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Evidence-based implementation of minimally invasive surgery

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Evidence-based implementation of Minimally Invasive Surgery

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Evidence-based implementation of Minimally Invasive Surgery

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Prof. dr. D. Oepkes

Prof. dr. M.Y. Bongers (MUMC, Maastricht)

Dr. C.A. Radder (OLVG, Amsterdam)

Voor Leon, Mees, Bregtje en mijn ouders

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Chapter 1

Introduction and outline of this thesis

Minimally invasive surgery

Surgery is a cornerstone of medical management, also in gynecology. Minimally invasive surgery (MIS) is a medical technology that intends to minimize surgical trauma. It encompasses surgical techniques that limit the size of incisions needed, resulting in lower postoperative patient morbidity compared with conventional open approaches. MIS is called a technology because it applies on scientific principles and keeps on advancing to make its appliances smarter and more efficient. The rapid evolution of this technology has led to the development of new surgical applications within the field of minimally invasive surgery.

As a result of technological developments, MIS evolved rapidly. Less visible scarring, less postoperative pain and rapid recovery after MIS have fuelled patient advocacy and enabled an increasing use of laparoscopy. For healthcare providers, laparoscopy has the benefit of shorter hospital stays and thus reduced inpatient costs. The benefits for the surgeon include the magnified optics and no-touch operative technique (1,2). There is indeed evidence that laparoscopy has advantages compared to the open abdominal technique (i.e. laparotomy), which include fewer surgical injuries, fewer postoperative complications, less postoperative pain and shorter hospital stays (3,4,5). At present, with advanced laparoscopic operations for pelvic organ prolapse, urinary incontinence and gynaecological cancers, laparoscopy has become completely integrated into the field of gynaecologic surgery.

Another minimally invasive technique that became popular in the late 1970s is hysteroscopy. Hysteroscopy is the inspection of the uterine cavity by endoscopy with a transcervical approach. With the evolvement of hysteroscopic procedures, female sterilization became one of the possibilities within the palette of hysteroscopic procedures. Hysteroscopic sterilization aims at the objective of minimally invasive surgery: less morbidity and a quicker return to normal activities, attempted through avoiding the transabdominal route.

The evolution of minimally invasive surgery has led to the development of many new technologies and techniques such as robot (-assisted) surgery, natural orifice transluminal endoscopic surgery (NOTES), and laparo-endoscopic single-site surgery (LESS). Robot surgery is a technological development where robotic systems are used to aid in surgical procedures (6). NOTES refers to surgery via natural orifices, where procedures are performed with transluminally placed instruments to gain access to the intra-abdominal cavity (7). LESS surgery is an advanced minimally invasive approach that allows laparoscopic operations to be undertaken through a single small incision, typically placed at the patient's umbilicus (8).

Evidence-based guidelines in MIS

Scientific evidence from clinical research supports us to acquire knowledge whether minimally invasive procedures serve their intended aims. Evidence-based medicine (EBM) aims to use scientific methods to guide interventions in healthcare. An evidence-based guideline is an instrument to integrate the best evidence from clinical research into clinical practice. Evidence-based guidelines also aim to reduce variations, to stimulate evidence-based clinical practice and to fulfil the internal and external (e.g. from health agencies and patient associations) need for transparency and controllability of healthcare.

In the Netherlands, the direct reason leading to development of an evidence-based guideline was the report of the Dutch Health Care Inspectorate '*Risico's minimaal invasieve chirurgie onderschat*' (9). The inspectorate had conducted a study of the risks presented by MIS procedures and observed many unsubstantiated pragmatic differences between general surgery, gynecology and urology. Though these specialisms practice relatively similar basic techniques, there was little cooperation to assure and improve the quality of MIS. Transcending the boundaries of monodisciplinary knowledge and skills and criticizing the differences between disciplines should result in multidisciplinary agreements to optimize patient safety. The involved professional bodies, mandated experts were to contribute to the development of the guideline.

Important topics that were identified from problem analysis for the MIS guideline were: laparoscopic entry techniques, intra-abdominal pressure, laparoscopic port instruments (i.e. trocars), port site closure, electrosurgical techniques, patient positioning, anesthesiology, perioperative care, patient information, multidisciplinary user consultation and complication registration. These problem topics were translated into clinical key questions. The scientific literature was systematically searched in collaboration with an information specialist. The scientific literature was summarised followed by a conclusion including the level of evidence. Then considerations, including patient preferences, availability of services, organization of care, impact of costs and legal consequences were discussed and recommendations were formulated. The recommendations in the guideline are the practical answer to the key question. They are based on 'evidence' (the summary of literature) and balanced with 'experience' (the considerations).

Evaluating the evidence of new techniques in MIS

One of the identified important topics concerned laparoscopic port instruments (i.e. trocars). In laparoscopic procedures, intraperitoneal access for laparoscopic instruments is provided via 'ports'. Specific cannulas, called trocars, are introduced through the abdominal wall to

create these ports. Trocars are commonly named in malpractice injury claims associated with laparoscopic procedures (10). The complications include intra-abdominal vascular and visceral injury, trocar site bleeding, herniation and infection. The incidence of trocar-related complications is estimated to be 3 to 4 per 1000 procedures (11,12). Of all trocar-related complications, vascular and visceral injuries are associated with the highest morbidity and mortality (11,13). Other trocar-related complications are trocar site herniation (TSH), trocar site bleeding and infection. It is important to determine how trocar-related complications may be prevented. It is hypothesized that trocar-related complications and pain may be attributable to certain types of trocars. Then, it would be possible to minimize trocar-related complications and pain. This question will receive further attention in this thesis.

The trocar designs illustrate the innovative character of MIS. To innovate, new designs and technologies are developed, introduced into surgical practice and evaluated for their clinical value. LESS was developed to extend the benefits of MIS: a single incision technique might offer advantages over the standard multiport laparoscopy as abdominal wall trauma is decreased, potentially leading to less postoperative pain and improved cosmesis (14,15,16). The potential drawbacks of the single port approach are a larger umbilical incision and the proximity of the instruments resulting in a technical challenge, especially for advanced surgery such as laparoscopic hysterectomy (17,18). Reports have currently shown the feasibility of LESS surgery in many benign gynecologic procedures (19,20). However, it remains debatable whether this new technology has added value over the existing conventional laparoscopic technique and whether it should be broadly implemented for hysterectomy.

Hysteroscopic sterilization is another MIS innovation aiming at the objectives of MIS: incision-free and with a reduced need for anesthesia which facilitates sterilization in an ambulatory setting. The initial techniques were difficult and inefficient. Failure rates were high, and serious complications by perforation and thermal bowel lesions were reported in clinical trials (21,22). Nevertheless there was continuing belief that hysteroscopic sterilization would be a suitable method for permanent contraception. In the past decades new systems became available, all with different mechanisms inducing fibrosis of the fallopian tubes leading to occlusion (23,24,25). These differing mechanisms may result in differences in feasibility, safety and effectiveness. Data from phase II and III clinical trials showed high feasibility and effectiveness, though their follow-up periods were relatively short (23,25,26). Hysteroscopic sterilization has limitations as well. Firstly, the likelihood of successful bilateral placement of the devices on first attempt varies from 76 – 96% (27). Secondly, hysteroscopic sterilization is not immediately effective; a period of 3 months is required for tubal fibrosis leading to tubal occlusion and contraceptive effectiveness. During these 3 months, women need to use alternative contraception until they can undergo a post procedure hysterosalpingogram (HSG). And thirdly, blockage does not occur in 5 – 16% of post procedural confirmation

tests (27). More than ten years after the introduction followed by broad clinical application, we question the feasibility, safety and effectiveness of current practice in hysteroscopic sterilization. Additionally, identifying risk factors for placement failure is important for patient selection and to identify cases at risk for failure of hysteroscopic sterilization. A review of the evidence of hysteroscopic sterilization techniques including an assessment of risk factors for failure is covered in this thesis.

Finally, a recently introduced innovation in MIS practice and to be evaluated is robotic-assisted surgery. In the late 1990s, MIS was introduced into urological surgical practice. Initially, surgeons adapting the laparoscopic radical prostatectomy (LRP) needed to overcome significant challenges and a significant learning curve (28). In 2000, the US company Intuitive Surgical Inc. launched the *da Vinci*® surgical system, leading to the development of robotic-assisted radical prostatectomy (RARP) in the early 2000s (29). This surgical system offered technological innovations such as 3D visualisation, articulated instruments and tremor filtration, which addressed some of the technical limitations of LRP. In 2016, the total worldwide procedure volume was approximately 653,000, therewith the *da Vinci*® dominates the market. However, the clinical implementation of robotic surgery in the Netherlands will be explored and discussed in the light of the available scientific evidence of RARP.

Randomised controlled trials in MIS

Clinical research generates knowledge that allows assessment whether the aims of MIS are targeted. Randomised controlled trials (RCTs) represent the best method to evaluate healthcare interventions (30). They are the most rigorous way of assessing the effectiveness of a treatment. RCTs aim to evaluate the (clinical) advances of new and existing medical technologies. The bundled outcomes of different RCTs should ultimately lead to a clear answer whether the new method should be used over the existing method. The Cochrane collaboration is globally known as an independent network where the best evidence from research is gathered and summarised for the use of high quality information to make health decisions (31). In the case of MIS, the question remains whether randomized controlled trials serve the clinical needs of MIS? Is the design of a RCT feasible to produce enough real data to inform clearly about the important clinical outcomes effectiveness and safety? It is suggested that RCTs might be less feasible in surgery than in other medical domains (32). Furthermore, concerns exist about the objectivity of the conclusions of published RCTs. The scientific literature on lung cancer and rheumatology showed substantial discordant conclusions in the abstract versus article (33) and misleading conclusions (34). In order to investigate the usefulness of RCTs on MIS, we explore the clinical importance of study outcomes in RCTs in MIS, whether these RCTs are set up sufficiently to answer the study question and if their conclusions correspond to their results.

Thus, the current thesis explores the evidence base of new techniques in minimally invasive surgery. For this purpose the main objectives of this thesis are:

- To present a multidisciplinary evidence-based guideline for MIS including the main topics in laparoscopic surgery;
- To identify the evidence of three new minimally invasive techniques: trocar types for laparoscopy, LESS-hysterectomy and hysteroscopic sterilization;
- To evaluate the course of introduction of a new minimally invasive technique (robot-assisted surgery) and the status of the evidence;
- To assess whether recent RCTs serve the clinical needs of the MIS approach.

Outline of this thesis

Chapter 2 describes the development of a multidisciplinary evidence-based guideline for minimally invasive surgery. Recommendations for clinical practice are formulated based on the evidence and a consensus of expert opinion aiming towards better patient care and safety.

Chapter 3 describes a systematic review of randomized controlled trials that aims to determine whether specific trocar designs can be recommended for use in people undergoing laparoscopy, with a goal to minimize trocar-related complications and postoperative pain.

Chapter 4 compares the safety and effectiveness of laparoendoscopic single-site surgery (LESS) and conventional laparoscopic hysterectomy using a systematic review and meta-analysis.

Chapter 5 contains a systematic review that assesses whether hysteroscopic sterilization is feasible and effective in preventing pregnancy. Secondly risk factors for failure of hysteroscopic sterilization are identified.

Chapter 6 evaluates the clinical implementation of robot-assisted surgery in the Netherlands. Furthermore the results of a systematic review on the effectiveness and safety of most frequently performed robot-assisted surgical procedure: radical prostatectomy is discussed.

In **Chapter 7** we inquire if randomised controlled trials serve the clinical needs of minimally invasive surgery. We critically appraise the clinical relevance, clearness and objectivity in randomised controlled trials on gynaecological minimally invasive surgery.

Finally, in the general discussion a summary of the most important findings of this thesis will be outlined and perspectives for future research will be given. Eventually, based on the evaluated evidence-base of new techniques in minimally invasive surgery guidance towards more useful research in minimally invasive surgery will be provided.

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PART 1



Chapter 2

A multidisciplinary evidence-based guideline for minimally invasive surgery

Part 1: Entry techniques and the pneumoperitoneum

Claire F. La Chapelle, Willem A. Bemelman, Bart M.P. Rademaker, Teus A. van Barneveld, Frank Willem Jansen, on behalf of the Dutch multidisciplinary guideline development group Minimally Invasive Surgery

Gynecol Surg (2012) 9:271-82

Part 2: Laparoscopic port instruments, trocar site closure and electrosurgical techniques

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Gynecol Surg (2012) 10:11-23

PART 1 ENTRY TECHNIQUES AND THE PNEUMOPERITONEUM

Abstract

Background: The Dutch Society for Endoscopic Surgery together with the Dutch Society of Obstetrics and Gynecology initiated a multidisciplinary working group to develop a guideline on minimally invasive surgery to formulate multidisciplinary agreements for minimally invasive surgery, aiming towards better patient care and safety.

Methods: The guideline development group consisted of general surgeons, gynecologists, an anesthesiologist and urologist authorized by their scientific professional association. Two advisors in evidence-based guideline development supported the group. The guideline was developed using the ‘Appraisal of Guidelines for Research and Evaluation’ instrument. Clinically important aspects were identified and discussed. The best available evidence on these aspects was gathered by systematic review. Recommendations for clinical practice were formulated based on the evidence and a consensus of expert opinion. The guideline was externally reviewed by members of the participating scientific associations and their feedback was integrated.

Results: Identified important topics were: laparoscopic entry techniques, intra-abdominal pressure, trocar use, electrosurgical techniques, prevention of trocar site herniation, patient positioning, anesthesiology, perioperative care, patient information, multidisciplinary user consultation and complication registration. The text of each topic contains an introduction with an explanation of the problem and a summary of the current literature. Each topic was discussed, considerations were evaluated and recommendations were formulated. The development of a guideline on a multidisciplinary level facilitated a broad and rich discussion, which resulted in a very complete and implementable guideline.

Introduction

Since the early 1990s, ‘minimally invasive surgery’ (MIS) or laparoscopic surgery has been rapidly implemented into a variety of surgical disciplines. Accordingly, new risks have emerged and complications of laparoscopic surgery are constantly being evaluated. The Dutch Healthcare Inspectorate (IGZ) conducted a study of the risks presented by MIS procedures and observed many unsubstantiated differences between general surgery, gynecology and urology. Although the basic knowledge and skills are identical regardless of specialism, multidisciplinary agreements were lacking. The Dutch Healthcare Inspectorate encouraged different specialties performing laparoscopy to work together and develop a multidisciplinary guideline for MIS.

This guideline represents a review of the evidence and consensus clinical opinion. The objective of this guideline is to provide guidance for MIS in daily practice. By formulating multidisciplinary agreements, the aim is to increase patient safety in MIS. It is intended primarily for all specialists performing laparoscopic surgery or those directly involved. This guideline can also be used as a standard by patients, patients’ organizations, hospital organizations, health insurances and government agencies. The scope of this guideline is laparoscopy in general, specific laparoscopic procedures are not addressed. Different aspects in MIS are described, including: laparoscopic entry techniques, pneumoperitoneum, trocar use, electrosurgical techniques, prevention of trocar site herniation, patient positioning, anesthesiology, perioperative care, patient information, multidisciplinary user consultation and the registration of complications.

In this first of two papers on the multidisciplinary guideline we present our literature reviews, conclusions and practical recommendations for entry techniques, and the pneumoperitoneum.

Methods

The Dutch Society for Endoscopic Surgery (NVEC) together with the Dutch Society for Obstetrics and Gynecology (NVOG) initiated a multidisciplinary working group to develop a guideline on MIS. Two general surgeons, two gynecologists, a urologist and an anesthesiologist participated in the guideline working group. All were authorized by their scientific professional association (the Dutch Society of Surgery, the Dutch Urological Association and the Dutch Association of Anesthesiologists respectively). Because of the surgical technical contents, patients were not involved in the guideline development.

The guideline was developed consistent with the 'Appraisal of Guidelines for Research and Evaluation' (AGREE) instrument (1). Initially, the working group performed a problem analysis to define the scope and topics of the guideline. These problem-topics were translated into clinical key questions and the scientific literature was searched for answering the key questions. Separate search strategies were developed for each problem-topic. Searches were conducted in collaboration with information specialists. Studies were limited to English and Dutch language in view of the limitations on time and resources. The search strategies are appended (see appendix). The developers selected relevant literature. The bibliographies of relevant articles were hand searched for other valuable references. The characteristics and methodological quality of the studies were assessed using the checklists from the Dutch Cochrane Center (2). The evidence was summarized in evidence tables and in the guideline text. The grading system of the Dutch Institute for Healthcare improvement CBO, was used to level the evidence (table 1). The guideline text is structured according to a prescribed Evidence Based Guideline Development (EBGD) format. Each defined key question has its own text-section that comprises the clinical key question followed by a summary of the literature and a conclusion including the level of evidence. Then, considerations (including: patient preferences, availability of services, organization of care, impact on costs, legal consequences) are discussed and each section ends with recommendations. The recommendations are the practical answer to the key question. They are based on 'evidence' (the summary of literature) and balanced with 'experience' (the paragraph considerations). An illustrative overview of the EBGD process is shown in figure 1.

Background

The incidence of laparoscopic complications described in the literature varies considerably. Reported complication rates vary from 1.0 to 12.5 per 1,000, depending on the retrospective or prospective nature of the study, the definition of 'complication', the experience of the surgeons, the characteristics of the study-participants and the complexity of the procedure. The largest reported studies on complication rates in laparoscopy are based on gynecologic procedures. The Finish National Insurance Association registered a total of 256 complications in 70,607 gynecologic laparoscopic procedures (3.6 / 1,000). The incidence of gastrointestinal injuries was 0.6 / 1,000, of urological injuries 0.3 / 1,000 and of vascular injury 0.1/1,000 (3). A Dutch prospective multicenter study reported 145 complications in a total of 25,764 gynecologic laparoscopies (5.7 / 1,000). Two fatal cases were described and in 84 procedures a complication resulted in conversion to laparotomy. The incidence of gastrointestinal injuries was 1.13 / 1,000, and of intra-abdominal vessels 1.05 / 1,000. 57% of the complications were entry-related (closed and open-entry techniques were included). Women who had undergone a prior history of laparotomy, had an increased risk of complications (4).

Table 1 Grading system for level of evidence

Level	Studies on therapy/prevention	Studies on diagnostic accuracy	Studies on harm, etiology or prognosis
A1	Systematic review/meta-analysis of at least two independent studies of A2 level with consistent results.		
A2	Double-blind randomized controlled trial of good quality and sufficient power	Study with respect to a reference test (gold standard) with pre-defined cut-off values, among large series consecutive persons that received both the index and the reference test and adequate blinding of interpretation of test results.	Prospective cohort study of sufficient power and follow-up, adequate control for confounding and selective follow up.
B	Randomized controlled trial of modest quality or insufficient power, or other analytic study (e.g. case-control study, cohort study)	A comparison with a reference standard that does not meet the criteria required for level A2 evidence.	Prospective cohort study that does not meet the criteria required for level A2 evidence. Or retrospective cohort study or case-control study.
C	Non-analytic study		
D	Expert opinion		
Level	Conclusion based on		
1	One systematic review (A1) or at least two independent randomized controlled trials of level A2.		
2	One study of level A2 or at least 2 independent studies of level B.		
3	One study of level B or C.		
4	Expert opinion		

Grading system used at the Dutch Institute for Healthcare Improvement CBO.

Other complications in laparoscopy are a pneumothorax or subcutaneous emphysema, with reported incidences of 1.9% and 2.3% respectively (5). Pneumothorax is frequently seen together with subcutaneous emphysema and associated with inadequate insufflation of CO₂ through an improperly placed trocar or Veress needle (6,7). Subcutaneous emphysema may also occur when pressurized CO₂ moves into pre-existing or iatrogenic defects in the diaphragm or retroperitoneum. Due to its good solubility, CO₂ is rapidly absorbed in the blood circulation and may lead to an increase in hypercapnia and acidosis. Subcutaneous emphysema located in the head and neck area can lead to airway obstruction. The airways should therefore be secured until all emphysema has been dissolved (8).

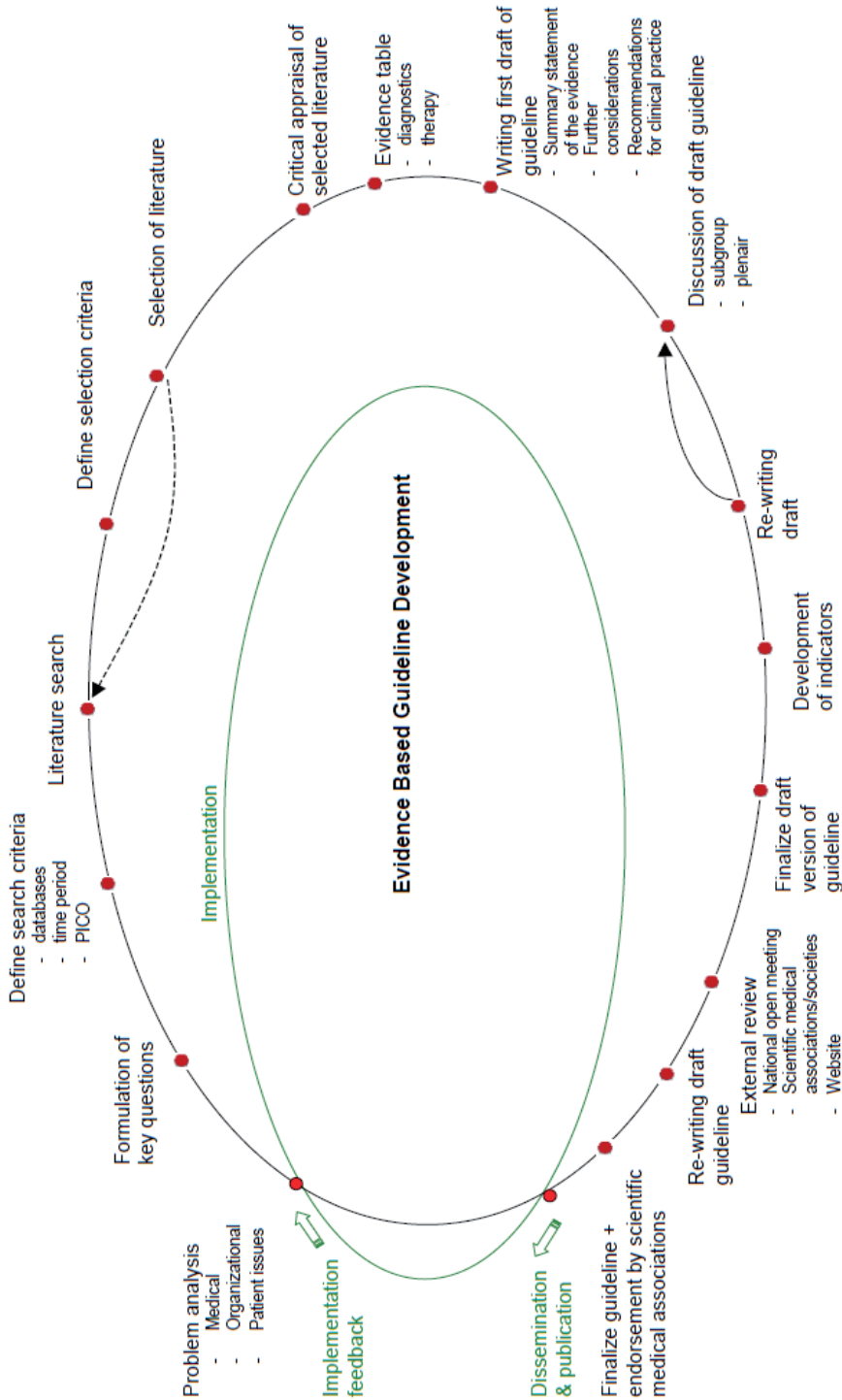


Figure 1 Overview of the developmental process in EBGD. Source: Dutch Institute for Healthcare Improvement CBO.

The incidence of complications related to laparoscopy is low; however they can be very severe. More than 50% of laparoscopic complications are entry-related and these occasionally require emergency surgery. Basically two different entry techniques can be distinguished: the open and closed-entry technique. Surgeons and urologists often use the open technique with Hasson trocar (also called the Hasson technique) (9) while gynecologists often use the closed technique with blind introduction of the Veress needle and primary trocar. The risks associated with the two different techniques are investigated and can be variously interpreted. The text below describes the strategies for a safe application of entry techniques in laparoscopy.

Key question

Which entry technique, open or closed, is associated with the lowest risks for complications?

Summary of the literature

Injuries of the intra-abdominal vessels and bowel are known entry-related complications. Since the incidences of these complications are low, a randomized controlled trial (RCT) would not be the appropriate design to detect risk differences. To detect a risk difference for bowel injury from 0.3 to 0.2%, over 800,000 patients would be needed for inclusion in a RCT (10).

In a Cochrane review different entry techniques were compared in terms of their influence on intraoperative and postoperative complications (11). The outcomes were divided into major complications (mortality, vascular injury, bladder injury, bowel injury, gas embolism, solid organ injury) and minor complications (e.g., extraperitoneal insufflation, trocar site bleeding). Two RCTs were included (a total of 210 patients enrolled) wherein open and closed-entry techniques were compared. No significant risk differences were found for major and minor complications, neither in more specified analyses. In 2001, the Australian College of Surgeons systematically reviewed the effectiveness and safety of entry techniques for establishing a pneumoperitoneum in laparoscopic surgery. Besides RCTs, other relevant studies with different study designs were included. The outcome data for bowel injury and vascular injury in five nonrandomized prospective and retrospective comparative studies were pooled. A higher risk of bowel injury showed for the open compared to the closed-entry technique (RR 2.17, 95% CI: 1.14 to 4.10). No statistical significant risk difference was found comparing the open versus closed-entry technique for vascular injury (RR 0.68, 95% CI: 0.16 to 2.84) (12).

Interpreting these results, the potential for selection bias should be taken into account. For example, the open-entry technique would often be the preferred technique in patients with

previous abdominal surgery. This selection bias may result in an increased relative risk of bowel injury for the open-entry technique compared to the closed-entry technique.

Conclusion

Level 1	No significant risk differences have been found for bowel and vascular injuries, when comparing the open-entry to the closed-entry technique. <i>Evidence level A1 (11)</i>
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Considerations

Theoretically, it could be claimed that retroperitoneal vascular injury can be prevented by using the open-entry technique and thereby eliminating the potential for abrupt and uncontrolled introduction of the primary trocar that may result in a deeper penetration than needed. This risk is inherent in the closed-entry technique and thus vigilance is needed. In practice, it shows that the risk of uncontrolled introduction reduces by gaining experience. No robust conclusions can be drawn from the results of nonrandomized studies because of insufficient power and a high risk of bias.

Recommendations

- In general, no completely safe entry technique can be recommended. Specialists should preferably practice the technique they have learned and with which they are familiar. According to expert opinion, experience with a particular entry technique will reduce the risks of complications. Exceptions to this rule are: patients with prior abdominal surgery, obese patients, very thin patients and pregnant patients.

Key question

How should the closed- and open-entry techniques be performed?

Summary of the literature

There are no comparative studies of good methodological quality about differing aspects in specifically closed- and open-entry techniques. The majority of the studies are descriptive and based on expert opinions.

Closed-entry technique: placement of the Veress needle

The Veress needle will be checked for its potency and spring action before inserting it into the abdomen. This is to ensure a free flow of CO₂ and the protective function of the blunt tip. The blunt tip emerges out of the sharp end to protect the bowel and other intra-abdominal organs from inadvertent puncture.

The abdominal wall is lifted until a 45° angle to the horizontal. This can be done by lifting the skin at the umbilicus by hand or with a towel clip. In the Cochrane review on laparoscopic entry techniques, one RCT was included comparing abdominal wall lifting versus not lifting for placement of the Veress needle. Not lifting the abdominal wall showed less failed entries, with no difference in complication rate. According to the experts however, abdominal wall lifting is aimed to prevent compression and thereby reduction of distance between instruments and retroperitoneal structures. The Veress needle is inserted perpendicular to the fascia and then directed towards the surgical field, avoiding the major vessels.

There are several tests to verify the correct position of the Veress needle tip. Different tests were evaluated in an observational study and it was concluded that a low initial gas pressure (< 10 mm Hg) followed by a free influx of CO₂ is the only valuable measure to reflect correct intraperitoneal Veress needle placement (13).

Conclusions

Level 3

A low initial gas pressures (< 10 mm Hg), followed by a free influx of CO₂, is a reliable indicator of correct intraperitoneal Veress needle placement.

Evidence level B (13)

Level 4

There are insufficient high-quality comparative studies on safety and effectiveness of the different aspects in the specific open- and closed-entry techniques.

Evidence level D (opinion of the guideline development group)

Considerations

In practice, for selected patients only specific entry techniques are applied. An adequate selection is required.

During every laparoscopic procedure, instruments to perform a laparotomy should be available. These could be necessary in case injury occurs for which a conversion is required. Prior to the closed-entry technique, the patient is catheterized or an indwelling catheter is inserted. A naso-gastric tube can be used. A filled stomach or bladder may hinder the placement of laparoscopic instruments or these structures can be damaged. Positioning the patient in Trendelenburg prior to the insertion of laparoscopic instruments could theoretically increase the risk of inadvertent aortic puncture. In most cases, the primary incision is preferred in the umbilicus because it overlies the location where the skin, fascia, and parietal peritoneum converge and fuse. Consequently, the distance between skin and abdominal cavity is short and an umbilical incision generally has a good cosmetic result. The skin incision should be large enough to prevent overshoot injury. In lean patients it must be avoided that the skin incision already involves the fascia. One should avoid stab incision. These precautions are not sufficiently investigated, but are considered common sense.

Closed-entry technique: insertion of the primary trocar

After the pneumoperitoneum is achieved and the Veress needle is removed, the primary trocar is inserted through the umbilical incision in the same directions as the Veress needle. When using a normal intra-abdominal pressure (IAP; 12 – 16 mm Hg), the umbilicus should be lifted and fixed as with the insertion of the Veress needle. Every move associated with introduction of the instrument should be well controlled. It is recommended to open the valve of the trocar to hear if the tip is located in the abdominal cavity. After inserting the laparoscope, visual inspection is intended to check for iatrogenic injuries and intraperitoneal aberrations.

Open-entry technique: insertion of the primary trocar

In the open-entry technique the introduction of sharp instruments is avoided. A small incision is created and the layers of the abdominal wall are incised. The peritoneum is opened bluntly or sharply. When reaching the peritoneal cavity this is often visible and can be verified by palpation with a finger. The primary trocar is then inserted and CO₂ is inflated to create the pneumoperitoneum. Today, balloon blunt-tip trocars are commonly used. The distal end of the sleeve has an inflatable balloon to create an air-tight fixation of the trocar.

Trocar removal

At the end of each laparoscopic procedure, the removal of all trocars should be under direct vision. As yet, unnoticed injuries, e.g. tamponaded hemorrhage or bowel perforation, can be detected. Thereby, trocar site herniation can possibly be prevented by avoiding bowel or omental tissue is pulled into the trocar site.

Recommendations for the closed-entry technique

- Prior to continuing the insufflation, the initial IAP should be <10 mm Hg (measured via Veress needle).
- Prior to the closed-entry technique, it is preferable to insert a nasogastric tube and to empty the urinary bladder.

General recommendations for primary entry

- Instruments to perform an emergency laparotomy should be available at close hand. These could be necessary in case a complication occurs for which conversion is required.
- During primary entry, the patient must be positioned horizontally until the primary trocar is safely inserted. The umbilicus can be stabilized by lifting it, this can prevent compression and consequent reduction of distance between instruments and retroperitoneal structures.
- After opening the peritoneum and prior to the introduction of the (blunt) primary trocar, it is important to ensure that the peritoneal cavity has been reached.
- The primary trocar must be introduced in a controlled manner, at an angle of 90 ° to the fascia. Once the peritoneal cavity has been reached, the insertion must be stopped immediately.
- After introduction of the laparoscope, the abdomen must be inspected for adjacent bowel by rotating the laparoscope 360°. If adjacent bowel is observed, it must be inspected for (signs of) hemorrhage, lesion and retroperitoneal hematoma.
- The removal of all trocars should occur under direct vision, to recognize a tamponaded hemorrhage or a bowel perforation that has not been noticed, and to prevent bowel or omental tissue to be pulled into the trocar site.

Key questions

Closed-entry technique and IAP:

1. What IAP should be achieved prior to insertion of the primary trocar?
2. What IAP should be applied once the insertion of trocars is complete?

Summary of the literature

When applying 'peritoneal hyperdistention', the abdomen is insufflated to 25 – 30 mm Hg before inserting the primary trocar. After introduction of the trocars, the IAP is reduced to a normal pressure (12 – 16 mm Hg).

Prospective observational studies have shown that the increased size of the 'gas bubble' has a splinting effect and allows the trocar to be more easily inserted through the layers of the abdominal wall. Furthermore, when force is applied to a hyper-distended abdomen (25 mm Hg), the depth under the umbilicus is larger, compared to a normally distended abdomen (10 mm Hg) (14). An increased IAP induces a hemodynamic stress response. The venous return from the lower extremities alters, cardiac output decreases and there is an increase in mean arterial pressure (MAP) systemic, pulmonary and vascular resistances (15-17). In a prospective observational study, significant hemodynamic changes were observed when the IAP was elevated above 12 mmHg. There was a decrease in stroke volume and cardiac output and an increase in MAP and systemic vascular resistance (18).

No studies were found that analyzed for the upper limit of IAP. Neither systematic reviews nor RCTs evaluating the clinically relevant consequences of 'peritoneal hyperdistention' were found. In a prospective cohort study including 100 women undergoing gynecological laparoscopy, hemodynamic changes were analyzed. High pressures (25 – 30 mm Hg) resulted in minimal changes in heart rate and blood pressure and a statistical significant decrease of pulmonary compliance, all without clinically relevant consequences (19). This study was conducted in healthy women with classified American Society of Anesthesiologists scores (ASA) I and II. The hemodynamic and pulmonary consequences of 'peritoneal hyperdistention' has not been studied in men and patients with higher ASA-scores. A larger prospective cohort study (1,150 consecutive ASA I patients undergoing gynecological laparoscopy) investigated the safety of the pressure technique for insertion of the primary trocar. No insertion complications or adverse clinical effects were noted during hospital stay (20).

In a Cochrane review, the harms and benefits of the low pressure pneumoperitoneum (< 12 mmHg) compared with standard pressure pneumoperitoneum (12 – 16 mmHg) were assessed in patients undergoing laparoscopic cholecystectomy (21). A total of 15 RCTs were included (690 patients), all with high risk of bias. There was no difference in mortality, postoperative complications, or conversion to open cholecystectomy between the groups. None of the trials reported any cardiopulmonary complications. Only patients with ASA I scores were included in the trials, together with a low overall incidence of cardiopulmonary complications (0.5% in a case series of 400 patients, 70% of the patients were scored ASA I) (22) the meta-analysis was under powered. In seven trials, the outcome data were incomplete: reasons for conversion were not reported. This caused a high risk of bias and thus the safety of the low-pressure pneumoperitoneum could not be ascertained (21).

Conclusions

Level 1

The safety of low pressure pneumoperitoneum (< 12 mm Hg) has only been studied in patients undergoing cholecystectomy. It is uncertain whether low pressures in comparison with conventional pressures, result in equal risks of morbidity and conversion to open surgery.

Evidence level A1 (21)

Level 2

Elevated IAP above 12 mm Hg is associated with significant hemodynamic effects. These effects did not demonstrate any clinically relevant consequences.

Evidence level A2 (18)

Level 3

‘Peritoneal hyperdistention’ has only been studied and found to be safe in healthy female patients with ASA scores I or II.

Evidence level C (19,20)

Level 3

‘Peritoneal hyperdistention’ (insufflation to IAP 25 – 30 mm Hg), results in an increased size of ‘gas bubble’ and a splinting effect of the abdominal wall, compared to the traditional, limited-volume pneumoperitoneum.

Evidence level C (14)

Considerations

The abdominal wall cannot be lifted when the abdomen is hyperdistended. Thus when using the ‘peritoneal hyperdistention’ technique, the primary trocar is inserted perpendicular to the abdominal wall.

‘Peritoneal hyperdistention’ can result in hemodynamic changes and compromise the respiratory ventilation of the patient. The anesthesiologist should therefore be informed when changing the IAP. ‘Peritoneal hyperdistention’ should last no longer than necessary: after introduction of the trocars, the IAP should be reduced to a normal pressure (12 – 16 mm Hg). High pressures did not result in any clinically relevant compromises in healthy patients but could possibly have more clinically significant effects in patients with ASA III and IV scores.

RCTs have shown that the use of a low pressure pneumoperitoneum results in less hemodynamic changes (22), less shoulder pain (23,24), less postoperative pain (25) and less use of analgesics (24,25). However, main criticism of low pressure pneumoperitoneum is its ability to provide adequate surgical exposure and its safety.

Recommendations for IAP

- Before blind introduction of the primary trocar, the IAP must be at least 12 – 16 mm Hg. The ‘pressure technique’ to 25 – 30 mm Hg may be applied briefly in selected patients.
- After introduction of the trocars, the IAP must be reduced to a normal pressure (12 – 16 mm Hg, depending on patient characteristics) creating sufficient distension to perform laparoscopy and where the anesthesiologist can provide safe and effective pulmonary ventilation.

Key question

What alternative entry techniques are available?

Summary of the literature

Direct trocar entry

The direct trocar entry has been described as an alternative to the Veress needle technique. The primary entry is initiated with one blind step instead of two (Veress needle and trocar). The direct trocar entry is faster than any other method of entry (26). In the Cochrane review on laparoscopic entry techniques, a meta-analysis was performed comparing direct trocar entry to Veress needle entry. A total of 1,909 participants in six RCTs were included and no major complications occurred with both techniques (27-32). There were however, statistically significant reductions in the risk of extraperitoneal insufflation and failed entry in the direct-entry group (OR 0.06; 95% CI 0.02 – 0.023) and 0.22; 95% CI 0.08 – 0.56 respectively) (11).

Other entry systems

Different entry-systems have been developed to reduce the risk of entry-related complications: direct-vision entry systems (33,34), radially expanding trocars (35), tapered blunt tipped trocars (TrocDoc, second generation Endotip®) (36). For the Cochrane review, no RCTs comparing direct-vision versus Veress needle entry were identified. There were no other observational studies with sufficient power to demonstrate a risk reduction for major complications when direct-vision entry was used. The Cochrane review on laparoscopic

entry techniques concludes that radially expanding access trocars offer advantages in terms of reduced trocar site bleedings, less extraperitoneal insufflations and failed entries (11,34,37,38). RCTs and other observational studies comparing tapered blunt tip-systems with the conventional Veress needle or open-entry technique did have insufficient power to demonstrate risk reductions for any complication.

Needlescopes are optical Veress needles with 1 – 2 mm diameter (39). There is as yet no evidence for their superiority compared to the conventional Veress needle entry.

Conclusions

Level 1

Direct-trocar entry leads to fewer extraperitoneal insufflations and failed entries when compared with Veress needle entry.

Evidence level A1 (11,27-32)

Level 1

For primary entry, radially expanding access trocars reduce the risks for trocar site bleedings, extraperitoneal insufflations and failed entries compared to conventional trocars.

Evidence level A2 (11,34,37,38)

Level 3

There is no evidence that use of direct vision systems, a tapered blunt tipped trocar or a needlescope for primary entry with is safer than the conventional open- or closed-entry techniques.

Evidence level C (26,40)

Considerations

Some RCTs excluded specific patient groups, e.g. patients with previous abdominal surgery, obese patients or patients at risk for subumbilical adhesions. Therefore, the results of these RCTs do not apply for the complete laparoscopic patient population. For a select patient group, the direct-trocar entry seems a safe and fast method with a lower risk of extraperitoneal insufflation and failed entry compared to Veress needle entry. This technique is not widely used in laparoscopic practice, probably because extensive experience is required for its use.

Moreover, high costs of newly developed systems could be a limiting factor for their use. Studies on cost effectiveness should be conducted to make informed choices for the use of specific instruments in laparoscopic practice.

Recommendations for alternative entry techniques

- The guideline development group does not recommend the use of direct trocar entry, since much experience is needed for safe application of this technique.
- The use of visual entry systems is only recommended when an adequate pneumoperitoneum (with the Veress needle) has been created.
- Radially expanding trocars are an expensive alternative to standard trocars. The use of these trocars may reduce trocar site bleedings and extraperitoneal insufflations.

Key question

What alternative sites can be safely used for insertion of the Veress needle and primary trocar?

Summary of the literature

The rate of adhesion formation at the umbilicus may occur up to 50% in patients following midline laparotomy and 23% following low transverse incision (41). A Veress needle or trocar should never be blindly inserted at a site where adhesions may be expected. In those cases, the umbilicus is not the appropriate site for closed-entry. The most usual alternative site following laparotomy, is in the left upper quadrant via Palmer’s point. Palmer’s point is located 3 cm below the costal margin in the midclavicular line. Adhesions are rarely formed in this area, though, in cases of previous surgery in this area or splenomegaly, Palmer’s point may as well be inappropriate.

It remains unclear what rates of adhesion formation are found in patients following laparoscopy and thus which entry location is most suitable following a prior laparoscopy.

Conclusion

Level 3	When periumbilical adhesions may be expected, Palmer’s point is the appropriate site for insertion of the Veress needle and primary trocar. <i>Evidence level C (41)</i>
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Considerations

When periumbilical adhesions are suspected, either an open-entry technique or a closed-entry at a different location (preferably Palmers' point) must be performed. It could be an option to insert the primary trocar subumbilical, after first having excluded periumbilical adhesions with a needlescoop (42).

Other sites for insertion of the Veress needle and trocar have been described (suprapubic, through the uterine fundus or posterior fornix) but, given the greater risks of complications, are to be avoided.

Recommendation for alternative entry site

- In the event of doubt or suspected periumbilical adhesions, the Veress needle and primary trocar should not be introduced at the umbilicus. An alternative technique (e.g., the open-entry technique or insufflation at the point of Palmer) should be chosen.

Key question

How should secondary ports be created?

Summary of the literature

The safety of different methods to create secondary ports has not systematically been studied. A prospective observational study showed that 64% of the superficial epigastric vessels could be identified with transillumination. Laparoscopic visualization successfully identified 82% of the inferior epigastric vessels. Both methods were less effective as patient's weight increased (43).

The insertion of secondary ports should be visualized laparoscopically, taking care to avoid injury to the vessels and viscera. Suprapubic insertion of a trocar puts the bladder at risk of damage; therefore the bladder should be visualized. If the margins of the bladder are unclear, the bladder can be filled retrograde.

