Delirium after surgery: prehabilitation, quality of life and risk factors in older patients

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Voor pap en mam

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General introduction

Population demographics

The world's population continues to grow and is expected to reach 10 billion people in 2050 and 12 billion in 2100.[1] Recent projections indicate that the percentage of persons above 65 years old will increase from almost 10% in 2019, to over 20% in 2100 (Table 1.1).[1, 2] Moreover, the number of persons aged 80 years or over is expected to have tripled by 2050.[2] Currently, almost 1 in 5 persons in Europe is over 65 years of age. Expectation are this will increase to almost 1 in 3 persons.[1]

Table 1.1. Percentage of population aged 65 years or over for the world in 2019, 2030, 2050 and 2100.

Region	2019	2030	2050	2100
World	9.1	11.7	15.9	22.6
Sub-Saharan Africa	3.0	3.3	4.8	13.0
Northern Africa and Western Africa	5.7	7.6	12.7	22.4
Central and Southern Asia	6.0	8.0	13.1	25.7
Eastern and South-Eastern Asia	11.2	15.8	23.7	30.4
Latin America and the Caribbean	8.7	12.0	19.0	31.3
Australia/New Zealand	15.9	19.5	22.9	28.6
Europe and Northern America	18.0	22.1	26.1	29.3

Department of Economic and Social Affairs, Population Division. World Population Prospects 2019. United Nations. New York, 2019.

Due to the demographic shift to an older population, new challenges for healthcare systems arise. Previous studies report an increasing median age, an age-distribution shift to older ages, and increasing life expectancy.[3] Because of this shift, 'successful aging' has become a topic of increasing interest. However, the specifics of successful aging remain unclear. Some studies mainly report 'health status' and define successful aging as growing older without disease and disability, maintenance of cognitive and physical function and social engagement.[4] Other studies report 'quality of life' and consider subjective well-being as successful aging.[5]

Nearly one third of the diseases in the 'Global Burden of Disease' study (92 of 293) were identified as age-related, but accounted for more than half of the age-related disease burden.[3] The current demographic projections will likely result in an increase in age-related diseases such as cancer and cardiovascular diseases, and the burden of these diseases. Successful aging therefore faces challenges in the upcoming years.

With increasing age, physiological changes result in a decrease in functional reserve and resilience. This makes it harder for older patients to withstand the stress that is associated with disease, hospital admission and surgery. When the body falls short in overcoming this stress, negative outcomes are likely to develop. 'Frail' patients, those with diminished physical reserves and high baseline vulnerability, are particularly prone to adverse outcomes. One of the most frequent complications in older surgical patients is delirium, with incidence rates of up to 50% after non-cardiac surgery.[6-9]

History of Delirium

Hippocrates first described mental abnormalities in the 5th century B.C. and used 'Phrenitis', 'Lethargus' and about fourteen other words to describe delirium 'avant la lettre'.[10-13] According to traditional humorism, which formed the basis of the 'father of medicine's' theories, these conditions were caused by an imbalance in yellow or black bile, depending on symptoms.[14, 15] For example: manic or wild behaviour (i.e. symptoms of hyperactive delirium) is caused by a surplus of black bile, for which valerian root was then advised to calm the patient.[14]

The term 'delirare' (meaning 'to deviate from the furrow') was first introduced by Aulus Cornelius Celsus in his second book of 'De Medicina' in the 1st century A.D.[11, 16] It comes from the combination of the Latin words 'de-' (meaning 'away') and 'lira' (meaning 'ridge between furrows').[13, 17] Celsus distinguished delirare, caused by yellow bile, from melancholia, caused by black bile.[11, 15] Back then, it was linked to fever or head trauma, as described by Celsus in his encyclopaedia: "Cui calor et tremor est, saluti delirium est."[11, 16]

The term 'Delirium' dates from the end of the 16th century and was firstly connected to surgery in the same century by Ambroise Pare, a surgeon.[11] "He described delirium as a transient condition that commonly followed fever and pain due to wounds, gangrene and operations involving severe bleeding of the patient."[11]

Many different names have been used to describe this sickness throughout the centuries due to its heterogeneous presentation.[13] Procopius, a 6th century historian, first recognised and described the different subtypes of delirium.[11, 18] Its clinical meaning remained the same up until the 18th century, mainly because most historians made use of the same sources.[11]