Conclusion

Level 3	Superficial epigastric vessels can be visualized with transillumination. Deeper epigastric vessels can be visualized laparoscopically. <i>Evidence level B (43)</i>
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Considerations

Secondary ports are inserted perpendicular to the skin to minimize the iatrogenic defect in the fascia. Once the tip has passed the peritoneum it is directed towards the surgical site. The inferior epigastric vessels should be visualized laparoscopically to ensure that the entry site is away from the vessels. The deep epigastric arteries and venae comitantes are located lateral to the lateral umbilical ligaments. The visualization can be difficult in obese patients. Then, the incision should be placed lateral to the rectus sheath, taking care to avoid injury of the pelvic side wall.

Recommendations for secondary ports

- The superficial epigastric vessels should be visualized by translumination prior to the insertion of secondary trocars. Deeper epigastric vessels should be visualized laparoscopically.
- When inserting the secondary trocars, this must be under direct vision and with presence of an adequate pneumoperitoneum. The trocars should be inserted perpendicular to the fascia and then directed towards the surgical site.
- When a suprapubic port is inserted, attention must be paid to the localization of the bladder. Retrograde filling of the bladder is possible.

Key question

What entry techniques should be applied for laparoscopy in a pregnant patient, a patient who is very thin or a patient with morbid obesity?

Summary of the literature

No trials that compare different entry techniques in pregnant patients or very thin patients or patients with morbid obesity have been described. There is some descriptive literature for these specific patient groups.

The pregnant patient

Concerning pregnant patients, there are specific concerns for a higher likelihood of injury to the uterus or other intra-abdominal organs. From 12 weeks of gestation, the fundal height of the uterus increases rapidly. The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) published a guideline on laparoscopy in pregnancy (44,45). In this guideline the authors recommend that in the second and third trimesters of pregnancy, the site of entry should be adapted to the fundal height: from the umbilicus towards subcostal regions (46). In their opinion, through this adjustment together with elevation of the abdominal wall during insertion, both the Hasson technique and Veress needle entry could be safely and effectively utilized.

The very thin patient

In children and extremely thin patients ($\text{BMI} < 18 \text{ kg/m}^2$), the aorta may lie less than 2.5 cm under the skin (47). These patients are at particular risk of retroperitoneal vascular injury during primary entry and for this reason, the open-entry technique or closed-entry at Palmer's point are preferable.

The obese patient

The site for primary entry, umbilicus or Palmer's point, in obese patients should depend on the body habitus and distribution of fat. The location where the thinnest subcutis is expected is best used for inserting the Veress needle or trocar. The open as well as the closed-entry technique can be applied. If the Veress needle is inserted vertically downward at the umbilicus, the mean distance from the lower margin of the umbilicus to the peritoneum is 6 cm (with a standard deviation of 3 cm). In this way it is possible to use a Veress needle with standard length, even in extremely obese patients.

Conclusion**Level 4**

There is insufficient qualitative data comparing the safety of different entry techniques in pregnant patients, very thin patients and patients with morbid obesity.

Evidence level D (opinion of the MIS guideline development group)

Considerations

In a pregnant patient, blind insertion of a Veress needle or trocar gives an additional risk of injury of the uterus. The SAGES describes a closed-entry can be considered, however, in our opinion, an open-entry technique is preferable. Since the fundal height can be increased in the first trimester due to a twin pregnancy or myomas, the open techniques is recommended in all trimesters. Attention should be paid to other aspects of laparoscopy in pregnancy as well: positioning, IAP, fetal monitoring and possibly medicinal tocolysis.

Recommendations for specific patient groups

- In pregnant patients, the open-entry technique or closed-entry technique via Palmers' point is preferred.
- In patients with underweight (BMI < 18 kg/m² and children) the open-entry technique or closed-entry via Palmers' point is preferred.
- In patients with morbid obesity (BMI > 40 kg/m²), the closed-entry technique via the umbilicus or Palmers' point is preferred.

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Appendix

Subject	Database	Search terms
Entry	Medline (OVID) 1950 – Aug 2010	1. Laparoscopy/ 2. exp *Laparoscopy/ 3. Surgical Procedures, Minimally Invasive/ 4. "lapar*scop*".m_titl. 5. "minimal invasive*".m_titl. 6. or/1-5 7. ("laparoscopic injur*" or "laparoscopic entr*" or "laparoscopic adj2 complication*" or "closed laparoscop*" or "open laparoscop*" or "direct-entry adj2 laparoscop*").ti,ab. 8. 6 and 7 9. limit 8 to yr="2006 -Current" 10. RCT (filter) 11. SR (filter) 12. exp epidemiological studies/
	Embase	laparoscop*:ti OR 'laparoscopy'/exp/mj OR 'minimal invasive':ti OR 'laparoscopic surgery'/exp AND ((laparoscopic NEAR/1 injur*):ab,ti OR (laparoscopic NEAR/1 entr*):ab,ti OR (laparoscopic NEAR/1 complication*):ab,ti OR (closed NEAR/1 laparoscop*):ab,ti OR (open NEAR/1 laparoscop*):ab,ti OR 'direct entry':ab,ti) AND [embase]/lim AND [2006-2011]/py
Pneumo-peritoneum	Medline (OVID) 1950 – March 2010	1. exp *Laparoscopy/ 2. Surgical Procedures, Minimally Invasive/ 3. "lapar*scop*".m_titl. 4. "minimal invasive*".m_titl. 5. or/1-5 6. Pneumoperitoneum, Artificial/ae [Adverse Effects] 7. 6 and 7
	Embase	laparoscop*:ti OR 'laparoscopy'/exp/mj OR 'minimal invasive':ti OR 'laparoscopic surgery'/exp AND (intraperitoneal NEAR/5 pressure OR intraperitoneal NEAR/5 insufflation) NOT [animals]/lim Searchfilter RCTs

The literature search for entry techniques was based on the search strategy of the Green-top Guideline 'Preventing entry-related gynaecological laparoscopic injuries' from the Royal College of Obstetricians and Gynaecologists. Medline and Embase were searched for relevant randomised controlled trials, systematic reviews and meta-analyses. The search was restricted to articles published in Dutch and English from 1966 to Augustus 2010.

PART 2 LAPAROSCOPIC PORT INSTRUMENTS, TROCAR SITE CLOSURE AND ELECTROSURGICAL TECHNIQUES

Abstract

Background: Minimally invasive surgery (MIS) is practiced by different surgical disciplines applying similar basic techniques. In 2007, the Dutch Healthcare Inspectorate indicated the need for a guideline including multidisciplinary agreements for MIS aiming towards better patient care and safety.

Methods: A multidisciplinary guideline development group was founded consisting of general surgeons, gynecologists, an anesthesiologist and a urologist. All members were authorized by their scientific professional associations. Clinically important aspects were identified and discussed. The best available evidence on these aspects was gathered by systematic review. Recommendations for clinical practice were formulated based on the evidence and a consensus of expert opinion. The guideline was externally reviewed by members of the participating scientific associations and their feedback was integrated.

Results: Identified important topics were: laparoscopic entry techniques, intra-abdominal pressure, laparoscopic port instruments, electrosurgical techniques, prevention of trocar site herniation, patient positioning, anesthesiology, perioperative care, patient information, multidisciplinary user consultation, and complication registration. The text of each topic contains an introduction with an explanation of the problem and a summary of the current literature. The current available evidence on safety aspects in minimally invasive surgery is limited. Few conclusions could be deduced from evidence-based data. This underscores the need for larger studies with adequate design and methodology to define conclusions of importance. Above all, the development of this multidisciplinary guideline facilitated a rich discussion, which resulted in a very complete and implementable guideline. This is the second of two papers on the multidisciplinary guideline for minimally invasive surgery, in which we present our literature reviews, conclusions, and practical recommendations for the use of specific port instruments, port site closure and electrosurgical and ultrasonic techniques.

Introduction and methods

Since the early 1990s, minimally invasive surgery (MIS) or laparoscopic surgery has been used extensively to diagnose and treat a variety of conditions. The advancing technology and methods of laparoscopic surgery offer increasing surgical possibilities. Laparoscopic surgery is practiced in different surgical disciplines, general surgery, gynecology and urology, using relatively similar basic techniques. Despite these similarities, there is little cooperation between the different disciplines to assure and improve the quality of minimally invasive surgery. A number of monodisciplinary gynecological guidelines on laparoscopic entry techniques do exist, a well-known one is the guideline from the Royal College of Obstetricians and Gynaecologists (1). Though, transcending the boundaries of monodisciplinary knowledge and skills and criticizing the differences between disciplines should result in multidisciplinary agreements to optimize patient safety. The Dutch Healthcare Inspectorate encouraged the national scientific associations representing laparoscopically oriented surgeons to work together and develop a multidisciplinary guideline on MIS.

In our previous paper we described the Evidence-Based Guideline Development (EBGD) methodology (2). In short, the EBGD-process includes the following steps: 1) problem analysis; 2) explicit formulation of the questions that the guideline is addressing (key questions); 3) defining eligibility criteria for evidence to be considered; 4) conducting a comprehensive search for evidence (search strategies are appended, see appendix); 5) evaluating study quality; 6) summarizing the evidence and drawing scientific conclusions; 7) balancing the benefits and downsides of the alternative management strategies, discussing values and preferences (other considerations); 8) formulating recommendations based on evidence and consensus clinical opinion; 9) discussion about the draft guideline within working group, 10) setting up a final draft guideline; 11) external review by members of the participating scientific associations; 12) revision and finalization of the guideline, and finally; 13) authorization and; 14) dissemination of the multidisciplinary guideline by the participating scientific professional associations.

In our first paper, we focused on primary entry techniques and the application of a pneumoperitoneum in laparoscopic surgery. The first technical step in laparoscopy is the primary entry: the introduction of a primary instrument (Veress needle or primary trocar) in the abdominal cavity, followed by the insufflation of carbon dioxide to create a pneumoperitoneum.

When the pneumoperitoneum is achieved, specific laparoscopic port instruments are introduced through the abdominal wall. Port instruments consist of several components: a central trocar, a corresponding peripheral cannula, a valve section, and a CO₂ stopcock. After insertion of this instrument, the central trocar is removed and the remaining cannula

functions as an access port for laparoscopic instruments. The primary port, generally created in or near the umbilicus, is used for the introduction of the laparoscope. The creation of the primary laparoscopic port is called “primary entry”. Secondary or ancillary ports are intended for the introduction of other laparoscopic instruments. The creation of secondary ports is called “secondary entry”. The method of port creation, the port instruments’ design and the port location influence the risk of port-related complications.

Laparoscopic port instruments include a myriad of device designs, including over 100 brands from more than 20 manufacturers (3,4). Differences in diameter, shape and material can result in an increased risk of laparoscopic port-related complications. An important postoperative port-related complication is port site herniation (PSH), a protrusion of intestine or omentum through a remaining defect at the laparoscopic port site. It is questionable whether closing the defect by suturing, can prevent these herniations. In the initial problem analysis for this guideline, differences in the use of port instruments and port site closure were identified as important topics within laparoscopic surgery as well as electrosurgical and ultrasonic modalities. These modalities are very useful for coagulation and hemostasis in laparoscopic surgery but have been associated with serious complications. In this second paper on the multidisciplinary guideline on MIS, we discuss the evidence and consensus clinical opinion for the use of specific port instruments, port site closure, and electrosurgical and ultrasonic techniques.

Laparoscopic port instruments

Background

Laparoscopic port instruments are the most common device named in malpractice injury claims associated with laparoscopic procedures, representing one-third of all claims (5). The incidence is estimated to be 4.24 per 1,000 procedures (3). Typical port-related complications are: intra-abdominal vascular injury, visceral injury, port site bleeding, port site herniation, port site infection, and pain. In the last few decades, there has been continuous innovation of the instrument design aimed at reducing these complications.

Distinguishing primary from secondary port entry and different entry techniques

A distinction between primary and secondary entry needs to be made. Within the primary entry technique it has to be taken into account whether the open/Hasson-, closed/Veress needle- or non-insufflated/direct entry technique has been used. Less frequently used instruments for the primary entry are: visual port systems and single port techniques. These different conditions may result in different outcomes. The type of primary port instrument

depends on the applied primary entry technique where the type of secondary port instrument generally does not. In the Veress needle entry technique or the direct insertion technique, the insertion of the primary port instrument is a blind procedure while secondary port instruments are mandatorily inserted under direct laparoscopic vision.

Laparoscopic port instruments

A distinction can be made between reusable and disposable port instruments. Reusable instruments are composed of metal. The perforator tip can be completely blunt (cone shaped), or sharp with a conical, pyramidal, triflanged or eccentric tip. Disposable instruments are usually made of plastic with bladed or bladeless tips. Shielded disposable port instruments are equipped with a retractable covering over the tip and were developed to protect against intra-abdominal vascular and visceral injury. These formerly called “safety trocars” are however also associated with major port-related complications (6). The FDA does not allow anymore that the shielded port instruments are called safety trocars.

Radially expanding access (REA) systems represent yet another alternative in design. These port instruments are equipped with a radially expanding sleeve that can be dilated from 5 mm to 12 mm in diameter. The REA instrument is developed to minimize tissue trauma and, in theory, its use could result in fewer vascular injuries. The optical access instruments are designed to decrease the risk of injury to the intra-abdominal structures by allowing the surgeon to visualize abdominal wall layers during placement (7). A visual system that should be distinguished is the threaded visual cannula (TVC). The TVC enables body cavity access by applying a blunt cannula where a pointed or sharp central trocar is not required, linear penetration force is realigned to radial and the cannula houses the laparoscope without an intervening pointed crystal that distorts visual layer enunciation (8). The diameters of port instruments vary from 2 mm to 12 mm, depending upon the largest instrument needed for a particular port. For exceptional indications (for example extirpation of large cysts), larger or modified trocars are available (4).

Despite continuous innovation in the design of port instruments to enhance patient safety, port-related complications do still occur. The guideline development group indicated a need for advices on the use of specific laparoscopic port instruments to ensure patient safety.

Key question

What specific port instrument can be recommended to minimize the risks of port-related complications?

Summary of the literature

Major port-related complications

Major complications are mortality, visceral injury (such as perforation of the intestines or stomach, or injury of the bladder or liver), vascular injury (such as perforation of the aorta, vena cava, iliac artery or iliac vein); and other injuries that required intensive care (IC) or intensive care unit (ICU) management or a subsequent surgical, endoscopic or radiological intervention. In the recently updated Cochrane review from Ahmad et al., different laparoscopic port instruments were studied (9). Eight RCTs were included comparing different port instrument designs. In four, REA instruments were compared with standard port instruments for primary port entry (10-13). Two RCTs compared cutting and blunt port instruments for primary and secondary port entry (14,15), and in two RCTs the REA instrument was compared to a conventional instrument with cutting tip for secondary port entry (16,17). Trials that analyzed major complications with low incidences, had too small sample sizes to identify any differences (10,12,15-17). Meta-analyses demonstrated no significant differences for major complications (table 1). Comparative prospective and retrospective studies on different laparoscopic port instruments did not evaluate major complications (18) or were underpowered (19).

Table 1 Results from meta-analyses in Ahmad et al. for major port-related complications comparing different port instruments (9)

Radially expanding instruments versus standard instruments for primary port entry	
Vascular injury	OR 0.24 (95% CI 0.05 – 1.21)
Visceral injury	OR 0.13 (95% CI 0.00 – 6.37)
Solid organ injury	OR 1.05 (95% CI 0.07 – 16.91)
Cutting instruments and blunt instruments for primary and secondary port entry	
Visceral injury	OR 7.67 (95% CI 0.15 – 386.69)

OR = odds ratio, 95% CI = 95% confidence interval.

Minor port-related complications

Minor port-related complications are port site herniation, port site bleeding or postoperative wound hematoma, port site infection, extraperitoneal insufflation and other injuries that did not require IC or ICU management or a subsequent surgical, endoscopic or radiological intervention under general anesthesiology. In the meta-analyses of the Cochrane review, some differences were found for minor port-related complications. REA instruments

compared to standard port instruments for primary entry were associated with a reduction of port site bleeding (OR 0.31 [95% CI 0.15 – 0.62] 3 studies, 421 participants). Comparing instruments with a cutting versus a blunt tip for primary port entry, no difference in port site bleeding (OR 0.33 [95% CI 0.09 – 1.23] two studies, 195 participants) or wound infection (OR 7.76 [95% CI 0.15 – 386.69] 1 study, 165 participants) was found. For secondary entry, radially expanding instruments were associated with lower rates of port site bleeding compared to conventional instruments with a cutting tip (OR 0.12 [95% CI 0.02 – 0.92] 1 study, 68 participants). No difference was found for port site infections after the use of REA instruments versus conventional instruments for secondary entry (OR 0.14 [95% CI 0.01 – 2.21] one study, 61 participants).

A prospective cohort study comparing REA instruments to conventional sharp-shielded pyramidal instruments for secondary entry was probably underpowered to identify a difference in port site bleeding (OR 0.18 [95% CI 0.01 – 4.00] 19 participants) (19). A retrospective cohort study compared reusable steel cone shaped non-cutting instruments to a historical group where disposable sharp cutting shielded instruments were used ($n = 600$) for secondary entry (18). A reduced risk was found for port site herniation (OR 0.09 [95% CI 0.01 – 0.69]) and for port site bleeding (OR 0.27 [95% CI 0.07 – 0.97]) when non-cutting instruments were used.

Port-related pain

No systematic reviews on pain related to laparoscopic port instruments were found. A total of seven RCTs evaluated postoperative pain after the use of REA instruments to standard port instruments for primary and/or secondary port entry. For primary and secondary ports, two RCTs found no differences ($n = 77$ and $n = 56$) (11,15) and one was in favor of REA instruments ($n = 87$) (12). For primary ports specifically, one RCT found no difference ($n = 244$) (10) whereas another RCT indicated less postoperative pain up to 12 h postoperative in patients where REA instruments were used ($n = 100$) (13). For secondary ports specifically, two RCTs reported less postoperative pain when REA instruments versus conventional instruments were used ($n = 68$ and $n = 54$) (16,17). Two RCTs found no differences for postoperative pain when blunt or cutting instruments were used (15;20). A prospective cohort study from Turner et al. ($n = 19$) found less pain at secondary ports where REA instruments were used compared to conventionally cutting instruments (19).

There is substantial clinical and statistical heterogeneity between these trials. Within the studies, factors that could have influenced the results in these studies are: fascial closure, manipulation at the port site and postoperative analgesics. In most of the studies on pain regarding the use of different laparoscopic port instruments, no intention was made to identify any confounders neither to correct for confounders in the analysis.

Conclusions

Level 1	There is no evidence to suggest that any type of laparoscopic port instrument is more or less safe in terms of reducing severe complications either during primary or secondary entry. <i>Evidence level A1 (9)</i>
Level 1	The use of radially expanding access instruments compared to standard (cutting) port instruments for primary and secondary port entry leads to fewer port site bleedings. <i>Evidence level A1 (9)</i>
Level 3	The use of blunt port instruments compared to cutting port instruments for secondary port entry possibly leads to fewer port site bleedings and port site herniations. <i>Evidence level C (18)</i>
Level 1	REA instruments compared to conventional port instruments result in a decrease in postoperative pain. This reduction was not consistently found for primary entry. <i>Evidence level A1 (10-13,16,17,19)</i>
Level 2	It remains unclear whether the use of cutting or blunt port instruments has different postoperative pain scores. <i>Evidence level A2 (15,20)</i>

Considerations

In the preceding text, we described the best available data on different laparoscopic port instruments and specific port-related risks. The studies available to analyze are of very small numbers and basically no definite conclusions of importance can be deduced from their

data. The expert's opinion in gynecology is that laparoscopic surgeons may continue to use their chosen technique for port creation (21).

Noticeably, the majority of trials compared REA instruments to conventionally cutting port instruments, even though they are not widely used in practice. A simple explanation could be encouragement by the pharmaceutical industry, though only two studies report that the REA instruments were supplied free of charge by the industry (15,16). REA instruments appear to have advantages in terms of less port site bleedings and postoperative pain. Reasons for their rare application probably are the higher cost price and a more complicated insertion technique of REA instruments compared to conventional instruments (15). No appropriate cost-benefit analysis for REA instruments is available; therefore, one should be careful with the wide implementation of these systems.

Laparoscopic port instruments are either intended for single use (disposable instruments) or multiple uses (reusable instruments). Environmental concerns and spiraling health care costs generally encourage reusable instruments (22). A disadvantage of reusable instrument is that their adequate function could diminish through repetitive use and sterilization. For example reusable sharp instruments lose their sharpness through repetitive insertion; consequently, a relatively high puncture force for penetration through the abdominal wall is required, which could result in an abrupt and uncontrolled introduction of the laparoscopic port instrument leading to serious visceral and vascular injury (23). No clinical trials comparing disposable to reusable laparoscopic port instruments were found. Multiple use of disposable port instruments is not recommended (24).

Another practical consideration that should not be overlooked is the use port instruments with a smaller diameter (e.g. with 5 mm diameter compared to 10 mm) resulting in less postoperative pain and shorter convalescence (25).

A study revealed that blunt-tipped conical port instruments have a significantly greater fixity to the abdominal wall compared to cutting port instruments, resulting in significantly lower numbers of spontaneous port dislodgement during surgery (14). Accordingly, the use of blunt-tipped instruments could reduce antecedent gas leak and loss of pneumoperitoneum and the need for port replacement with its associated increase in risk of trauma to the abdominal wall. On the other side, it appeared from animal studies that the entry force needed to perforate the abdominal wall is higher for conical blunt-tipped than pyramidal sharp port instruments (26). The higher entry force could increase the risk of injuries to the intra- or retroperitoneal organs during insertion. The use of optical-access port instruments does not avoid serious injury despite having the ability to visualize tissue layers during insertion (7). The TVC is a different system of which some experts consider it could be a less damaging approach (8). We found insufficient evidence to formulate clear recommendations for safe

and cost-effective use of laparoscopic port instruments. Larger comparative studies, with good methodological quality, are needed to clarify the important safety issues. The guideline development group supposes that the selection of a port instrument should, above all, be based on weighing the advantages against disadvantages of its characteristics and the experience of the surgeon with a safe application.

Recommendations

- The selection of a laparoscopic port instrument should be based on the benefits of its characteristics to the individual patient and the experience of the surgeon in a safe application of the particular instrument.
- The use of blunt-tipped instruments is preferred for laparoscopic ports with a 10 – 12 mm diameter.
- Whenever possible, it is recommended to use port instruments with small diameters.

Port site closure

Background

The introduction of a port instrument through the abdominal wall creates a fascial defect. The estimated prevalence of PSH is 0.5% (27). Closure of the fascial defect could reduce the risk of port site herniation. In clinical practice, there is a wide variety of suturing methods. No consensus exists regarding the closure of the fascial defect according to the port instrument diameter. Also, risk factors for PSH should be defined. Below, the available evidence on fascial closure of port sites is discussed.

Key questions

Does fascial closure of port sites prevent or reduce the risk of port site herniation?

What is the minimal port site diameter whereby fascial closure should be advised?

What fascial closure technique can be recommended?

Summary of the literature

No RCTs or prospective observational studies were found that investigated fascial closure as a measure to prevent PSH. In two retrospective cohort studies, the PSH prevalence among patients with or without fascial closure were compared (28,29). Mayol et. al. observed that PSH in 10 mm umbilical ports occurred among patients with (3.3%, n = 151) or without (1.9%, n = 52) fascial closure (OR 1.8, [95% CI 0.2 to 15]). Kadar et al. neither identified a difference in prevalence of PSH in 12 mm extraumbilical ports when the fascia was closed or left open (8.0%, n = 25 versus 2.2% n = 136, OR 3.9, [95% CI 0.6 to 24]). The study does show that PSH could not completely be prevented by fascial closure: three hernias were found in 136 patients. Both studies were underpowered to detect statistically significant differences.

We then performed a search to identify the port site diameter from which the risk of herniation becomes significant. The majority of reported cases on PSH occurred at ≥ 10 mm ports (30,31) however, these studies did not compare this with the prevalence of PSH in ports with different diameters. Only one retrospective cohort study shows a relationship between port instrument size and PSH (28). The prevalence of PSH was higher when instruments with a diameter of 12 mm compared to 10 mm were used (OR 13.7 [95% CI 1.6 – 118.3]). For 5 mm instruments compared to 10 mm trocars, no differences were found.

Closure technique

The standard closure technique for the fascia at the port site is a hand-sutured figure-of-eight. A variety of other methods have been described (32). We found two comparative studies wherein different port-closure techniques were compared with the standard technique (33,34). No PSHs were observed as the studies were underpowered to analyze for differences in prevalence of PSH.

More recently, cases of intrafascial incisional hernia were found in patients where 12 mm bladeless radially dilating instruments (without fascial closure) had been used (35). In this type of hernia, also called partial-wall hernia, bowel herniates through a defect in the transversal and internal oblique fasciae, but the external oblique fascia is intact. These patients present with symptoms of bowel obstruction but lack the typical signs of herniation during physical examination. This could be an argument for full thickness closure of the port site, including all abdominal layers (27).

Conclusions

Level 3	It is unclear whether fascial closure of port sites reduces the risk of PSH. <i>Evidence level B (28,29)</i>
Level 3	The prevalence of PSH is significantly increased in port sites where instruments with a diameter of 12 mm are used compared to sites where instruments with a diameter of 10 mm are used. <i>Evidence level B (28,29)</i>
Level 4	It is unclear which fascial closure technique results in the least PSHs. <i>Evidence level D (opinion of guideline development group)</i>
Level 4	Full-thickness closure of port sites could reduce the risk of intrafascial herniation. <i>Evidence level D (opinion of the guideline development group)</i>

Considerations

From data obtained from current literature, it is generally recommended to close fascial defects ≥ 10 mm to reduce the risk of PSH (28,31). However, current information is inadequate and no evidence confirms that fascial closure reduces PSH. On the other hand, the risk of nerve injury, superficial vascular injury, and inadvertent injury of the bowel should be taken into account. Some suggested risk factors for PSH are preexisting umbilical hernia (36) or a history of port site hernia, history of postoperative wound infection, poor wound healing (e.g., diabetes mellitus, wound infection, chemotherapy, steroid use or poor nutrition), ascites, obesity, cachexia, asthma, connective tissue disorders and manipulation of the port (e.g., to retrieve specimens) (31). The extent in which these factors may pose a risk has been insufficiently researched.

In daily laparoscopic practice, some variety exists in the cutoff point of the port site diameter which should be closed; however the fascia at port sites > 10 mm are generally closed in all laparoscopic disciplines. In the literature, it appears that the risk of PSH is significantly

increased in port site diameters ≥ 12 mm and it is supposed that fascial closure reduces the risk. The working group aligned their recommendation with current practice and recommends to close the fascia of port sites > 10 mm diameter. The closure of smaller port site diameters should be considered, specifically when assumed risk factors are present.

As previously noted, the use of blunt trocars compared to cutting trocars for secondary port entry possibly leads to fewer TSHs. This is explained through the stretching and separating of tissues by blunt trocars rather than cutting through tissue layers by cutting trocars. This could be a reason for not closing a fascial defect with a diameter ≤ 12 mm, where a blunt trocar has been used.

It should be noted that single port surgery and robot assisted surgery is not included in this guideline. It should be anticipated that in those techniques, a different port creation method is applied, probably increasing the occurrence of port site herniation and other port-related complications.

Recommendations

- Fascial closure is recommended for port sites with a diameter > 10 mm. It could also be considered to close fascial defects of smaller ports, especially when assumed risk factors are present.
- When blunt port instruments of ≤ 12 mm diameter are applied, it is an option not to close the fascial defect.
- There are no recommendations for a specific fascial closure technique. Full-thickness closure of the port site could be considered, since it possibly reduces the risk of PSH.

Electrosurgical and ultrasonic energy techniques

Background

Electrosurgical and ultrasonic energy techniques have become indispensable in minimally invasive procedures. These techniques are used for coagulation, cutting and hemostasis. The traditional modalities are monopolar and bipolar electrosurgery. Bipolar vessel sealing systems and ultrasonic technologies further improved the efficiency of operations and facilitated the surgical abilities to perform certain procedures. However, each of these energy sources can be associated with distressing complications. Compared to open surgery, a hazard in laparoscopic procedures is the visual field: the electrical current may damage adjacent structures outside the view of the laparoscope. Laparoscopic surgery

presents additional hazards for electrosurgery, the primary ones being direct application, insulation failure, direct- and capacitive coupling. Both electrosurgical instruments and ultrasonic instruments generate heat with the risk of thermal injury. It is important for users to have knowledge of the principles, applications, and safety aspects of the energy sources used in laparoscopy. We reviewed the literature concerning hazards of electrosurgical and ultrasonic energy sources in laparoscopy. Here we describe the specific complications and offer guidance to minimize the risks.

Monopolar electrosurgery

Monopolar electrosurgery is used for cutting, coagulation, and hemostasis. With monopolar electrosurgery, the active electrode is located at the surgical site while the return electrode (a dispersive pad) is attached elsewhere to the patient's body. The current flows from the active electrode, into the target tissue, through the patient, the dispersive pad, and subsequently returns to the generator. With the dispersive pad properly placed, the electrosurgical effects occur at the active electrode.

General surgeons rely more on monopolar than on bipolar electrosurgery because of its ease of use (37). Monopolar electrosurgery provides a better penetration of the current density, which can be advantageous for hemostasis in certain tissues. A “blended cut” (blend of surgical effects) can be applied with a combined modus of cutting and coagulation. Additional capabilities are enhanced cutting, rapid dissection and non-contact fulguration. With fulguration, a high voltage electric current is used to destroy tissue; this may be useful to control diffuse bleedings.

Bipolar electrosurgery

With bipolar electrosurgery, both active and return electrodes are located close together within the tip of the surgical instrument. The current flows from one tip to the other; only the tissue between the two electrodes is exposed to the electric current. Tissue thermal energy can be localized more precisely and is effective at a lower voltage and power. This enables electrosurgical safety. Bipolar instruments cannot be used effectively for pure cutting, and for coagulating the tissue should be gripped between the two electrodes. Because of lower power settings, bipolar coagulation of large areas and dense tissues requires more time. In addition, spray coagulation (fulguration) is not possible.

Vessel sealing

Vessel sealing technology is a type of bipolar electrosurgery developed to coagulate blood vessels from a diameter of 2 – 3 mm and with minimized collateral tissue damage. An electrothermal bipolar vessel sealer (EBVS) combines an advanced electrical current with

mechanical pressure, in order to fuse the vessel walls and create a seal. The EBVS allows the secure sealing of vessels with a diameter of up to 7 mm (38,39). The seals obtained with EBVS have proven to be stronger compared to those obtained with traditional bipolar and ultrasonic technology (40,41). The available instruments have a diameter of either 5 or 10 mm (40). EBVS rely on a computer-controlled tissue feedback system that senses tissue impedance or resistance and adjusts the current and output voltage: a consistent electrosurgical effect is obtained through all tissue types.

Ultrasonic technology

With ultrasonic technology, electrical energy is converted into vibration and heat. The combination of a vibrating blade together with the produced heat forms the mechanism by which the instrument cuts and coagulates tissue. The heat generated by ultrasonic instruments is typically less compared to mono- and bipolar electrosurgery, resulting in less thermal injury to surrounding tissues. This optimizes the histopathology assessment of surgical margins. An ultrasonic instrument ensues less smoke emission and probably less toxin production since tissue destruction is by vaporization and avoid charring (42). As no electrical current is applied, there is no risk of direct coupling or capacitive coupling injuries. There are some disadvantages of ultrasonic technology: the formation of steam from tissues being treated can interfere with visualization through a laparoscope. After prolonged use, the vibrating blade may remain hot for a long period and create a risk of inadvertent thermal injury.

The ultrasonic technology enables the coagulation and sealing of blood vessels from 2 – 5 mm in diameter (43). It has been shown that this modality can be used safely and effectively in different laparoscopic procedures such as myomectomy, hysterectomy, cholecystectomy and colorectal laparoscopic surgery (43-46).

Key questions

What are the potential complications related to electrosurgery and what is the incidence of recognized injuries?

What measures can be taken to reduce the risk of electrosurgery-related complications?

Summary of the literature

Electrosurgery-related complications

Although electrosurgery-related complications are widely described, no systematic reviews, prospective or retrospective cohort studies or case-control studies were identified that collected data on the incidence of electrosurgery-related complications in laparoscopy. Several studies retrospectively analyzed data on laparoscopic electrosurgery-related complications limited to specific procedures (47-49). Consequently, a reliable incidence rate of electrosurgery-related complications is missing. The estimated incidence is 2 to 5 per 1000 procedures (50). One of the most serious complications is bowel perforation caused by an electrosurgical burn, frequently unrecognized at the time of occurrence. Symptoms of peritonitis are usually seen 4 to 10 days later and often lead to long term complications.

Several RCTs comparing different electrosurgical and ultrasonic techniques were identified (41,43,45,51-53). There is considerable heterogeneity in the investigated surgical procedures between studies. In the majority of the trials, no difference in electrosurgery- and ultrasonic-related complications was found. However, the studies were generally underpowered to identify differences in complications. The use of distinct electrosurgical and ultrasonic instruments depends on the suitability of the instruments characteristics in the type of surgical procedure. Therefore, the following text is a delineated description of the electrosurgical mechanisms that may lead to complications and how to avoid potentially dangerous situations.

Hazards in monopolar electrosurgery

With monopolar electrosurgery, the patient forms a major part of the electrical circuit. This causes additional risks: stray currents, insulation failure, direct coupling and capacitive coupling.

Stray currents through insulation failure

Insulation failure occurs when the insulation covering of the shaft of the active electrode is damaged. This allows the current to flow through alternative pathways and non-target-tissue. Breakdown of insulation can be caused by the use of high-voltage currents, repeated use, frequent re-sterilization, inappropriate use, or mechanical damage of instrumentation. The small and undetectable defects in the insulation are more dangerous, because this creates a higher current density.

Open circuit and detachment of the dispersive pad

When the electrosurgical unit is activated without the active electrode in contact with the tissue (i.e. open circuit activation) a high-voltage level emerges at the active instrument. This may cause stray currents. Poor quality of contact between the dispersive pad and the patient's skin compromises a safe return of the current to the generator. The dispersive pad must be of low resistance with a large enough surface ($> 20 \text{ cm}^2$). When the dispersive pad is (partially) detached through bony prominences, adipose, excessive hair, scar tissue, presence of fluid or lotions or dryness of the pad, the current exiting the body can have a high density. This may produce heat and unintended burns at the site of the dispersive pad. The use of a return electrode monitoring (REM) system averts these burns. This system inactivates the electrosurgical unit if the resistance between the patient's body and the dispersive pad is too high.

Direct coupling and capacitive coupling

Direct coupling occurs when the electrosurgical unit is accidentally activated while the active electrode is in close proximity to another secondary non-insulated instrument (e.g., a metal laparoscope). Electrical current flows from the active electrode to the secondary instrument, and potentially damages adjacent structures.

Capacitive coupling occurs when current is transmitted from the active electrode through intact insulation and into adjacent materials without direct contact. Activation of the active electrode produces an alternating current inducing an electrostatic field between two 'conductors' (conductive elements). When the net charge exceeds the insulator's capacity, that current is transferred from one conductor to the other. Hybrid cannulas are prone to induce capacitive coupling, since the plastic parts prevent the current dissipating from the metal part into the abdominal wall. This can result in electrical current passing through nearby structures. Longer instruments, thinner insulation, higher voltages, and narrow trocars increase the risk of injury (43,50,54).

Interference with (cardiac) implantable electronic device and prosthetics

Implantable devices that use electric current may be affected by the use of electrosurgery. In monopolar surgery, interaction of the current with a cardiac implantable electronic device (CIED) may have life-threatening consequences. Adverse effects include damage to the device, inability to deliver pacing or shocks, lead-tissue interface damage, and electrical reset. The preoperative management of the CIED function should be guided by the cardiologist or anesthesiologist (42). The risk of interference is low in procedures where the path between the active electrode and dispersive pad does not cross the CIED or its leads. There may be some diffusion of current and it is therefore safer to use bipolar electrosurgery

or ultrasonic technology in patients with implantable electronic devices (55,56). Conductive prosthetics should as well be placed out of the direct path of the circuit since activation of the electrosurgical unit may cause heating of the prosthetic material.

Thermal injuries in electrosurgery and ultrasonic technology

Prolonged activation of both mono- and bipolar electrosurgical instruments as well ultrasonic instruments generate heat (up to 80 – 100 °C). The instrument can remain hot for some time after activation with the risk of thermal injury when it unintentionally touches surrounding tissue.

Conclusions

Level 4	Bowel perforation, biliary- and urinary tract injuries are among the most serious electrosurgical injuries. <i>Evidence level D (opinion of guideline development group)</i>
Level 2	There is insufficient evidence to define the differences in electrosurgery- versus ultrasonic-related complications. <i>Evidence level A2 (41,44,45,51-53)</i>
Level 4	Exact incidence rates of electrosurgery-related complications are unknown. The estimated incidence is 2 to 5 per 1,000 procedures. <i>Evidence level D (opinion of guideline development group)</i>
Level 3	Additional risks of monopolar electrosurgery, compared to bipolar electrosurgery and ultrasonic technology, include: stray currents, insulation failure, direct coupling and capacitive coupling. <i>Evidence level C (37,43,50,54)</i>

Level 4

Based on electrophysiology, the following factors increase the risk of electrosurgical injuries:

- The use of high-power and high-voltage settings
- Inadequate placement of the dispersive pad
- Hybrid cannulas
- The intermingling use of plastic and metal cannulas
- Long instruments and narrow cannulas
- Insulation failure
- Char of coagulated tissue on the instrument
- Prolonged activation of an electrosurgical instrument
- Activation of an electrosurgical instrument in an open circuit

Evidence level C (37,42)

Level 4

When using electrosurgery, cardiac implantable electronic devices and conductive prosthetics are additional hazards.

Evidence level D (55,56)

Considerations

The current available evidence on electrosurgical and ultrasonic energy techniques is inadequate to formulate definite evidence-based conclusions. Therefore, larger scale studies are needed. With the current information available, a safe application of these techniques can be achieved by adequate education of the surgical team and supporting staff. The team should be aware of the physics and hazards associated to the use of different energy sources used in MIS. Another obstacle in safety is that biomechanical engineers involved in the purchase of minimally invasive instruments, are not routinely involved in the maintenance. Reusable trocars and instruments are often used until defects appear; this might represent a danger to the patient. Participation of biomechanical engineers in maintaining and testing instruments in use could possibly prevent those dangers. Instead of reusable instruments, disposable instruments could be used to prevent insulation failure through wear and tear. However, disposable instruments are often more expensive and not immune from insulation failures.

Finally, postoperative vigilance is required when a patient does not easily recover. The surgeon, physicians, and nurses on duty should be highly alert to the early manifestations of peritonitis. The warning signs may be insidious with atypical or mild symptoms such as

slight abdominal discomfort, slight temperature increase, and inability to void. Symptoms of bowel perforation following electrothermal injury are usually seen 4 to 10 days after surgery, leading to a delay in diagnosis and treatment, with sometimes fatal consequences (54). Laboratory results are often normal with a slight leukocytosis. Expedient evaluation and early intervention is demanded when a patient's recovery is below what should be expected (50).

Recommendations

- When using electrosurgical or ultrasonic techniques, one must have knowledge of electrophysiological functioning and effects.
- To reduce the risk of electrosurgical complications, the following precautions are recommended:
 - When both mono- and bipolar instruments are used, pedals and connections should be checked for accuracy before activating the electrosurgical units.
 - Instrument electrodes should be kept smooth and clean from char, to avoid disruption of current transfer.
 - To prevent capacitive coupling, an isolated position of metal trocars from the abdominal wall should be avoided. Use all-metal or all-plastic cannula systems, the use of metal-plastic hybrids is discouraged.
 - An instrument should be activated only when its electrode is fully visible and in contact with the target tissue. Do not activate in an open circuit.
 - Preferably use brief intermittent activation versus prolonged activation.
 - Use the lowest possible power setting and low-voltage waveform for the desired effect.
- Prior to each MIS procedure, monopolar instruments should be tested for insulation failure with a porosity detector at the central sterilization department.
- With monopolar electrosurgery, the dispersive pad should be applied to well-perfused, dry skin over a large muscle away from bony prominences and conductive prostheses. When disinfecting the skin, be cautious no fluid leaks under the dispersive pad.
- In patients with conductive prosthesis, it is strongly recommended to place the prosthesis out of the direct path of the electrical circuit.
- For procedures in patients with a CIED, the use bipolar over monopolar electrosurgery is preferred.
- Alertness for electrothermal injury is needed when a patient presents with mild symptoms such as slight abdominal discomfort or slight temperature increase.

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Appendix

Table Literature searches

Subject	Database	Search terms
Laparoscopic port instruments	Medline (OVID) 1950 – March 2012	1. *Laparoscopy/ 2. (trocar* or troicar* or trocard*).ti. 3. ((secondary adj trocar*) or (classical adj trocar*) or cannula or (disposable adj3 trocar*) or (radially adj expanding adj trocar*) or (STEP adj trocar*) or (visual adj entry) or systems or (conical adj trocar) or (pyramidal adj trocar*) or (reusable adj trocars*) or (disposable adj trocar*) or (single adj2 trocars) or optiview or endotip or visiport or (bladeless adj trocar*) or (sharp adj trocar*) or (trocar adj valve*)).ab,ti. 4. 2 or 3 5. *Surgical Instruments/ 6. "Equipment Design"/ 7. exp Gynecologic Surgical Procedures/is [Instrumentation] 8. Laparoscopy/mt [Methods] 9. or/5-9 10. 1 and 4 and 9 11. systematic reviews (filter) 12. randomized controlled trials (filter) 13. exp longitudinal studies/ 14. 10 and 13 (trocar* OR troicar* OR trocard* OR 'secondary trocar' OR 'classical trocar' OR 'radially expanding trocar' OR 'step trocar' OR 'visual entry system' OR 'conical trocar' OR 'pyramidal trocar' OR 'reusable trocar' OR 'disposable trocar' OR 'single trocar' OR optiview OR endotip OR visiport OR 'bladeless trocar' OR 'sharp trocar' OR 'trocar valve' OR 'secondary trocars' OR 'classical trocars' OR 'cannula'/exp OR 'radially expanding trocars' OR 'step trocars' OR 'visual entry systems' OR 'conical trocars' OR 'pyramidal trocars' OR 'reusable trocars' OR 'disposable trocars' OR 'single trocars' OR 'bladeless trocars' OR 'sharp trocars' OR 'trocar valves') AND 'surgical instrument'/exp/mj NOT [animals]/lim) AND ([dutch]/lim OR [english]/lim AND [embase]/lim
Port site closure	Medline (OVID) 1950 – Nov 2009	1. exp *Laparoscopy/ 2. "laparoscop*".m_titl. 3. "minimal invasive*".m_titl. 4. 1 or 2 or 3 5. Surgical Wound Dehiscence/ Obesity/"obes*".m_titl./ Body Mass Index 6. deep sheath closure*.mp. or Surgical Wound Infection/ 7. port closure*.mp. 8. port site hernia*.mp. 9. port infection*.mp. 10. hernia/ or hernia, abdominal/ 11. herniation.mp. 12. fascia defects.mp. or Hernia, Ventral/ 13. or/5-15 14. exp *Sutures/ 15. exp *Suture Techniques/ 16. "suture*".m_titl. 17. 17-19 18. 4 and 16 and 20 19. 9 or 10 or 11 or 12 or 14 or 15

Table 2 continues on next page

Table *Continued*

Subject	Database	Search terms
		20. *Laparoscopy/ae [Adverse Effects] 21. 22 and 23 22. 21 or 24 23. "ventral hernia repair*".m_titl. 24. 25 not 26 25. Roux-en-Y Gastric Bypass.m_titl. 26. (suture* or closure* or port*).m_titl. 27. 27 and 29 28. 30 not 28 Embase (Elsevier) 1974 – Nov 2009 (laparoscop*:ti OR 'laparoscopy'/exp/mj OR 'minimal invasive':ti AND ('deep sheath closure' OR 'port closure' OR 'port site hernia' OR 'port infection' OR 'herniation'/exp OR 'fascia defect' OR 'deep sheath closures' OR 'port closures' OR 'port site hernias' OR 'port infections' OR herniations OR 'fascia defects' OR 'wound dehiscence'/exp OR 'obesity'/ exp OR 'body mass'/exp OR 'surgical infection'/exp OR 'abdominal wall hernia'/exp) AND ('suture'/exp/mj OR 'suture'/exp OR suture*:ti)) NOT ('roux en y' AND gastric AND bypass:ti) AND filter randomized controlled trials
Electrosur- gical and ultrasonic techniques	Medline (OVID) 1950 – Nov 2009	1. Laparoscopy/ 2. Laparoscopy.ti. 3. 1 or 2 4. Electrosurgery/ 5. Electrosurgery.ti. 6. 4 or 5 10. 3 and 6 11. limit 10 to (dutch or english) 12. limit 11 to (clinical trial, all or clinical trial or review or comparative study or consensus development conference or controlled clinical trial or evaluation studies or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or research support, nih, extramural or research support, nih, intramural or research support, non us gov't or research support, us gov't, non phs or research support, us gov't, phs or technical report or validation studies) 13. exp Epidemiologic Studies/ 14. 11 and 13 15. systematic reviews (filter) 43. randomized controlled trials (filter) 68. 12 or 14 69. 68 not (66 or 67)
	Embase (Elsevier) 1974-Nov 2009	'clinical study'/exp OR 'comparative study'/exp OR 'controlled study'/ exp OR 'observational study'/exp AND ('electrosurgery'/exp/mj OR electrosurg*:ti) AND ('laparoscopy'/exp/mj OR laparoscop*:ti) NOT [animals]/lim) AND ([dutch]/lim OR [english]/lim AND [embase]/lim

Medline (OVID) and Embase were searched for relevant literature on the topics trocar use, trocar site closure and electrosurgical and ultrasonic techniques. The search was restricted to articles published in Dutch and English from 1966 to November 2009, with exception to the search for trocar use which we updated in March 2012. Additionally, the reference lists of all included studies and systematic reviews pertinent to this topic were screened. Methodological filters of the Scottish Intercollegiate Guidelines Network (<http://www.sign.ac.uk/methodology/filters.html>) were used to identify potential systematic reviews and randomized controlled trials.



PART 2

Chapter 3

Trocar types in laparoscopy

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Abstract

Background: Laparoscopic surgery has led to great clinical improvements in many fields of surgery; however, it requires the use of trocars, which may lead to complications as well as postoperative pain. The complications include intra-abdominal vascular and visceral injury, trocar site bleeding, herniation and infection. Many of these are extremely rare, such as vascular and visceral injury, but may be life-threatening; therefore, it is important to determine how these types of complications may be prevented. It is hypothesised that trocar-related complications and pain may be attributable to certain types of trocars. This systematic review was designed to improve patient safety by determining which, if any, specific trocar types are less likely to result in complications and postoperative pain.

Objectives: To analyze the rates of trocar-related complications and postoperative pain for different trocar types used in people undergoing laparoscopy, regardless of the condition.

Search methods: Two experienced librarians conducted a comprehensive search for randomised controlled trials (RCTs) in the Menstrual Disorders and Subfertility Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO, CINAHL, CDSR and DARE (up to 26 May 2015). We checked trial registers and reference lists from trial and review articles, and approached content experts.

Selection criteria: RCTs that compared rates of trocar-related complications and postoperative pain for different trocar types used in people undergoing laparoscopy. The primary outcomes were major trocar-related complications, such as mortality, conversion due to any trocar-related adverse event, visceral injury, vascular injury and other injuries that required intensive care unit (ICU) management or a subsequent surgical, endoscopic or radiological intervention. Secondary outcomes were minor trocar-related complications and postoperative pain. We excluded trials that studied non-conventional laparoscopic incisions.

Data collection and analysis: Two review authors independently conducted the study selection, risk of bias assessment and data extraction. We performed sensitivity analyses and investigation of heterogeneity, where possible.

Main results: We included seven RCTs (654 participants). One RCT studied four different trocar types, while the remaining six RCTs studied two different types. The following trocar types were examined: radially expanding versus cutting (six studies; 604 participants), conical blunt-tipped versus cutting (two studies; 72 participants), radially expanding versus conical blunt-tipped (one study; 28 participants) and single-bladed versus pyramidal-bladed (one study; 28 participants). The evidence was very low quality: limitations were insufficient power, very serious imprecision and incomplete outcome data.

Primary outcomes: Four of the included studies reported on visceral and vascular injury (571 participants), which are two of our primary outcomes. These RCTs examined 473 participants where radially expanding versus cutting trocars were used. We found no evidence of a difference in the incidence of visceral (Peto odds ratio (OR) 0.95, 95% confidence interval (CI) 0.06 to 15.32) and vascular injury (Peto OR 0.14, 95% CI 0.0 to 7.16), both very low quality evidence. However, the incidence of these types of injuries were extremely low (i.e. two cases of visceral and one case of vascular injury for all of the included studies). There were no cases of either visceral or vascular injury for any of the other trocar type comparisons. No studies reported on any other primary outcomes, such as mortality, conversion to laparotomy, intensive care admission or any re-intervention.

Secondary outcomes: For trocar site bleeding, the use of radially expanding trocars was associated with a lower risk of trocar site bleeding compared to cutting trocars (Peto OR 0.28, 95% CI 0.14 to 0.54, five studies, 553 participants, very low quality evidence). This suggests that if the risk of trocar site bleeding with the use of cutting trocars is assumed to be 11.5%, the risk with the use of radially expanding trocars would be 3.5%. There was insufficient evidence to reach a conclusion regarding other trocar types, their related complications and postoperative pain, as no studies reported data suitable for analysis.

Authors' conclusions: Data were lacking on the incidence of major trocar-related complications, such as visceral or vascular injury, when comparing different trocar types with one another. However, caution is urged when interpreting these results because the incidence of serious complications following the use of a trocar was extremely low. There was very low quality evidence for minor trocar-related complications suggesting that the use of radially expanding trocars compared to cutting trocars leads to reduced incidence of trocar site bleeding. These secondary outcomes are viewed to be of less clinical importance.

Large, well-conducted observational studies are necessary to answer the questions addressed in this review because serious complications, such as visceral or vascular injury, are extremely rare. However, for other outcomes, such as trocar site herniation, bleeding or infection, large observational studies may be needed as well. In order to answer these questions, it is advisable to establish an international network for recording these types of complications following laparoscopic surgery.

Plain language summary

Complications of trocar types for laparoscopic surgery

Review question

Laparoscopy is a modern operative technique to perform abdominal (belly) surgery through small incisions in the skin. Specific instruments, called trocars, are used to gain access to the abdominal organs through the skin. We reviewed the evidence to find out whether the use of different types of trocar for laparoscopic surgery leads to fewer complications and less pain in the first month following surgery.

Background

In laparoscopic surgery, trocars are needed to seal the skin openings, while permitting entry and removal of the surgical instruments. The introduction of trocars through the skin into the abdominal cavity is usually safe, yet, in a small minority of people, life-threatening complications can occur. The two most serious complications are puncture into a large blood vessel (occurs 0.9 times per 1,000 operations) and puncture into abdominal organs (e.g. the intestine, stomach or liver) (occurs 1.8 times per 1,000 operations). Less serious but more frequent complications include bleeding or infection of the skin at the trocar insertion site. Also, the degree of pain following laparoscopy could depend on the type of trocar used. It is unclear whether specific trocar types are less likely to be associated with complications and postoperative pain.

Study characteristics

We identified seven randomised controlled studies (clinical studies where people are randomly put into one of two or more treatment groups) that compared two or more different trocar types in 654 people undergoing laparoscopy. The evidence is current to May 2015.

Key results

From the data available in these studies, there appears to be no advantage from one trocar type over another for serious complications, which include visceral and vascular injury. However, caution is urged when interpreting these results because very few cases were identified for these types of complications.

Quality of the evidence

Most of our results are based on very low quality evidence, mostly due to the limited number of studies identified and low number of complications. Therefore, no specific trocar type can be recommended over another for laparoscopic surgery.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON

Radially expanding trocars compared to cutting trocars for laparoscopy						
Patient or population: people undergoing laparoscopy Settings: surgical Intervention: radially expanding trocars Comparison: cutting trocars						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Cutting trocars	Radially expanding trocars				
Visceral injury	4 per 1000	4 per 1000 (0 to 60)	OR 0.95 (0.06 to 15.32)	473 (4 studies)	⊕○○○ very low ^{1,2}	-
Vascular injury	4 per 1000	1 per 1000 (0 to 28)	OR 0.14 (0.00 to 7.16)	473 (4 studies)	⊕○○○ very low ^{1,2}	-
Trocar site herniation Follow-up: 6-46 months	No events reported	No events reported	Not estimable ³	463 (4 studies)	⊕○○○ very low ^{2,4}	-
Trocar site bleeding	115 per 1000	35 per 1000 (18 to 66)	OR 0.28 (0.14 to 0.54)	553 (5 studies)	⊕○○○ very low ^{2,4}	-
Trocar site haematoma ⁵	See comment ⁵	See comment ⁵	Not estimable ⁵	238 (2 studies)	⊕○○○ very low ^{2,4}	-
Postoperative pain ⁶	See comment ⁶	See comment ⁶	Not estimable ⁶	306 (4 studies)	See comment ⁶	-

*The basis for the assumed risk is the <i>mean control group risk</i> across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; OR: odds ratio.	
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.	

- ¹ Downgraded one level due to high risk of attrition bias.

² Downgraded two levels due to imprecision: the number of events was fewer than 300 (the threshold rule-of-thumb value).

³ No events reported.

⁴ Downgraded one level due to risk of bias: in all included studies, high risk of performance bias, due to differences between groups for fascial closure or other types of port manipulation. Method of assessment mostly unclear.

⁵ Data could not be pooled because of clinical heterogeneity.

⁶ All studies provided insufficient statistical data, making it inappropriate to pool the data.

Background

Description of the condition

Surgery is by nature invasive and inevitably associated with complications and trauma. Laparoscopic surgery, also known as minimally invasive surgery, was developed to minimise surgical trauma as opposed to the open abdominal surgical technique (i.e. laparotomy). A laparoscopic procedure is an abdominal or pelvic operation conducted through small incisions in the abdominal wall. In gynaecology, laparoscopy began in the late 1970s and was primarily used for diagnostic procedures. The first widely accepted laparoscopic procedure was tubal ligation (Hulka 1977). Thereafter, gynaecological surgeons began to explore other applications, including diagnostic procedures for pelvic pain and ectopic pregnancy. In the early 1980s, additional operative procedures were introduced including adnexal surgery, uterine myomectomy and hysterectomy (DeSimone 2008). Less visible scarring, less postoperative pain and rapid recovery have fuelled patient advocacy and enabled an increasing use of laparoscopy. For healthcare providers, laparoscopy has the benefit of shorter hospital stays and thus reduced inpatient costs. The benefits for the surgeon include the magnified optics and no-touch operative technique (Ahmad 2015; DeSimone 2008). There is indeed evidence that laparoscopy has advantages compared to laparotomy, which include fewer surgical injuries, fewer postoperative complications, less postoperative pain and shorter hospital stays (Kulier 2004; Medeiros 2009; Metwally 2012). At present, with advanced laparoscopic operations for pelvic organ prolapse, urinary incontinence and gynaecological cancers, laparoscopy has become completely integrated into the field of gynaecologic surgery. In general surgery and urology, laparoscopy is increasingly being used for different purposes as well.

Description of the intervention

The first step in a laparoscopic procedure involves the introduction of a primary instrument (i.e. a Veress needle or trocar) followed by the insufflation of carbon dioxide into the peritoneal cavity. This is called the primary entry, which is applied to create a pneumoperitoneum. Different primary entry techniques are used in practice. Ahmad et al. performed a Cochrane review on laparoscopic entry techniques and compared the different techniques in terms of their influence on intraoperative and postoperative complications (Ahmad 2015). They found no evidence of benefit in terms of safety of one technique over another. Intraperitoneal access for laparoscopic instruments is provided via 'ports'. Specific cannulas, called trocars, are introduced through the abdominal wall to create these ports. A distinction needs to be made between primary and secondary trocar ports. The first port for primary entry is located in or near the umbilicus. This port is used for the introduction of the laparoscope. Secondary or

ancillary ports are intended for the introduction of laparoscopic instruments. The secondary port locations depend upon the location in the abdomen where the surgical procedure is to take place. In general, a minimum of two secondary ports are created. The trocars are placed to facilitate operating in line with the camera while maintaining a comfortable operating position for the surgeon with triangulation of the instruments around the surgical focal point within the abdomen. The rapid evolution of instrumentation has led to the development of new minimally invasive techniques such as natural orifice transluminal endoscopic surgery (NOTES), laparo-endoscopic single-site surgery (LESS) and mini laparoscopy. NOTES refers to surgery via natural orifices, where procedures are performed with transluminally placed instruments to gain access to the abdominal cavity. Transvaginal, transanal, transvesical, transoesophageal, transgastric and transoral approaches for NOTES are described (Moris 2012). LESS surgery is an advanced minimally invasive approach that allows laparoscopic operations to be undertaken through a single small (12 mm to 15 mm) incision, typically placed at the person's umbilicus (Rao 2011). Mini laparoscopy involves the use of smaller incisions, smaller instruments and fewer ports to reduce perioperative morbidity further and enhance cosmesis. Other terms for mini laparoscopic surgery include mini port or micro laparoscopic surgery (Thakur 2011). NOTES, LESS and mini laparoscopy are in their early stages of development. NOTES, LESS and mini laparoscopy are not included in this review since these techniques are different from traditional laparoscopy.

How the intervention might work

Trocar designs include a myriad of device designs, including over 100 brands from more than 20 manufacturers (Fuller 2003). There is a distinction between reusable and disposable trocars. Reusable trocars are made of metal and have a perforator tip. Completely blunt trocars, with a cone-shaped perforator tip, and sharp or cutting trocars with a conical, pyramidal, triflanged or excentric tip can be differentiated. Disposable trocars are made of plastic materials and are provided with bladed or blade-less tips. Shielded disposable trocars have a retractable shield that covers the tip before and after insertion. Dilatation systems represent yet another technical alternative in trocar techniques. These trocars are equipped with a radially expanding sleeve that can be dilated from 5 mm to 12 mm in diameter. This radially expanding access (REA) trocar was developed to minimise tissue trauma and, in theory, its use would result in fewer vascular and visceral injuries. Optical access trocars allow laparoscopists to view the cutting tip as it penetrates the tissues. Many other different trocar designs are described, for example trocars with a threaded sleeve or an expandable arm (Fuller 2005; Leibl 2001; Ternamian 1998; Vilos 2007). The diameters of trocars vary from 2 mm to 12 mm, depending on the largest instrument needed for a particular port. For exceptional indications (e.g. extirpation of large cysts) larger or modified trocars are available (Leibl 2001).

Why it is important to do this review

Laparoscopic trocars are the most common device named in malpractice injury claims associated with laparoscopic procedures, representing one-third of all claims (Fuller 2005). The incidence is estimated to be 3 to 4 per 1,000 procedures (Cardin 2011; Champault 1996). Trocar-related complications represent all types of complications due to the contribution of the trocar, including intra-abdominal vascular injury, intra-abdominal visceral injury, trocar site bleeding, trocar site herniation and trocar site infection. Of all trocar-related complications, vascular and visceral injuries are associated with the highest morbidity and mortality (Jansen 1997). By inserting a trocar, the trocar tip can damage abdominal wall vessels (e.g. the epigastric artery), intra-abdominal vessels (e.g. the aorta, vena cava, iliac artery or iliac vein) or visceral organs (e.g. bowel, stomach and bladder). Although vascular injury is often noticed directly during laparoscopy, bowel injuries are more likely to go undetected during the procedure (Fuller 2005). When vascular or visceral injury occurs, additional surgical intervention is often required. Cardin et al. reported vascular and visceral injuries in 51 out of 4,007 (1.3%) people undergoing a laparoscopic procedure. At least 14 (27.5%) of these people required a subsequent surgical, endoscopic or radiological intervention under general anaesthesia (Cardin 2011). Mortality is reported occasionally after vascular or visceral injury (Cardin 2011; Jansen 2004).

An important postoperative trocar-related complication is trocar site herniation. A trocar site hernia (TSH) is a protrusion of intestine or omentum through a remaining defect in the peritoneum, abdominal fascia or musculature at the trocar insertion site. TSHs occur postoperatively, which can vary from shortly following surgery to several years postoperation. Whereas TSH is uncommon, with an estimated prevalence of 0.5% in people operated on laparoscopically, it is a potentially serious complication. People with TSH may require emergency re-operation for bowel obstruction or strangulation (Swank 2012). Less severe trocar-related complications are trocar site bleeding, trocar site infection and pain. Although pain is not always classified as a complication, it is considered clinically important and is an indicator for recovery.

The use of trocars inevitably leads to risks of trocar-related complications. Major complications such as vascular and visceral injury can have serious consequences including conversion from laparoscopy to laparotomy, other invasive interventions, medical therapies and prolonged hospitalisation. When discovered postoperatively, occasionally emergency or revision surgery is required, resulting in longer hospital stay or re-admission and additional costs. Minor complications might also result in the need for additional pharmacological treatment and compromise postoperative recovery. All these deviations from a normal intra- and postoperative course after laparoscopy potentially have a negative effect on people's quality of life and satisfaction.

A difference in trocar-related complications may be attributable to different types of trocars and the experience of the surgeon according to the trocar type. The Cochrane review from Ahmad et al. studied different trocar systems. They found eight randomised controlled trials (RCTs) where different trocar designs were compared. In four RCTs, REA trocars were compared with standard trocars. One meta-analysis demonstrated fewer trocar site bleeding episodes when using REA trocars compared to standard trocars for the primary laparoscopic entry (Ahmad 2015). Two RCTs compared cutting trocars to blunt trocars for primary and secondary port insertion, and there was no difference in any type of complication. Two RCTs compared the REA trocar to a conventional cutting tip trocar for secondary port entry. REA trocars were associated with lower rates of trocar site bleeding compared to standard secondary port trocars. Our review differs from Ahmad et al. in that we searched for differences in the outcome of postoperative pain. Specific types of trocars could relate to higher or lower risks on any of the trocar-related complications or for postoperative pain. The sharpness of disposable cutting trocars is usually better compared to that of reusable cutting trocars. This sharpness of disposable trocars facilitates smooth insertion. Reusable trocars do lose their sharpness through repetitive insertion. Reusable trocars require a relatively high puncture force for penetration through the abdominal wall. Increased entry force could result in an abrupt and uncontrolled introduction of the trocar that may result in a deeper penetration and potential serious visceral and vascular injury (Tansatit 2006). The cutting trocar mechanism of sharp trocars may result in occasional bleeding from the trocar port. Conical blunt-tipped trocars are designed to stretch, rather than cut, the abdominal wall to enable port placement. The use of conical reusable trocars compared to sharp cutting disposable trocars was associated with fewer trocar-related bleeding events and TSHs in one non-randomised prospective study (Leibl 1999). A larger trocar diameter creates a larger defect in the abdominal wall and potentially results in an increased risk of trocar site herniation. In 1993, one retrospective study demonstrated an increased risk of trocar site herniation when trocars with a diameter of 12 mm were used compared to 10 mm (Kadar 1993).

This Cochrane review aimed to determine whether specific trocar designs can be recommended for use in people undergoing laparoscopy, with a goal to minimise trocar-related complications and postoperative pain.

Objectives

To analyse the rates of trocar-related complications and postoperative pain for different trocar types used in people undergoing laparoscopy, regardless of the condition.

Methods

Criteria for considering studies for this review

Types of studies

We included only RCTs. We excluded quasi-randomised (e.g. randomised by birth date, chart number, alternating inclusion), cluster randomised studies and studies with a 'split-mouth design'.

Types of participants

Inclusion criteria

We included adults (aged 18 years and older) who underwent elective or emergency diagnostic, therapeutic or mixed laparoscopy for surgical, gynaecological or urological conditions.

Exclusion criteria

We excluded animal studies.

Types of interventions

Inclusion criteria

- Studies on different trocar designs used in laparoscopy, performed by either surgeons, gynaecologists or urologists;
- Studies on trocars used for both primary and for secondary entry.
- All variations of trocar types, for example, sharp-tipped trocars, blunt-tipped trocars, pyramidal-tipped or conical-tipped trocars, disposable (plastic) trocars, reusable (metal) trocars, trocars with a shielded tip, radially expanding trocars, trocars with a threaded sleeve, an expandable arm or an optical view.

Exclusion criteria

- Studies wherein other (than conventional) laparoscopic incisions were made (e.g. single port surgery (single-incision laparoscopic surgery (SILS), LESS), natural orifice surgery (NOTES) and mini laparoscopy).

Types of outcome measures

Primary outcomes

- Major trocar-related complications:
 - mortality;
 - conversion to laparotomy due to any trocar-related adverse event;
 - visceral injury (such as perforation of the intestines or stomach, or injury of the bladder or liver);
 - vascular injury (such as perforation of the aorta, vena cava, iliac artery or iliac vein); and
 - other injuries that required intensive care (IC) or intensive care unit (ICU) management or a subsequent surgical, endoscopic or radiological intervention.

Secondary outcomes

- Minor trocar-related complications, such as trocar site herniation, trocar site bleeding or postoperative wound haematoma, trocar site infection, extraperitoneal insufflation and other injuries that did not require IC or ICU management or a subsequent surgical, endoscopic or radiological intervention under general anaesthesia.
- Postoperative pain, expressed on a self reported scale (e.g. visual analogue scale (VAS), numerical rating scale (NRS)).

Search methods for identification of studies

Electronic searches

Search methods for identification of studies

The clinical librarian (MW) developed a comprehensive literature search strategy in consultation with the Trials Search Co-ordinator of the Cochrane Gynaecology and Fertility Group (formerly Cochrane Menstrual Disorders and Subfertility Group). We based the search strategy on that in the Cochrane Gynaecology and Fertility Group module. We identified the relevant subject indexing terms used within individual databases and added them to the strategy as appropriate. Where databases offered facilities such as truncation, explosion and proximity searching, we used these as appropriate. We focused the searches to the study designs of interest by using RCT search filters. We used no publication or language restrictions.

We searched the following databases:

- Gynaecology and Fertility Group Specialised Register (inception to 26 May 2015) (Appendix 1);

- Ovid Cochrane Central Register of Controlled Trials (CENTRAL) (inception to 26 May 2015) (Appendix 2);
- Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE® (1950 to 26 May 2015) (Appendix 3);
- Ovid EMBASE (January 2010 to 26 May 2015) (Appendix 4);
- Ovid PsycINFO (inception to 26 May 2015) (Appendix 5);
- CINAHL via EBSCO (inception to 26 May 2015) (Appendix 6);
- Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE, Wiley) (inception to 26 May 2015) (Appendix 7).

We used both indexed and free-text terms. The MEDLINE search was combined with the Cochrane highly sensitive search strategy to identify randomised trials (Higgins 2011). The EMBASE and CINAHL searches were combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/methodology/filters.html#random).

Searching other resources

We also:

- screened the reference lists of all included studies and systematic reviews pertinent to this topic;
- searched the main electronic sources of ongoing trials, World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/), Current Controlled Trials (www.controlled-trials.com/), Clinicaltrials.gov (federally and privately supported clinical trials conducted in the US) and European Clinical Trials database (EudraCT) (www.clinicaltrialsregister.eu/ctr-search/); and
- searched the US Food and Drug Administration (FDA) website (www.fda.gov/MedicalDevices) and contacted the US FDA by email for regulatory trial data.

Data collection and analysis

Two review authors (HS and CC) independently performed the selection of studies, risk of bias assessment, and extraction of qualitative and quantitative data. They had a background in surgery (HS), gynaecology and clinical epidemiology (CC). A third review author (FWJ or SMR) acted as arbiter when necessary.

Selection of studies

We screened the titles and abstracts from the search results and obtained potentially relevant studies in full text and independently assessed them for inclusion. We evaluated full papers, abstracts, proceedings from congresses and any other 'grey literature'. A third review author (FWJ or SMR) resolved disagreements by discussion.

Data extraction and management

Two review authors (HS and CC) independently extracted data, applying the inclusion and exclusion criteria. We used a pre-defined and tested data selection list. We extracted the methodological details (concealed assignment, technique of randomisation, time of randomisation (pre- or intraoperatively), number of randomised participants, number of participants not randomised with explanation, the presence of blinding) and descriptive study characteristics (e.g. country where the study was conducted, recruitment modality, source of funding), characteristics of the participants (e.g. age, gender, body mass index (BMI), previous abdominal surgery), description of the trocar type and size (diameter), description of the entry method, description of the port creation and closure (desufflation, closure of peritoneum, fascia and skin), co-interventions (e.g. local anaesthetics at trocar sites), and outcomes (types of outcomes, documentation of drop-outs, follow-up, standardisation of outcome assessment, and whether an intention-to-treat analysis was employed), and the authors' results and conclusions. We discussed disagreements and consulted an arbiter (FWJ or SMR) when necessary. We summarised key findings in a narrative format. We extracted the outcome per study. We made a differentiation of outcomes regarding primary trocar ports and secondary trocar ports and differentiated primary port outcomes for open, Veress needle and direct entry methods. We assessed data relating to the defined outcomes for inclusion in the meta-analyses. We extracted final scores for means and measures of variance for continuous outcomes (e.g. VAS) while we extracted the number of participants experiencing an event and the number randomised for adverse events (e.g. incidence of trocar site bleeding).

Assessment of risk of bias in included studies

We used Cochrane's tool for assessing risk of bias (Higgins 2011, Section 8.5) and produced a 'Risk of bias' summary. We evaluated: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, intention to treat analysis, selective reporting, group similarity at baseline, co-interventions and timing of outcome assessment. We judged for the presence of a 'high', 'low' or 'unclear' risk of bias. When trials appeared to meet the eligibility criteria but aspects of the methodology were unclear or unsuitable for statistical analysis, we contacted the authors of those trials and asked for the additional information. We resolved any disagreements of

opinion by discussion, and when necessary we included the input from a third independent review author (FWJ or SMR).

Measures of treatment effect

We conducted the review using the standard Cochrane software Review Manager 5 (RevMan 2014). For dichotomous data (rates of trocar-related complications), we used the number of events in the control and intervention groups of each study to calculate Peto estimated odds ratios (ORs). The Peto method, which uses an inverse variance approach but utilises an approximate method of estimating the log OR, and uses different weight, works well when intervention effects are small (OR are close to one), events are not particularly common and the studies have similar numbers in experimental and control groups (Higgins 2011). We expected this would match our findings. For continuous data (pain scales), we planned to calculate mean difference (MDs) between treatment groups. We allowed pain scales other than VAS if we thought that the construct measured was consistent with the evaluated outcome. We would have used standardised mean difference (SMD) instead of MD if studies used multiple scales to measure the same outcome (e.g. VAS and verbal scale). We presented 95% confidence intervals (CIs) for all outcomes.

Unit of analysis issues

Analysis was per person randomised. We excluded trials where body parts or sites were randomised for trocar introduction.

Dealing with missing data

To deal with missing data, we planned to use the strategies described in Chapter 16, Section 16.1 (missing data) and Section 16.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). When summary data were missing, we attempted to contact the author. In the absence of additional information, we looked for statistics that allowed calculation or estimation of the standard deviation (e.g. test statistics, P values). When these were not available, we planned that imputation could be reasonable for a small proportion of studies comprising a small proportion of the data if it enabled the data to be combined with other studies for which full data were available, but that was not the case.

We collected and reported drop-out rates in the 'Risk of bias' table. For dichotomous data, we assumed that all missing participants did not experience the event (based on clinical judgement). We could not perform sensitivity analyses to assess how sensitive results were to changes in the drop-out rates since there were too few study data.

Assessment of heterogeneity

We identified and qualified statistical heterogeneity among the results informally by visual inspection (eye-ball test) and formally by calculating the I^2 statistic. The decision regarding heterogeneity was dependent upon the I^2 statistic, with a value of 50% or greater indicating substantial heterogeneity. Where I^2 was 50% or greater, we did not pool results, but described the effect of the interventions.

Assessment of reporting biases

We used online trial registers to investigate trials that had not been published. There were not sufficient studies to construct funnel plots to investigate possible publication bias.

Data synthesis

If studies were sufficiently similar, we planned to combine the data using Peto's method in a fixed-effect model, for the dichotomous outcomes of trocar-related complications. For the continuous outcome pain, we planned to combine data for meta-analysis using a random-effects model. An increase in the odds of a particular outcome, which may be beneficial (e.g. live birth) or detrimental (e.g. adverse effects), is displayed graphically in the meta-analyses to the right of the centre-line and a decrease in the odds of an outcome to the left of the centre-line.

Subgroup analysis and investigation of heterogeneity

We intended to perform subgroup analyses for type of surgery (e.g. general versus gynaecological versus urological surgery), age groups, gender, obesity, presence of co-morbidities, primary entry technique, secondary entry technique and differing trocar diameters. However, there were insufficient details to extract data about separate participant types.

Sensitivity analysis

We planned the following sensitivity analyses a priori to determine whether the conclusions were robust to arbitrary decisions made regarding the eligibility of studies and analysis. We considered if conclusions would have differed if:

- eligibility were restricted to studies without high risk of bias: this analysis was not possible because of insufficient data;
- eligibility were restricted to studies with blinded outcome assessment; this analysis was not possible because of insufficient data;
- alternative imputation strategies had been adopted; this analysis was not possible since we could not impute any data;
- a random-effects model had been adopted for meta-analysis of dichotomous data.

Overall quality of body of evidence: 'Summary of findings' table

We generated 'Summary of findings' tables for analyses of all primary and secondary outcome measures. When statistical heterogeneity was present, we noted this. We used GRADEpro to prepare the tables (GRADEpro).

We used GRADE (Grading of Recommendations, Assessment, Development and Evaluation) to evaluate the overall quality of the evidence and strength of recommendations (Guyatt 2008). We based the quality of evidence for a specific outcome upon performance against five principal domains:

- limitations in design (downgraded when more than 25% of the participants were from studies with a high risk of bias);
- inconsistency of results (downgraded in the presence of substantial statistical heterogeneity (I^2 greater than 50%) and inconsistent findings (in the presence of widely differing estimates of a specific trocar type A versus type B);
- indirectness (i.e. generalisability of the findings; downgraded when a participant-important outcome is represented by a surrogate);
- imprecision (downgraded when the total number of participants was insufficient to determine any significant statistical difference. The required power of a study depended on the questioned outcome);
- other (e.g. publication bias).

The quality of the evidence was defined as:

- high quality: further research is very unlikely to change the estimate of effect or our confidence in it. There were sufficient data with narrow CIs. There were no known or suspected reporting biases;
- moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; one of the domains was not met;
- low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change it; two of the domains were not met;
- very low quality: great uncertainty about the estimate, three of the domains were not met;
- no evidence: no evidence for this outcome from RCTs.

Results

Description of studies

Results of the search

We identified 1,858 references of possible interest by searching the Menstrual Disorders and Subfertility Group Specialised Register (31 references), CENTRAL (552 references), MEDLINE (540 references), EMBASE (434 references), PsycINFO (10 references), CINAHL (135 references), Cochrane Database of Systematic Reviews (69 references), DARE (24 references) and other sources (63 references). We excluded 448 duplicates and 1397 clearly irrelevant references by reading the abstracts. Accordingly, we retrieved 13 references for further assessment. Of these, we excluded six references because they were not RCTs or did not fulfil our review protocol inclusion criteria. In total, seven RCTs fulfilled our inclusion criteria (figure 1). We contacted four study authors to ask for the missing information and received answers from two authors.

Included studies

Trial characteristics

All the included trials randomly assigned participants individually. Three trials were multi-centre (Bhoyrul 2000; Feste 2000; Mettler 2000), and four were single centre (Bisgaard 2007; Hamade 2007; Lam 2000; Venkatesh 2007). The trials were published from 2000 to 2007. The trials were conducted in the US (Feste 2000; Venkatesh 2007), Australia (Mettler 2000), China (Lam 2000), the UK (Hamade 2007), Denmark (Bisgaard 2007), and Germany (Feste 2000; Mettler 2000). In one trial the study location was not specified (Bhoyrul 2000). In two trials, the study trocars were supplied free of charge by a pharmaceutical company (Lam 2000; Venkatesh 2007). The other five trials did not report funding.

Participants

The trials included 654 participants. Sample size ranged from 30 to 250. The age range of participants was from 18 to 80 years. A total of 314 women and 90 men were included; one study did not report sex of the 250 participants (Bhoyrul 2000). Three studies reported a mean or median BMI (Bisgaard 2007; Hamade 2007; Venkatesh 2007), while the other four other studies did not report any data on body mass (Bhoyrul 2000; Feste 2000; Lam 2000; Mettler 2000). Laparoscopic procedures included surgical (405 procedures), gynaecological (187 procedures) and urological (56 procedures). Three studies did not refer to exclusion criteria (Feste 2000; Hamade 2007; Venkatesh 2007). The other trials excluded people on the presence of acute inflammatory conditions (Bhoyrul 2000; Lam 2000; Mettler 2000),

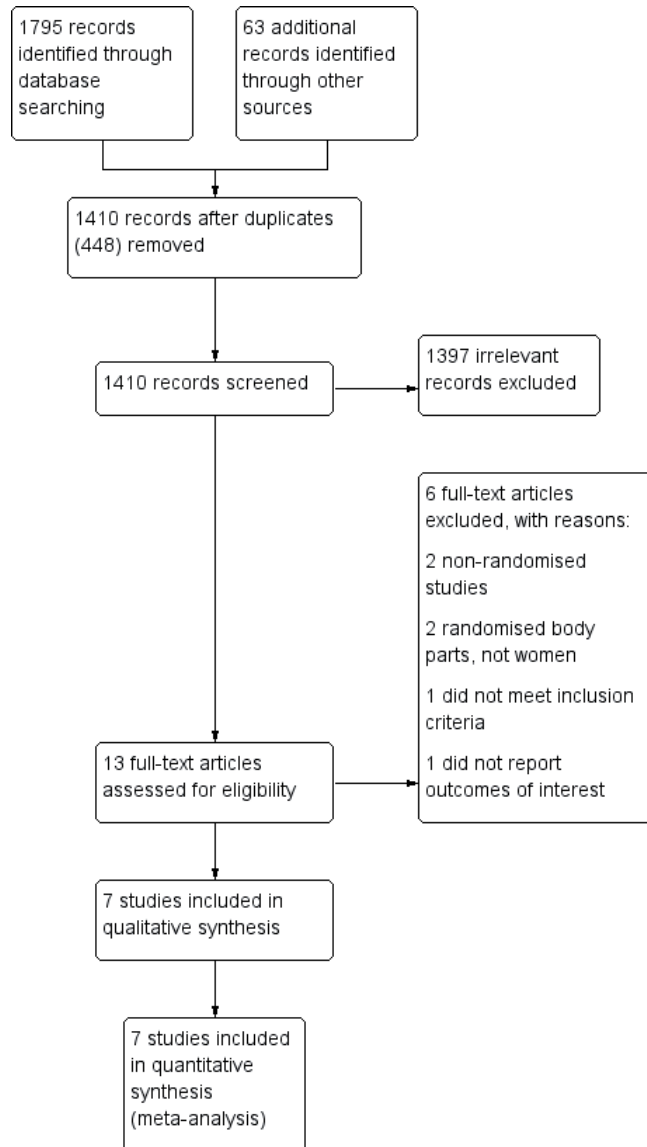


Figure 1 Study flow diagram.

and conversion to laparotomy (Bhoynul 2000; Bisgaard 2007). Exclusion was also based on gallbladder malignancy (Lam 2000), American Society of Anaesthesiologists (ASA) physical class 4, pregnancy, participant age, chronic pain diseases, use of opioids or tranquillisers, foreign language, mental disorder and history of alcoholism or drug abuse (Bisgaard 2007).

Interventions

Trials compared the following trocar types:

- radially expanding trocar versus cutting trocar: two studies used reusable cutting trocars (Lam 2000; Mettler 2000), three studies used disposable cutting trocars (Bhojrul 2000; Bisgaard 2007; Venkatesh 2007), and one study used both reusable and disposable cutting trocars were used (Feste 2000);
- conical blunt-tipped versus cutting trocar (Hamade 2007; Venkatesh 2007);
- radially expanding trocar versus conical blunt-tipped trocar (also called axially dilating) (Venkatesh 2007);
- single-bladed trocar versus pyramidal-bladed trocar (Venkatesh 2007).

Three studies did not refer to the diameter of the trocars (Bhojrul 2000; Feste 2000; Mettler 2000), two studies evaluated 5 mm and 10 mm trocars (Bisgaard 2007; Hamade 2007), one study evaluated 10 mm trocars (Lam 2000) and one study evaluated 12 mm trocars (Venkatesh 2007).

Four studies examined primary entry and secondary entry ports (Bisgaard 2007; Feste 2000; Mettler 2000; Venkatesh 2007), two studies examined secondary ports only (Hamade 2007; Lam 2000), and one study examined primary ports only (Bhojrul 2000). Primary entry used the Veress needle technique.

Co-interventions

Two studies reported gallbladder extraction through a port (Bhojrul 2000; Lam 2000), one study documented the morcellation site, specimen extraction, and hand-assist device site location (Venkatesh 2007). The other studies did not report specimen extraction or other mechanisms of port manipulation. The indications for fascial closure were specified in five studies (Bhojrul 2000; Bisgaard 2007; Feste 2000; Mettler 2000; Venkatesh 2007), two studies did not report on fascial closure (Hamade 2007; Lam 2000). Intraoperative anaesthesia was not described in five studies (Bhojrul 2000; Feste 2000; Hamade 2007; Mettler 2000; Venkatesh 2007), two studies reported that the participants received general anaesthesia (Bisgaard 2007; Lam 2000). A standardised postoperative analgesics regimen was mentioned in two studies (Bisgaard 2007; Lam 2000) and in Bisgaard 2007 the amount of postoperative analgesics was clearly specified. Other studies did not report the use of postoperative analgesics.

Outcomes

Studies reported the following outcome measures.

Primary outcomes: major trocar-related complications

- Visceral injury (e.g. perforation of the intestines or stomach, or injury of the bladder or liver) (571 participants) (Bhoyrul 2000; Feste 2000; Mettler 2000; Venkatesh 2007).
- Vascular injury (e.g. perforation of the aorta, vena cava, iliac artery or iliac vein) (571 participants) (Bhoyrul 2000; Feste 2000; Mettler 2000; Venkatesh 2007).

No studies reported mortality, conversion to laparotomy and other injuries that required IC or ICU management or a subsequent surgical, endoscopic or radiological intervention.

Secondary outcomes: minor trocar-related complications

- Minor trocar-related complications (trocar site herniation (533 participants), trocar site bleeding (583 participants) or postoperative wound haematoma (161 participants) and trocar site infection (56 participants) (Bhoyrul 2000; Bisgaard 2007; Feste 2000; Hamade 2007; Lam 2000; Mettler 2000; Venkatesh 2007).
- Postoperative pain, expressed on a self reported scale (e.g. VAS, NRS (348 participants) (Bhoyrul 2000; Bisgaard 2007; Feste 2000; Mettler 2000; Venkatesh 2007).

No studies reported measures for extraperitoneal insufflation and other injuries that did not require IC or ICU management or a subsequent surgical, endoscopic or radiological intervention under general anaesthesia.

Excluded studies

We excluded five studies from the review, for the following reasons:

- two were not RCTs (Herati 2011; Huang 2012);
- two had randomised different sites of the abdomen to different trocars ('Split-mouth' design) (Stephanian 2007; Yim 2001);
- one study did not examine the types of outcome measures defined for this review (Tchartchian 2010).

Risk of bias in included studies

The results for risk of bias for the individual studies are summarised in figure 2, for assessment with GRADE see the 'Summary of findings' tables. See also figure 3.

Allocation

Five RCTs reported that they used randomisation tables or lists (Bhoyrul 2000; Bisgaard 2007; Hamade 2007; Lam 2000; Mettler 2000). Two RCTs did not describe the method used for sequence generation (Feste 2000; Venkatesh 2007).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Intention-to-treat analysis	Selective reporting (reporting bias)	Group similarity at baseline (selection bias)	Co-interventions (performance bias)	Timing of outcome assessment (detection bias)
Bhoyrul 2000	+	+	+	+	-	+	?	+	-	+
Bisgaard 2007	+	+	+	+	+	+	?	+	-	+
Feste 2000	?	?	+	+	?	+	?	-	-	+
Hamade 2007	+	+	+	?	+	+	?	+	?	+
Lam 2000	+	?	+	+	-	+	?	+	?	+
Mettler 2000	+	?	+	+	+	+	?	?	-	+
Venkatesh 2007	?	?	+	+	?	+	?	?	-	?

Figure 2 Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.

Allocation concealment

Three studies described that their allocation concealment was performed by independent investigators using sealed envelopes (Bhoyrul 2000; Bisgaard 2007; Hamade 2007). The other four studies did not report their method of concealment (Feste 2000; Lam 2000; Mettler 2000; Venkatesh 2007).