Despite being introduced over 2500 years ago, fully understanding, recognising and preventing delirium remains a challenge.[11] Current views on delirium emerged in the end of the 19th century and shifted to delirium as a psychopathological syndrome.[11, 12] Old terms for delirium disappeared and focus of describing this disease turned towards clinical symptoms rather than aetiology, since the latter was since then considered organic.[11, 12]

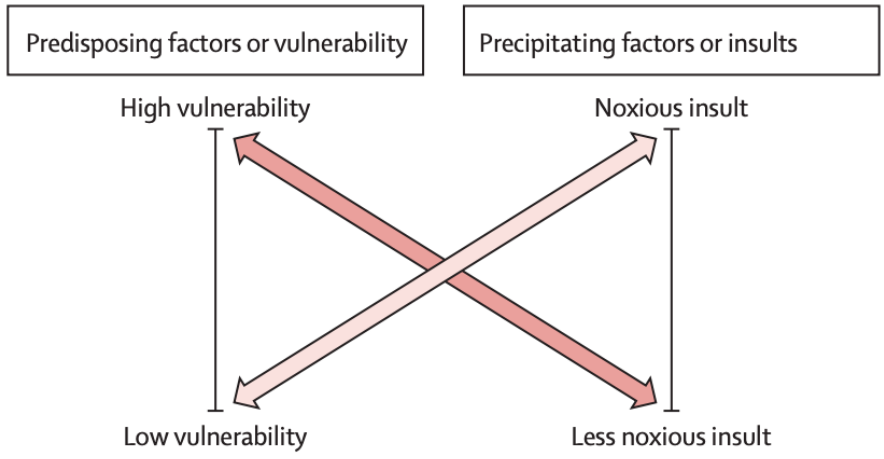
The clouding of consciousness was introduced as an important characteristic of the disease in 1817[11] and the intermittent course and reversibility of symptoms were described in the mid-1830's.[12] The connection with an organic cause was first described in 1904[11]. Zbigniew J. Lipowski, a Polish psychiatrist and historian, extensively investigated delirium in the second half of the 20th century and his theories are the basis of current insights on delirium.[11] Crucial to the development of these modern insights is the demographic shift to an increasing number of older patients.[11]

Standardised criteria for delirium were introduced in the DSM-III criteria (1980). Since then, criteria for delirium have changed in the DSM-III-R and DSM-IV.[19] The most recent DSM-5 criteria describe delirium as a condition with a disturbance in attention, awareness and cognition, which developed over a short period of time and tends to fluctuate in severity. Historical evidence must suggest that this condition is a direct physiological consequence of (an)other medical condition(s), and cannot be better explained by a pre-existing neurocognitive disorder.[20]

Present day delirium

Delirium is a direct physiologic consequence of a somatic condition, substance overuse or substance withdrawal.[20] It has a multifactorial aetiology and is an expression of decreased physiological reserves.[21] This physiological reserve, baseline vulnerability, or 'frailty' is set by a combination of predisposing risk factors. Delirium is an expression of this baseline vulnerability and is elicited by stressors (i.e. precipitating risk factors) in susceptible patients (Figure 1.1).[7] Delirium has three main subtypes: 1) hyperactive, which main symptoms are arousal, agitation and hallucinations, 2) hypoactive, which is more common in older patients and remains unrecognised in 60% of the cases due to lethargy and agnosia of the patient,[9, 18, 22] and 3) mixed, which alternates between the hyperactive and hypoactive form.

Figure 1.1. Theory of the aetiology of delirium



Risk factors for delirium have been investigated in a wide variety of populations. In non-cardiac surgical patients, the following predisposing (fixed) risk factors have been identified: older age, dementia, cognitive impairment, history of delirium, functional impairment, sleep- and sensory deprivation, severity of comorbidity and alcohol misuse. Psychoactive drugs, polypharmacy, use of physical restraints, a bladder catheter or lines, infection, dehydration, malnutrition, pain, bleeding and iatrogenic events have been identified as important precipitating (modifiable) risk factors.[7, 8, 23, 24]