Blinding

There was a low risk of performance bias through blinding issues. Six studies reported that blinding of participants and outcome assessors was well performed. Six studies blinded the participants for the type of trocars used (Bhoyrul 2000; Bisgaard 2007; Feste 2000; Lam 2000;

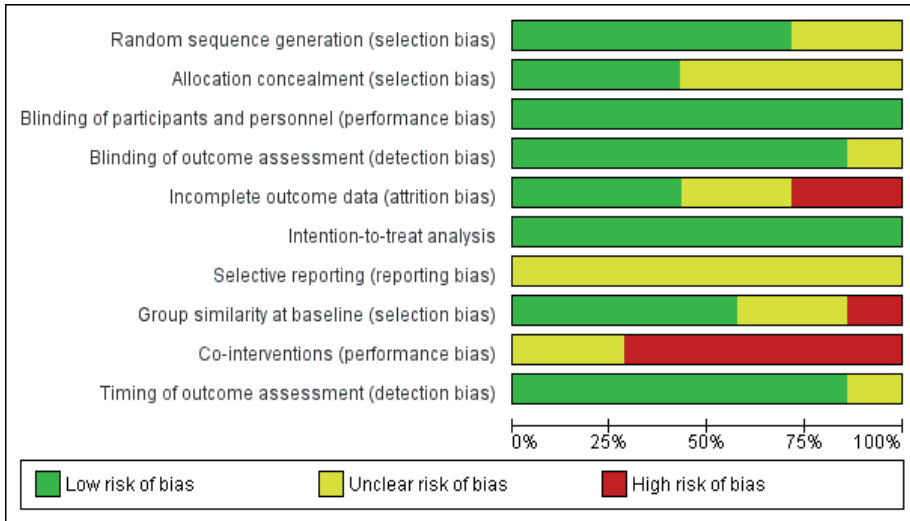


Figure 3 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Mettler 2000; Venkatesh 2007). One study did not report details on blinding of participants. This study did not have subjective outcomes that could be influenced by the participant (Hamade 2007). Blinding of the surgical personnel was not applicable in any of the studies. Blinding of the outcome assessors was reported in the six studies that performed participant blinding (Bhoyrul 2000; Bisgaard 2007; Feste 2000; Lam 2000; Mettler 2000; Venkatesh 2007). One study did not report the use of a blinded outcome observer. This study measured objective outcomes only (Hamade 2007).

There was a substantial risk of performance bias through variance in co-interventions in all studies. None of the studies specified the applied degree of port manipulation during the operation, for example for morcellation or extraction of a surgical specimen. Only two authors reported the intra- or postoperatively applied standard analgesics (Bisgaard 2007; Lam 2000). We judged there to be a high risk of performance bias in five of the studies, because of significant differences between study groups in the application of fascial closure (Bhoyrul 2000; Bisgaard 2007; Feste 2000; Mettler 2000; Venkatesh 2007). Two other studies did not provide details on the application of fascial closure (Hamade 2007; Lam 2000). There was a low risk of detection bias for short-term outcomes. These were all equally assessed between the groups. We rated three studies that performed a long-term assessment of TSH at high risk on detection bias: the duration and completeness of follow-up was unclear or uneven between the studied groups (Bhoyrul 2000; Bisgaard 2007; Venkatesh 2007).

Incomplete outcome data

We rated two studies at a substantial risk of attrition bias (Bhoyrul 2000; Lam 2000). In one of these studies, data on intraoperative complications, postoperative pain and wound complications (trocar site bleeding and haematoma) were either missing or unclear (Bhoyrul 2000). In the second of these studies, approximately 10% of the laparoscopies in both groups were converted to open surgery and a substantial percentage of outcome data from the radially trocar group was missing (Lam 2000). It remained unclear how they dealt with the missing data and data of converted procedures. We rated two studies at unclear risk of attrition bias, because they did not present the numbers of participants that were excluded for participation (Feste 2000) or analysis (Venkatesh 2007). No loss of data or participants was apparent in the remaining studies and we judged them at a low risk of attrition bias (Bisgaard 2007; Hamade 2007; Mettler 2000). However, loss to follow-up was unclear and thus resulted in a high risk for attrition bias on long-term outcomes (Bisgaard 2007; Mettler 2000). Six studies applied an intention-to-treat analysis, and analysed all data according to the randomisation result (Bhoyrul 2000; Bisgaard 2007; Feste 2000; Hamade 2007; Lam 2000; Mettler 2000). In one study, unit-of-analysis issues were evident: the trocar sites rather than the participants were analysed (Venkatesh 2007).

Selective reporting

We judged all included studies at unclear risk of selective reporting. One study had published a study protocol; however, they published it after finishing the study (Hamade 2007). All studies analysed their outcomes as they planned in the methods sections.

Other potential sources of bias***Surgeon's experience***

Two trials described the surgeons as “experienced” (Bisgaard 2007) and “well trained” (Feste 2000). Only one study reported that the surgeons were equally distributed between the two study groups (Bisgaard 2007). The other five studies were unclear about the experience of the surgeons (Bhoyrul 2000; Hamade 2007; Lam 2000; Mettler 2000; Venkatesh 2007). Two studies provided the number of surgeons that had performed the laparoscopies: seven (Feste 2000) and 16 (Bhoyrul 2000). The remaining studies did not report the number of surgeons. This substantial lack of clarity of the number and experience of surgeons created a potential risk of bias. This limits the external validity of the included studies.

Source of funding

Two studies reported their sources of funding. Lam 2000 received all radially trocars from Kojima Healthcare Asia Ltd; Venkatesh 2007 received all the trocars used in the study from manufacturing companies.

Effects of interventions

See: Summary of findings for the main comparison Radially expanding trocars compared to cutting trocars for laparoscopy; Summary of findings 2 Conical blunt-tipped trocar compared to cutting trocar for laparoscopy; Summary of findings 3 Radially expanding trocar compared to conical blunt-tipped trocar for laparoscopy; Summary of findings 4 Single-bladed trocar compared to pyramidal-bladed trocar for laparoscopy.

1. Radially expanding trocar versus cutting trocar

Primary outcomes: major trocar-related complications

1.1 Visceral injury

Four studies with 473 participants provided data for analysis of visceral injury (Bhoyrul 2000; Feste 2000; Mettler 2000; Venkatesh 2007). One study reported two cases of visceral injury, one in each group (Bhoyrul 2000). The combined results from the four trials showed no evidence of a difference in visceral injury between the use of the two trocars (Peto OR 0.95, 95% CI 0.06 to 15.32).

1.2 Vascular injury

Vascular injuries were infrequent in the four studies that reported them (473 participants) (Bhoyrul 2000; Feste 2000; Mettler 2000; Venkatesh 2007). There was only one case of vascular injury in a participant where a disposable cutting trocar was used for primary entry (Bhoyrul 2000). The combined results from the four trials showed no evidence of a difference in vascular injury (Peto OR 0.14, 95% CI 0.00 to 7.16).

Secondary outcomes: minor trocar-related complications

Six studies provided data for analysis of minor trocar-related complications (Bhoyrul 2000; Bisgaard 2007; Feste 2000; Lam 2000; Mettler 2000; Venkatesh 2007).

1.3 Trocar site herniation

There was no trocar site herniation in four studies (463 participants) (Bhoyrul 2000; Bisgaard 2007; Mettler 2000; Venkatesh 2007).

1.4 Trocar site bleeding

See figure 4. Five trials (553 participants) reported trocar site bleeding within radially expanding versus cutting trocar use (Bhoyrul 2000; Bisgaard 2007; Feste 2000; Lam 2000; Mettler 2000). There was a decreased risk for trocar site bleeding in the radially expanding trocar group (Peto OR 0.28, 95% CI 0.14 to 0.54) without substantial heterogeneity ($I^2 = 46\%$).

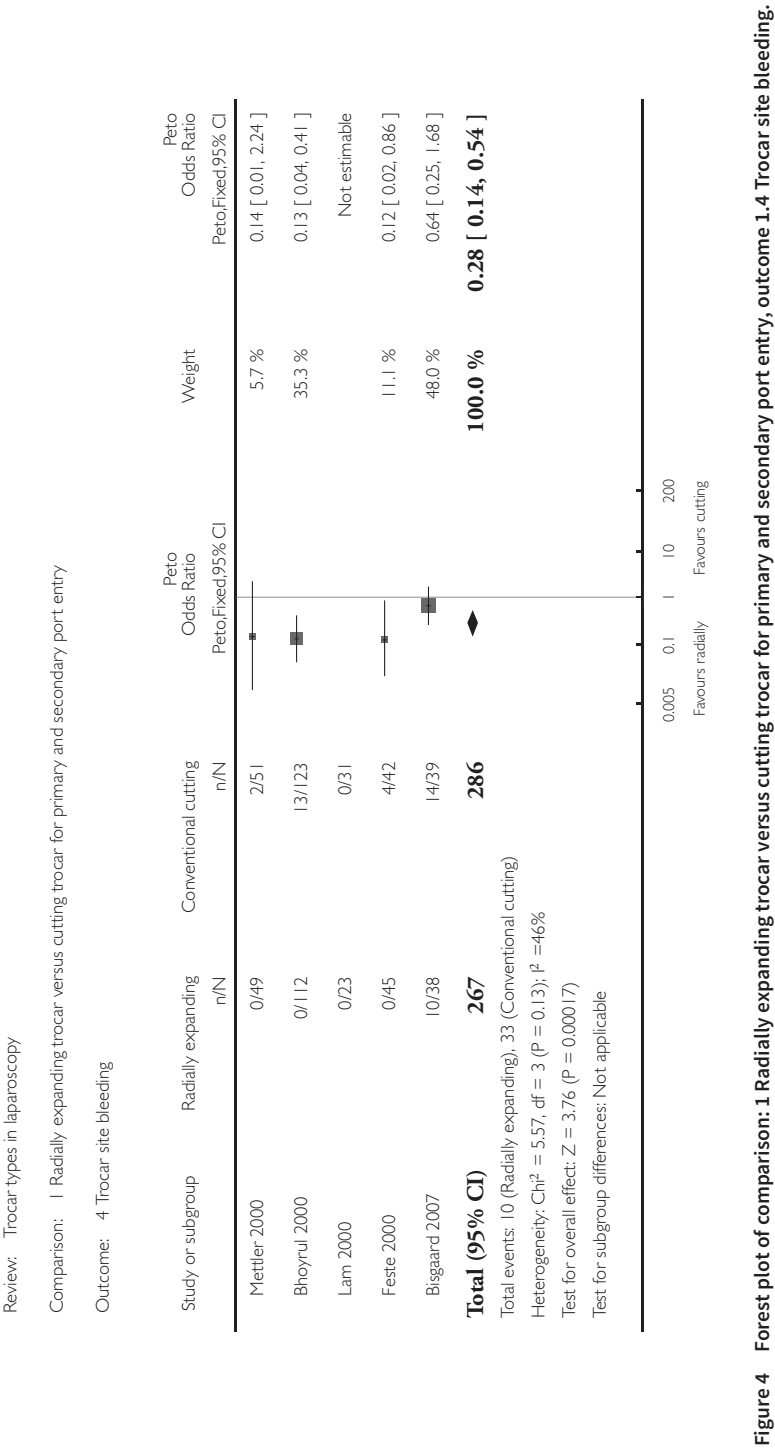


Figure 4 Forest plot of comparison: 1 Radially expanding trocar versus cutting trocar for primary and secondary port entry, outcome 1.4 Trocar site bleeding.

Subgroup analyses for surgical and gynaecological participants revealed a beneficial effect for the use of radially expanding trocars in people undergoing general surgery (Peto OR 0.29, 95% CI 0.15 to 0.58) but not for people undergoing gynaecological surgery (Peto OR 0.14, 95% CI 0.01 to 2.24). We could not perform a subgroup analysis for primary entry, secondary entry or trocar diameter because there were too few data. One included study reported a remarkably high incidence of bleeding at radially expanding trocar sites. More participants in the radially expanding trocar group had needed an additional incision to retract the gallbladder compared to the cutting group. One study reported one single trocar site bleeding at 43 radially trocar sites versus five at 84 cutting trocar sites. Because of unit-of-analysis issues, we could not use these data for statistical analysis (Venkatesh 2007).

1.5 Trocar site haematoma

See figure 5. Two studies described trocar site haematoma (Bhoirul 2000; Bisgaard 2007). One study (77 participants) reported no evidence of a difference between radially expanding trocars and cutting trocars in the occurrence of trocar site haematoma at two days postoperative (Peto OR 0.96, 95% CI 0.39 to 2.36) (Bisgaard 2007). However, in this study, more participants in the radially expanding group needed an additional incision to retract the gallbladder compared to the cutting group. The other study (161 participants) reported no evidence of a difference four hours postoperative, but at 24 hours postoperative fewer participants in the radially expanding trocar group compared to the cutting trocar group, had haematomas (Peto OR 0.32, CI 0.13 to 0.80) (Bhoirul 2000). We could not pool these data because of the clinical heterogeneity.

1.6 Trocar site infection

One study reported indistinct findings on a single trocar site infection (Venkatesh 2007).

1.7 Postoperative pain

Four studies reported statistical data on postoperative pain. None of these studies provided sufficient data, making it inappropriate to pool the data (Bisgaard 2007; Feste 2000; Mettler 2000; Venkatesh 2007). Two studies found no evidence of a difference in pain at six hours, one day and two days postoperative (Bisgaard 2007), and three hours, 24 hours and one week postoperative (Venkatesh 2007). One study found no evidence of a difference four hours postoperative, but did find differences in pain eight, 12 and 24 hours postoperative (Feste 2000). The other study found differences for pain at four, eight and 12 hours, but no evidence of a difference at 24, 48 and 72 hours postoperative (Mettler 2000). The differences all favoured the participants that had received radially expanding trocars for primary and secondary ports. Another study reported no evidence of differences at four, eight, 12 and 24 hours postoperative, no statistical data were provided (Bhoirul 2000).

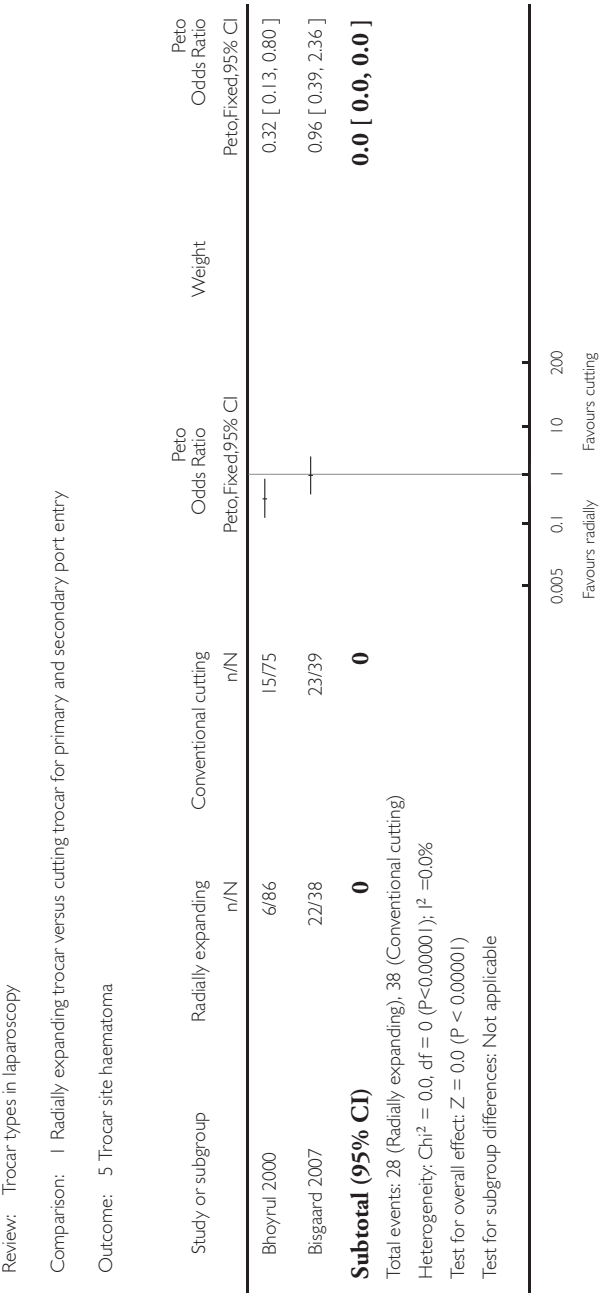


Figure 5 Forest plot of comparison: 1 Radially expanding trocar versus cutting trocar for primary and secondary port entry, outcome 1.5 Trocar site haematoma.

2. Conical blunt-tipped trocar versus cutting trocar

Primary outcomes: major trocar-related complications

2.1 Visceral injury

One study provided data on visceral injury, and reported no visceral injuries in either the conical blunt-tipped trocars or cutting trocars groups (42 participants) (Venkatesh 2007).

2.2 Vascular injury

One study provided data on vascular injury, and reported no vascular injuries in either the conical blunt-tipped trocars or cutting trocars groups (42 participants) (Venkatesh 2007).

Secondary outcomes: minor trocar-related complications

2.3 Trocar site herniation

One study provided data on trocar site herniation, and reported no herniations in either the conical blunt-tipped trocars or cutting trocars groups (42 participants) (Venkatesh 2007).

2.4 Trocar site bleeding

Two studies reported occurrences of trocar site bleeding (Hamade 2007; Venkatesh 2007). One study with 30 participants, found no evidence of a difference between conical blunt-tipped trocars and cutting trocars (Peto OR 0.13, 95% CI 0.01 to 2.12) (Hamade 2007). The other study reported one single trocar site bleeding at 43 conical blunt-tipped trocar sites versus five trocar site bleedings at 84 cutting trocar sites. Because of unit-of-analysis issues, we could not use these data for statistical analysis (Venkatesh 2007). The trocar site of a single wound infection is indistinct (Venkatesh 2007).

2.5 Postoperative pain

One study reported mean VAS scores at three hours, 24 hours and one week postoperative (Venkatesh 2007), and found no evidence of a difference between conical blunt-tipped and cutting trocars. The data provided were insufficient for calculation of adequate measures and also unit of analysis issues are present.

3. Radially expanding trocar versus conical blunt-tipped trocar

Primary outcomes: major trocar-related complications

3.1 Visceral injury

One study (28 participants) provided data on visceral injury, and reported none within either the radial expanding trocar or conical blunt-tipped trocar groups (Venkatesh 2007).

3.2 Vascular injury

One study (28 participants) provided data on vascular injury, and reported none within either the radial expanding trocar or conical blunt-tipped trocar groups (Venkatesh 2007).

Secondary outcomes

3.3 Minor trocar-related complications

One study provided data on minor trocar-related complications. It reported no herniations and two ports with trocar site bleeding: one out of the 43 radially trocar sites and one out of the 38 conical blunt-tipped trocar sites. These study data presented unit-of-analysis issues and data were insufficient to present in meta-analysis (Venkatesh 2007).

3.4 Postoperative pain

One study reported mean VAS scores at three hours, 24 hours and one week postoperative (Venkatesh 2007), and found no evidence of a difference between radially expanding and conical blunt-tipped trocars. We could not calculate adequate measures because of insufficient statistical data and issues on unit-of-analysis.

4. Single-bladed trocar versus pyramidal-bladed trocar

Primary outcomes: major trocar-related complications

4.1 Visceral injury

One study (28 participants) provided data on visceral injury, and reported none within either the single-bladed trocar or pyramidal-bladed trocar groups (Venkatesh 2007).

4.2 Vascular injury

One study (28 participants) provided data on vascular injury, and reported no vascular injuries within either the single-bladed trocar or pyramidal-bladed trocar groups (Venkatesh 2007).

Secondary outcomes: minor trocar-related complications

One study provided data on minor trocar-related complications and postoperative pain (Venkatesh 2007). There were no herniations and five ports with trocar site bleeding (one of the 41 single-bladed trocar sites and four of the 43 pyramidal-bladed trocar sites). This study reported mean VAS scores at three hours, 24 hours and 1 week postoperative. They found no evidence of a difference between single-bladed and pyramidal-bladed trocars. We could not calculate adequate measures because of insufficient statistical data and issues on unit-of-analysis.

Sensitivity analyses

We could not perform planned sensitivity analyses due to the small number of included studies.

ADDITIONAL SUMMARY OF FINDINGS

Conical blunt-tipped trocar compared to cutting trocar for laparoscopy						
Patient or population: people undergoing laparoscopy Settings: surgical Intervention: conical blunt-tipped trocar Comparison: cutting trocar						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Cutting trocar	Conical blunt-tipped trocar				
Visceral injury	No events reported	No events reported	Not estimable ¹	42 (1 study)	⊕○○○ very low ^{2,3}	-
Vascular injury	No events reported	No events reported	Not estimable ¹	42 (1 study)	⊕○○○ very low ^{2,3}	-
Trocar site bleeding	133 per 1000	20 per 1000 (2 to 246)	OR 0.13 (0.01 to 2.12)	30 (1 study)	⊕○○○ very low ^{3,4}	-
Postoperative pain ⁵	See comment ⁵	See comment ⁵	Not estimable ⁵	42 (1 study)	⊕○○○ very low ^{2,6,7}	-
*The basis for the assumed risk is the <i>mean control group risk</i> across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; OR: odds ratio.						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						

- ¹ No events reported.
- ² Downgraded one level due to high risk of selection bias: unclear randomisation and allocation.
- ³ Downgraded two levels due to imprecision: the number of events was fewer than 300 (the threshold rule-of-thumb value).
- ⁴ Downgraded one level due to high risk of performance bias: personnel not blinded, unclear type and frequency of port manipulation.
- ⁵ Study provided insufficient statistical data, making it inappropriate to calculate adequate measures.
- ⁶ Downgraded one level due to risk of bias: attrition bias due lack of clarity on completeness of the outcome data and 'unit of analysis' issues and performance bias due to lack of clarity on degree and frequency of port manipulation.
- ⁷ Downgraded one level due to imprecision.

Radially expanding trocar compared to conical blunt-tipped trocar for laparoscopy							
Patient or population: people undergoing laparoscopy Settings: surgical Intervention: radially expanding trocar Comparison: conical blunt-tipped trocar							
Outcomes	Illustrative comparative risks* (95% CI)			Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk					
	Conical blunt-tipped tro- car	Radially expanding tro- car					
Visceral injury	No events reported	No events reported	No events reported	Not estimable ¹	28 (1 study)	⊕○○○ very low ^{2,3}	-
Vascular injury	No events reported	No events reported	No events reported	Not estimable ¹	28 (1 study)	⊕○○○ very low ^{2,3}	-
Trocar site herniation	No events reported	No events reported	No events reported	Not estimable ¹	28 (1 study)	⊕○○○ very low ^{3,4}	-
*The basis for the assumed risk is the <i>mean control group risk</i> across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; OR: odds ratio.							
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.							

¹ No events reported.

² Downgraded one level due to high risk of selection bias: unclear randomisation and allocation.

³ Downgraded two levels due to imprecision: Only 28 participants.

⁴ Downgraded one level due to risk of bias: attrition bias due to unclear loss to follow-up and performance bias.

Single-bladed trocar compared to pyramidal-bladed trocar for laparoscopy						
Patient or population: people undergoing laparoscopy Settings: surgical Intervention: single-bladed trocar Comparison: pyramidal-bladed trocar						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Pyramidal-bladed trocar	Single-bladed trocar				
Visceral injury	No events reported	No events reported	Not estimable ¹	28 (1 study)	⊕○○○ very low ^{2,3}	-
Vascular injury	No events reported	No events reported	Not estimable ¹	28 (1 study)	⊕○○○ very low ^{2,3}	-
Trocar site herniation	No events reported	No events reported	Not estimable ¹	28 (1 study)	⊕○○○ very low ^{3,4}	-
*The basis for the assumed risk is the <i>mean control group risk</i> across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval. OR: odds ratio.						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						

¹ No events reported.

² Downgraded one level due to high risk of selection bias: unclear randomisation and allocation.

³ Downgraded two levels due to imprecision: only 28 participants.

⁴ Downgraded one level due to risk of bias: attrition bias due to unclear loss to follow-up and performance bias.

Discussion

Summary of main results

This systematic review evaluated the rates of trocar-related complications and postoperative pain for different trocar types used in people undergoing laparoscopy. We divided the outcomes into primary outcomes (including major trocar-related complications), and secondary outcomes (including minor trocar-related complications and postoperative pain). For major trocar-related complications, the studies reported events of vascular and visceral injury. The reported minor trocar-related complications were trocar site herniation, trocar site bleeding and trocar site infection. The trocar designs assessed in this review were radially expanding, cutting, conical blunt-tipped, single-bladed and pyramidal-bladed trocars. The result of seven RCTs (654 participants) showed no advantage of the use of a specific trocar design to minimise major trocar-related complications. Concerning minor trocar-related complications, very low quality evidence demonstrated a lower risk of trocar site bleeding with the use of radially expanding trocars in comparison to cutting trocars (five studies, 553 participants). There was no advantage of a specific trocar design in terms of reducing the incidence of trocar site herniation, haematoma and infection with very low quality evidence (five studies, 477 participants). Very low quality evidence suggested less postoperative pain after the use of radially expanding trocars compared to cutting trocars (two studies, 187 participants). However, these findings could not be imputed in a meta-analysis because of incompleteness and heterogeneity of the statistical data. Very low quality evidence indicated no difference in postoperative pain between participants who had received conical blunt-tipped trocars, radially expanding trocars, single-bladed trocars or pyramidal-bladed trocars.

Overall completeness and applicability of evidence

Vascular and visceral injuries are the most serious trocar-related complications and therefore our main interest. These major complications often require additional surgical intervention, conversion to laparotomy and are associated with postoperative morbidity and mortality (Jansen 1997). This review included seven studies (654 participants), representing insufficient power to demonstrate a beneficial effect of one trocar type over another effectively. Minor trocar-related complications, such as trocar site herniation, trocar site bleeding or postoperative wound haematoma and trocar site infection, are generally more common and can be studied with smaller study populations. This could also be applied to the outcome of postoperative pain, depending on the clinically relevant difference in pain score that should be identified. However, with the exception of trocar site bleeding, the studies were not sufficient to address (all of) the defined outcomes in this review.

Apparently, the included studies focused on short-term outcomes as their primary outcome parameter. The study data particularly concerned complications that occurred intraoperatively or within the first 24 hours after surgery. Longer-term complications such as haematoma, wound infection and trocar site herniation, were studied with very limited precision.

The trocar types included in this review for comparisons were limited to the radially expanding trocar, the cutting trocar, the conical blunt-tipped trocar, the single-bladed trocar and the pyramidalbladed trocar. A myriad of device designs exists (Fuller 2003), but this review only evaluated a small number of these types. RCTs have not studied other types of trocars. Remarkably, we found no comparison between reusable and disposable trocars. The sharpness of disposable cutting trocars is usually better compared to that of reusable cutting trocars, which may lose their sharpness through repetitive insertion. Therefore, reusable trocars may require a relatively high puncture force for penetration through the abdominal wall, with a higher chance of resulting in an abrupt and uncontrolled introduction of the trocar that may result in a deeper penetration and potentially serious visceral and vascular injury (Tansatit 2006). None of the studies analysed the disposability of the trocars as a confounding factor for trocar-related complications. It is notable that six of the seven included RCTs studied radially expanding trocars, which does not seem in proportion to current practice. In view of the higher cost of radially expanding devices, it can be questioned whether this scientific attention can be regarded as clinically relevant. Another shortcoming was that many studies did not report the diameter of the trocars used. In the studies that did report diameters, there was much variety. To assess whether the trocar diameter affects the outcome of trocar-related complications, future studies should analyse individual participant data. A larger trocar diameter creates a larger defect in the abdominal wall and probably results in an increased risk of trocar site herniation and bleeding. In 1993, one retrospective study demonstrated an increased risk of trocar site herniation when trocars with a diameter of 12 mm were used compared to 10 mm (Kadar 1993). More recent studies on cholecystectomy did not show clear clinical advantages of mini laparoscopy (Gurusamy 2013; Sajid 2009).

We studied trials on traditional laparoscopy. We did not include newer techniques such as robot-assisted laparoscopy, LESS and NOTES. The results of this review should not be extrapolated to these other techniques.

Various types of participants were included in the studies for this review, all undergoing laparoscopy. The vast majority of the participants underwent laparoscopy for surgical indications, fewer for gynaecological conditions and fewer for renal conditions. Many different exclusion criteria were applied in the included studies and there was a wide age range. This large heterogeneity of included studies means there were too few data to perform a sensitivity analysis. From a clinical perspective, we do not expect a difference in

trocar-related complications in people undergoing laparoscopy for different conditions. This should be examined when more studies become available and adequate sensitivity analyses can be conducted.

Quality of the evidence

The quality of the evidence was generally very low as shown in the 'Summary of findings' tables, the main limitation being very serious imprecision. This systematic review did not allow a robust conclusion regarding the rates of trocar-related complications and postoperative pain for different trocar types used in people undergoing laparoscopy. The main methodological limitation was the small number of included participants, due to the small number of RCTs included in this review. The incidences of trocar-related complications are low; particularly the incidence of major trocar-related complications is very low. To detect a risk difference for bowel injury from 0.3% to 0.2%, over 800,000 participants would be needed for inclusion in a trial (Garry 1999). Obviously, RCTs are not the design of choice to detect risk differences for major trocar-related complications. In our opinion, interventions to prevent events that occur only infrequently may be best assessed by good-quality observational studies such as cohort and case-control studies.

With respect to minor complications with a higher incidence (trocar site herniation, trocar site bleeding and haematoma) and postoperative pain, other study limitations came into view: heterogeneity of intervention and comparator within and between studies. Within the included studies, there was a considerable risk of performance bias: differences or ambiguities between study groups for closure of the fascial defect at trocar sites. This could have resulted in the inconsistencies in outcome trocar site bleeding, haematoma and postoperative pain. A third type of risk of performance bias resulted from limited reporting on the use of analgesics to prevent postoperative pain. In three of the studies, the type and amount of used analgesics was not reported, while pain was one of the evaluated outcomes. Another notable limitation was the high risk of attrition bias in most studies: short-term outcome data were incomplete, and this is even more pronounced for longer-term outcomes including trocar site infection and herniation.

One issue particularly arose in the analysis of the outcome postoperative pain, which was heterogeneity in the measures of postoperative pain. This was caused by different timings of measurements, use of different assessment tools and different presentations of data. No single study provided sufficient pain data, making it inappropriate to pool the data. Contacting the authors for missing data did not result in sufficient data for pooling.

Potential biases in the review process

There was a number of limitations to this review. The primary limitation was the lack of studies with a low risk of bias. The second limitation was the possibility of publication bias, which we attempted to minimise through an extensive database search. We also searched the main electronic sources for ongoing trials and contacted the US FDA for regulatory trial data without relevant result. Surprisingly, with the exception of one study, all studies did not have a published protocol and, to our knowledge, had not registered their study in one of the many trial registries. This indicates that many trials conducted in the 21st century still do not conform to international procedure as outlined by the International Committee of Medical Journal Editors (ICJME). The third weakness is the outcomes information in the included studies. Most outcome measures were not properly defined. The reliability of meta-analyses is depending on the reliability with which these complications were measured by the authors. Furthermore, we could not obtain all relevant data. We were unable to obtain some data on the outcome of postoperative pain and missing data to calculate or estimate the standard deviations were not available even though we contacted the study authors. Since this concerned the majority of the pain data, imputation was not possible. Strengths of this review include the methodological rigor applied according to our published protocol: the search was guided and adapted by the Cochrane Menstrual Disorders and Subfertility Group. Two review authors independently conducted the study selection, risk of bias assessment and data collection. We resolved any disagreements by discussion with a third review author. We attempted to deal with missing information and data by contacting the primary authors of Bhoyrul 2000, Bisgaard 2007, Feste 2000, and Mettler 2000, and we received partial responses.

Agreements and disagreements with other studies or reviews

We identified two systematic reviews that have included this topic (Ahmad 2015; Antoniou 2013). In an update of their Cochrane review on laparoscopic entry performed during the development of this review, Ahmad et al. also included the outcomes of secondary ports, and, as a result, there is agreement between their review and ours. Their results are consistent with this review in finding an advantage of radially expanding trocars compared to standard trocars in terms of trocar site bleeding (Peto OR 0.31, 95% CI 0.15 to 0.62). They found no other evidence suggesting more or less safety of radially expanding, cutting or blunt trocars (Ahmad 2015). Antoniou 2013 evaluated the risk of abdominal wall bleeding, visceral injuries and overall complications with the use of bladed and blunt-tipped laparoscopic trocars. Radially expanding trocars were included in the 'blunt-tipped' group. Meta-analysis resulted in a lower risk of abdominal wall bleeding for the blunt-tipped trocar group (OR 0.42, 95% CI 0.21 to 0.88). We believe that the expanding function of the radially expanding trocar may have a different effect

on trocar-related complications and, therefore, did not pool data from blunt-tipped trocars with radially expanding trocars. However, their results for trocar site bleeding are consistent with the results in this review since most of their included studies used radially expanding trocars.

Authors' conclusions

Implications for practice

We found no evidence of a difference in the incidence of major trocar-related complications, such as visceral or vascular injury, when comparing different trocar types with one another. However, caution is urged when interpreting these results because the incidence of serious complications following the use of a trocar is extremely low. There was very low quality evidence for minor trocar-related complications suggesting that the use of radially expanding trocars compared to cutting trocars leads to reduced incidence of trocar site bleeding. These secondary outcomes are viewed to be of less clinical importance.

Implications for research

Large, well-conducted observational studies are necessary in order to answer the questions addressed in this review because serious complications, such as visceral or vascular injury, are extremely rare. However, for other outcomes, such as trocar site herniation, bleeding or infection, large observational studies may be needed as well. In order to answer these questions, it is advisable to establish an international network for recording these types of complications following laparoscopic surgery.

Acknowledgements

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Appendices

Appendix 1. Menstrual Disorders and Subfertility Group (MDSG) search strategy

Keywords CONTAINS “laparoscopic” or “laparoscope size” or “laparoscopy” or “laparoscopically assisted hysterectomy” or “laparoscopically assisted vaginal hysterectomy” or “laparoscopy-assisted vaginal hysterectomy” or “mini-laparoscopy” or Title CONTAINS “laparoscopic” or “laparoscope size” or “laparoscopy” or “laparoscopically assisted hysterectomy” or “laparoscopically assisted vaginal hysterectomy” or “laparoscopy-assisted vaginal hysterectomy” or “mini-laparoscopy”

AND

Keywords CONTAINS “trocar” or “trocar - dilating-tip” or “trocar - non-shielded-bladed” or “trocar ports” or “pneumoperitoneum” or Title CONTAINS “trocar” or “trocar - dilating-tip” or “trocar - non-shielded-bladed” or “trocar ports” or “pneumoperitoneum”

Appendix 2. Ovid Cochrane Central Register of Controlled Trials (CENTRAL)

Database searched 28 February 2011, 1 February 2012, 15 January 2014, 24 July 2014 and 26 May 2015.

1. exp Laparoscopy/ (3605)
2. exp Laparoscopes/ (92)
3. (Laparoscop\$ or Laparascop\$).tw. (7064)
4. (minimal\$ adj invasive).tw. (1544)
5. or/1-4 (8532)
6. (trocar\$ or troicar\$ or trochar\$).tw. (306)
7. cannula\$.tw. (1757)
8. (visual adj2 entry system\$).tw. (3)
9. pneumoperiton\$.tw. (455)
10. exp Pneumoperitoneum, Artificial/ (225)
11. (optiview\$ or endotip\$).tw. (3)
12. visiport\$.tw. (0)
13. access technique\$.tw. (22)
14. (Veress or veress-needle\$).tw. (35)
15. Hasson.tw. (8)
16. or/6-15 (2535)
17. 5 and 16 (729)

Appendix 3. Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1950 to present)

Database searched 28 February 2011, 1 February 2012, 15 January 2014, 24 July 2014 and 26 May 2015.

1. exp Laparoscopy/ (72404)
2. exp Laparoscopes/ (3453)
3. (Laparoscop\$ or Laparascop\$).tw. (88645)
4. (minimal\$ adj invasive).tw. (40910)
5. or/1-4 (132344)
6. (trocar\$ or troicar\$ or trochar\$).tw. (5224)
7. cannula\$.tw. (35322)
8. (visual adj2 entry system\$).tw. (6)
9. pneumoperiton\$.tw. (5927)
10. exp Pneumoperitoneum, Artificial/ (3860)
11. (optiview\$ or endotip\$).tw. (38)
12. visiport\$.tw. (15)
13. access technique\$.tw. (530)
14. (Veress or veress-needle\$).tw. (387)
15. Hasson.tw. (153)
16. or/6-15 (47827)
17. randomized controlled trial.pt. (395860)
18. controlled clinical trial.pt. (89548)
19. randomized.ab. (321300)
20. placebo.tw. (167185)
21. clinical trials as topic.sh. (173005)
22. randomly.ab. (231296)
23. trial.ti. (138894)
24. (crossover or cross-over or cross over).tw. (64217)
25. or/17-24 (984055)
26. exp animals/ not humans.sh. (4043807)
27. 25 not 26 (906186)
28. 5 and 16 and 27 (774)

Appendix 4. Ovid EMBASE

Ovid EMBASE (January 2010 to present)

Database searched 28 February 2011, 1 February 2012, 15 January 2014, 24 July 2014 and 26 May 2015.

1. exp Laparoscopy/ (108007)
2. (Laparoscop\$ or Laparoscop\$).tw. (131384)
3. (minimal\$ adj invasive).tw. (59604)
4. exp laparoscope/ (2885)
5. or/1-4 (199188)
6. exp trocar/ (5725)
7. (trocar\$ or troicar\$ or trochar\$).tw. (9064)
8. (Veress or veress-needle\$).tw. (657)
9. Hasson.tw. (270)
10. gastrointestinal radiography/ (4308)
11. pneumoperiton\$.tw. (7441)
12. cannula\$.tw. (42077)
13. (visual adj2 entry system\$).tw. (6)
14. (optiview\$ or endotip\$).tw. (99)
15. visiport\$.tw. (43)
16. access technique\$.tw. (777)
17. or/6-16 (62302)
18. Clinical Trial/ (844393)
19. Randomized Controlled Trial/ (370996)
20. exp randomization/ (66369)
21. Single Blind Procedure/ (20206)
22. Double Blind Procedure/ (120351)
23. Crossover Procedure/ (42869)
24. Placebo/ (256309)
25. Randomized controlled trial\$.tw. (116070)
26. Rct.tw. (16937)
27. random allocation.tw. (1411)
28. randomly allocated.tw. (22280)
29. allocated randomly.tw. (2019)
30. (allocated adj2 random).tw. (726)
31. Single blind\$.tw. (15724)
32. Double blind\$.tw. (150401)

- 33. ((treble or triple) adj blind\$.tw. (449)
- 34. placebo\$.tw. (213796)
- 35. prospective study/ (290100)
- 36. or/18-35 (1459024)
- 37. case study/ (31673)
- 38. case report.tw. (281336)
- 39. abstract report/ or letter/ (923420)
- 40. or/37-39 (1230185)
- 41. 36 not 40 (1419880)
- 42. 5 and 17 and 41 (1495)

Appendix 5. Ovid PsycINFO

Ovid PsycINFO (inception to present)

Database searched 28 February 2011, 1 February 2012, 15 January 2014, 24 July 2014 and 26 May 2015.

- 1. (Laparoscop\$ or Laparascop\$).tw. (282)
- 2. (minimal\$ adj invasive).tw. (284)
- 3. or/1-2 (542)
- 4. (trocar\$ or troicar\$ or trochar\$).tw. (7)
- 5. cannula\$.tw. (1976)
- 6. (visual adj2 entry system\$).tw. (0)
- 7. (optiview\$ or endotip\$).tw. (0)
- 8. visiport\$.tw. (0)
- 9. pneumoperiton\$.tw. (3)
- 10. or/4-9 (1986)
- 11. 3 and 10 (6)

Appendix 6. CINAHL, Cumulative Index of Nursing and Allied Health Literature

CINAHL search for CC1505 15 January 2014, and updated on 26 May 2015.

#	Query	Results
S27	S11 AND S25	18
S26	S11 AND S25	97
S25	S12 OR S13 or S14 or S15 OR S16 OR S17 OR S18OR S19 OR S20 OR S21 OR S22 OR S23 OR S24	Display

S24	TX allocat* random*	Display
S23	(MH "Quantitative Studies")	Display
S22	(MH "Placebos")	Display
S21	TX placebo*	Display
S20	TX random* allocat*	Display
S19	(MH "Random Assignment")	Display
S18	TX randomi* control* trial*	Display
S17	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	Display
S16	TX ((trebl* n1 blind*) or (trebl* n1 mask*))	Display
S15	TX ((trebl* n1 blind*) or (trebl* n1 mask*))	Display
S14	TX clinic* n1 trial*	Display
S13	PT Clinical trial	Display
S12	(MH "Clinical Trials+")	Display
S11	S4 AND S10	471
S10	S5 OR S6 OR S7 OR S8 OR S9	892
S9	TX Pneumoperiton*	572
S8	TX endotip*	2
S7	TX visual entry system*	2
S6	TX trochar*	14
S5	TX trocar*	329
S4	S1 OR S2 OR S3	16,899
S3	(MM "Minimally Invasive Procedures") OR "tx minimal* invasive"	2,714
S2	TX Laparoscop*	14,593
S1	(MM "Laparoscopy"# OR "laparoscopy" OR #MH "Surgery, Laparoscopic"#	11,161

Appendix 7. Cochrane Database of Systematic Reviews, DARE, Wiley – Database of Abstracts of Reviews of Effects (reference lists)

- #1 MeSH descriptor Laparoscopy explode all trees
- #2 MeSH descriptor Laparoscopes explode all trees
- #3 (Laparoscop* or Laparoscop*):ti,ab,kw
- #4 (minimal* invasive*):ti,ab,kw
- #5 (#1 OR #2 OR #3 OR #4)
- #6 (trocar* or troicar* or trochar):ti,ab,kw

- #7 MeSH descriptor Pneumoperitoneum, Artificial explode all trees
- #8 (pneumoperiton*):ti,ab,kw
- #9 (access technique*):ti,ab,kw
- #10 (cannula*):ti,ab,kw
- #11 (“visual entry system” or “visual entry systems”):ti,ab,kw
- #12 (optiview* or endotip*):ti,ab,kw
- #13 (visiport*):ti,ab,kw
- #14 (Veress or veress-needle*):ti,ab,kw
- #15 (Hasson*):ti,ab,kw
- #16 (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
- #17 (#5 AND #16)

Chapter 4

Laparoendoscopic single-site surgery versus conventional laparoscopy for hysterectomy: a systematic review and meta-analysis

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Jan W. Schoones
Frank Willem Jansen

Abstract

Purpose: To assess the safety and effectiveness of LESS compared to conventional hysterectomy.