The pathophysiology of delirium is still not fully understood. Consequently, several different theories currently exist to explain the onset of delirium. In line with the multifactorial aetiology of delirium, these theories likely intertwine; neuronal aging, changes in the neuronal network connectivity, glucocorticoid stress response, neuroinflammation, activation and deactivation of specific cytokines, and an imbalance of the neurotransmitters acetylcholine, dopamine and glutamate, together cause the complex syndrome of delirium.[21, 23, 25] Depending on the interaction between these pathways and which pathway is dominant, delirium is expressed as one of the different phenotypes of delirium.[25]

Delirium is associated with an increased rate of complications, cognitive decline, institutionalisation, morbidity and mortality, increased health care costs, prolonged length of hospital stay and a decreased quality of life.[9, 23, 26, 27] New developments in treatment protocols and surgical techniques such as minimally invasive surgery allow more older patients to undergo surgery. The incidence of delirium is likely to increase together with the increasing number of older patients, causing an increased burden on economies and health care systems due to its serious negative short- and long-term outcomes.

Primary prevention is the most effective method for treating delirium, because no treatment or intervention can effectively reduce its severity, duration or recurrence.[7, 22] Over one third of delirium cases is said to be preventable,[7] which emphasizes the importance of tackling precipitating risk factors and optimising circumstances for predisposing risk factors. Examples of widely-used delirium prevention programs are the Hospital Elder Life Program, the NICE guidelines and the American Geriatrics Society abstracted clinical practice guideline for postoperative delirium in older adults.[28-30] Despite current prevention programs, delirium remains a frequent complication in older surgical patients and therefore requires additional preventive methods.

Prehabilitation

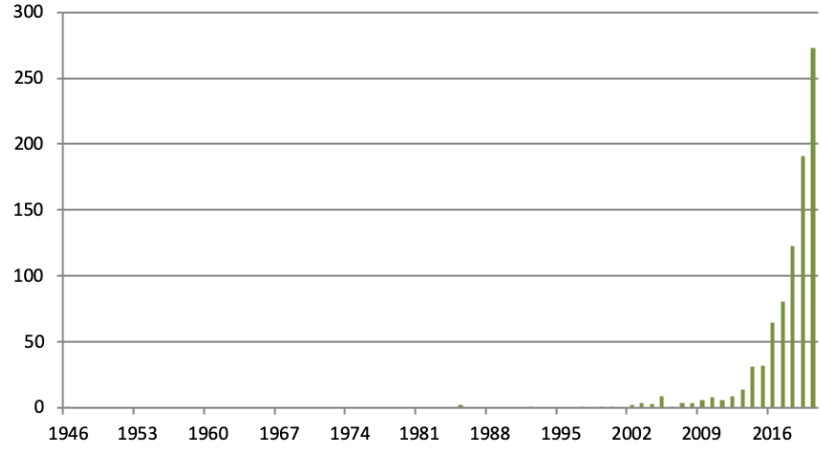
The term 'prehabilitation' was first introduced in an article from 1946.[31] Many men who enlisted for the U.S. army during the Second World War were rejected because of poor physical and mental fitness, attributes that were directly related to the socio-economic conditions they lived in. By setting-up training programs to improve physical and nutritional health (and by educating these men), roughly 10.000 men (85 percent of those who entered these prehabilitation programs) were eventually considered fit for battle.[32]

Although the program could be considered a success, prehabilitation is only sporadically referenced to in the second half of the 20th century. It again pops up in the mid-1980's, in journals related to sports medicine, as a way to "allow an athlete to withstand the inherent demands imposed by the particular sport."[33]

Since the turning of the century, interest in prehabilitation as a means of preventing adverse outcomes after medical treatment has been increasing exponentially (Figure 1.2).

Prehabilitation is the preoperative optimisation of a patient's overall fitness and resilience in order to make them able to withstand the stress that is associated with surgery and provide fast recovery (Figure 1.3).[34, 35] Surgery, especially in older patients, may lead to loss of muscle mass (sarcopenia), reduced functional capacity, hypoxemia, psychological distress, fatigue and sleep disorders.[34, 36, 37] These effects, in combination with a baseline vulnerability due to comorbidities, make older patients specifically prone to postoperative adverse events.

Figure 1.2. Number of publications related to 'prehabilitation'

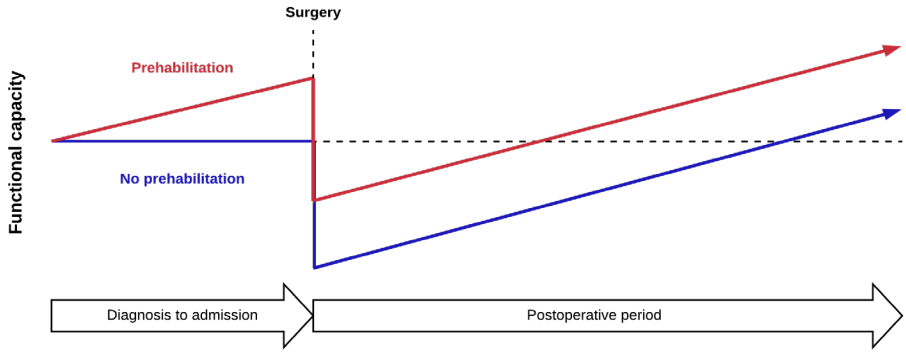


In order to prevent these postoperative adverse events, new treatment protocols, surgical site infection protocols and Enhanced Recovery After Surgery protocols have been developed over the years. These interventions mainly focus on the postoperative period; a period in which patients experience fatigue, weakness and anorexia due to surgery.[37] The period prior to admission, especially in elective surgery, may therefore be a more ideal time to anticipate to the upcoming stressor by optimising patients' physiological reserve. Therefore, prehabilitation programs which focus on optimisation of physical health, psychological health, nutritional status or smoking cessation in the pre-admission phase have been developed.[34]

Physical exercise may consist of cardiopulmonary fitness training, resistance training, musculoskeletal strengthening, breathing exercises and inspiratory muscle training.[36, 38] Each of these exercises can be performed at either low or high intensity and either supervised in a clinic or unsupervised at home.[38] Patients receive nutritional support by providing them with dietary advise, supplementary protein and caloric intake and supplementation of vitamins. Cognitive intervention, information provision, relaxation techniques, anxiety reduction and coping strategies are the main components of psychological prehabilitation.[39, 40]

Previously published systematic reviews and meta-analyses concluded that physical prehabilitation can effectively reduce the number of postoperative complications, but does not shorten the length of hospital stay. However, the included studies in these meta-analyses were very heterogeneous in type of surgical procedure, physical optimisation method and additional components of the programs.[38, 41, 42] A large meta-analysis provided clear evidence of the importance of a nutritional component by demonstrating a significant reduction in length of hospital stay when providing patients with nutritional counselling and protein supplementation alone.[43] Outcome studies on psychological interventions lacked clear reporting and were too heterogeneous to draw hard conclusions, but suggest that these interventions may result in improvements in traditional surgical outcomes, depressive symptoms and quality of life.[39, 44]

Figure 1.3 Theory behind prehabilitation



Carli F, Silver JK, Feldman LS, McKee A, Gilman S, Gillis C, et al. Surgical Prehabilitation in Patients with Cancer: State-of-the-Science and Recommendations for Future Research from a Panel of Subject Matter Experts. Phys Med Rehabil Clin N Am. 2017;28(1):49-64.

Above-mentioned studies are mainly unimodal programs, focusing on a single component. In recent years, physicians have reached general consensus on superiority of multimodal- over unimodal prehabilitation. By optimising multiple domains at once, a complementary effect may be achieved, resulting in faster return to baseline fitness and greater improvement in endurance and strength.[42, 45, 46] Additionally, they may help to reduce the incidence of delirium and other common postoperative complications. Struggling with low adherence rates and non-compliance however, these studies have yet to show conclusive evidence that these interventions also lead to a reduction in conventional surgical outcomes (length of hospital stay, readmissions or short-term mortality) and a better quality of life.[42, 47, 48]

Aims and outline of this thesis

This thesis aimed to establish the best possible approach to prevent postoperative delirium (part I), to design a new delirium prevention method and determine its effectiveness (part II), to assess the impact of surgery and subsequent delirium on quality of life of patients and its strain on caregivers (part III), and to develop new theories on how to optimally improve these methods of prevention (part IV).

Part I. Insights on current methods to prevent delirium

Evidence supporting effective treatment of delirium is still lacking. In the late nineties, it had already been established that primary prevention is the most effective method of lowering the incidence of delirium. Since then, many studies have investigated a wide number of methods to lower its incidence, both pharmacological and non-pharmacological. In Chapter 2, we provide an overview of these methods and pool results to examine which method is the most effective.