Methods: The systematic review and meta-analysis was performed according to the MOOSE guideline, and quality of evidence was assessed using GRADE. Different databases were searched up to 4th of August 2016. Randomized controlled trials and cohort studies comparing LESS to the conventional laparoscopic hysterectomy were considered for inclusion.

Results: Of the 668 unique articles, 23 were found relevant. We investigated safety by analyzing the complication rate and found no significant differences between both groups [OR 0.94 (0.61, 1.44), $I^2 = 19\%$]. We assessed effectiveness by analyzing conversion risk, postoperative pain, and patient satisfaction. For conversion rates to laparotomy, no differences were identified [OR 1.60 (0.40, 6.38), $I^2 = 45\%$]. In 3.5% of the cases in the LESS group, an additional port was needed during LESS. For postoperative pain scores and patient satisfaction, some of the included studies reported favourable results for LESS, but the clinical relevance was non-significant. Concerning secondary outcomes, only a difference in operative time was found in favor of the conventional group [MD 11.3 min (5.45 – 17.17), $I^2 = 89\%$]. The quality of evidence for our primary outcomes was low or very low due to the study designs and lack of power for the specified outcomes. Therefore, caution is urged when interpreting the results.

Conclusion: The single-port technique for benign hysterectomy is feasible, safe, and equally effective compared to the conventional technique. No clinically relevant advantages were identified, and as no data on cost effectiveness are available, there are currently not enough valid arguments to broadly implement LESS for hysterectomy.

Introduction

Since the early 1990s, “minimally invasive surgery” (MIS) has been rapidly implemented into a variety of surgical disciplines. The main advantage of minimally invasive procedures is the absence of a large abdominal wound, which results in fewer wound-related complications, less postoperative pain, and a shorter hospital stay (1). In an effort to extend these benefits, an increasing enthusiasm has emerged for the laparoendoscopic single-site surgery (LESS). In LESS, multiple laparoscopic instruments are placed through one single abdominal incision at the place of the umbilicus. The hypothesis is that single incision technique might offer advantages over the standard multi-port laparoscopy as abdominal wall trauma is decreased, potentially leading to less postoperative pain and improved cosmesis (2-4). The potential drawbacks of the single-port approach are a larger umbilical incision and the proximity of the instruments resulting in a technical challenge, especially for advanced surgery (5,6). It was only in 1991 that Pelosi et al. performed the first LESS hysterectomy (7), more than 20 years after the first publication on the LESS procedure in 1969 (6). Reports have currently shown the feasibility of LESS surgery in many benign gynecologic procedures (8,9). However, it remains debatable whether this new technology has added value over the existing conventional laparoscopic technique and whether it should be broadly implemented for hysterectomy.

The proportion of laparoscopic hysterectomies (LH) has significantly increased the last decades: from 3% in 2002 to 36% in 2012 in the Netherlands (10), and similar numbers have been observed in other countries (United States (11) and Finland (12)). Regarding the proportion of hysterectomies performed using the LESS approach, no national overviews have been published on this topic so far. In some parts of the world, single-port hysterectomy seems well implemented. A retrospective single-hospital study from Korea showed for example that in 2013, 80% of their hysterectomies were LESS hysterectomies (13). Hysterectomy in general is one of the most performed advanced surgeries in gynecology with approximately 600,000 procedures a year in the United States (11). As a result, defining the surgical approach with the most advantages is essential. In this light, the aim of this study is to provide a systematic review and meta-analysis of the current comparative studies evaluating specifically LESS hysterectomy and conventional laparoscopy. We particularly focused on the safety and effectiveness of the two techniques.

Materials and methods

Eligibility criteria, information source, search strategy

This systematic review was conducted according to the MOOSE guidelines (14). We identified original published studies through a search of Medline (PubMed version), EMBASE (Ovid version), Cochrane, Web of Science, Central, CINAHL, Academic Search Premier and Science Direct up to 4th of Augustus 2016 without restriction. The search terms included 'gynecology', 'hysterectomy', and all acronyms of LESS. The exact search terms are presented in supplemented material (Appendix 1). In addition, relevant studies cited in the reference lists of the selected papers were evaluated. Only comparative studies (randomized controlled trials, prospective and retrospective cohort studies) evaluating LESS versus hysterectomy for benign indications were considered for inclusion. LESS procedures had to be strictly performed through one single (umbilical) port as opposed to the conventional laparoscopic hysterectomy performed through more than one port. Studies on animals or patients aged < 18 years were excluded as well as studies comprising endoscopic surgery with different techniques (e.g., hand- or robot-assisted, isobaric pneumoperitoneum). We also excluded descriptive review articles, surveys, technical reports, published abstracts without a full manuscript, reports from meetings, and trials with less than ten included participants per arm or 20 in total.

Study selection

Two reviewers independently screened the titles and abstracts for their relevance (ES and CC). Potentially relevant studies were obtained in full text and assessed for inclusion. We included studies wherein the effectiveness and/or safety of LESS compared to conventional laparoscopy for hysterectomy were investigated. To assess the safety of a procedure, we considered complication rates as primary outcome. Effectiveness refers to the potential success of a surgical procedure, and therefore, we considered: success rate (defined by the chance for a successful procedure without conversion to laparotomy and for the use of an additional port in the single-site group), postoperative pain scores, cosmetic outcomes, and patient satisfaction (including sexual function) as relevant primary outcomes. The following secondary perioperative outcomes were considered: operative time, intraoperative blood loss, and length of hospital stay. Although less important, these are also relevant identifiers for the effectiveness of a procedure.

Complications were defined according to the classification of the Dutch Society of Obstetrics and Gynecology and further divided into 'major complications' and 'minor complications' (15). Major complications included: major hemorrhage or hematoma (requiring transfusion);

urinary tract or bowel injury; pulmonary embolism; major anesthesia problems; vaginal cuff dehiscence; port site hernia; and re-operation. Minor complications were defined as hemorrhage (not requiring transfusion) or hematoma (with spontaneous drainage); infection to the chest, urinary tract, wound, pelvic, other, or pyrexia 38 °C; deep vein thrombosis; and other minor complication requiring treatment (including voiding dysfunction and ileus). We distinguished two types of conversion: an unintended conversion to laparotomy and the need for an additional port in the single-site group. The postoperative pain should be expressed on a self-reported scale (16) (e.g., visual analogous scale (VAS), numerical rating scale (NRS)), and for cosmetic outcomes, validated questionnaires should be used.

Data extraction

Outcome data as mentioned in the previous heading as well as study and patient characteristics were extracted from the included studies. These baseline findings included study design, number of included participants, country where the study was conducted, source of funding, relevant characteristics of the participants (age, body mass index, and uterine weight), description of the procedural setting, and experience of the physician. Data related to the defined outcomes were assessed for inclusion in the meta-analysis. Sensitivity analyses were performed for randomized studies and cohort studies when relevant subgroup analyses were accomplished for TLH and LAVH.

Assessment of risk of bias

The study limitations in randomized trials and observational studies were assessed using the checklists adapted from Guyatt et al. (17): (1) random sequence generation; (2) allocation concealment; (3) blinding of participants, surgeons, and investigators; (4) attrition bias: loss to follow-up (5) reporting bias: selective reporting and/or missing per protocol analysis; (6) other, e.g., use of non-validated outcome measures, difference in baseline characteristics between the groups and influence of co-interventions, or differing surgical experience in the compared procedures. For the first three points of the checklist, retrospective studies were rated as 'high risk', whereas attrition bias and reporting bias were marked as 'unclear', unless there was an additional reason to judge them as 'high risk'. The quality of evidence was then rated following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (18). The quality of evidence was classified into one of four categories: high quality, moderate quality, low quality, or very low quality. We used the online GRADE program (GRADEpro Guideline Development Tool [Software], McMaster University, 2015, developed by Evidence Prime, Inc., available from grade.pro.org). Any discrepancies between reviewers were addressed by an open discussion.

Evidence synthesis and statistical analysis

Meta-analysis was conducted using Review Manager (Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). For continuous data, we calculated mean differences (MDs) and standard deviations (SDs); for dichotomous data, we calculated odds ratio (OD) with their 95% confidence intervals (CIs). When summary data were missing, e.g., only the median and range were available, data were transformed as appropriate according to the definitions described by Hozo (19). We applied the random-effects model to combine data for meta-analysis.

Results

Study selection

Figure 1 shows the flow diagram of the literature selection for this review. The initial search yielded 668 unique references, and twenty-three studies fulfilled our inclusion criteria. Eleven studies compared LESS hysterectomy to conventional TLH (13,20-29), eleven studies compared LESS hysterectomy to LAVH (30-40), and in one study, both procedures were included (41). Two studies also included supra-cervical hysterectomies (20,21). The study by Koyanagi (42) was excluded as all data were already included in another study by the same author (40). The selected papers were published between 2010 and 2015.

Study characteristics

A total of 1,985 women in the LESS group and 2,466 women in the conventional hysterectomy were included in six randomized controlled trials (23,24,26,30,39,41), five prospective cohort studies (21,27,32,36,37), and 12 retrospective cohort studies (13,20,22,25,28,29,31,33-35,38,40). Twenty of the studies (86.9%) were performed in Asia (fifteen in Korea (13,23-25,27,28,31,32,34,35,37-39,41), one in China (26), two in Japan (29,40), and two in Taiwan (30,33), and the other three studies originated from the United States (20), Italy (22), and France (21). Fourteen studies had a single center design (20-24,26-30,33,36,37,39), one RCT was multi-center (41), and in the other eight studies, the setting was unclear (13,25,31,32,34,35,38,40). Fifteen studies stated that there was no potential conflict of interest to disclose (13,20-27,30-33,35,38), five studies reported financial support (from a grant of Samsung Medical Center (39), from a grant of Korea Health Care technology (36,37), from Covidien (41), and from Kyung Hee University Research Fund (34)), and three studies remained unclear about their potential conflicts (28,29,40).

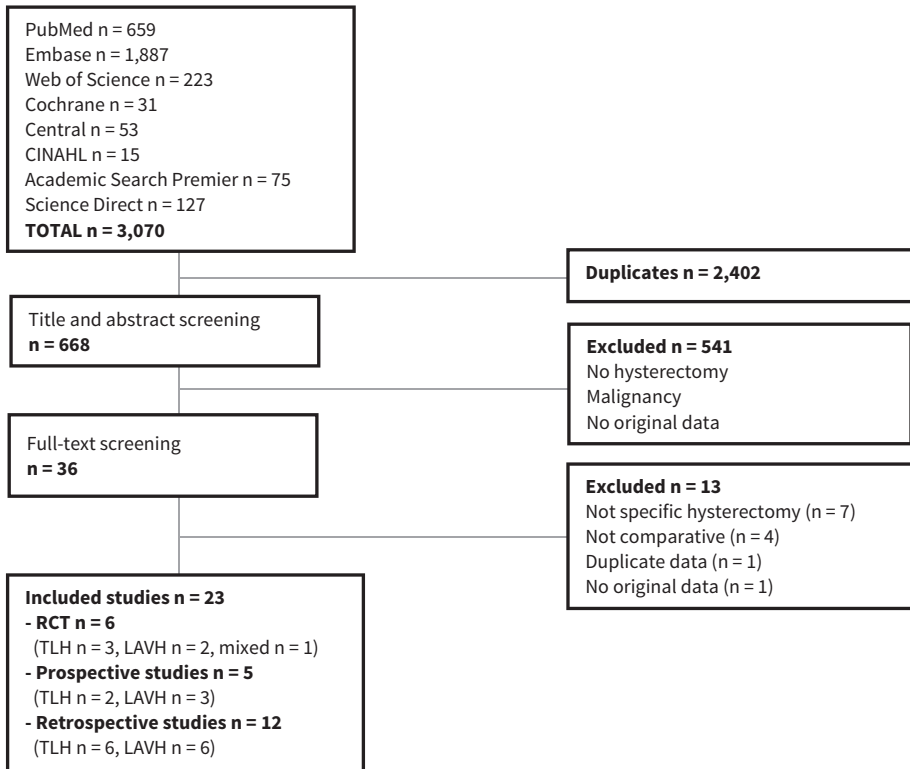


Figure 1 Flow diagram of the study selection.

Women in the LESS group aged between 40.3 and 53 years, their BMI ranged from 22.0 to 28.7 kg/m², and their uterine weight ranged from 105 to 642 grams. In the conventional group, the age range of the patients, their BMI, and uterine weight varied, respectively, between 41.26 and 63 years; 22.0 – 28.8 kg/m² and 9 – 613 g. In two studies from Lee et al., the same cohort was partially used: the smaller cohort study focused on outcomes of sexual function. We used the data from the largest cohort (37), but for analysis of the outcome ‘sexual function’, we extracted the data from the partial cohort (36).

Risk of bias of the included studies

A summary of risk of bias for the individual studies is depicted in figure 2. For the overview of GRADE findings, see table 1.

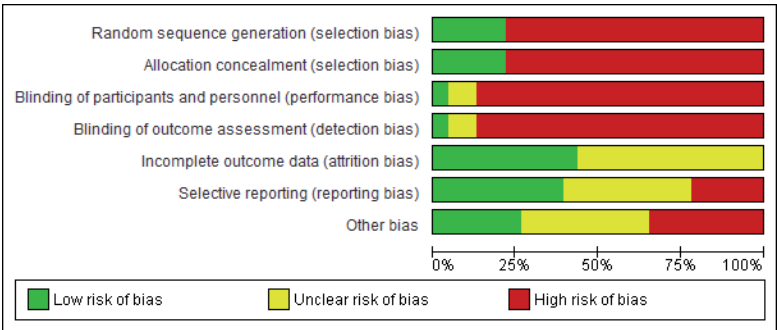


Figure 2a Risk of bias summary LESS versus conventional laparoscopic hysterectomy.

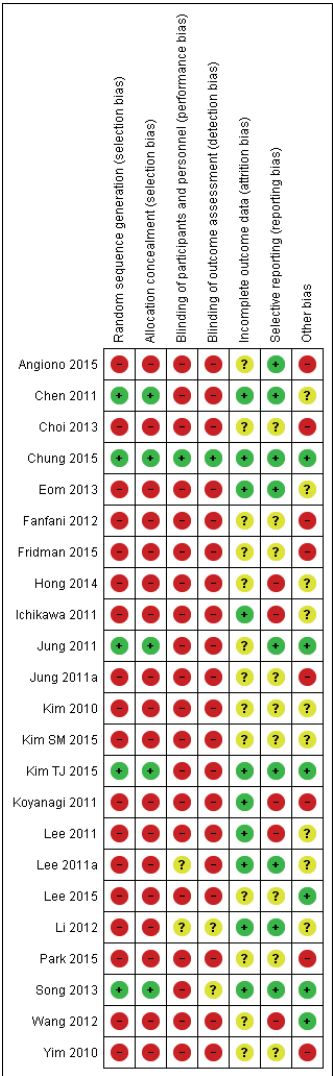


Figure 2b Risk of bias per study, LESS versus conventional laparoscopic hysterectomy.

Table 1 GRADE evidence LESS versus conventional laparoscopic hysterectomy

LESS compared to conventional laparoscopic hysterectomy										
Quality assessment						Summary of findings				
N ^o of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Anticipated absolute effects	
							With conventional	With LESS	Relative effect (95% CI)	Risk with conventional
Complications MAJOR										
3,943 (23 observational studies)	serious ¹	not serious	not serious	serious ²	none	⊕○○○ VERY LOW	121/2,153 (5.6%)	94/1,790 (5.3%)	OR 0.94 (0.61 to 1.44)	56 per 1,000 3 fewer per 1,000 (21 fewer to 23 more)
Complications MINOR										
2,555 (13 observational studies)	serious ¹	not serious	not serious	serious ²	none	⊕○○○ VERY LOW	61/1,368 (4.5%)	40/1,187 (3.4%)	OR 0.76 (0.46 to 1.27)	45 per 1,000 10 fewer per 1,000 (24 fewer to 11 more)
Conversion to laparotomy										
4,124 (21 observational studies)	serious ¹	not serious	not serious	very serious ²	none	⊕○○○ VERY LOW	8/2,289 (0.3%)	22/1,835 (1.2%)	OR 1.60 (0.40 to 6.38)	3 per 1,000 2 more per 1,000 (2 fewer to 18 more)

Table 1 continues on next page

Table 1 Continued

LESS compared to conventional laparoscopic hysterectomy										
Quality assessment						Summary of findings				
N ^o of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Anticipated absolute effects	
							With conventional	With LESS	Relative effect (95% CI)	Risk with conventional
VAS score 24 h postoperatively										
512 (5 RCTs)	serious ³	serious ⁴	not serious	not serious	none	⊕⊕⊕⊕ LOW	257	255	-	The mean VAS score 24 hours post-operatively was -0.15 VAS
				serious						MD 0.14 VAS lower (0.58 lower to 0.28 higher)
Cosmetic outcomes										
353 (3 RCTs)	serious ³	not serious	not serious	serious ^{5,6}	none	⊕⊕⊕⊕ LOW	179	174	-	The mean cosmetic outcomes was 0
										MD 0 (0 to 0)
Operative time										
620 (5 RCTs)	not serious	not serious	not serious	serious ⁷	none	⊕⊕⊕⊕ MODERATE	313	307	-	The mean operative time was 119.6 min
										MD 13.14 min more (1.69 more to 24.59 more)

Blood loss									
620 (6 RCTs)	not serious	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	313	307 - The mean blood loss was 158 mL (0.42 more to 10.82 more)
Length of stay									
562 (4 RCTs)	not serious	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	284	278 - The mean length of stay was 3.81 days (0.74 fewer to 0.17 more)

CI: Confidence interval; OR: Odds ratio; MD: Mean difference.
1 Majority of studies are retrospective cohort studies.
2 Wide confidence interval, crossing the line of no effect.
3 No blinding.
4 Differences between studies (in favor of conventional LH; in favor of LESS).
5 Different questionnaires.
6 Underpowered.
7 For TLH vs LESS a significant difference of 21 min was observed. For LAVH vs LESS a non significant difference of 2 min was observed.

Safety: complications

We found no differences between complication rates when comparing LESS hysterectomy to conventional hysterectomy when clustering into major complications (23 studies, OR 0.94 (0.61, 1.44), $I^2 = 19\%$, figure 3a) and minor complications (13 studies, OR 0.76 (0.46 – 1.27), $I^2 = 11\%$, figure 3b). Sub-analysis specific for TLH and LAVH showed no difference (data not shown). None of the studies reported a port site herniation, though only one study mentioned that they had collected data on herniation (26).

Effectiveness: success rate, postoperative pain scores, cosmetic results, and patient satisfaction

Conversion to laparotomy occurred in 22 of 1,835 patients (1.2%) in the LESS group, compared to 8 of 2,289 (0.35%) patients in the conventional group, which was not statistically significant (total 21 studies, OR 1.60 (0.40, 6.38), $I^2 = 45\%$, figure 3c). The six RCTs included reported two conversions in both groups. For the 15 cohort studies, 17 of the 20 conversions in the LESS

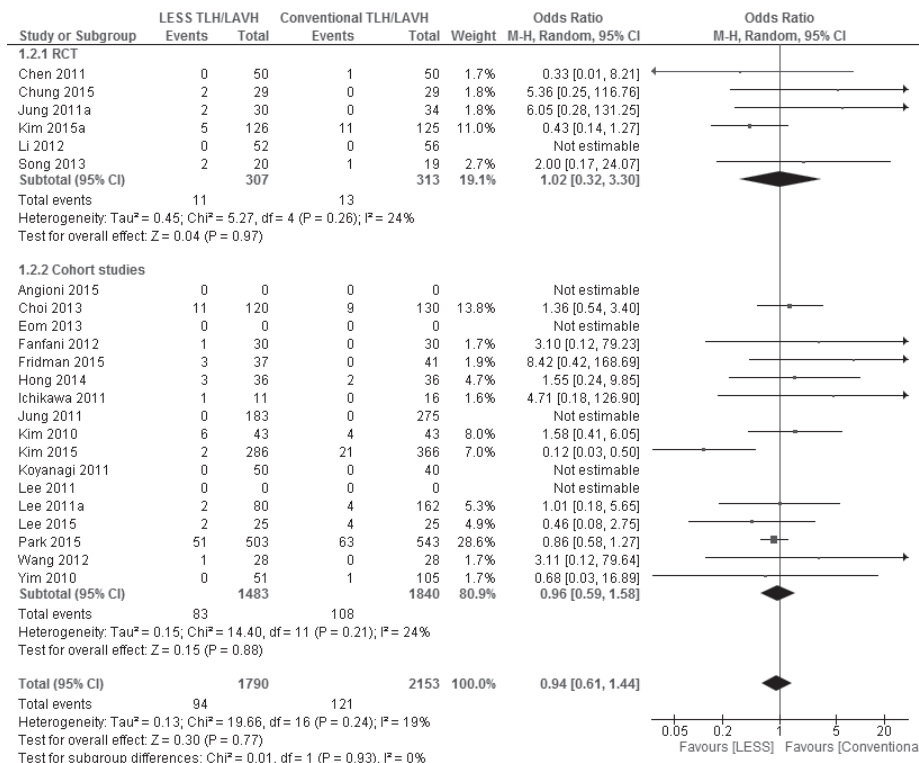


Figure 3a Major complications, LESS versus conventional laparoscopic hysterectomy.

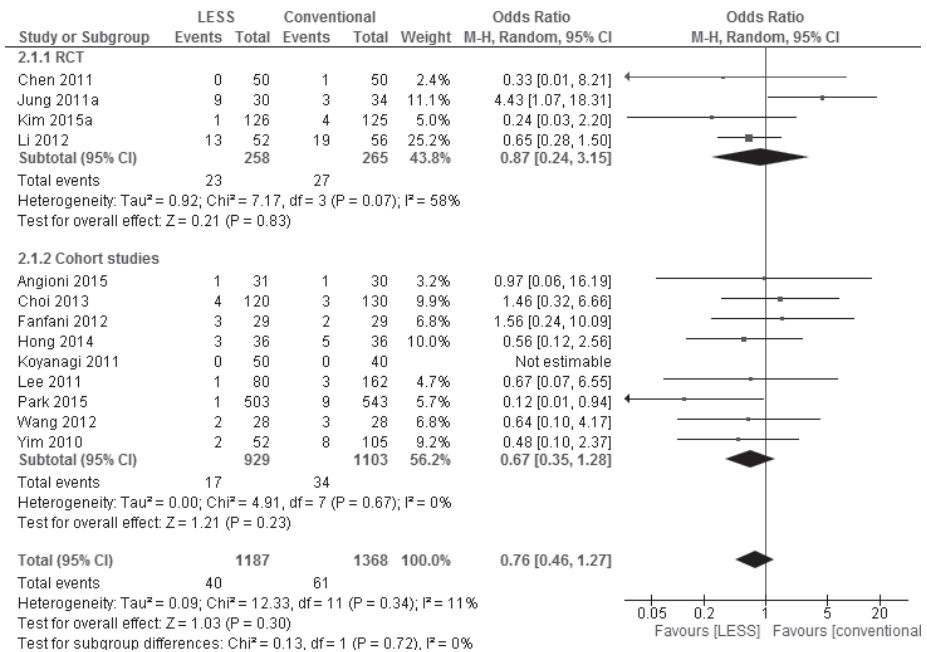


Figure 3b Minor complications, LESS versus conventional laparoscopic hysterectomy.

group were observed in one study (13). Reason for conversions was extensive adhesions ($n = 18$), bladder injury ($n = 1$), bladder and bowel injury ($n = 1$), retroperitoneal bleeding ($n = 1$), and unspecified ($n = 9$). When evaluating the rate of additional ports needed during LESS surgery, 48 of the 1344 (3.5%) patients included had at least one additional port during LESS surgery versus one in the conventional group (0.06%) (38). Fourteen of these cases can be attributed to Fridman et al. where additional port was needed in 38% of the cases (20). In the study by Jung et al. one patient had an additional port due to an incidental finding of an appendiceal mucinous adenoma (34).

Thirteen studies assessed the pain scores of their patients at various postoperative moments (direct after surgery up to one week) using VAS scores. Five of these studies were RCTs and one had appropriate double blinding. That specific RCT found no difference between the two groups at any of the reported moments (direct, 12, 24, and 48 h post-operative) (23). The pain scores direct, 12 and 24 h after surgery were most frequently studied and, therefore, pooled for meta-analysis. Data that analyzed pain scores in the recovery unit, thus immediately after surgery, showed significantly lower pain scores after LESS hysterectomy compared to conventional hysterectomy (5 studies, MD -1.09 (-1.66, -0.52), $I^2 = 80\%$, figure 4a) (21-23,28). The only randomized controlled trial included in this sub-analysis showed no difference between the two groups. At 12 h, a non-significant difference was observed (5

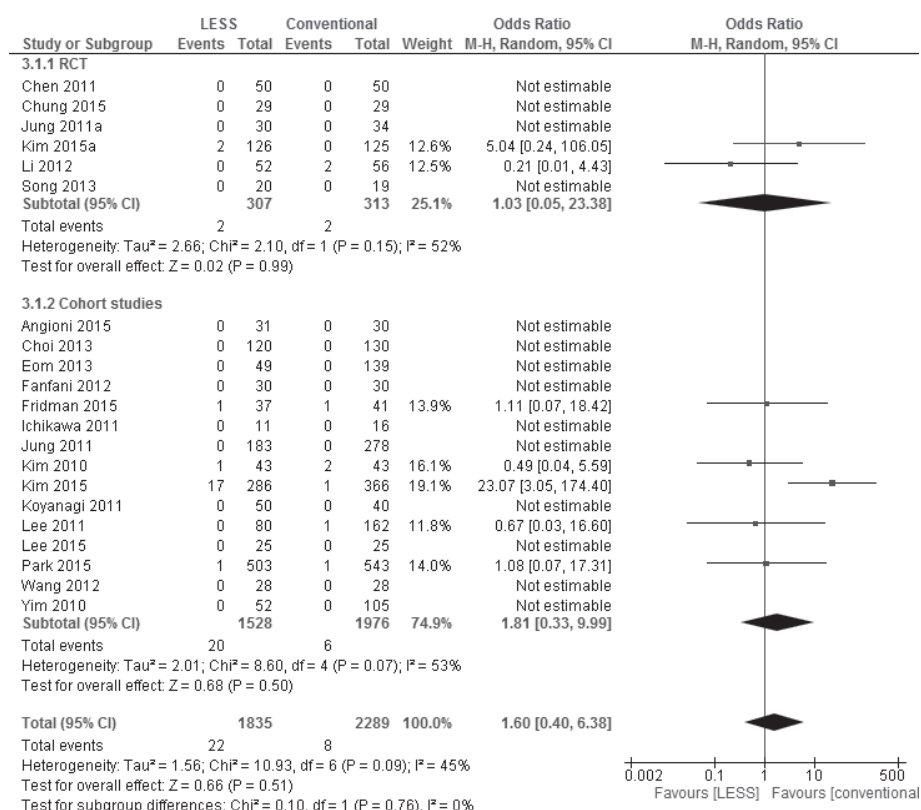


Figure 3c Conversion to laparotomy, LESS versus conventional laparoscopic hysterectomy.

studies, MD -0.19 (-0.41, 0.03), $I^2 = 0\%$, figure 4b). At 24 h, meta-analysis showed a significant difference between the two groups (11 studies, MD -0.45 (-0.87, -0.03), $I^2 = 90\%$, figure 4c) (21,23,25,28). Though, the subgroup analysis including five RCTs showed non-significant results (MD -0.15 [-0.58, 0.28], $I^2 = 64\%$). Ten studies reported on data regarding analgesic use (22-25,28,30,33,38,39,41). Chung et al. and Jung et al. showed that the LESS group requested significantly more (additional) analgesics, but the VAS scores revealed no difference (23,24). In contrast, the (rescue) analgesic requirement was significantly lower in the LESS group in four studies (22,28,30,38). Similarly, Hong et al. calculated a pain-relief score based on the amount and type of analgesic used and the effectiveness on pain relief and their results were also in favor of the single-port surgery (33). Finally, Lee et al., Kim et al. and Song et al. showed no difference in analgesic use between the two groups (25,39,41).

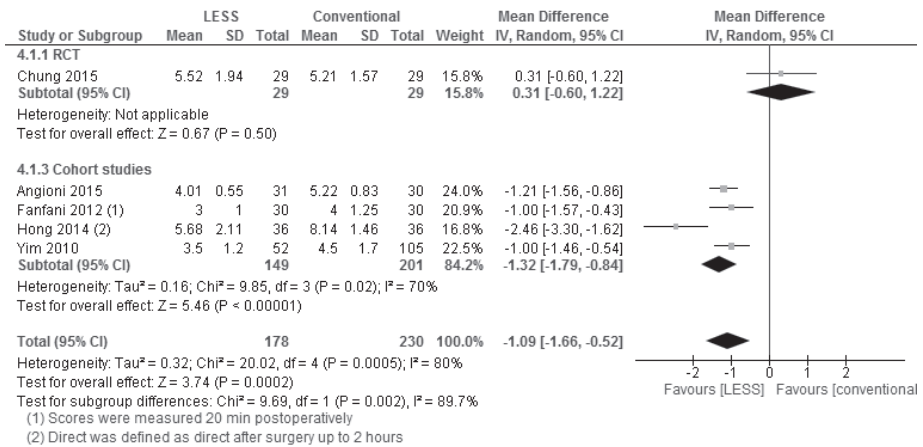


Figure 4a Pain scores direct postoperative, LESS versus conventional laparoscopic hysterectomy.

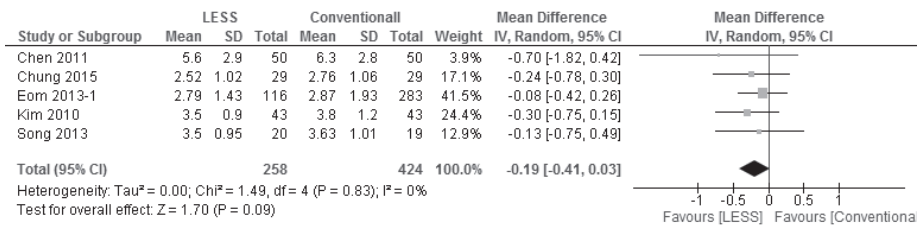


Figure 4b Pain scores 12 hours postoperative, LESS versus conventional laparoscopic hysterectomy.

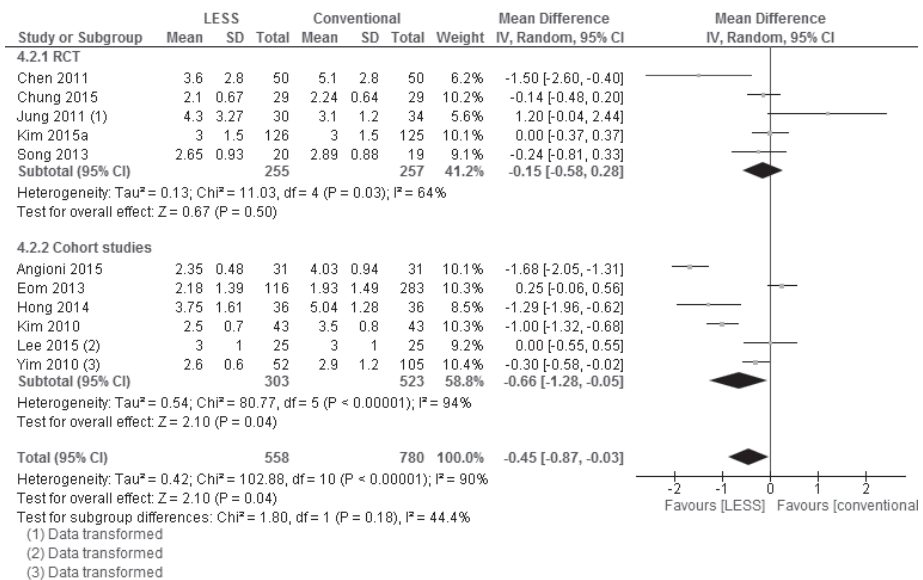


Figure 4c Pain scores 24 hours postoperative, LESS versus conventional laparoscopic hysterectomy.

Three studies reported on cosmetic results (21,39,41), and two used the validated Body Image Questionnaire at one, four and 24 week postoperative. Patients in the LESS group were significantly more satisfied with their scars and had higher satisfaction with their own body at the three measured moments. Kim et al. studied the scar satisfaction using the patient and observer scar assessment scale (POSAS) one week and two months after surgery and showed no difference between the single-site group and the multi-port one. Li et al. studied patient satisfaction and demonstrated a higher patient satisfaction rate in the single-port group, although it was unclear which questionnaire was used (26). Lee et al. compared the sexual function of premenopausal women by using the female sexual function index and showed no difference between women that underwent LESS compared to LAVH (36).

Secondary outcomes

The operative time was significantly longer in the single-port group compared to the multi-port group (20 studies, MD 11.3 min (5.45 – 17.17), $I^2 = 89\%$, figure 5a. When comparing

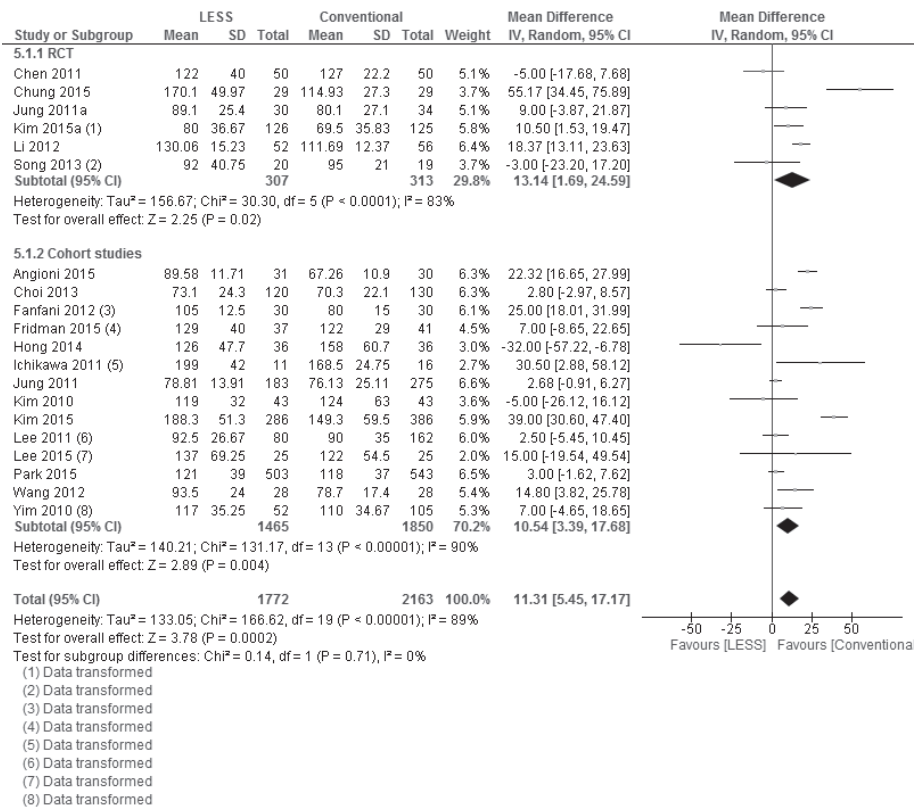


Figure 5a Operative time, LESS versus conventional laparoscopic hysterectomy.

separately TLH and LAVH, a significant difference of 21 minutes was seen in favor of the TLH group, compared to a non-significant difference of two minutes after LAVH (data not shown). No difference was seen for the intraoperative blood loss (19 studies, MD 1 mL (-6.03, -7.81), $I^2 = 27\%$, figure 5b). For the length of hospital stay, a small significant difference was seen (15 studies, MD -0.22 (-0.43, -0.01), $I^2 = 86\%$, figure 5c). This difference was not seen when looking separately at the RCTs and cohort studies.

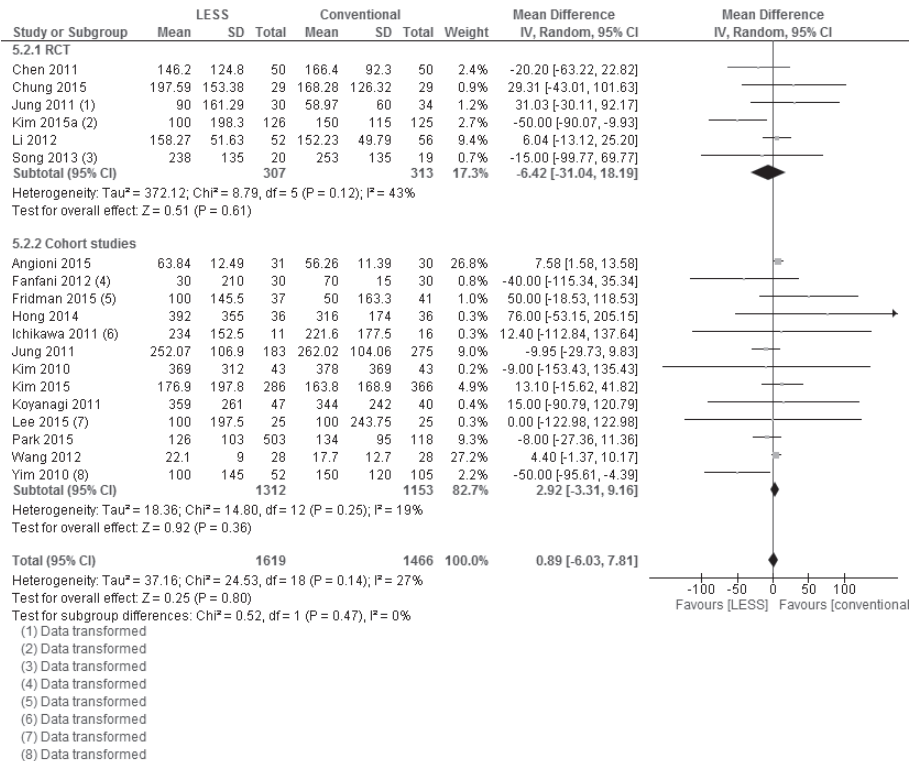


Figure 5b Total blood loss, LESS versus conventional laparoscopic hysterectomy.

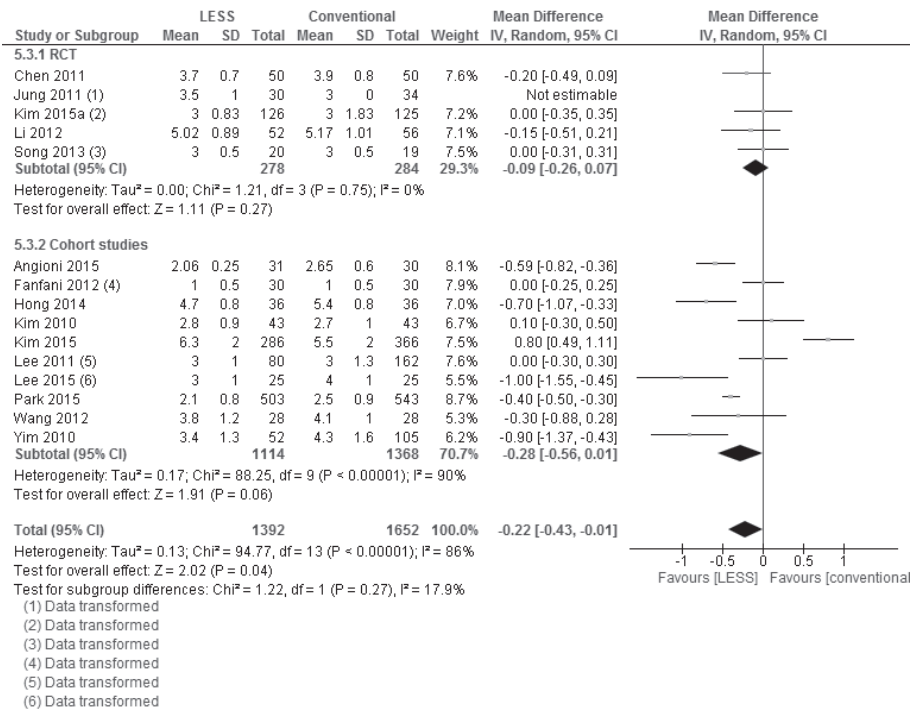


Figure 5c Length of hospital stay, LESS versus conventional laparoscopic hysterectomy.

Discussion

Main findings

In this systematic review, we evaluated the safety and effectiveness of LESS hysterectomy compared to the conventional laparoscopic hysterectomy (TLH and LAVH). Twenty-three studies on LESS versus conventional hysterectomy showed no differences for safety with very low quality evidence. Concerning effectiveness, very low quality evidence indicated no difference for the risk of conversion to laparotomy in the LESS group compared to TLH and LAVH. In 3.5%, the LESS approach failed as an additional port was needed. For postoperative pain, low quality of evidence indicated a lower VAS score of 1.09 and 0.45, respectively, directly and 24 h after LESS hysterectomy, though with substantial statistical heterogeneity. Two out of three studies with low-quality evidence indicated a better cosmetic outcome after LESS versus conventional hysterectomy. A major shortcoming in these studies is the lack of a pre-operative assessment. Without a pre-operative assessment, it remains unclear whether

there were any differences between the groups prior to their surgery. The third study, a RCT showed no difference with respect to scar satisfaction.

Strengths and limitations

Though there are some RCTs available comparing LESS to conventional hysterectomy, we decided to include other comparative study designs as well. The inclusion of non-RCT designs results in less homogenous groups, but when outcomes of interest are infrequent (e.g., conversion to laparotomy risk, complication risks); RCTs are rarely large and lengthy enough to measure infrequent outcomes accurately. Cohort studies facilitate a larger study population and adequate power to identify significant differences. Therefore, the inclusion of study designs other than RCTs can be seen as a limitation but also as strength. In addition, to limit bias, we performed sensitivity analysis for the study design for the meta-analysis. Another strength of this review is the assessment of the quality of evidence using GRADE methodology. We believe that the use of GRADE results in additional clinical value of this review: GRADE optimizes the presentation of evidence for clinical practice. The results of this systematic review are strengthened through the findings of other reviews published on the subject that as well found no significant difference in the frequency of perioperative complications and postoperative pain scores (8,9,43). Though, other reviews described a higher rate of 'failures' in the LESS group. These studies defined 'failure' as the need to convert to laparotomy and/ or to add an extra port, without differentiating. We found that in 3.5% of the LESS procedures, an additional port was needed compared to < 1% in the conventional procedures.

Interpretation

The feasibility of LESS surgery for benign gynecologic procedures seems proven.^{8;9} The meta-analyses in this review showed no significant differences in complication and conversion rate to laparotomy between LESS and conventional hysterectomy. Without substantial statistical heterogeneity, we consider these findings reliable. Besides complication risk, the pain experienced after surgery is an important consideration and usually an important argument in favor of LESS. Though, we did not find any clinically significant differences in postoperative pain. Directly and 24 h after LESS hysterectomy, a significant lower VAS score was observed. This difference was not observed when analyzing only the RCTs. Furthermore, the mean difference did not exceed 1.09 and studies have shown that a mean difference of 2 points on a 10-point scale should be considered as clinically relevant (44). In addition, it cannot be excluded that enrolled patients in the study are biased with respect to their pain outcomes as, except in one study, the included patients were not blinded to the type of

surgery. One single randomized controlled trial applied accurate blinding (23): patients and anesthesiology staff who measured the postoperative pain scores did not know which type of approach had been performed and similar pain scores were found. Cosmetic outcomes are also suggested as important improvement in the single-site approach but surprisingly few studies on LESS hysterectomy reported on this topic (21,39,41). We judged the assessment in the two studies on patient satisfaction insufficient, since baseline assessment of body image and cosmetic satisfaction was not performed. The largest RCT published so far for hysterectomy reported no significant differences regarding scar satisfaction between the LESS and 'conventional' hysterectomy group (41). When looking at studies published in other fields than benign gynecology, inconsistent results are found for the self-scar rating in patients who underwent LESS or conventional laparoscopic surgery (45-47). In Tuschy et al. patients who underwent conventional gynecological laparoscopy were asked which scar they would prefer to eliminate, and for most patients, it was the umbilical one (48). In the study by Bush et al. patients were asked their aesthetic preference regarding scars, and no differences were observed between the single-site and conventional incisions (6). In LESS surgery, higher forces are applied on the umbilical port during tissue handling and irreversible umbilical deformation has been described (29). It is also suggested that LESS would lead to a higher risk of port herniation as the opening of the umbilical port is larger (49-51). Though, this could not be confirmed in the current literature, as within the short study follow-up, only one case of port herniation was reported (31).

Evaluating the secondary surgical outcomes, a notable finding is the increased operative time found in the LESS versus conventional hysterectomy group: an overall mean difference of 11 minutes was observed, though with substantial heterogeneity. For the TLH, the mean difference was 21 minutes, whereas for the LAVH, a non-significant difference of two minutes was observed. The reason for the prolonged operative time during TLH is most probably related to the difference in surgical experience. For the LAVH, it makes sense that the operative time was similar as a large part of the LESS and conventional procedure is performed vaginally, thus using exactly similar techniques. It is well known that LESS surgery is technically more challenging (8,9,43) and studies reporting on the learning curve in LESS have suggested that sufficient skills are acquired after 10 to 15 (3) up to 40 cases (52), especially when surgeons are already well-trained in laparoscopy. In five studies included in this review, the surgical experience of the surgeons was not described (13,28,30,35,38). In the other included studies, the experience of surgeons was defined by terms, such as 'very experienced', 'senior surgeon', or by the number of laparoscopic and/or LESS surgeries performed in one's career. Hence, it is difficult to interpret the impact of the skills on the outcomes. It is noteworthy mentioning that we found substantial differences in baseline characteristics between compared groups in the non-randomized studies (uterine weight

(20,21,28), age (20), BMI (31), previous surgeries, and co-morbidities (28,38)). This could be explained by the surgeon's specific selection when performing a new technique in a non-randomized setting. Yet, an increased uterine weight, a high BMI, and/or previous surgical interventions are known to directly influence surgical outcomes (53) and this could lead to an overestimation of effectiveness, safety, and secondary outcomes (e.g., operative time, blood loss) for LESS outcomes. In addition, it should also be taken into account that 20 of the 23 studies originated from Asian, and therefore, the impact of Asian demographics should not be underestimated.

Remarkably, none of the included studies has taken the costs of the surgery into account, and currently, it is unknown if the LESS approach is cost effective. Despite the lack of data for LESS versus conventional hysterectomy, it can be reasoned that implementing the LESS technique in a hospital is costly as the conventional instruments do not fit and new instruments need to be purchased.

As seen with previous devices and or techniques (54), implementing new technologies in the medical field is a challenge. In contrast to the introduction of new drugs, the latest techniques and devices are usually implemented in clinical practice without proper systematic evaluation regarding their safety, effectiveness, costs, and benefits. Advantages and disadvantages only become clear with the passage of time and after the implantation phase. Considering this, it is complex to answer the question whether the single-port surgery should be an additional possibility for the minimally invasive surgery. Most of studies in the review were single center and from the same region in the world, where a lot of experience has already been acquired with the LESS technique. Despite the amount of experience with LESS in these centers, there is still no clear added value.

In conclusion, current evidence shows that the single-port technique for benign hysterectomy (TLH and LAVH) is feasible, safe, and equally effective compared to the conventional technique. Caution is urged when interpreting the results of studies on LESS because the evidence is of low to very low quality. Potential benefits are sought in patient satisfaction, cosmetic satisfaction, and postoperative pain, but the small differences for these outcomes appear not to be of clinical relevance. Furthermore, surgeons and patients should be aware that in up to 3.5% of LESS hysterectomies an additional port is required resulting in failure of the "single-site" approach and affecting the less invasive purpose. As no clinically relevant advantages were identified, and no data on cost effectiveness were available, there are currently no solid arguments to implement the single-port technique worldwide.

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Appendix 1 Search up to 4th of August

PubMed:

("gynaecology"[All Fields] OR "gynecology"[MeSH Terms] OR "gynecology"[All Fields] OR gynaecologic[All Fields] OR gynecologic[All Fields] OR "Genital Diseases, Female"[Mesh] OR "female genital disease"[all fields] OR "female genital diseases"[all fields] OR "Gynecologic Surgical Procedures"[Mesh]) AND (("Single Incision Laparoscopic Surgery"[All Fields] OR "laparo-endoscopic single-site surgery"[all fields] OR "One port umbilical surgery"[all fields] OR "Natural orifice transluminal endoscopic surgery"[all fields] OR "Single-incision minimally invasive surgery"[all fields] OR "Single laparoscopic incision transabdominal surgery"[all fields] OR "Single-port access"[all fields] OR "Single-port laparoscopy"[all fields] OR "Single-port incisionless conventional equipment-utilizing surgery"[all fields] OR "Umbilical laparoendoscopic single-site surgery"[all fields]) OR ("laparoscopy"[MeSH Terms] OR "laparoscopy"[All Fields] OR "laparoscopic"[All Fields] OR laparoendoscopic[All Fields]) AND (("single"[All Fields] AND (site[All Fields] OR port[all fields] OR incision[all fields] OR umbilical[all fields] OR transumbilical[all fields])) OR (single-port[all fields] OR single-site[all fields] OR single-incision[all fields])) AND ("surgery"[Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms])) AND ("2012/05/01"[PDAT] : "3000/12/31"[PDAT])

Embase:

(gynaecolog*.mp. OR gynecolog*.mp. OR exp gynecology/ OR exp gynecologic disease/ OR female genital disease*.mp. OR exp gynecologic surgery/) AND (("Single Incision Laparoscopic Surgery".mp. OR "laparo-endoscopic single-site surgery".mp. OR "One port umbilical surgery".mp. OR "Natural orifice transluminal endoscopic surgery".mp. OR "Single-incision minimally invasive surgery".mp. OR "Single laparoscopic incision transabdominal surgery".mp. OR "Single-port access".mp. OR "Single-port laparoscopy".mp. OR "Single-port incisionless conventional equipment-utilizing surgery".mp. OR "Umbilical laparoendoscopic single-site surgery".mp.) OR ((exp laparoscopy/ OR exp laparoscopic surgery/ OR "laparoscopy".mp. OR "laparoscopic".mp. OR laparoendoscopic.mp.) AND ("single".mp. AND (site.mp. OR port.mp. OR incision.mp. OR umbilical.mp. OR transumbilical.mp.)) OR (single-port.mp. OR single-site.mp. OR single-incision.mp.)) AND (exp surgical technique/ OR surgery.mp. OR surgical.mp.)) AND (201236 OR 201237 OR 201238 OR 201239 OR 20124* OR 20125* OR 2013* OR 2014* OR 2015* OR 2016*).ew

Chapter 5

**Effectiveness and feasibility of
hysteroscopic sterilization techniques:
a systematic review and meta-analysis**

Claire F. La Chapelle
Sebastiaan Veersema
Hans A.M. Brölmann
Frank Willem Jansen

Abstract

Objective: To assess whether hysteroscopic sterilization is feasible and effective in preventing pregnancy. Secondly to identify risk factors for failure of hysteroscopic sterilization.

Design: A systematic review and meta-analysis.

Setting: Not applicable.

Patients: Women undergoing hysteroscopic sterilization.

Intervention: Hysteroscopic sterilization with a commercially available system (Ovabloc Intra Tubal Device, Essure system or Adiana Permanent Contraception system).

Main outcome measures: Successful placement at first attempt, confirmed correct placement, complications, incidence of pregnancy and risk factors for placement failure in hysteroscopic sterilization.

Results: Of the 429 citations identified, 45 articles were eligible for analyses, no randomised controlled trials (RCTs) were identified, just cohort studies. Six articles concerned Ovabloc, 37 Essure and two Adiana sterilization. The probabilities for successful bilateral placement in a first attempt for Ovabloc, Essure and Adiana, were respectively ranging: 78% – 84%, 81% – 98% and 94%. The probabilities of successful bilateral placement could not be pooled because of substantial heterogeneity. The 36 months cumulative pregnancy rate of Adiana was 16/1,000. Reliable pregnancy rates after sterilization with Ovabloc or Essure method could not be calculated. For all three hysteroscopic techniques, the incidence of complications and their severity has not been studied adequately and remains unclear. We also found too little evidence to identify risk factors for placement failure.

Conclusion(s): Sterilization by hysteroscopy seems feasible, but the effectiveness and risk factors for failure of sterilization remain unclear due to the poor quality evidence. Both currently applied hysteroscopic sterilization techniques and the coming new techniques must be evaluated properly for feasibility and effectiveness. Appropriate RCTs and observational studies with sufficient power and complete and long-term (> 10 years) follow up data on unintended pregnancies and complications are needed.

Introduction

The hysteroscopic approach to female sterilization has been studied for more than a century. The initial techniques often proved to be difficult and inefficient. Failure rates were high and serious complications by perforation and thermal bowel lesions were reported in clinical trials (1,2). Nevertheless there was continuing belief that hysteroscopic sterilization would be a suitable method for permanent contraception. This was prompted by the fact that the hysteroscopic route avoids the transabdominal route and the risks of entering the peritoneal cavity are thereby avoided. Hysteroscopic sterilization is supposed to result in less morbidity and a quicker return to normal activities. Another advantage of hysteroscopic sterilization compared to laparoscopic sterilization is the reduced need for anaesthesia, which facilitates sterilization in an ambulatory setting. These advantages make that hysteroscopic sterilization is a good option for women with contraindications to laparoscopy (e.g. with a history of laparotomy) or who just wish to avoid incisional surgery or general anaesthesia.

In the past decades, three systems became available on the commercial market: in 1988 the Ovabloc Intra Tubal Device (Advanced Medical Grade Silicones BV, Reeuwijk, the Netherlands) (3), in 2002 the Essure system (Conceptus Incorporated, Mountain View, CA, USA) (4,5) and in 2009 the Adiana Permanent Contraception system (Hologic, Inc, Bedford, MA, USA) (6). The Ovabloc device is a silicon mixture that is instilled into the tubal ostium and solidifies within five minutes into a rubber plug. The Essure device is a 4 cm expanding spring made of a nitinol outer coil and stainless steel inner coil with PET fibres, placed in the proximal section of the fallopian tube. The Adiana sterilization technique is a combination of 60 seconds of radiofrequency applied to the mucosa of the fallopian tube followed by deployment of a 3.5 mm matrix into the created lesion. These distinct mechanisms of action may lead to differences in feasibility and effectiveness.

The above described techniques all require a so called 'confirmation test' three-months post-procedure to verify proper placement. While conventional laparoscopic approach and sterilization via mini-laparotomy are considered to be effective immediately, hysteroscopic systems require a period of three months after the procedure for the fallopian tubes to undergo fibrosis leading to occlusion and contraceptive effectiveness (5,6,7). During these three months women have to use alternative contraception. A hysterosalpingogram (HSG), pelvic X-ray or ultrasound is used to verify correct placement, depending on the instructions for use supplied by the manufacturer.

Long-term studies on large cohorts of women have assessed laparoscopic sterilization and sterilization via mini-laparotomy, though less is known about the feasibility and effectiveness of the hysteroscopic approach. Data from phase II and III clinical trials with Adiana and Essure showed high feasibility and effectiveness (4,5,6). It is questionable if daily practice results are

comparable with these earlier results. Additionally, identifying risk factors for placement failure will be important in patient selection and to identify cases at risk for failure of hysteroscopic sterilization. We conducted a systematic review to examine the feasibility and effectiveness of hysteroscopic sterilization. Secondly, we tried to identify risk factors for failure of hysteroscopic sterilization.

Methods

This systematic review was conducted according to the PRISMA guidelines. All longitudinal studies addressing hysteroscopic sterilization were considered for inclusion, both prospective and retrospective. Studies were included if successful placement rate, safety, effectiveness or risk factors for failure of hysteroscopic sterilization were investigated. Only original studies with > 20 consecutively included participants were selected to allow pooling of data. Descriptive articles, case-series (with non-consecutively included participants), reviews, surveys, technical reports and congress abstracts were excluded. No language restriction was applied. All types of participants undergoing tubal sterilization by hysteroscopy were included. Animal studies and studies wherein electrocoagulation or chemicals (e.g. quinacrine) were used to obliterate the tubes were excluded.

To assess feasibility we considered successful placement rate, percentage of confirmed proper placements and the occurrence of procedural complications as important outcomes. As effectiveness refers to the ability to prevent conception, we evaluated the rate of unintended pregnancies after confirmation of correctly placed devices. Hence we formulated the following research questions:

1. What is the probability of a successful bilateral placement at the first attempt of a hysteroscopic sterilization?
2. What percentage of women have a confirmed correct bilateral placement of the devices three months after the procedure?
3. What are the risk factors for placement failure of the devices used for hysteroscopic sterilization?
4. What are the complications of hysteroscopic sterilization and what are the corresponding incidences?
5. What is the incidence of pregnancy after confirmed correct bilateral placement?

We defined successful placement rate as the percentage of women that had successful bilateral procedures in a first attempt. There are some differences in the definitions of successful placement applied by the manufacturers. For Ovabloc the bilateral instillation

is immediately followed by a satisfactory X-ray showing adequate filling, continuous from the tip to the ampulla. For Essure, successful placement is a hysteroscopically verified bilateral correct position of the inserts during the procedure, by counting the number of coils protruding in the uterine cavity. For Adiana successful bilateral placement includes bilateral insertion and confirmation of placement at one week post-procedure using transvaginal ultrasonography.

Confirmed correct placement rate was recorded as the percentage of women with good results of the three-months post-procedure 'confirmation test', out of the total number of women who had a successful placement. There are also differences in the confirmation tests prescribed by the manufacturers. After the Ovabloc procedure the required confirmation test is a second X-ray to evaluate for correct position of the devices. After Essure procedures, an X-ray or transvaginal ultrasonography to confirm appropriate retention and location of both devices or confirmed bilateral tubal occlusion on HSG is required. For Adiana the confirmation test includes verification of bilateral occlusion with an HSG. For all techniques, we excluded successful single placements in patients with a history of salpingectomy, because the higher chance for successful single placement would confound the outcome successful placement.

The related risk factors for placement failure were abstracted from both uni- and multi-variate analyses. We studied safety (covered by feasibility) through recording intra- and post procedural complications other than failed sterilization. We defined complications as an unintended and undesirable event or condition during or following medical intervention to such an extent it is disadvantageous to the patient's health that medical intervention is necessary and/or irreparable damage has occurred. Symptoms related to patient tolerance of the procedure (e.g. pain, vasovagal reaction, nausea, vaginal spotting or post procedure bleeding) were not classified as complications. Ineffectiveness was recorded as the cumulative pregnancy rate per specified unit of time as part of the total number of participants. All outcomes were evaluated per specific sterilization technique.

Search methods for identification of studies

Medline (PubMed version), EMBASE (OVID version), Web of Science and the Cochrane library were searched by a clinical librarian up to February the 25th 2014 without language restriction or methodological filters. The exact search is supplemented to this article (supplement 1).

Two reviewers (C.C. and S.V.) independently screened titles and abstracts for relevance. The bibliographies of included articles were then hand-searched for other relevant references. The same reviewers independently extracted study and patient characteristics and outcome data. The methodological details, number of included patients and descriptive study

characteristics (country where the study was conducted, recruitment modality, source of funding), characteristics of the participants (age, body mass index, parity), description of the device (type, version), description of the procedural setting (in-office or Operation Room, type of anaesthesia, experience of the physician), co-interventions (for example polypectomy, endometrial ablation), and outcomes (types of outcomes, documentation of drop-outs, follow-up, standardization of outcome assessment) were extracted. Disagreements were reconciled by discussion with an arbiter (F.W.J or H.B.). Data related to the defined outcomes were assessed for inclusion in the meta-analyses.

The methodological quality of the included studies was assessed using a checklist adjusted from the Newcastle-Ottawa Scale (8). We customized the items to the review questions of interest. Study limitations were reviewed for appropriate eligibility criteria (item selection), adequate measurement of outcomes (item outcome), selective reporting and other bias (e.g. confounding factors) (item comparability). Pooled probability of successful placement, confirmed placement and pregnancy were conducted using 'R' version 3.0.2. (<http://www.r-project.org>). Statistical heterogeneity among the results of the included studies was identified and quantified formally with I^2 statistic. A value of $\geq 50\%$ indicates substantial heterogeneity. Where $I^2 \geq 50\%$, results were not pooled but described. The probabilities are shown with their 95 per cent confidence interval (CI). Outcomes for dichotomous risk factors for placement failure are expressed as odds ratios (OR), continuous outcomes for risk factors are expressed as mean difference (MD), both with 95% CI.

Results

The search produced 429 unique references, of which 66 were considered relevant to the topic based on title and abstract. Figure 1 shows the flow diagram of the selection process. Finally, a total of 45 articles were eligible for analyses: six articles concerned Ovabloc, 37 Essure and two Adiana sterilization. The eligible studies included: no RCTs, 30 prospective, 13 retrospective, one partly retro- and partly prospective cohort study and one study with unclear perspective.

Ovabloc

A total of 2,039 women were included in two prospective and four retrospective studies (7,9,10,11,12). The articles were published between 1983 and 1999. Two studies were multi-centre and four were single-centre. Two articles included cohorts that had overlap with each other (7,12). None of the studies reported a potential conflict of interest. The number of participants in each trial ranged from 115 to 438. The age range

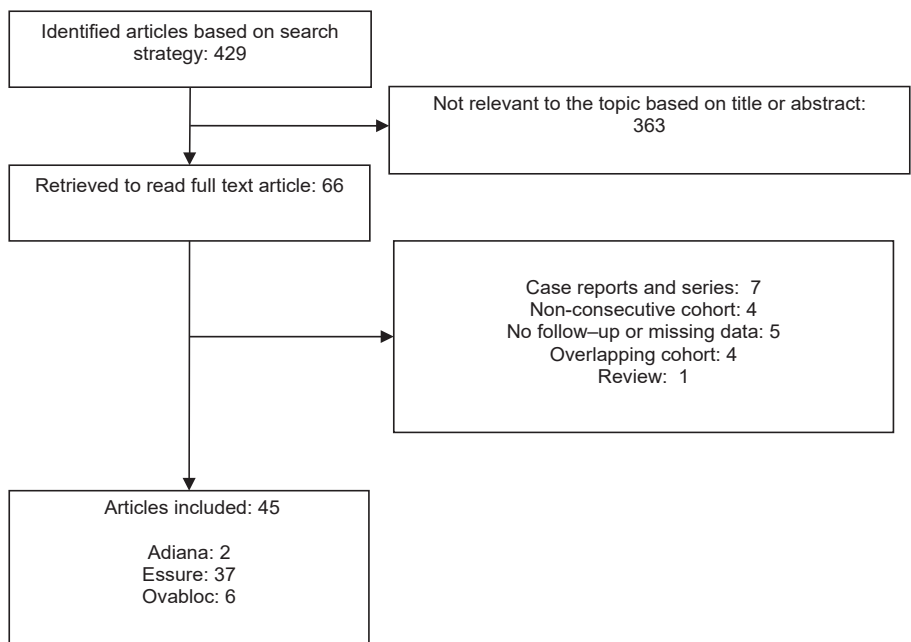


Figure 1 Flow diagram.

was 18 to 46 years. The exclusion criteria were clearly defined in five articles. Three studies included nulliparous women (9,12,13). There were considerable differences in exclusion criteria between studies. In one study tubal patency was tested with perfusion of diluted methylene blue dye (MBPT) before instillation. Women with no tubal patency in one or both tubes were excluded for an installation attempt (13). All procedures were performed with a paracervical block. One study reported pre-medication of naproxen 12 hours and 2 hours before the procedure and intramuscularly atropine 30 minutes before the procedure (9). In three studies office hysteroscopy was performed with an 8 mm single flow (SF) system (Hyskon or CO₂) (7,11,12), while in two studies a continuous flow (CF) system with low viscosity distension medium was used (10,13). In one study both SF and CF techniques were used (9).

Figure 2 shows the risk of bias graph for included Ovabloc studies. Follow-up data for pregnancies and complications other than failed sterilization were undefined, mainly based on self-reporting, and presumably incomplete.

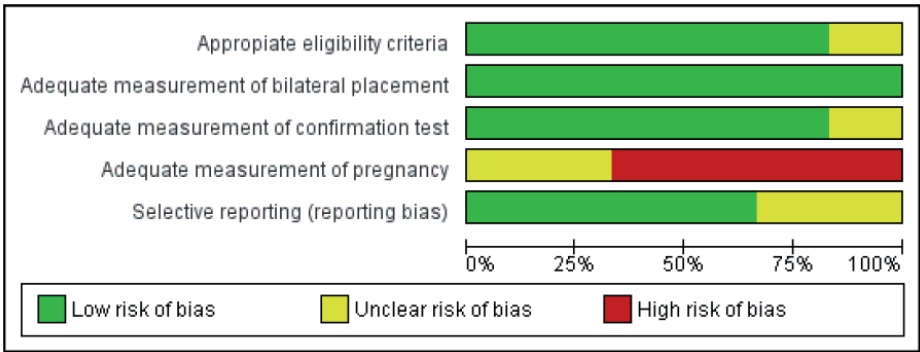


Figure 2 Risk of bias graph: review authors’ judgements about each risk of bias item presented across all included Ovabloc studies.

Feasibility of Ovabloc

The number of successful bilateral Ovabloc placements at first attempt was reported in five studies (n = 1,601 women) (9,10,11,12,13) (table 1). The probability varied between 78% and 84%. Due to substantial statistical heterogeneity, the results could not be pooled. In one study, the lower success rate was explained by the inclusion of women with retroflexed uterus, minor intrauterine pathology and nulliparity, resulting in a more difficult catheterization of the tubes. Also the use of single flow hysteroscopy was cited as explanation (9). In a second study with a lower probability for successful placement, 50/411 (12.2%) of women were did not undergo an installation attempt because the methylene blue perfusion test showed no tubal patency in one or both tubes or because of technical problems (13). One study reported uterine wall perforation during the procedure in 5/438 cases (7).

Table 1 Feasibility of Ovabloc, Essure and Adiana. Feasibility includes the success rates for placement at the first placement attempt and confirmed correct placement assessed with the three-month confirmation test. The last column shows the cumulative number of unintended pregnancies.

Technique	Successful bilateral procedure rates at the first attempt	Satisfactory outcome rates at 3 months confirmation	Cumulative number of pregnancies after satisfactory confirmation
Ovabloc	range 78 – 84% (5 studies, n = 1,601)	range 91 – 100% (5 studies, n = 1,312)	N.A.
Essure	range 81 – 98% (31 studies, n = 12,961)	range 90 – 100% (24 studies, n = 9,112)	N.A.
Adiana	94% (1 study, n = 645)	91% (1 study, n = 551)	12 months: 6/ 547 24 months: 9/ 523 36 months: 9/ 505

After successful bilateral placement the probability for confirmed correct placement three months post-procedure varied between 91% and 100%, there was substantial statistical heterogeneity between the results.

Effectiveness of Ovabloc

Approximately 46/1,312 (3.5%) of women could not rely on Ovabloc after successful placement, based on results of three-months confirmation tests. A pooled total of 12/1212 (1.0%; 95% CI: 1 – 2%; $I^2 = 0\%$) pregnancies were reported in women who passed the three-months confirmation test (figure 3) (7,9,10,12,13). The majority of pregnancies (n = 8; 67%) was registered in the first three to 24 months after the procedure. Other reasons for discontinuation of reliance on Ovabloc sterilization were spontaneous expulsions or migrations (n = 26/750) (10,13) and removal or damage by D & C of the silicon plugs (n = 36/870) (7,12,13).

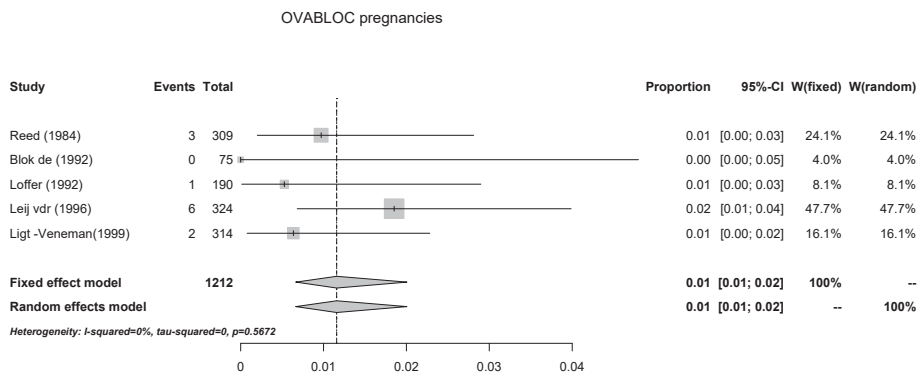


Figure 3 Number of pregnancies for included Ovabloc studies. Probabilities are shown with 95% CIs.

Risk factors for Ovabloc placement failure

Univariate analyses for risk factors were performed in two studies (9,13). Van der Leij et al. compared 71 failed to 340 successful procedures and found nulliparity (OR 3.87, 95% CI: 1.89 – 7.92), intrauterine pathology (OR 4.5, 95% CI: 2.38 – 8.51) and an asymmetric uterine cavity (OR 3.65, 95% CI: 1.50 – 8.91) to be associated with failure (13). De Blok et al. compared Ovabloc sterilizations performed with single flow to continuous flow hysteroscopies. Procedures performed with continuous flow hysteroscopy had lower failure rates due to failed instillation of silicon in the tubes or insufficient visualization. The failed procedure rate decreased from 29% to 12% when continuous flow hysteroscopy was used (OR 0.33, 95% CI: 0.12 – 0.97) (9).

Essure

A total of 14,126 women were included in 37 studies: 26 prospective, nine retrospective, one partly retro- and partly prospective and one with unclear relation between enrolment and occurrence of the outcomes. The articles were published from 2003 to 2012. Ten studies were multi-centre, 27 were single-centre. Nine articles studied a cohort that overlapped with a cohort in another article: seven of these were performed in centres in France (14,15,16,17,18,19,20) and two in Spain (21,22). In thirteen studies a potential conflict of interest was reported, in four studies it was stated there was no potential conflict and in twenty studies this remained unclear.

The number of participants in each trial ranged from 24 to 4,306. The age ranged from 19 to 57 years. The exclusion criteria were not described in 26 articles, in 11 articles the exclusion criteria were reported, three studies (14,23,24) referred to the criteria defined in the instructions for use. The version of the device used was not defined in 29 articles, ESS 305 was used in three articles (19,24,25), ESS 205 in one article (26), and the version known as STOP (Selective Tubal Occlusion Procedure) was used in two articles (4,5). In two articles both the ESS 205 and 305 (20) and the ESS 105 and 205 (27) were used. In one study concomitant procedures were excluded (23), seven studies included patients whom received concomitant procedures (16,17,18,19,20,28,29), all other studies did not specifically report on concomitant procedures. The type of analgesics differed from only pre-medication to paracervical block, intravenous analgesics or general anaesthesia.

Figure 4 shows the risk of bias graph of included Essure studies. The methods of assessment for follow-up data on pregnancies were unspecified and primarily based on self-reporting. In some studies the risk of bias was judged high for assessment of confirmation because it was unclear whether single placements were also included in the evaluation (14,16).

Feasibility of Essure

Successful placement and successful confirmation rates were reported in 31 and respectively 24 of the included Essure studies (table 1). The successful placement rate at first attempt varied between 81% and 98%, with substantial statistical heterogeneity. There seems to be a tendency for higher successful placement rates for studies published since 2007. The chance of confirmed correct placement after successful bilateral placement ranged from 90% to 100%, with substantial statistical heterogeneity between the results. One cervical perforation (30) and one fundal perforation (31) during the procedure were reported. In one case the microinserts were removed because of the suspicion of a nickel allergy (32).

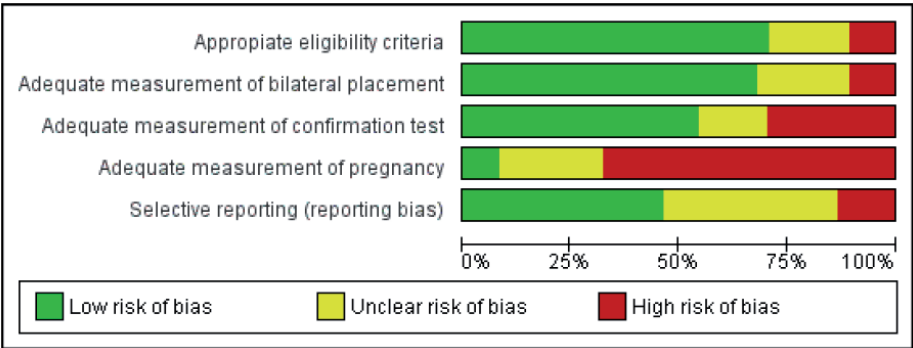


Figure 4 Risk of bias graph: review authors' judgements about each risk of bias item presented across all included Essure studies.

Effectiveness of Essure

In figure 5 the number of pregnancies after a confirmed Essure procedure are shown. Eight pregnancies were registered in 7,706 patients who relied on the sterilization after a satisfactory confirmation (22,29). In one case, the three-months control pelvic X-ray and vaginal ultrasound scan had suggested well placed devices, and an HSG performed post-partum showed an apparent bilateral occlusion. Though, at laparoscopy a unilateral tubal perforation was found.

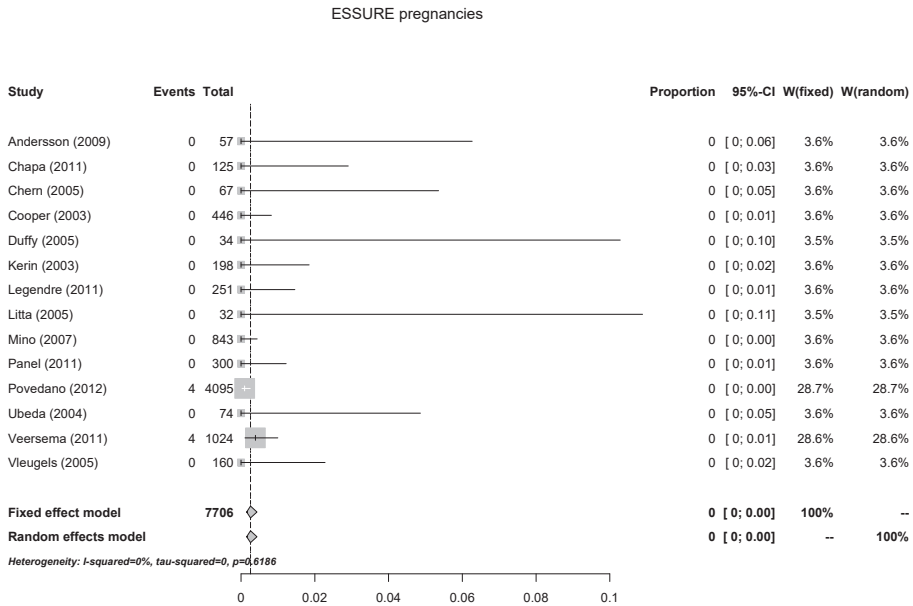


Figure 5 Number of pregnancies for included Essure studies. Probabilities are shown with 95% CIs.

In a second case, a post-partum radiographic examination demonstrated complete expulsion of one device. In a third case the pregnancy was terminated and followed by laparoscopic sterilization, where one device was found located intramurally under the serosa due to partial perforation. In a fourth case of pregnancy, the Essure device was only placed in one tube as placement in the contralateral tube was unsuccessful. The patient underwent HSG at which time the contralateral tube appeared occluded and the patient was instructed incorrectly to cease alternative contraception (23). A fifth patient became pregnant 32 months after the procedure, the 3-month control pelvic X-ray and vaginal ultrasound scan suggested correct placement of both devices and the HSG performed after delivery showed an apparent bilateral occlusion. However, laparoscopy demonstrated a unilateral tubal perforation (29). No data were available for analysis of the other three pregnancies. In all analyzed cases, pregnancy was related to incorrect position of at least one device.

Risk factors for Essure placement failure

In ten studies the risk factors for placement failure of Essure microinserts were analysed (5,15,17,23, 24,25,26,30,33,34). Age was examined as a risk factor for placement failure in five studies. In one prospective multicentre study on 578 women seeking hysteroscopic sterilization a statistically significant difference in the average age of patients was observed: 35.3 years for patients with successful placement versus 39.4 years for patients with failures (MD 4.1 95% CI: 1.45 – 6.75) (24). Four other studies did not find any relation between age and placement failure (23,25,26,33). The influence of body mass index on placement failure was examined in five studies and no significant difference was found (24,25,26,30,33). Five studies examined parity as a risk factor for placement failure, no differences between nulliparous compared to multiparous women were found (17,24,25,26,33). In the majority of the studies, the procedures were scheduled in the follicular phase or women should be taking oral contraceptives. Three studies explored the cycle phase at the time of the procedure as a risk factor for failure. Two studies: a phase II study (5) and phase III study (26) found no differences between placements timed in the follicular versus luteal phase. One study reported higher odds for successful placement in the follicular phase with both a uni- and multi-variable analyses (OR 11.2, 95% CI: 1.35 – 92.6 and OR 10.2, 95% CI: 1.13 – 91.0) (30). One study examined the effect of hormonal contraception and concluded that a receipt of hormonal contraception before the procedure was not significantly related to higher bilateral placement rates (23). In two articles a history of sexually transmitted infection (STI) or pelvic inflammatory disease (PID) was studied (25,26). One study (n = 316) found no statistically significant differences in the prevalence of women with a history of STI or PID between the group with successful placement and failed placement (26). The other study (n = 310) reported a remarkable high percentage of women who reported to have had a STI (26.8%) and found a higher risk of placement failure in these women (OR 2.64, 95% CI:

1.01 – 6.90) (25). In another study the rates of successful bilateral placement in relation to uterine size was analysed. Both uni- and multi-variable analyses found significantly better success rates in women with uterine sizes ≤ 8 weeks compared to uterine sizes > 8 weeks (OR 15.7, 95% CI: 3.19 – 77.1 and OR 14.0, 95% CI: 2.5 – 79.5 respectively) (30). This single study examined the effect of uterine axis, which was not associated with failure of placement. One case control study found no lower placement rates in patients with concomitant bipolar endometrial ablation (17).

In almost all Essure studies patients received premedication, generally a combination of non-steroidal anti-inflammatory medications combined with diazepam. In three studies the effect of premedication was investigated (17,23,34). Two studies showed that the use of NSAIDs before the procedure significantly reduces the risk for failure of bilateral placement (OR 0.44, 95% CI: 0.21 – 0.93, respectively OR 0.17, 95% CI: 0.03 – 0.89) (23,34). Whereas one study did not find a difference (17). In this last study a relatively small group of women had not received NSAIDs pre-procedure (OR 1.71, 95% CI: 0.22 – 13.35) (17). Four studies examined the effect of different analgesic regimes, such as general anaesthesia, IV sedation, spinal anaesthesia, paracervical block or nothing, no statistically significant differences in placement failure were found (15,17,24,26).

In three studies, the influence of experience with Essure sterilization on successful placement was evaluated and no statistically significant differences were calculated (24,26,33). Three studies compared the influence of the inpatient versus outpatient setting on the success of placement (23,24,33). In two studies ($n = 319$ and $n = 578$) no differences in placement rates were observed (23,24). One study reported a significantly higher successful placement rate in the outpatient setting (97.3% versus 92.8%, no CIs provided, $p = 0.004$) (33).

Adiana

The included articles for Adiana both concerned the Evaluation of the Adiana System for Transcervical Sterilization (EASE) trial from 2002 through May 2005, a prospective, single-arm, international study, involving 18 investigators at 16 sites (6,35). A total of 645 women participated in the study. Women were eligible to participate if they were 18 – 45 years of age, generally healthy, had established fertility, and were seeking permanent contraception. Exclusion criteria included major medical conditions, use of cortisone or cytostatic medication, any underlying health condition that would adversely affect the ability to undergo surgical procedures (e.g. cardiovascular conditions), pelvic inflammatory disease, intrauterine conditions that may affect tubal access (e.g., synechiae), significant cervical or uterine pathology, or any condition that might compromise compliance or long-term study follow-up. Each participant underwent a complete physical examination, with documentation

of normal cervical cytology, negative testing for sexually transmitted infections, and a negative pregnancy test to confirm study eligibility. The mean age was 31 years (range: 20 – 45 years), with a mean parity of 2.2 (range: 0 – 7). Different analgesic regimes used during the procedure ranged from topical or local to intravenous sedation. Three months post-procedure a HSG was performed to confirm bilateral occlusion. Thereafter, women were evaluated by office visits at three, six, and nine months and at one, two and three years. Women with an unsuccessful sterilization (n = 75) were excluded from the study or were followed for safety evaluation only. The assessment of successful placement was clearly defined. A small number of women were lost to follow up for the three-months HSG (7/ 611). Of the 570 women who were able to rely on the sterilization, 97% (n = 547), 92% (n = 523), and 89% (n = 505) were compliant with the follow up at one, two and three years respectively. Concerning safety, the method of assessing and recording complications is unclear. Additionally, it remains unclear how many women unable to rely on Adiana sterilization were followed for safety evaluation. We found a low risk of bias for the outcome measurements of successful placement, confirmed correct placement and incidence of pregnancy and an unclear to high risk of bias for outcome complications.

Feasibility of Adiana

The results on feasibility and effectiveness are presented in table 1. Successful bilateral placement in a first attempt was achieved in 607 of 645 women (94%). In seven women successful placement was achieved in a second attempt. An HSG was used to confirm reliability in 604 women. In 91% (n = 551) bilateral occlusion after a successful first placement was confirmed three months post procedure (table 1). Re-evaluation of the remaining women by HSG at six months confirmed bilateral occlusion in an additional 19 women. According to the protocol 611 women with successful bilateral placement, 93% (n = 570) were able to rely on Adiana for pregnancy prevention and cease additional contraception. No uterine or tubal perforations or injuries related to RF energy or matrix placement were reported. No analysis for risk factors in placement or failures or learning curve were performed in the selected studies.

Effectiveness of Adiana

A total of six pregnancies were reported in the first 12 months of the reliance phase, three in the second year and none in the third year (table 1). Three pregnancies that occurred during the first year were determined to be due to misinterpretation of the HSG.

Discussion

Though the first studies on hysteroscopic sterilization date back to the turn of the century, and the approach is widely applied in female sterilization, it is remarkable that the currently available evidence is still poor. To evaluate the effectiveness of an intervention a RCT is the appropriate design. We did not find any RCT. When the outcomes of interest are infrequent and/or far in the future (e.g. 0.5% pregnancies in the first year post sterilization) RCTs are rarely large and lengthy enough to accurately measure infrequent outcomes. A prospective cohort study will facilitate a larger study population and adequate power to identify significant differences. In this review, the available evidence on effectiveness of hysteroscopic sterilization techniques comes from observational studies. Unfortunately, these studies are lacking sufficient power, complete and long term (> 10 years) follow up data on unintended pregnancies and complications.

Additional to the methodological quality of the included studies, another limitation is the inclusion of nine Essure articles and two Ovabloc articles that probably included women who may also be included in other included articles. We could not correct our calculations for this potential overlap. The potential conflict of interest in a large portion of the studies is a third limitation.

Considering feasibility, the 78% – 98% probability of successful placement at first attempt and 90% – 100% verified by a proper confirmation test, all three hysteroscopic sterilization techniques have sufficient feasibility. With a low risk of bias for these outcomes, we consider these rates reliable. Adiana and Essure have the highest successful placement rates, 94% and range: 81% – 98% respectively versus Ovabloc range: 78% – 84%. This is explained by differences in patient selection and different hysteroscopic systems. For all three techniques, complications during the procedures were incidentally reported. The reported complications concerned perforations or expulsions typically related to incorrect placements. The quality of evidence for the outcome complications is very low, since the definition and assessment of this outcome is not clear in the majority of the studies.

The reported incidence of unintended pregnancies after confirmed successful hysteroscopic sterilization with Adiana are considered reliable, though this does not apply to the Essure and Ovabloc studies. To demonstrate the effectiveness of a sterilization technique, pregnancy rates may be calculated by either life table analysis or the Pearl Index. The latter, also called the Pearl rate is the most common technique used in clinical trials for reporting the effectiveness of a birth control method but it assumes a constant failure rate over time. In the U.S. Collaborative Review of Sterilization, a prospective study that included 10,685 women who underwent tubal sterilization, the risk of pregnancy was assessed by cumulative life-table probabilities. Cumulative 1-year probabilities of pregnancy ranged from 0.6 – 18.2 per 1,000 procedures, cumulative 2-year probabilities ranged from 2.3 – 23.8 per 1,000 procedures

(36). The highest probabilities were calculated for the spring clip application (Hulka) and the interval partial salpingectomy, techniques that are not commonly used in daily practice anymore. Today, laparoscopic sterilizations using Filshie Clips are performed more frequently. A prospective study that followed 822 women after a laparoscopic sterilization with Filshie clips found a cumulative 1-year probability of 1.2 per 1,000 procedures. Compared to the cumulative 1-year and 2-year probabilities of Adiana which are 11 and 17.2 respectively per 1,000 procedures, these latter probabilities are relatively high. Both for Essure and Ovabloc, but as well for Adiana, better quality of longer term (up to ten years) follow up is needed to assess the cumulative risk of failure and effectiveness.

Many factors have been explored as a risk factor for placement failure. In single Ovabloc studies it is suggested that intrauterine pathology, an asymmetric uterine cavity, nulliparity (13) and single flow compared to continuous flow (9) are risk factors for placement failure. These findings are however, not confirmed with multivariate analysis or within other studies.

For Essure, single studies found timing of placement in the follicular phase compared to luteal phase (30), a history of sexually transmitted infections (25) and uterine size of more than 8 weeks (30) to be associated with a higher risk for placement failure. These findings are again not supported by other studies. Two retrospective studies found a higher risk for placement failure in women that had not received NSAIDs before the procedure (23,33). A Cochrane review in 2012 concluded that the available literature insufficient is to determine the appropriate pain regimen for outpatient sterilization by hysteroscopy (37). Patient-related risk factors should be investigated in prospective cohort studies with good methodological quality. Technical risk factors e.g. timing of the procedure should preferably be analysed in RCTs. In clinical practice it is preferable to perform a hysteroscopic sterilization prior to ovulation in order to minimize the risk of pregnancy occurring following ovulation.

Future perspectives

Since 1988 three methods have become commercially available. Two methods were later withdrawn from the market. In 2009, reports of disappointing results, technical problems with the cold storage of the silicon and a histological study that could not confirm the claim of reversibility of the technique resulted in withdrawal of Ovabloc. In March 2012, Adiana was withdrawn as part of an agreement to settle ongoing patent infringement litigation (38). Currently, Essure is the only system used for hysteroscopic sterilization. There is continuing innovation of hysteroscopic sterilization devices. In the near future, two new hysteroscopic sterilization methods will be launched. Both methods are based on an intra-tubal device with immediate mechanical occlusion of the fallopian tubes, which should eliminate the need for a three-months confirmation test (39,40).

A third new hysteroscopic sterilization method has been announced. It is described as a redesigned Ovabloc Intratubal Device System. Challenges related to the design include storage under room temperature and incorporating a contrast agent to facilitate visibility for evaluation. For every new technique, we adhere an appropriate evaluation of feasibility and effectiveness, including well defined, complete and long term (≥ 10 years) follow up for unintended pregnancies and complications.

For some techniques, it is argued that the post-procedure imaging should be eliminated based on the fact that in the original clinical trials, 96% and 100% of patients with successful bilateral placement had complete tubal occlusion at respectively three and six months (4,5). Since reliable cumulative long term probabilities for pregnancy could not be calculated, it is still not justifiable to rely on an uncomplicated bilateral successful procedure. At least confirmation tests are indicated to detect failed hysteroscopic sterilization and reduce the risk of pregnancy.

Alternative, less invasive diagnostic tests, like 3D ultrasound, have yet to replace HSG for confirmation of proper placement, though the results from preliminary studies are promising (29,41). Other new non-radiation techniques such as Contrast Infusion Sonography or Hysterosalpingo Contrast Sonography (HyCoSy) (42) or Hysterosalpingo-Foaminfusion Sonography (HyFoSy) also have potential as confirmation tests for tubal occlusion (43,44). Above all, appropriate RCTs and observational studies with sufficient power and follow up are needed for relevant and complementary information to the body of evidence on the effectiveness of hysteroscopic sterilization techniques.

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Supplement 1

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PART 3



Chapter 6

Robotchirurgie in Nederland
Hoogwaardig bewijs voor effectiviteit ontbreekt

Claire F. La Chapelle
Frank Willem Jansen
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Ned Tijdschrift Geneeskde (2013) 157:A5145
[Robotic surgery in the Netherlands: lack of high quality proof of efficacy]

Abstract

More than 10 years after its first introduction, robot-assisted surgery is now performed in 17 Dutch hospitals. Robotic-assisted radical prostatectomy (RARP) is the most frequently performed, though its clinical superiority compared to open (RRP) and laparoscopic prostatectomy (LRP) has not been demonstrated. One randomized controlled trial showed better outcome in erectile function after RARP compared to LRP. The quality of the other studies into RARP is too limited to draw reliable conclusions on clinically relevant outcome measures such as survival, disease-free survival and quality of life. Given the high costs and small scientific evidence, the introduction of robotic surgery has been irresponsibly quick. Better scientific research of robotic surgery is needed before this technology can be broadly applied in clinical practice.

Samenvatting

Robot geassisteerde operaties worden, ruim 10 jaar na de introductie ervan, in 17 Nederlandse ziekenhuizen uitgevoerd. De meest uitgevoerde robot geassisteerde operatie is de radicale prostatectomie (RARP), maar de meerwaarde van deze ingreep ten opzichte van de open en de laparoscopische variant is niet aangetoond. 1 RCT, laat een betere uitkomst van de erectiele functie na RARP vergeleken met LRP zien. Verder is de kwaliteit van het onderzoek naar RARP te beperkt om betrouwbare conclusies te kunnen trekken over klinisch relevante uitkomstmaten als overleving, ziektevrije overleving en kwaliteit van leven. De introductie van de robotchirurgie verloopt gezien de hoge kosten en de geringe wetenschappelijke evidentie onverantwoord snel. Er is beter wetenschappelijk onderzoek nodig voordat robotchirurgie breed kan worden ingezet in de klinische praktijk.

De oorspronkelijke vraag naar een operatierobot waarmee artsen op een veilige afstand ingrepen op het slagveld konden verrichten, kwam vanuit het Amerikaanse leger in de jaren 80 van de vorige eeuw. In 2000 bracht het Amerikaanse bedrijf Intuitive Surgical Inc. de *da Vinci*-operatierobot, vernoemd naar Leonardo da Vinci, de eerste ontwerper van een robot. Met wereldwijd circa 360.000 ingrepen per jaar domineert deze operatierobot momenteel de markt (1). Naar verwachting zullen er de komende jaren ook andere fabrikanten met operatierobots op de markt komen, omdat de patenten op de *da Vinci*-operatierobot binnenkort aflopen (2).

In dit artikel geven we een overzicht van het gebruik van de operatierobot in Nederland en bespreken we onze resultaten van een systematische review naar de effectiviteit en de veiligheid van de robotgeassisteerde radicale prostatectomie (RARP).

Robotchirurgie in Nederland

De eerste robot geassisteerde operatie in Nederland was een cholecystectomie en deze werd verricht in het Universitair Medisch Centrum Utrecht in 2000 (3). 2 jaar later werd in datzelfde ziekenhuis de eerste RARP in Nederland uitgevoerd, gevolgd door de eerste hysterectomie met robotassistentie in het Vrije Universiteit Medisch Centrum te Amsterdam in 2006.

Inmiddels is in 17 Nederlandse ziekenhuizen een *da Vinci*-operatierobot operationeel, maar er is weinig zicht op het beloop van de klinische implementatie van deze nieuwe technologie. Vanuit de Nederlandse Vereniging voor Urologie (NVU) wil men de nationale registratie van alle prostatectomieën, die tot nu toe op vrijwillige basis geschiedt, verplicht gaan stellen. De NVU liet ons echter weten dat de registratie tot nu toe nog onvoldoende betrouwbaar en onvolledig is. Ook de Dutch Gynecologic Robotics Society, die begin 2012 werd opgericht, streeft ernaar om alle robot geassisteerde gynaecologische ingrepen die in Nederland worden verricht te registreren en te evalueren. Ondanks deze ontwikkelingen is er tot op heden geen inzichtelijke nationale registratie. Intuitive Surgical Inc. beschikt als enige over een database waarin alle ingrepen geregistreerd worden die met hun systemen worden uitgevoerd, maar het bedrijf geeft deze informatie niet vrij.

Om een overzicht te verkrijgen van de toepassing van robotchirurgie in de Nederlandse ziekenhuizen, namen wij contact op met de Nederlandse ziekenhuizen die met de *da Vinci*-operatierobot werken. Op www.ntvg.nl/A5145 is een tabel te raadplegen waarin voor verschillende ziekenhuizen in Nederland het jaar van aanschaf van de operatierobot, de specialismen die gebruik maken van de operatierobot en de ingrepen dat daarmee verricht worden zijn weergegeven.

Tot 2008 verliep de groei van het aantal centra met een operatierobot gestaag. Sindsdien is er een explosieve toename geweest: momenteel beschikken 5 academische en 12 niet-

academische ziekenhuizen over een da Vinci-operatierobot. In het Maastricht Ziekenhuis zijn zelfs 2 robotsystemen operationeel. In 17 centra maken urologen gebruik van de da Vinci-operatierobot voor het verrichten van de RARP. In 11 centra gebruiken gynaecologen de operatierobot, met name voor het uitvoeren van hysterectomieën. De overige specialismen die een operatierobot tot hun beschikking hebben zijn de gastro-intestinale chirurgie (6 centra), de cardio-thoracale chirurgie (4 centra) en de hoofd-halschirurgie (2 centra).

In Nederland is de meest uitgevoerde robot geassisteerde operatie de RARP. Naar schatting worden er jaarlijks circa 1200 RARP's verricht, circa 70% van het totale aantal prostatectomieën per jaar (4). Het Nederlands Kanker Instituut-Antoni van Leeuwenhoek Ziekenhuis, het Jeroen Bosch Ziekenhuis, het Canisius-Wilhelmina Ziekenhuis en het Maastricht Ziekenhuis voeren jaarlijks ieder meer dan 200 RARP's uit (La Chapelle, schriftelijke mededeling, 2013). De resterende 400 operaties komen op het conto van de overige 13 centra.

Systematische reviews

Wij vroegen ons af of de massale introductie van robotchirurgie wel gerechtvaardigd is in het licht van de kennis over de klinische effectiviteit en veiligheid van deze techniek. Om die vraag te beantwoorden zochten we naar artikelen over de effectiviteit en de veiligheid van de RARP. Recent werden in 4 systematische reviews de resultaten – oncologische uitkomsten, perioperatieve uitkomsten en complicaties, herstel van de urinecontinentie, en erectiele functie – van RARP vergeleken met die van de retropubische radicale prostatectomie (RRP) en de laparoscopische radicale prostatectomie (LRP) (5-8). In totaal werden er 44 vergelijkende en 136 niet-vergelijkende studies geëvalueerd; in elk van deze studies waren meer dan 100 patiënten geïncludeerd. Op basis van het wetenschappelijke bewijs uit de 4 systematische reviews is het tot op heden niet duidelijk of RARP tot betere klinische resultaten leidt dan RRP en LRP. Hieronder bespreken wij de resultaten van de vergelijkende studies uit elk van de 4 reviews.

Oncologische uitkomsten

Er zijn nog te weinig data over de kankerspecifieke overleving na een robot geassisteerde radicale prostatectomie. In plaats daarvan werd in de eerste review het percentage tumor-positieve snijranden als indirecte maat voor de overleving genomen (5). In 18 studies, 6 prospectieve studies en 12 retrospectieve studies werden de percentages tumor-positieve snijranden na RRP en RARP met elkaar vergeleken; in 1 RCT, 1 prospectieve cohortstudie en 9 retrospectieve studies werd LRP vergeleken met RARP. De cumulatieve analyses lieten geen statistisch significante verschillen zien tussen RRP en RARP (respectievelijk 21 en 20%

tumor-positieve snijranden); bij de vergelijking tussen LRP en RARP waren deze percentages respectievelijk 18 en 18.

In 3 retrospectieve studies werden de aantallen biochemische recidieven na RRP en RARP met elkaar vergeleken; in 2 andere retrospectieve studies werden RRP, LRP én RARP met elkaar vergeleken. Er werden geen verschillen gevonden in de biochemisch bepaalde recidief-vrije overleving, met hazardratio's van 0,9 (95%-BI: 0,7–1,2) voor RRP versus RARP en 0,5 (95%-BI: 0,2–1,3) voor LRP versus RARP.

De auteurs van de review merken op dat er naast methodologische beperkingen van de individuele studies ook enkele bezwaren kleven aan de analyse van de studies. Zo was het niet mogelijk om de invloed van de chirurgische kundigheid te evalueren, terwijl verschillen hierin aanzienlijke gevolgen kunnen hebben voor de oncologische en functionele uitkomsten (9,10). Daarnaast is er niet gestratificeerd voor ziekte-specifieke karakteristieken als tumorstadium, Gleason-score en prostaatvolume, en is er geen rekening gehouden met verschillen in de pathologieprotocollen voor het beoordelen van de chirurgische preparaten. Deze aspecten kunnen een grote invloed hebben op de percentages tumor-positieve snijranden (5).

Perioperatieve uitkomsten en complicaties

In de tweede review werd de veiligheid van robotchirurgie onderzocht aan de hand van de volgende parameters: het aantal complicaties, de operatieduur, de hoeveelheid bloedverlies en het risico op een bloedtransfusie (6). Er werden 3 prospectieve en 9 retrospectieve cohortstudies gevonden waarin deze parameters vergeleken werden tussen RRP en RARP; in 1 RCT en 6 retrospectieve studies werden deze parameters vergeleken tussen LRP en RARP.

De cumulatieve analyses toonden significant minder bloedverlies bij RARP dan bij RRP, met een gewogen gemiddeld verschil ('weighted mean difference', WMD) van 582,77 ml (95%-BI: 435,25–730,29). Daarnaast was het risico op een bloedtransfusie significant lager bij RARP dan bij RRP (OR: 7,55; 95%-BI: 3,56–15,64). Tussen deze operaties werden geen significante verschillen gevonden in de duur van de operatie (WMD: -15,81; 95%-BI: -68,65–37,03) en in het aantal complicaties (OR: 1,25; 95%-BI: 0,53–2,93).

Tussen LRP en RARP werden geen significante verschillen gevonden in het aantal complicaties (OR: 1,4; 95%-BI: 0,73–2,69), in de hoeveelheid bloedverlies (WMD: 54,21; 95%-BI: -75,17–183,59) en in de operatieduur (WMD: 34,78; 95%-BI: -1,36–70,93). Daarentegen was er bij LRP wel een hoger risico op een bloedtransfusie dan bij RARP (OR: 2,56; 95%-BI: 1,32–4,96).

Naast de methodologische beperkingen – vooral retrospectieve studies met onvoldoende statistische 'power' – zijn er nog een aantal zaken die de resultaten minder betrouwbaar

maken. In de meeste studies werden de complicaties niet accuraat geregistreerd. Verder zijn de analyses niet gecorrigeerd voor verschillen in patiëntkarakteristieken als BMI, eerdere abdominale chirurgie of prostaatchirurgie, prostaatvolume en de kundigheid van de chirurg.

Herstel van de urinecontinentie

In de derde review werden 4 prospectieve en 4 retrospectieve cohortstudies gevonden waarin het herstel van de urinecontinentie na RARP en na RRP met elkaar werden vergeleken (7). Een cumulatieve analyse van 5 van deze studies toonde een significant hoger aantal patiënten bij wie 12 maanden postoperatief sprake was van herstel van de urinecontinentie, in het voordeel van RARP (OR: 1,51; 95%-BI: 1,04–2,25). 1 RCT en 7 retrospectieve studies bestudeerden het herstel van de urinecontinentie na LRP en na RARP. De RCT toonde geen significant voordeel in het herstel na RARP ten opzichte van LRP (OR: 3,27; 95%-BI: 0,85–12,59). Een cumulatieve analyse van 5 van de 8 studies toonde een significant hoger aantal patiënten bij wie 12 maanden postoperatief sprake was van herstel van de urinecontinentie, opnieuw in het voordeel van RARP (OR: 2,39; 95%-BI: 1,29–4,45).

Erectiele functie

In de vierde review werden 4 prospectieve en 3 retrospectieve cohortstudies gevonden waarin de erectiele functie na RRP en na RARP met elkaar werden vergeleken (8). In 6 studies werd voor beide operaties 12 maanden na de ingreep het percentage patiënten met erectiele disfunctie gescoord: erectiele disfunctie werd vastgesteld bij 47,8% van de patiënten na RRP en bij 24,2% na RARP (OR: 2,84; 95%-BI: 1,48–5,43).

In 1 RCT en 3 retrospectieve studies werden de erectiele functie na LRP en na RARP met elkaar vergeleken (8). De RCT toonde significant betere uitkomsten na RARP dan na LRP: 77 versus 32% van de patiënten had 12 maanden na de ingreep een goede erectiele functie (OR: 7,19; 95%-BI: 3,09–16,73). De cumulatieve analyse liet een niet-significant verschil zien in het voordeel van RARP (OR: 1,89; 95%-BI: 0,70–5,05).

Zowel de onderzoeken naar het herstel van de urinecontinentie als die naar de erectiele functie bij patiënten na prostaatchirurgie gaan gepaard met aanzienlijke methodologische beperkingen: het merendeel van de studies heeft een retrospectieve studieopzet en de definities en toegepaste methoden voor het beoordelen van urinecontinentie en erectiele functie verschillen tussen de studies. Informatie over de urinecontinentie en de erectiele functie voorafgaand aan de ingreep wordt in geen van de studies beschreven. Ook is er geen rekening gehouden met de kundigheid van de chirurg en met variaties in de chirurgische techniek.

Kostenafwegingen

Bij de introductie van een nieuwe technologie spelen naast effectiviteit ook kosten een rol. De aanschafprijs van de da Vinci-operatierobot is ongeveer 1,7 miljoen euro en de jaarlijkse onderhoudskosten bedragen ongeveer 10% van de cataloguswaarde. Daarbovenop komen de kosten voor wegwerpmateriaal en voor specifieke instrumenten die na 10 ingrepen door nieuwe moeten worden vervangen. Een laparoscopische radicale prostatectomie kost 8000–9000 euro, terwijl de RARP 2000–4500 euro per ingreep méér kost (11).

Een Nederlands ziekenhuis dat de aanschaf van een da Vinci-operatierobot overwoog, schatte dat de totale kosten ongeveer 1 miljoen euro per jaar zouden bedragen. Daarmee liggen de jaarlijkse kosten om in 17 ziekenhuizen in totaal 18 operatierobots operationeel te houden rond de 18 miljoen euro. Mogelijk dat de extra materiele kosten van een operatierobot gecompenseerd kunnen worden door een afname van het aantal postoperatieve bloedtransfusies, door de kortere opnameduur en door betere functionele uitkomsten bij robotchirurgie. Daarnaast kunnen de veel genoemde voordelen van robotchirurgie als de kortere leercurve en de betere ergonomie voor de chirurg, met name ten opzichte van conventionele laparoscopische chirurgie, een rol spelen bij de kosten-batenanalyse van een robotsysteem. Wij zijn echter van mening dat deze potentiële voordelen van robotchirurgie eerst moeten worden aangetoond voordat ze kunnen worden meegenomen in de beschouwingen over de kosten rond de robotchirurgie.

Beschouwing

In september 2011 werd tijdens een bijeenkomst van de European Association of Urology een internationaal consensusdocument opgesteld als aanvulling op de 4 eerder genoemde systematische reviews. Ondanks het gebrek aan RCT's van hoge kwaliteit, waarin de effectiviteit en de veiligheid van RARP worden vergeleken met die van de open radicale prostatectomie, werd vastgesteld dat robotgeassisteerde prostaatchirurgie al op grote schaal is geïmplementeerd in de klinische praktijk (12).

Ook in Nederland is er sprake van een snelle groei van het aantal ziekenhuizen met een operatierobot, met een geschatte kostenpost van 18 miljoen euro per jaar. Dusdanig hoge kosten zijn naar onze mening alleen maatschappelijk verantwoord als de effectiviteit van de operatierobot evident superieur is aan de conventionele technieken. De geringe methodologische kwaliteit van de studies die wij vonden en het ontbreken van data over (ziektevrije) overleving genereren wat ons betreft twijfel over de juistheid van de massale introductie van de robotchirurgie in Nederland.

De academische ziekenhuizen die de robotsystemen introduceerden hebben weinig bijgedragen aan de evaluatie van de effectiviteit daarvan. In het Nederlands Trial Register vonden wij 1 onderzoek naar robotchirurgie (13). Als argument tegen het opzetten van een gerandomiseerde studie wordt gesteld dat het grootste deel van de patiënten desgevraagd voor de operatierobot zou kiezen, waardoor een gerandomiseerd onderzoek niet meer mogelijk is (14). Naar onze mening zijn dergelijke studies wel mogelijk als patiënten goed worden voorgelicht over de onzekere verschillen in klinische uitkomsten tussen de diverse operatietechnieken. Dit blijkt ook uit de meer dan 10 geregistreerde en lopende RCT's naar robotchirurgie in het metaregister voor klinische trials (bron: www.controlled-trials.com/mrct/).

Wij vinden dat zorgprofessionals en ziekenhuizen de verantwoordelijkheid hebben om ervoor te zorgen dat data over de effectiviteit en de veiligheid van robotchirurgie bekend zijn voordat er massale introductie plaatsvindt. De juiste volgorde waarin een klinisch vraagstuk om een technologische oplossing vraagt ('clinical driven approach') is hier omgekeerd toegepast. De technologie heeft gezocht naar een medische indicatie ('technical driven approach') en geresulteerd in een brede suboptimale inzet van een wellicht veelbelovende nieuwe technologie (15). Vanuit dat perspectief valt de door ons geïnventariseerde situatie te omschrijven als een bijna gemiste kans. De gedane investeringen kunnen immers niet meer teruggedraaid worden, maar onder het motto 'beter ten halve gekeerd dan ten hele gedwaald' hebben de ziekenhuizen met een operatierobot nu nog de gelegenheid de handen ineen te slaan voor een systematische evaluatie van de robotchirurgie.

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PART 4

Chapter 7

**Randomised controlled trials in minimally
invasive surgery: an evaluation of clinical
relevance, clearness and objectivity**

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Submitted

Abstract

Background: Minimally invasive surgery (MIS) is a medical technology that intends to minimize surgical trauma as opposed to the conventional surgical techniques. MIS has been assessed in randomized controlled trials (RCTs), that aim to evaluate the clinical advances of these new medical methods. The aim of this study is to critically appraise clinical relevance, clearness and objectivity in randomised controlled trials (RCTs) on gynaecological MIS.

Methods: We searched the Cochrane Library for systematic reviews on minimally invasive procedures in gynaecology. We browsed the topic 'gynaecology' for RCTs wherein MIS procedures were evaluated: i.e. different approaches and different techniques within a minimally invasive procedure. Data on various methodological traits were extracted from the included studies within a pre-defined assessment tool, with a view to investigate the clinical relevance, clearness and objectivity of RCTs.

Results: Out of the 566 systematic reviews found in the Cochrane database, we selected 47 RCTs eligible for further assessment. Procedural and costs outcomes were set as primary outcome in 32%, patient comfort in 29%, effectiveness in 15% and safety in 12% of these RCTs. Sufficient sample size, adequate distribution of participants arms and sufficient follow up duration were reached in 24 RCTs (51%) RCTs. We found a complete match between the authors' conclusion and the results in eight (17%) RCTs. None of the RCTs provided sufficient data supporting superiority of a new MIS method over the existing method.

Conclusions: This study shows that the clinical relevance, clearness and objectivity of RCTs on gynecological MIS is suboptimal. RCTs do have large difficulties to provide sufficient information for decisions on implementation of new MIS techniques. The validity of observational studies should be further explored to provide additional evidence. Furthermore, it is of clinical importance that authors, reviewers and editors criticize the consistency between results and conclusions of their forthcoming study publications.

Introduction

Minimally invasive surgery (laparoscopy) is a medical technology that intends to minimize surgical trauma as opposed to the open abdominal surgical technique (laparotomy). With advanced laparoscopic operations for pelvic organ prolapse, urinary incontinence and gynaecological cancers, laparoscopy has become completely integrated into the field of gynaecologic surgery. Minimally invasive surgery is called a technology because it applies on scientific principles and keeps on advancing to make its appliances smarter and more efficient. The rapid evolution of this technology has led to the development of new technologies and techniques within the field of minimally invasive surgery such as Robot (-assisted) surgery, natural orifice transluminal endoscopic surgery (NOTES), laparo-endoscopic single-site surgery (LESS) and minilaparoscopy. Robot surgery is a technological development where robotic systems are used to aid in surgical procedures. It was developed to overcome the limitations of pre-existing minimally-invasive surgical procedures (1). NOTES refers to surgery via natural orifices, where procedures are performed with transluminally placed instruments to gain access to the abdominal cavity (2). LESS surgery is an advanced minimally invasive approach that allows laparoscopic operations to be undertaken through a single small incision, typically placed at the patient's umbilicus (3). Minilaparoscopy involves the use of smaller incisions, smaller instruments and fewer ports to further reduce perioperative morbidity and enhance cosmesis (4).

Physicians and patients often embrace new technologies before their clinical and economic implications are fully evaluated (5). There are numerous examples of recalled "new methods" that were already broadly applied in clinical practice but proved to be insufficiently safe or cost-effective (6). Medical technology is often driven by commerce, though its driving force should primarily be what clinical practice is demanding for (7). Firstly, commercial pressure can lead to new methods being implemented too quickly, for another thing clinical research is slow at adopting new clinical applications. Secondly, the conduct of clinical research for new methods is often of limited size and could be more targeted to relevant clinical questions. A third weakness can be found in the presentation of research results. It is questionable whether the conclusions drawn from clinical research match the actual reported data. As the minimally invasive procedures are usually evaluated by the same people who developed and introduced those techniques, the results are potentially interpreted with overoptimism.

To determine what the main conclusions of trials are, studying the abstract of the paper is not enough, but can serve as a starting point. It is supposed that reading only the abstract or conclusions of a study is insufficient and may lead to an overstatement of study findings (8). We think that commercially driven medical technology, insufficient clinical research and overstatement of study findings could lead to incautious implementation of new methods in clinical practice.

Randomised controlled trials (RCTs) represent the best method to evaluate the effectiveness of healthcare interventions (9). They are the most rigorous way of assessing the effectiveness of a treatment. RCTs aim to evaluate the (clinical) advances of new and existing medical technologies. The bundled outcomes of different RCTs should ultimately lead to a clear answer whether the new method should be used over the existing method. The Cochrane collaboration is a globally known as an independent network where the best evidence from research is gathered and summarised for the use of high quality information to make health decisions (10).

In this study, we inquire if randomised controlled trials serve the clinical needs of minimally invasive surgery. We assessed the clinical importance of primary and secondary study outcomes, whether studies are set up sufficiently to answer their research question and if the conclusions of the articles corresponded to their actual results. The aim of this study is to critically appraise clinical relevance, clearness and objectivity in randomised controlled trials (RCTs) on gynaecological minimally invasive surgery. We aim to provide guidance towards more useful (less wasteful) future research in minimally invasive surgery.

Methods

Search methods for the selection of studies

We searched the Cochrane Library for systematic reviews on minimally invasive procedures in gynaecology. Two assessors (SV and CC) browsed the topic 'gynaecology' independently and screened titles and abstracts for reviews addressing minimally invasive gynaecologic surgery. We included RCTs comparing laparoscopic surgery with other surgical approaches (e.g., laparotomy or different minimally invasive techniques) and newer techniques within minimally invasive surgery (e.g., laser vs diathermy, different trocar design). In order to focus on current scientific literature, we excluded RCTs published before 2005. We also excluded trials that compared substantially different treatment techniques (e.g. excision versus ablation of cysts) or a minimally invasive surgical approach to a conservative or pharmacological approach. Furthermore, cohort studies were excluded. We only assessed full text manuscripts. Studies reported in abstracts-only were excluded.

Data collection and assessment

Two assessors (SV and CC) independently assessed the selected RCTs. Each article was read and examined for clinical relevance, clearness and objectivity. We focussed on the following aspects:

1. clinical relevance: what are the defined study outcomes and what is their clinical relevance?
2. clearness: does the RCT comprise a sample size calculation for the defined outcome(s) of the trial? Is the study power and follow up sufficient to ensure distinctiveness to provide a clear answer to the study objective?
3. objectivity: represents the conclusion the actual results of the RCT?

The assessors evaluated the RCTs independently with use of a pre-defined assessment tool (figure 1) To evaluate the clinical relevance of a RCT, the defined primary and secondary study outcomes were assessed. To do so, we categorized these study-outcomes into: 1) effectiveness, 2) safety, 3) patient-comfort, 4) procedural and costs, 5) surgeon comfort and 6) other outcomes. For outcomes of effectiveness, a distinction was made between clinical effectiveness (e.g. reduction of the complaints of urinary incontinence) and technical effectiveness (technical success of the procedure, e.g. correction rate of the anatomical position of the bladder). This distinction is important for the clinical interpretation of effect measures. We denoted *conversions* as an outcome measure of technical effectiveness since a conversion indicates that the intended procedure has not been successful (11). Safety-outcomes were defined as complications and adverse events. For patient-comfort outcomes we included all outcomes directly relating to or affecting the comfort of the patient (i.a. quality of life, postoperative pain, duration of postoperative paralytic ileus). Procedural and cost outcomes concerned organizational aspects that are principally more important to healthcare institutions than to patients. For surgeon comfort, all aspects directly influencing the comfort of the surgeon were included. The remaining outcomes that we could not classify were assigned to *other* outcomes.

The clearness of a RCT was investigated by determining whether the achieved sample size, follow up duration and completeness provided enough power to detect significant differences in the studied outcomes.

We studied the objectivity of the RCT by assessing the results per outcome. Preferably odds ratios, risk ratios, and mean differences were collected all including confidence intervals (CI) or p-values. We indicated whether the result for the new versus existing method is positive, indifferent, or negative. Based on the obtained overview of investigated and missing clinically important outcomes, we considered if the “newer method” would be sufficiently effective and safe to be implemented in daily surgical practice. In the context of objectivity we examined the abstract conclusion compared to the full-text conclusion. These were judged being concordant or discordant. Thereafter, we extracted the overall conclusion of the authors of the RCT and classified the style as “nuanced” or “outspoken”. “Nuanced” signified that the specific findings are subtly described in the conclusion. Conversely, an “outspoken”

Study:	Effectiveness: How is the effect of the intervention on the disease or condition assessed? Make a clear distinction between technical effectiveness and clinical effectiveness:	Safety: How is the safety of the intervention assessed (complication rate)?	Patient- comfort: How are factors on patient- comfort assessed (e.g. adverse effects, pain, fatigue, satisfaction)?	Procedural and costs: How are organizational or economical aspects assessed (e.g. operative time, hospital stay)?	Surgeon- comfort: How are aspects that aim advantages for the surgeon assessed (ergonomics, technical difficulties)	Other: What other outcomes are assessed (e.g. secondary outcomes or indirect outcomes)?
1. If applicable, describe the outcome(s) and its assessment	Clinical effectiveness: Technical effectiveness:					
2. Is the number of participants, the length and completeness of follow-up sufficient to detect significant differences in the outcome(s) described above?						
N = ...						
3. What are the results of the above described outcomes for the MIS-procedure compared to the control-intervention? What are the actual results per outcome measure? (if applicable, report their statistical outcome measure (Risk Ratio/ Odds Ratio and Confidence Interval or rates/ percentages/ times and P-value.) Define: positive/ indifferent/ negative effect.						
	• Positive effect • Indifferent • Negative effect Explanation:	• Positive effect • Indifferent • Negative effect Explanation:	• Positive effect • Indifferent • Negative effect Explanation:	• Positive effect • Indifferent • Negative effect Explanation:	• Positive effect • Indifferent • Negative effect Explanation:	• Positive effect • Indifferent • Negative effect Explanation:

4. Based on the results described in section 3, should the newer intervention be implemented in surgical practice?
- ☐ Yes, completely acceptable in surgical practice
 - ☐ No, not (yet) acceptable, more important outcomes should be evaluated
 - ☐ No, not at all, the newer intervention has more disadvantages and less advantages compared to the control- intervention
5. Are the abstract- conclusion and full- text conclusion concordant?
- ☐ concordant
 - ☐ discordant
6. How would you describe the style of the author's conclusions?
- ☐ "Nuanced" → skip question 7. Go to question 8.
 - ☐ "Outspoken"
7. What are the author's conclusions?
- ☐ The new method is superior
 - ☐ The new method is indifferent to the conventional method
 - ☐ The new method is inferior to the conventional method
8. Do the conclusions match the reported results?
Assess the findings for each outcome measure and if applicable, criticize the clinical relevance of a demonstrated difference.
- | | | | |
|--------------------------|--------------------------|--------------------------|--------------------------|
| no | partly | largely | completely |
| ☐ | ☐ | ☐ | ☐ |
- Explain:

Figure 1 Assessment form for critical appraisal of RCTs on new procedures in MIS.

conclusion postulates the newer method either showed to be superior, comparative or inferior to the conventional method. We labelled “outspoken” conclusions as superior, indifferent or inferior. The authors’ conclusions were independently scored for consistency with the results. The possible scores to be assigned were: “no”- “partly”- “largely”- and “completely”, the motivation for judgement was included. Completed assessment forms were compared and any disagreements were solved by a third author (FWJ). We investigated whether the style of the conclusions was related to differences in consistency between conclusion and results.

Statistical analysis

Data were initially analysed descriptively to estimate frequencies and percentages for the number of RCTs and categorical variables. Differences between groups were tested by using the Fisher’s exact test (Freeman-Halton extension) for categorical data. A p-value < 0.05 (two-sided) was considered statistically significant. <http://vassarstats.net/fisher2x4.html> was used for statistical analysis.

Results

We identified a total of 566 items by browsing for topic gynaecology in the Cochrane database. We considered 23 items potentially relevant based on their title. We excluded five items with abstract screening: three were a review protocol and two reviews compared substantially different treatments. This resulted in 18 reviews including a total of 257 RCTs considered feasible for inclusion in this study. Of these 257 RCTs, 97 were published between 2005 – May 2017. After further selection 47 RCTs remained eligible for assessment (figure 2).

Clinical relevance: study-outcomes

In 34 out of the 47 RCTs (72%) the primary outcome was indicated (figure 3a). In five RCTs the primary outcome was a measure for effectiveness (15%), in four RCTs for safety (12%), in 10 RCTs for patient comfort (29%), 11 RCTs used procedural and cost outcomes (32%) and four defined primary outcomes were categorized as “other” outcomes (12%). None of the RCTs was carried out with a primary focus on surgeon-comfort outcomes.

Two RCTs assessed clinical effectiveness as primary outcome, two other RCTs clinical and technical effectiveness and one RCT technical effectiveness. A total of 32 RCTs reported measures of effectiveness as a secondary outcome including nine times clinical and respectively 14 times technical measures. Seventeen trials reported conversions.

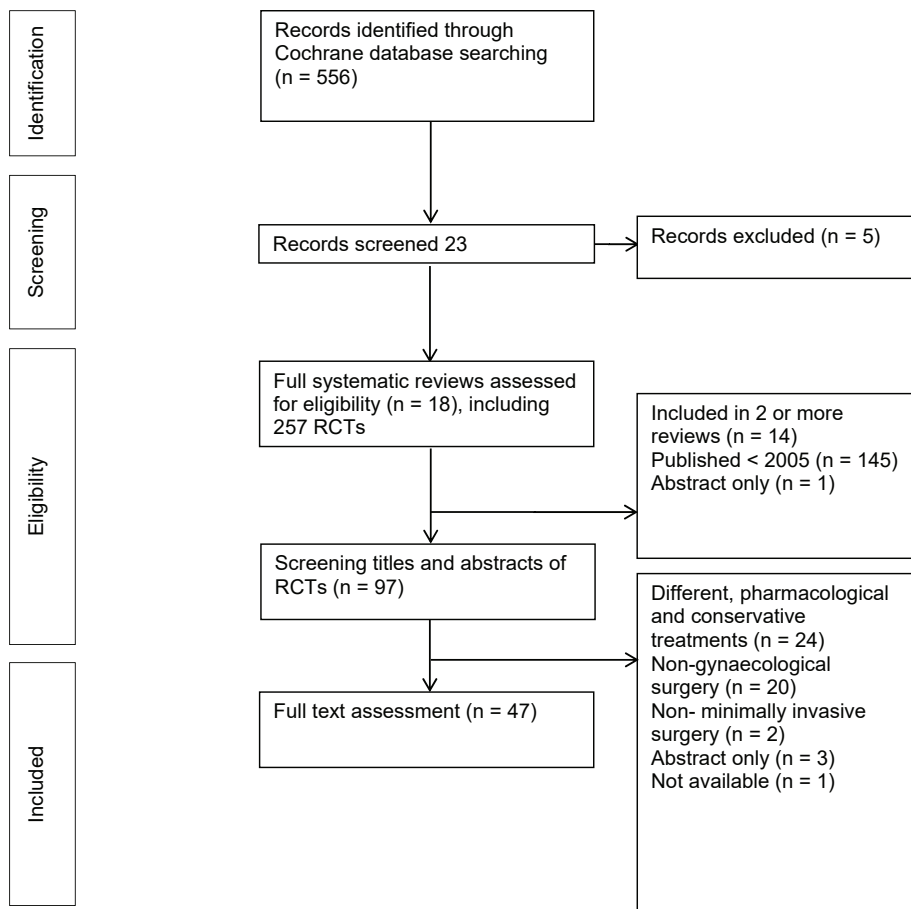
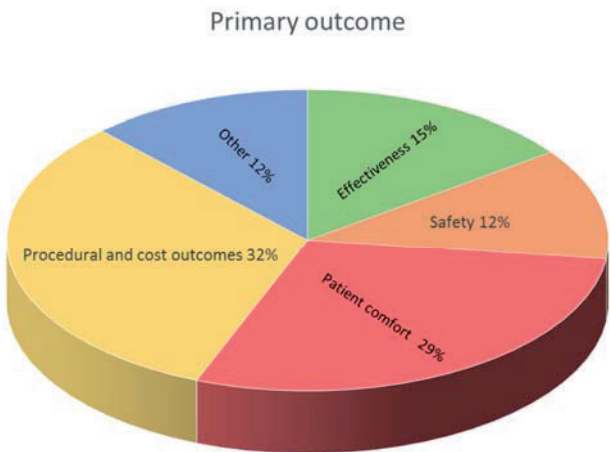


Figure 2 Flowchart of selection of studies. last searched may 22th 2017, Cochrane Library, Cochrane Reviews, Browse by topic, Gynaecology 566 HITS.

The distribution of secondary outcomes was as follows: 24% of the secondary outcomes were set at safety, 22% at procedural and costs, 19% at effectiveness 17% at 'other', 15% at patient comfort, and 3% at surgeon comfort (figure 3b).

Based on the particular findings of each individual RCT we judged none of the RCTs providing sufficient evidence supporting the newer method should be implemented in daily surgical practice. From the results of 40 RCTs we found the newer method not (yet) acceptable since more important outcomes should be evaluated. From the results of seven RCTs we judged the newer method should not be implemented at all because the newer method showed more disadvantages and less advantages.

a



b

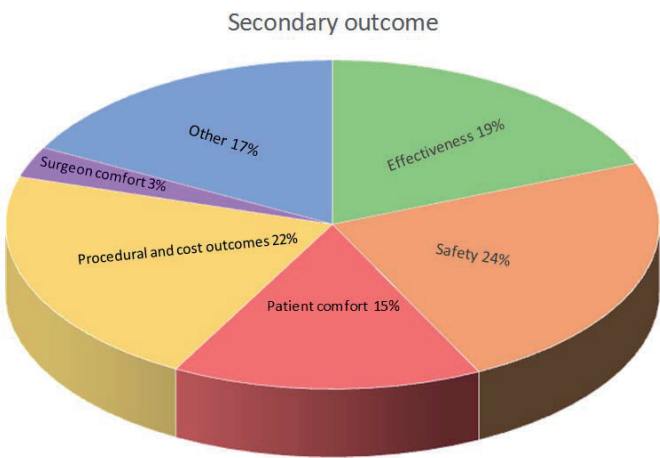


Figure 3 a) Primary study outcomes, categorized. b) Secondary study outcomes, categorized.

Clearness

A total of 31 RCTs (66%) performed a sample size calculation for the primary study outcome (figure 4). The total calculated sample size was included in 25 RCTs. One RCT did not achieve the calculated sample at all, in four RCTs the distribution of the sample size across the groups was inadequate resulting and the distribution was unclear in one RCT. For all 25 RCTs with sufficient sample size the intended duration of follow-up was estimated to be appropriate for the analysis.

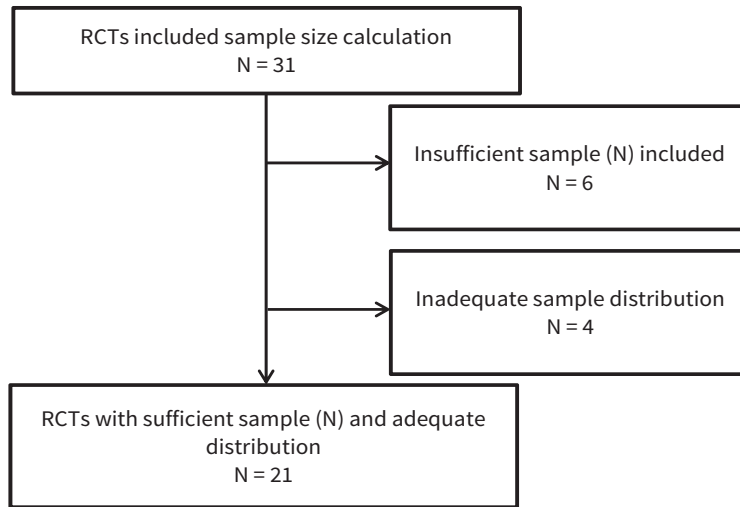


Figure 4 Sample size and follow up flowchart.

Objectivity

We found 39 (83%) abstract conclusions concordant with the conclusions in the full text of the article. In eight RCTs (17%) we judged the abstract conclusion discordant with the full text conclusion. Six abstract conclusions were more positive compared to the conclusion in full text. One full-text conclusion described extra advantages compared to the abstract conclusion. And in one RCT word usage differed between the abstract and full text conclusion leading to confusion about what was actually meant.

In eight (17%) RCTs we found the conclusion completely matching with the results. From 10 RCTs (21%) we criticized the conclusion “largely” matching the results, in 22 (47%) this was “partly” and in seven (15%) the conclusion did not match the results at all. The conclusion of 24 (51%) RCTs was labelled having a “outspoken” style. In 16 of these the authors concluded the “newer” method being “superior” to the existing method. In six RCTs the methods were concluded to be “indifferent” and in two the newer method was judged “inferior”. In the conclusions of the remaining 23 (49%) RCTs a more nuanced judgement was postulated, where the pros and cons were more specifically described. The RCTs with “nuanced” conclusions showed statistically different scores for consistency of conclusion with results compared to RCTs with “outspoken” conclusions ($p = 0.01$).

Discussion

Main results

Concerning the clinical relevance, in this cohort of 47 recent RCTs on gynecological minimally invasive surgery, over 60% focussed their primary study outcomes on patient comfort, procedural and cost aspects. Outcomes on effectiveness and safety remained underexposed. The results of individual RCTs showed insufficient evidence to support implementation of a new method into surgical practice. The ability to provide clarity was suboptimal: slightly more than 50% of the RCTs paid sufficient attention to an adequate sample size calculation followed by sufficient inclusion and distribution across the study groups. The objectivity of the studies is also debatable: we found discordance in the conclusions stated in the full articles compared with those in the accompanying abstracts in more than 15% of the RCTs. We also found that a substantial percentage of the conclusions in RCTs were not (15%) or just partly (47%) matching the actual results. The conclusions were formulated in different styles: we could distinguish a “nuanced” style and an “outspoken” style. The style of the conclusion and the degree of consistency between study-results and conclusion seems to be associated.

Importance to clinicians and researchers

These findings inform the readers of medical scientific literature that the clinical relevance, clearness and objectivity of RCTs on gynecological MIS can be unsatisfactory. It appears that RCTs do not provide sufficient information for decisions on implementation of new MIS techniques. Furthermore, it is of clinical importance that authors, reviewers and editors criticize the consistency between results and conclusions of their forthcoming study publications.

Additionally, these findings should alert researchers. The usefulness of RCTs on new techniques in MIS could be improved. Study objectives should be considered clinically relevant. A proper RCT focusses on relevant outcome measures and applies a careful weighting to assess the importance of related clinical outcomes. Study outcomes should be chosen for their clinical relevance and study designs should fit the study objective. This study shows that RCTs are not necessarily the appropriate design to study effectiveness and safety in MIS: the reality shows it is challenging to recruit sufficient participants and to achieve long-term follow-up to provide clearness. Observational studies can provide evidence additional to that available from randomised trials about long term outcomes, rare events, adverse effects and populations that are typical of real world practice (12).

Other publications and concerns on this topic

This is not the first study that identifies the shortcomings in clinical relevance, clearness and objectivity of RCTs. From among 114 published RCTs of systemic therapy in lung cancer, 10% of the articles presented discordant conclusions in the abstract versus article (13). Another study compared the abstract conclusions and results sections of 144 RCTs in rheumatology and reported almost one quarter contained misleading conclusions (14). The issues even extend far beyond invalid research conclusions: concerns about poor clinical research design and the arbitrary choice of analyses and an overemphasis on random extremes affecting reported findings have been growing increasingly (15,16). Statements and networks have been designed to increase the value in research design, conduct and analysis (such as the Equator network, REWARD statement and CONSORT STATEMENT) (17,18,9). All with the purpose of making clinical research more useful.

Alternative explanations for the observations

We already discussed one reason why the RCTs tended to refrain from studying the most clinically relevant outcomes of effectiveness and safety: - RCTs are not necessarily the appropriate design. This methodological challenge is also represented where half of the effectiveness-outcomes were set for technical effectiveness and the other half respectively for clinical effectiveness. In trials on surgical procedures, technical effectiveness is more often evaluated since it has less methodological barriers compared to clinical effectiveness. Another underlying reason might be that there already is sufficient knowledge of these outcomes (and these outcomes did not need to be studied anymore). Two other possible reasons we did not explore, could be publication bias and conflicts of interest. Ocana et al. also suggested the choice to investigate less relevant outcome measures might be the consequence of the quest for adequate statistical power (at the cost of generalizability) (18).

The assessment objectivity: consistency between study results and conclusions, is a complex process that relies on subtle interpretations of language used to convey a bottom-line message from the study. To minimize the impact of subjectivity, two authors independently categorized the conclusions, with any disagreements being resolved by consensus. The inconsistencies we found between study results and conclusions could be subject to our self-designed assessment tool and personal interpretation. The validity of our assessment may be improved by expanding such an evaluation, with multiple reviewers and a more sensitive assessment scale (e.g. 7-point Likert scale).

Limitations of the study

As described, the assessment of objectivity should be viewed with caution, because interpretation is subject to differences in individual perception. Thereby, the assessors were not blinded for information that could lead to conscious or unconscious bias on their part. This was not feasible because blinding would hinder adequate evaluation of the relevance of outcome measures. Additional to the validity of our assessment of objectivity, there are some other limitations. We focused on RCTs in one medical field (minimally invasive surgery). We restricted our selection of articles because of our particular experience in this specialty. The results of this study may, accordingly, not be generalizable to other medical areas. Furthermore, we selected RCTs that were included in Cochrane reviews. We assumed the Cochrane database as a helpful base for our study: the methodological quality of included trials is already systematically and critically assessed (e.g. risk of bias assessment and prioritizing outcome measures). However, this selection results in the risk for a selection bias: non-Cochrane RCTs may have different outcomes. To get more insight in the clinical relevance, clearness and objectivity of RCTs, studies are needed to see whether our results are confirmed in more randomly selected RCTs and within other medical areas.

Finally, determining the clinical relevance of the outcome measures gives difficulties. Clinical relevance is subject to several factors, including the severity and consequences of the type of disease, patient's context (e.g. age) and cultural values. To explain this: in the case of an oncological disease, long-term patient comfort may be more important than recurrence free survival (effectiveness). And: "should paralytic ileus time", "febrile morbidity" or "blood loss" be categorized as a safety concern or patient comfort? This should of course depend on the impact on the patient's quality of life. These difficulties can be resolved when outcomes for RCTs are carefully weighted for their clinical importance and thoroughly specified at the set-up of an RCT.

Conclusion

The findings of our study show that the clinical relevance, clearness and objectivity of RCTs on gynecological MIS can be unsatisfactory. It appears that RCTs do have large difficulties to provide sufficient information for decisions on implementation of new MIS techniques. The validity of observational studies should be further explored to provide additional evidence. Furthermore, it is of clinical importance that authors, reviewers and editors criticize the consistency between results and conclusions of their forthcoming study publications.

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Chapter 8

General discussion

Minimally invasive surgery (MIS) aims to achieve at least similar clinical effectiveness for a quicker recovery compared to the conventional surgical approaches. In the last decades, MIS has led to great clinical improvements in many fields of surgery; however the invasive and innovative character also entails additional risks. Starting something new is often more difficult and risky than doing things the old familiar way. Clinical research generates knowledge that allows assessment whether the aims of MIS are targeted. Gathering the best evidence from clinical research and subsequently integrating it into daily practice gives valuable input to evolve MIS.

This thesis describes the multidisciplinary guideline for minimally invasive surgery, identifies the scientific evidence of four recent innovations within MIS, addresses the quest for evidence supporting surgical practice and appraises the clinical relevance, clearness and objectivity of recent randomized controlled trials in MIS.

The translation from evidence to practice: evidence-based guidelines

Evidence-based guidelines facilitate integration of the best evidence into surgical practice. Guidelines are developed by groups of experienced individuals who carefully weigh syntheses of evidence and the strength of the evidence before developing recommendations for interventions (1). In **Chapter 2** we present the multidisciplinary evidence-based guideline for MIS. At the initiation of the development of this guideline, the problem analysis revealed the following main problem topics in laparoscopic surgical practice: entry-techniques, the pneumoperitoneum, port instruments, trocar site closure and electrosurgical techniques. Based on the available evidence we formulated general recommendations for minimally invasive surgery. However, the majority of recommendations in the guideline was based on the findings of descriptive studies and expert opinion. To date, high quality evidence is lacking to formulate clear answers to important clinical questions. The unanswered questions offer interesting opportunities for future research. This illustrates the dynamic and cyclic process of an evidence-based guideline: pragmatic clinical questions lead to a review of the evidence, the best evidence is extracted, balanced with other considerations to formulate recommendations for clinical practice and future research. In a later stage, new research will potentially provide answers to the outstanding questions resulting in new recommendations for clinical practice. Eventually leading to better surgical care.

Gathering evidence of new techniques in minimally invasive surgery

The evolution of instrumentation leads to the development of new applications for minimally invasive surgery. As shown in the evidence-based guideline, questions about the safety of

different port instruments persisted (i.e. trocars). The aim to make the use of trocars more effective and safe results in continuing development of different trocar types. In **Chapter 3**, we present a systematic review that assesses the evidence of trocar types. We used GRADE (Grading of Recommendations Assessment, Development and Evaluation), as a tool that facilitates the translation from evidence to recommendations (2). This method optimizes the presentation of evidence per clinically important outcome. The review on trocar types showed a lack of data from randomized controlled trials (RCTs) on the incidence of major trocar-related complications. The incidence of these serious complications was extremely low and a RCT is therefore not the most appropriate design of choice. Adaptations in the design of trocars to prevent adverse events that occur only infrequently may be best assessed by good-quality observational studies such as cohort and case-control studies. Minor trocar-related complications (trocar site bleeding, trocar site infection and trocar site herniation) were generally more common: low quality evidence suggested the use of radially expanding trocars compared to cutting trocars leads to reduced incidence of trocar site bleeding. Though this outcome is viewed with less clinical importance. The review particularly illustrates the importance of focussing on the outcome measures when selecting a study design. Studies on outcomes that can be expected shortly after the intervention and with high incidence rates, do fit in an experimental (RCT) design. Though, studies on outcomes that are extremely rare, need large well-conducted observational studies. The disadvantage of observational studies is however the risk of bias. This emphasizes the importance of proper methodology to reduce the risk of bias. It is finding the balance, on one hand, the most rigorous method (RCT) though with usually insufficient power to draw conclusions and, on the other hand, observational studies to gain more power to draw conclusions though with an increase in risk of bias.

Returning to the trocar types, the systematic review of RCTs provided advantageous evidence for the radially expanding trocar concerning minor complications, however, the clinical importance of this finding is debatable. To get more clarity upon possible risk-differences between trocar types, a systematic review including (non-randomized) observational studies may provide more information.

We explored the latter, investigating the possible advantages of laparoendoscopic single-site surgery (LESS) for hysterectomy over the conventional laparoscopic approach.

LESS was designed to decrease abdominal wall trauma resulting in less postoperative pain and better cosmetic outcomes. In **Chapter 4** we primarily investigated the safety, effectiveness (including conversion rate, postoperative pain and patient satisfaction) of LESS hysterectomy. A total of 23 comparative studies (RCTs plus comparative cohort studies) with approximately 4000 participants did not reach sufficient power to measure differences for infrequent outcomes,

such as major complications and conversions. Where statistically significant advantages for the outcomes postoperative pain, operative time and hospital stay appeared, these results show significant statistical heterogeneity and should be interpreted with caution. The evidence regarding the advantages of LESS-hysterectomy is not a sufficient base for broad implementation of this surgical technique. It can be stated that this technique is still under evaluation. Future RCTs with adequate power are mandatory to identify the possible benefits in patient satisfaction and cosmetic satisfaction. Furthermore a better understanding of its effectiveness and costs is needed. Remarkably, more than 85% of the included studies on LESS originated from Asia. This remark also applies to the Natural Orifice Translumenal Endoscopic Surgery (NOTES)- hysterectomy. NOTES is another new approach for hysterectomy, where the transvaginal access route is used to perform intra-abdominal surgery. Also here, the effectiveness of NOTES could not be fully demonstrated. The scant available evidence for NOTES was found to be retrieved from Asian tertiary centres with a high proficiency for doing this kind of advanced surgery (3). Publication bias could be the underlying reason or reasons causing Asian surgeons to be more inclined to use such new approaches. Those motives could be technological advancement, commercial drives or maybe cultural motives regarding cosmetics.

Another new minimally invasive technique that was enthusiastically introduced in the United States and Europe is hysteroscopic sterilization. Also within the purposes of MIS, hysteroscopic sterilization aims to avoid incisional surgery and further reduce morbidity compared to the conventional techniques (laparoscopic sterilization). An additional advantage of hysteroscopic sterilization is the reduced need of anesthesia, which facilitates the procedure in an ambulatory setting. To verify the effectiveness (i.e. reliability) and safety of the hysteroscopic sterilization we performed a systematic review, presented in **Chapter 5**. The review was performed in 2015, all data from available observational studies that involved more than 20 participants were included. Three types of devices that have been available on the market were evaluated: Ovabloc, Essure and Adiana. At the time of performing the review, Ovabloc and Adiana were no longer available, Essure still was. From a total of 37 articles concerning Essure (counting over 14,000 women), the effectiveness (i.e. reliability), long term safety and risk factors for failure of sterilization could not be identified.

From evaluation to introduction into practice

In 2002, the U.S. Food and Drug Administration (FDA) approved the Essure technique for clinical use. The approval was based on two short-term safety studies, 92% of the participants were followed up at one year, and 25% for two years (4,5). More than ten years after the approval an estimated 750,000 women that had received Essure, even though the effectiveness and long-term safety remained unclear. Indeed, the clinical research with regards to Essure has

not gone beyond demonstrating feasibility. Hence, since 2013 Essure has been the subject of controversy raised by large numbers of women with these devices who complained of adverse events (6). In 2015, the FDA reconvened its Obstetrics and Gynecology Devices Panel to evaluate its safety and effectiveness and to investigate the need for additional post marketing studies (7). In 2017, the manufacturer withdrew the product from the Dutch market.

A similar situation concerning the clinical introduction of robotic-assisted surgery is described in **Chapter 6**. We questioned the progress of introducing robotic-assisted surgery, given the high costs and small scientific evidence. In the Netherlands, the robotic-assisted radical prostatectomy (RARP) is the most frequently performed robotic-assisted procedure. We found robotic-assisted surgery being increasingly applied into Dutch urological surgical practice, although the clinical superiority compared to the existing techniques (open and laparoscopic prostatectomy) had not been demonstrated. Robotic assistance for performing radical prostatectomy was introduced in the early 2000s with the aim to overcome significant challenges and learning curve for laparoscopic radical prostatectomy (LRP) (8). The surgical system currently used for RARP, is called the *da Vinci*® surgical system and offers additional technological innovations (3D visualisation, articulated instruments, tremor filtration) addressing some of the technical limitations of LRP. A recent systematic review showed the lack of high-quality evidence from RCTs for prostate cancer-specific survival and other oncological outcomes (9). Other systematic reviews of non-RCTs concluded that the quality of the evidence base in observational studies is low (10,11). RARP is still under evaluation: understanding of the impact of risk of LRP/RARP on oncological outcomes is needed. The robotic-assisted technology is likely to provide useful benefits. But still, it appears difficult to prove the effectiveness compared to the conventional laparoscopic techniques. For example in gynecologic oncology concerns were raised about the minimally invasive hysterectomies for endometrial cancer. In 2010, in the United States, around 60% were performed robotically, despite the limited available evidence (12). The highlighted examples illustrate a self-regulated process of surgical innovation: following FDA approval or a CE marking (Conformité Européene) products may be legally placed on the market. Thereafter, the extent of clinical implementation and evaluation depends on its users, manufacturers and local authorities. The extent of clinical implementation of a new technique is subject to different forces. Commercial drives of the industry, funders of research and development, characteristics of early users, perceptions and medical publishing industry are elements influencing the innovation environment. In general, sales of new devices and instruments are permitted in most jurisdictions on the basis of proof of safety (e.g. the FDA, CE marking), rather than of efficacy or effectiveness. Implementation of new appliances just after CE marking exposes health care to risks of unexpected patient harm, suboptimal treatments and higher costs. On the other hand, a vigorous ongoing process of innovation is central to continuing improvement of surgical care. Delaying the introduction of an 'effective' technique into surgical practice, may withhold benefits to patients.

Challenges for RCTs in minimally invasive surgery

In clinical research, RCTs are still considered the gold standard for establishing data about safety and effectiveness of an intervention. A proper RCT, focusses on relevant outcome measures and applies a careful weighting to assess the importance of related clinical outcomes. Secondly, it has the potential to provide a clear and distinctive answer to its research question. Thirdly, it is objective and based on facts. Therefore the ingredients for an appropriate trial are:

1. clinical relevance: it includes a consideration of assessing effectiveness, safety, patient comfort, procedural aspects (i.e. costs) and surgeon comfort of a surgical procedure.
2. clearness: it considers an adequate power and follow up, calculated for the defined outcome(s) of the trial. Adequate study power and follow up to ensure sufficient distinctiveness and to provide a clear answer to the study objective.
3. objectivity: it includes a conclusion that represents the actual study results.

In **Chapter 7** we examined recent RCTs on gynecological MIS for clinical relevance, clearness and objectivity. We found more than 60% of RCTs had focussed their primary outcome on patient comfort, procedural and cost aspects. Clinically more relevant outcomes for effectiveness were underrepresented. Primary outcomes for effectiveness were set in only 15% of the included RCTs. With regards to clearness, slightly 50% of the RCTs included sufficient participants in both study arms, meeting the calculated sample size. With these little study-powers, nearly half of the RCTs could not ensure sufficient distinctiveness to provide a clear answer to the study objective. A third weakness was identified in the objectivity in presenting results and conclusions of a RCT. In 15% of the RCTs the conclusion was inconsistent with the actual study results. As previously mentioned, and supported by these findings, RCTs are not necessarily the appropriate design to study effectiveness and safety in MIS. The reality shows it is challenging to recruit sufficient participants and to achieve long-term follow-up to provide clearness. Furthermore, to improve the clinical relevance of forthcoming study publications it is of clinical importance that authors, reviewers and editors criticize the consistency between results and conclusions of their manuscripts.

Conclusions

MIS is introduced with the aim to achieve at least similar clinical effectiveness with a quicker recovery compared to the conventional surgical approaches. The last decades, MIS has led to great clinical improvements in many fields of surgery. The advent of evidence-based medicine has led to increasingly more clinical research (including RCTs) which has been carried out within the field of MIS. This brings great possibilities to acquire knowledge whether

the targets in MIS are achieved and how MIS should be applied to improve healthcare. The acquired knowledge can subsequently be reviewed and summarized to synthesize a practical guideline. In this way, the “multidisciplinary evidence-based guideline for minimally invasive surgery” facilitates the integration of the best evidence into MIS practice. The guideline additionally identifies a substantial lack of high quality evidence for important clinical questions. These unanswered questions offer interesting opportunities for future clinical research. Evidence-based guidelines would thus be a good addition to the innovation cycle: by reviewing the existing evidence and indicating which innovation and research are needed.

We reviewed three innovations within MIS: trocar types, LESS and hysteroscopic sterilization. These reviews typically provide data on short term outcomes. For all three subjects, it showed lack of evidence for infrequent outcomes and long term outcomes. These concerned in particular outcomes as major complications and long-term effectiveness (contraceptive). The latter information should probably be searched in well-conducted observational studies. Although these three innovations and robotic -assisted surgery have promising advantages, their clinical superiority has not (yet) been demonstrated. Therefore, these techniques should be considered under evaluation.

MIS continues to evolve through innovation, though appropriate frameworks for regulation and evaluation of innovation in MIS are needed. The usefulness of RCTs on new techniques in MIS could be improved. Eventually, we have seen that a RCT is not necessarily the most appropriate design to evaluate new techniques. Study designs should fit the study objective and thus focus on the primary outcome measure.

There is a lot of activity in clinical research for MIS. MIS has brought clinical improvement through innovation and research. There still is substantial room to optimize the implementation of evidence-based MIS. There are many opportunities from different perspectives to pursue improvement, several are described in the future perspectives.

Future perspectives

Extracting clinically driven research questions from evidence-based guidelines

Within the development and maintenance of guidelines, good opportunities are provided to identify knowledge gaps and formulate clinically driven questions for research. A useful distinction can be made for the type/direction of research questions: developmental, explanatory or pragmatic: developmental questions seek new methods or devices, explanatory questions seek whether a new method can work and pragmatic questions seek to inform clinical decisions. The advantages of this method for extracting research questions

are: focus on the needs of MIS practice and specification of important clinical outcomes to be addressed. Currently, robotic-assisted surgery and hysteroscopic sterilization are, with many others, interesting subjects for the development of evidence-based guidelines and subsequently extract research questions.

(Re)organizing research for MIS

Incorporating different experts into research teams, representing the necessary disciplines (including clinicians, methodologists, statisticians, patients, research nurses) enables a better match between clinically-driven research questions and study-design and conduct. Much research has been done by individuals for whom it is not their main sphere of activity; notably, clinicians are expected to conduct some research early in their careers. Methodological experts name this as one of the factors related to poor quality research (13,14). The importance of involving methodologists and statisticians also applies to accomplishment of systematic reviews. Cochrane is a global independent network, concerned with the methodology of systematic review. Their aim is to summarize the best health evidence from research (15). Though Cochrane groups principally conducted systematic reviews only on RCTs, recently Cochrane members became more interested in considering nonrandomized studies for systematic reviews. Debate about the validity of observational studies versus randomized trials for estimating effectiveness and safety of interventions has continued for decades (16,17). This thesis contains two systematic reviews where it showed that the included RCTs were not large enough to accurately measure outcomes of interest that are infrequent and/or in distant future. Observational studies can provide evidence additional to that available from randomised trials about long term outcomes, rare events, adverse effects and populations that are typical of real world practice (18). Methodologists are continuously exploring the validity of observational studies (19).

The above described developments apply to evidence-based medicine in general and should be passed through to MIS. Within MIS, additional emphasis should be placed on the need for (re)organizing surgical research. Formal assessment (RCTs) might even be less feasible in surgery than in other medical domains (20). Widespread use of prospective databases and registries for MIS have the potential to provide solutions.

Close involvement with innovating industry and technology

Various forces are involved with the introduction of surgical innovations into clinical practice. Commercial drives play a major role: it is in the interest of the manufacturer to increase the market share. Though clinicians primarily have pragmatic objectives: to improve health care

through innovation. The first drive is called a commercially driven approach, the second a clinically driven approach and a third drive is the technically driven approach, where indications are searched to use an existing technology (for example robotic surgery, laser surgery) (21). Enhancing the communication between these forces, potentially leads to better alignment of their efforts and would make the process of surgical innovation more efficient.

Frameworks for evidence-based MIS

The intricate relation between innovation and daily practice in MIS needs a formalised evaluative framework. The last decade, various attempts have been made to develop a framework for regulation and evaluation of surgical innovation: 'IDEAL', 'NOSCAR' (22), 'Leidraad nieuwe interventies in de klinische praktijk'. The IDEAL (Idea, Development, Exploration, Assessment, Long term study) recommendations called for modifications to systems for regulating surgical innovation and for a change to the standard against which these innovations should be measured before being approved for general use, from demonstration of safety, to evidence of efficacy (20,23,24). They proposed recommendations for the assessment of surgery based on a five-stage description of the surgical development process. In 2014, in the Netherlands, a framework for new techniques was developed (25). The Dutch framework describes the conditions for careful introduction and evaluation of new methods in clinical practice. Potential roles for medical specialists and other healthcare professionals in this process are suggested. The above perspectives fit into these frameworks. Paramount is proper communication and collaboration between stakeholders and the implementation of these or similar frameworks.

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Chapter 9

Summary
Nederlandse samenvatting

Summary

In the last decades, minimally invasive surgery (MIS) has led to great clinical improvements in many fields of surgery, achieving at least similar clinical effectiveness for a quicker recovery compared to the conventional surgical approaches. However, the invasive and innovative character also entails additional risks. Clinical research generates knowledge that allows assessment whether the aims of MIS are targeted. Gathering the best evidence from clinical research and subsequently integrating it into practice gives valuable input to evolve MIS.

In 2007, the Dutch Health Care Inspectorate published the report “*Risico’s minimaal invasieve chirurgie onderschat*”. They had conducted a study of the risks presented by MIS procedures and observed many unsubstantiated pragmatic differences between general surgery, gynecology and urology. Though these specialisms practice relatively similar basic techniques, there was little cooperation to assure and improve the quality of minimally invasive surgery. The Dutch Health Care Inspectorate encouraged the specialties practising laparoscopic surgery to develop a multidisciplinary guideline for MIS, with the purpose to reduce large variations in surgical care.

In this thesis we presented the multidisciplinary guideline for minimally invasive surgery. With the development of this guideline, multidisciplinary recommendations were formulated, based on ‘evidence’ and balanced with ‘experience’. An evidence-based (EB) guideline is an instrument supporting integration of the best evidence into clinical practice. Eventually this guideline as well identified knowledge gaps for future research. Thereafter, we identified the scientific evidence for four recent innovations within MIS and addressed the quest for evidence supporting surgical practice. Finally we appraised the clinical relevance, clearness and objectivity of recent randomized controlled trials in MIS.

In **Chapter 2**, the multidisciplinary evidence-based guideline is presented. The following main problem topics in laparoscopic surgical practice discussed were: entry-techniques, the pneumoperitoneum, port instruments (i.e. trocars), trocar site closure and electrosurgical techniques. Remarkably, the majority of recommendations in the guideline was based on the findings of descriptive studies and expert opinion. High quality evidence to formulate clear answers to important clinical questions was lacking. For example, questions about the safety of different trocar types remained unanswered.

In **Chapter 3**, we assessed the evidence of trocar designs for laparoscopy. Trocar designs are continuously being innovated to improve the safety of trocar use. We analysed the rates of trocar-related complications and postoperative pain for different trocar types. The examined trocar types were: radially expanding, cutting, conical blunt-tipped, single-bladed and pyramidal-bladed. Data were lacking on the incidence of major trocar-related complications, such as visceral or vascular injury, when comparing different trocar types with one another. However, caution is urged when interpreting these results because the

incidence of serious complications following the use of a trocar was extremely low. There was very low quality evidence for minor trocar-related complications suggesting that the use of radially expanding trocars compared to cutting trocars leads to reduced incidence of trocar site bleeding. These secondary outcomes are viewed to be of less clinical importance. Regarding postoperative pain, there was insufficient evidence to draw a conclusion. Here, we encountered the problem of a RCT design for assessing complications that occur infrequently. RCTs are rarely large enough to measure accurately infrequent outcomes. We advise to establish an international network for recording infrequent but clinically important complications following laparoscopic surgery.

In **Chapter 4** we systematically reviewed the evidence of a second innovation in MIS: laparoendoscopic single-site surgery (LESS) for hysterectomy. RCTs and observational studies comparing LESS versus conventional laparoscopy for hysterectomy were included for analysis.

We found very low quality evidence suggesting LESS – hysterectomy to be equally safe compared to conventional laparoscopic hysterectomy. This results should be interpreted with caution: very low quality evidence means the estimated effect is very uncertain and the number of participants ($n = 4,000$) does not provide sufficient power to measure differences for infrequent outcomes. We found the outcomes of effectiveness discussable, since in 3.5% of the LESS procedures an additional port was needed. No clinically relevant advantages were identified regarding postoperative pain, patient satisfaction (including cosmetic satisfaction) and operative time. We concluded that there are no current valid arguments to broadly implement LESS for hysterectomy.

A third innovation in MIS, hysteroscopic sterilization, was evaluated in **Chapter 5**. We performed a systematic review of the literature to assess the feasibility and effectiveness of hysteroscopic sterilization and to identify risk factors for failure of sterilization. No RCTs comparing hysteroscopic sterilization with laparoscopic sterilization (the conventional technique) were found. Very low quality evidence from observational studies (prospective as well retrospective) demonstrated that hysteroscopic sterilization is feasible. However, the effectiveness and risk factors for failure remained unclear. Studies on hysteroscopic sterilization are lacking sufficient power and complete long-term (> 10 years) follow-up on unintended pregnancies and complications. Chapter 3, 4, and 5 do all support that RCTs are not necessarily the appropriate design to study effectiveness and safety in MIS. Therefore, when choosing a study design it is important to focus on the primary outcome. Outcome measures to be expected shortly after the procedure and with high incidence rates could best be investigated in a RCT. Though, research questions on outcomes that are extremely rare need large well-conducted observational studies.

In **Chapter 6** we evaluated a fourth innovation in MIS, robotic-assisted surgery. In the Netherlands, robotic-assisted radical prostatectomy (RARP) is the most frequently performed robotic-assisted procedure. At the same time, the clinical superiority of RARP compared to open (RRP) and laparoscopic prostatectomy (LRP) has not been demonstrated. Given the high costs and small scientific evidence, the introduction of robotic surgery has been irresponsibly quick. Better scientific research of robotic surgery is needed before this technology can be broadly applied in clinical practice.

Clinical research generates knowledge that allows assessment whether the objectives in MIS are targeted. RCTs are considered the *gold standard* in clinical research. In **Chapter 7** we examined recent RCTs in MIS and appraised their value in generating useful knowledge for the implementation of MIS innovations into daily surgical practice. Concerning the clinical relevance of these RCTs we found primary outcomes for effectiveness were set in 15% and for safety in 12% of the included RCTs. Nearly 50% of the RCTs could not ensure sufficient distinctiveness, due to inadequate study-power to provide clear answers to their study objectives. At last, we observed substantial inconsistencies between conclusions drawn and the actual reported results.

To conclude,

MIS has led to great clinical improvements in many fields of surgery; however the invasive and innovative character also entails additional risks. Clinical research generates knowledge that allows assessment whether the aims of MIS are targeted. A guideline facilitates the integration of the best evidence into clinical practice. Thereby, with the development of a guideline, knowledge gaps can be identified for future research. This thesis provides insight in the evidence of MIS and its limitations. Therewith, we provide guidance to optimize research and evidence-based implementation of MIS towards better minimally invasive surgical care.

Nederlandse samenvatting

De introductie van de minimaal invasieve chirurgie (MIC) in het chirurgisch palet heeft de afgelopen decennia gezorgd voor een revolutie in het oplossen van chirurgische problemen. Zo heeft deze techniek ertoe geleid dat minimaal invasieve chirurgische ingrepen vergeleken met de bestaande conventionele ingrepen een kortere herstelperiode hebben bij tenminste gelijke effectiviteit. Het minimaal invasieve en innovatieve karakter brengt echter ook risico's met zich mee. Klinisch onderzoek kan bewijzen of met deze techniek de beoogde doelen daadwerkelijk behaald worden. Door het beste beschikbare wetenschappelijke bewijs uit klinisch onderzoek te verzamelen en vervolgens te integreren in de praktijk, wordt waardevolle input gegeven aan de evolutie van deze chirurgische techniek om haar zo op haar merites te kunnen beoordelen. Ook voor de introductie van nieuwe technieken in deze, zal nader klinisch onderzoek noodzakelijk zijn.

In 2007 bracht de Inspectie voor de Gezondheidszorg (IGZ) het rapport "*Risico's minimaal invasieve chirurgie onderschat*" uit. Hierin rapporteerde de inspectie haar onderzoek naar de risico's van minimaal invasieve chirurgie. Onder de verscheidene disciplines die MIC uitoefenen (chirurgie, gynaecologie en urologie), bleken er veel ongegronde verschillen in de uitoefening te bestaan. Hoewel de basistechnieken van MIC in grote mate overeenkomen, bestond er weinig *multidisciplinaire* samenwerking om de kwaliteit van de MIC te borgen en te verbeteren. De in het IGZ-rapport beschreven problematiek noodzaakte de beroepsverenigingen tot het opstellen van een *multidisciplinaire richtlijn*, met als doel het reduceren van de praktijkvariatie binnen de MIC.

In dit proefschrift presenteren we allereerst de *multidisciplinaire richtlijn Minimaal Invasieve Chirurgie*. Deze richtlijn omvat multidisciplinaire aanbevelingen die gebaseerd zijn op *evidence* (wetenschappelijk bewijs) gecombineerd met de kennis, ervaring en mening van deskundigen. De *evidence-based* richtlijn MIC biedt ondersteuning bij het integreren van het beste beschikbare wetenschappelijke bewijs in de klinische praktijk. Daarnaast geeft de *Richtlijn MIC* inzicht in de kennishiaten die er bestaan en die interessant zijn voor toekomstig onderzoek. In het tweede deel van dit proefschrift spitsen we ons toe op drie recente innovaties binnen de MIC, te weten:

1. trocartypes voor laparoscopische chirurgie
2. single port chirurgie
3. hysteroscopische sterilisatie.

Van deze innovaties presenteren we een systematisch overzicht (*systematic review*) van het beschikbare wetenschappelijke bewijs en identificeren we de behoefte aan wetenschappelijk onderzoek met een goede methodologische kwaliteit. Vervolgens wordt in het derde deel de introductie van de robotchirurgie in Nederland beschreven in het licht van de kennis over de klinische effectiviteit en de veiligheid van deze techniek. Tot slot worden in het vierde

deel van dit proefschrift de klinische relevantie, duidelijkheid en objectiviteit van recente gerandomiseerde gecontroleerde studies over MIC beoordeeld.

De *multidisciplinaire richtlijn Minimaal Invasieve Chirurgie* wordt in **hoofdstuk 2** van dit proefschrift beschreven. Belangrijke knelpunten uit de klinische praktijk van de MIC worden in de richtlijn behandeld. Deze knelpunten betreffen de volgende onderwerpen: entreetechnieken, het pneumo-peritoneum, poort-instrumenten (trocars), het sluiten van insteekopeningen en elektrochirurgische technieken. Opvallend is dat de meerderheid van de aanbevelingen in de richtlijn gebaseerd is op de bevindingen uit beschrijvende studies en de meningen van deskundigen. Er ontbrak hoogwaardig wetenschappelijk bewijs voor het formuleren van duidelijke antwoorden op belangrijke klinische vraagstellingen. Zodoende bleven onder andere vragen over de veiligheid van verschillende typen trocars onbeantwoord.

Er vindt continue innovatie plaats om veiligere trocars te ontwerpen. In **hoofdstuk 3** gaan we in op de vragen over de veiligheid van de verschillende typen trocars. We analyseerden de incidenties van trocar-gerelateerde complicaties en de mate van postoperatieve pijn in relatie tot het gebruik van verschillende trocartypes. De onderzochte trocartypes zijn: radiaal expanderend, snijdend, conisch met stompe tip, trocars met een mes (zgn. *single-bladed*) en trocars met een piramidaal mes. Er waren onvoldoende data over de incidenties van ernstig trocar-gerelateerde complicaties (zoals visceraal en vasculair letsel) bij het vergelijken van verschillende trocartypes. Deze bevindingen moeten echter met voorzichtigheid worden geïnterpreteerd, omdat de incidentie van ernstige trocar-gerelateerde complicaties überhaupt erg laag is (kleiner dan 1 op de 1000). Wetenschappelijk bewijs van ‘zeer lage kwaliteit’ suggereert dat het gebruik van radiaal expanderende trocars, vergeleken met snijdende trocars, tot minder poortbloedingen leidt. Vanwege de lage klinische relevantie worden poortbloedingen echter als een *secundaire uitkomstmaat* gezien. Er konden geen conclusies worden getrokken betreffende trocar-gerelateerde postoperatieve pijn, omdat ook daar onvoldoende wetenschappelijk bewijs over was. Dit hoofdstuk illustreert duidelijk het probleem van het gebruik van een gerandomiseerd gecontroleerd studie-ontwerp (RCT), wanneer bij het onderzoek de incidentie van complicaties zeer laag is, cq. zelden voorkomen. RCT’s zijn daarom zelden van voldoende omvang om incidentieverschillen in zeldzame uitkomsten accuraat te kunnen bepalen. Een oplossing voor een dergelijk probleem is om een internationaal onderzoeks netwerk of datacollectie op te zetten om niet-frequente doch klinisch relevante complicaties na MIC-ingrepen te registreren.

Een recente andere innovatie binnen de MIC is de *Laparoendoscopic single-site surgery* (LESS). In **hoofdstuk 4** presenteren we een systematische review van de evidence voor de LESS benadering bij de hysterectomie (LESS-hysterectomie). Voor de analyse hiervan werden RCT’s en observationele studies vergeleken met de conventionele laparoscopische hysterectomie.

Ook hier werd wetenschappelijk bewijs van zeer lage kwaliteit gevonden, wat suggereert dat de LESS-hysterectomie en de conventionele laparoscopische hysterectomie even veilig zijn. Er is echter voorzichtigheid geboden bij de interpretatie van deze bevindingen: dat het bewijs van lage kwaliteit is betekent dat het geschatte effect zeer onzeker is en tevens geeft het aantal deelnemers ($n = 4.000$) onvoldoende studie *power* om de verschillen voor zeldzame uitkomsten te kunnen meten. Ook de uitkomsten betreffende de effectiviteit zijn discutabel, in 3,5% van de LESS procedures was er een extra toegangspoort nodig voor het uitvoeren van de ingreep. Ten slotte konden wij geen voordelen vinden ten aanzien van postoperatieve pijn, patiënttevredenheid (inclusief tevredenheid over de cosmetische resultaat) en de operatieduur. We concludeerden dat er momenteel geen valide argumenten zijn om de LESS benadering bij de hysterectomie breed te implementeren in de dagelijkse chirurgische praktijk.

In **hoofdstuk 5** evalueren we een derde innovatie in de MIC, de hysteroscopische sterilisatie. Aan de hand van een systematische review van de literatuur werd de haalbaarheid (*feasibility*) en effectiviteit van deze sterilisatiemethode beoordeeld. Tevens werden zo de risicofactoren voor het falen van een hysteroscopische sterilisatie geïdentificeerd. Er werden geen RCT's gevonden waarin de hysteroscopische sterilisatie met de (conventionele) laparoscopische sterilisatie wordt vergeleken. Wetenschappelijk bewijs was van zeer lage kwaliteit (uit prospectieve en retrospectieve studies) en laat zien dat hysteroscopisch steriliseren haalbaar is. Echter, de effectiviteit en risicofactoren voor het falen van deze vorm van steriliseren blijven echter vanuit de literatuur onduidelijk. In de studies over hysteroscopische sterilisatie ontbreekt het tevens aan voldoende *power* en complete follow-up voor de lange termijn (> 10 jaar) ten aanzien van zwangerschappen na de sterilisatie en complicaties ten gevolge van de ingreep. De hoofdstukken 3, 4 en 5 illustreren dat een RCT niet per se het meest geschikte design is om effectiviteit en veiligheid van de MIC te bestuderen. Bij het selecteren van een studiedesign is het daarom van belang de karakteristieken van de primaire uitkomsten in ogenschouw te nemen. Zo kunnen uitkomstmaten die kort na de interventie worden verwacht en een hoge incidentie hebben het best worden onderzocht in een RCT. Terwijl onderzoeksvragen over zeldzame uitkomsten het beste kunnen worden beantwoord middels (grote) goed uitgevoerde observationele studies.

De robot-geassisteerde chirurgie, een vierde recente innovatie binnen de MIC, wordt in **hoofdstuk 6** geëvalueerd. In Nederland is de meest frequent uitgevoerde robot-geassisteerde operatie de robot-geassisteerde radicale prostatectomie (RARP). Tegelijkertijd is de klinische superioriteit van RARP vergeleken met de open radicale prostatectomie (RP) en de laparoscopische radicale prostatectomie (LRP) niet bewezen. Gezien de hoge kosten en de geringe wetenschappelijke evidentie verloopt de introductie van de robotchirurgie onverantwoord snel. Er is beter wetenschappelijk onderzoek nodig voordat robotchirurgie breed kan worden ingezet in de klinische praktijk.

Klinisch onderzoek genereert kennis waarmee beoordeeld kan worden of de door de MIC beoogde doelen daadwerkelijk behaald worden. Binnen klinisch onderzoek wordt de RCT beschouwd als de *goudstandaard* van onderzoek. In **hoofdstuk 7** onderzochten we recente RCT's binnen de MIC en beoordeelden de waarde van deze RCT's voor het genereren van bruikbare kennis voor de implementatie van innovaties in de dagelijkse chirurgische praktijk. De klinische relevantie van deze RCT's betreffende, zagen we dat in 15% van de RCT's de primaire uitkomst een maat voor effectiviteit was en in 12% een maat voor veiligheid, hoewel wij deze twee uitkomsten als de meest belangrijke beschouwden. Bijna 50% van de RCT's hadden onvoldoende studiepower en daarmee onvoldoende onderscheidend vermogen om een duidelijk antwoord te kunnen geven op de onderzoeksvraag. Tenslotte observeerden we substantiële inconsistenties tussen de beschreven conclusies en de gerapporteerde resultaten.

Concluderend,

De MIC heeft vele klinische voordelen voor de patiënt gebracht binnen verscheidene chirurgische vakgebieden. Het invasieve en innovatieve karakter van MIC brengt echter additionele risico's met zich mee. Met het uitvoeren van klinisch onderzoek kan uitgezocht worden of met de MIC techniek daadwerkelijk de beoogde doelen behaald worden. Een *evidence-based* richtlijn biedt ondersteuning bij het integreren van het best beschikbare wetenschappelijke bewijs in de klinische praktijk. Daarnaast geeft het ontwikkelen van een richtlijn inzicht in de kennishiaten die er bestaan en die voortgang geven aan toekomstig onderzoek. Dit proefschrift geeft inzicht in het wetenschappelijke bewijs waarmee de MIC techniek werd geïmplementeerd en geeft tevens de beperkingen weer van het klinisch onderzoek doen naar de MIC techniek. Hiermee bieden we mogelijkheden voor het optimaliseren van klinisch onderzoek en het *evidence-based* implementeren van MIC, met als hoger doel de beste minimaal invasieve chirurgische zorg naar de patiënt uit te kunnen rollen.

Chapter 10

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Curriculum vitae

Claire La Chapelle was born on September 16th 1982 in Soest. From the age of 7 years she grew up in Waddinxveen. In 2000 she graduated from secondary school (VWO) at the Coenecoop College. In the same year she started with the curriculum Medicine at Leiden University. She chose to spend her third year abroad at the faculty of Medicine of the University of Oviedo in Spain as part of the ERASMUS program. In 2007 she attained her medical degree and started to work as a physician at the department of Obstetrics and Gynecology at the Groene Hart Ziekenhuis, Gouda (Dr. H. van Huisseling). Subsequently in 2009 she worked at the department of Obstetrics and Gynecology at the Leiden University Medical Center. She was seconded to the Dutch Society of Obstetrics and Gynecology (NVOG), where she advised professional workgroups during the development of evidence-based guidelines from 2010 until 2012. In addition to this work, she completed the Master's program to Epidemiologist A, and made her first steps that led to her thesis under supervision of Professor dr. F.W. Jansen and Professor dr. B.W.M. Mol. In October 2012 she started her official residency program in Obstetrics and Gynecology at the Haaglanden Medisch Centrum, the Hague (Dr. M.J. Kagie). She is currently continuing her residency at the department of Obstetrics and Gynecology, LUMC, Leiden (Prof. dr. J.M.M van Lith).

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