Part II. A new multicomponent delirium prevention program

In Chapter 3, we build on previous results and propose a new method to reduce the incidence of delirium by means of primary prevention. Previous interventions have focused mainly on the intraoperative, perioperative and postoperative period. Multicomponent interventions such as HELP have provided specific interventions to prevent delirium during admission. The pre-admission period however, from diagnosis to admission, may be an ideal period to implement new ways of prevention. We hypothesised that prehabilitation may be able to decrease the incidence of delirium and therefore designed a new multicomponent, multidisciplinary prehabilitation pathway. The aim of this pathway was to reduce the incidence of delirium in colorectal cancer patients and abdominal aortic aneurysm patients, two conditions associated with age and with high rates of delirium as a complication. Results on the effectiveness of this program in preventing delirium, preventing other postoperative complications and institutionalisation, and in reducing the length of hospital stay and short-term mortality rates are presented in Chapter 4. Long-term mortality rates and the effects of this program on functional outcomes up to one year are demonstrated in Chapter 5. The effectiveness and safety of using intravenous ferric carboxymaltose in our prehabilitation program to correct preoperative anaemia and to prevent postoperative delirium were assessed in Chapter 6.

Part III. Impact of surgery and subsequent delirium on patients' quality of life and informal caregivers' strain

When conventional outcomes as the ones mentioned in the previous paragraph started decreasing due to advances in anaesthesiological and surgical techniques, new outcomes have been gaining interest. Decreased quality of life has been associated with delirium in the past. In Chapter 7, we investigate the impact of surgery and subsequent postoperative delirium on quality of life, cognitive impairment and depression in our prehabilitated cohort. In contrast to previous studies which have often used 'health status' (e.g. a patient's ability to climb a stairs) as an outcome, a patient-reported subjective quality of life (e.g. a patient's opinion on whether or not he or she can climb a stairs) was used in this study. Surgery may not only impact the elderly patient, but may also burden family or friends who provide informal care for these patients. In our society, current healthcare systems

rely on these informal caregivers to provide additional care. Chapter 8 provides an overview of the perceived burden of these caregivers and of factors that may influence the perceived burden.

Part IV. Future delirium prevention programs

Risk factors that increase the risk for postoperative delirium, and with that patients who are most likely to develop a delirium in the future, were identified in Chapter 9. Future prehabilitation programs may focus on patients with these characteristics specifically. In the last part of this thesis, Chapter 10 and 11, we elaborate on the results of the previous studies by discussing these in the light of our current and future society and provide directions for future research on preventing delirium.

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CHAPTER 2

Prevention of postoperative delirium in elderly patients planned for elective surgery: Systematic review and meta-analysis.

Janssen TL, Alberts AR, Hooft L, Mattace-Raso F, Mosk CA, van der Laan L
Clin Interv Aging. 2019;14:1095-117.

Abstract

Introduction

Vulnerable or 'frail' patients are susceptible to the development of delirium when exposed to triggers such as surgical procedures. Once delirium occurs, interventions have little effect on severity or duration, emphasizing the importance of primary prevention. This review provides an overview of interventions to prevent postoperative delirium in elderly patients undergoing elective surgery.

Methods

A literature search was conducted in March 2018. RCT's and before-and-after studies on interventions with potential effects on postoperative delirium in elderly surgical patients were included. Acute admission, planned ICU admission and cardiac patients were excluded. Full-texts were reviewed and quality was assessed by two independent reviewers. Primary outcome was the incidence of delirium. Secondary outcomes were severity and duration of delirium. Pooled risk ratios (RR) were calculated for incidence of delirium where similar intervention techniques were used.

Results

Thirty-one RCT's and four before-and-after studies were included for analysis. In nineteen studies intervention decreased incidences of postoperative delirium. Severity was reduced in three out of nine studies which reported severity of delirium. Duration was reduced in three out of six studies. Pooled analysis showed a significant reduction in delirium incidence for dexmedetomidine treatment and bispectral index (BIS)-guided anaesthesia. Based on sensitivity analyses by leaving out studies with high risk of bias, multicomponent interventions and antipsychotics can also significantly reduce the incidence of delirium.

Conclusion

Multicomponent interventions, the use of antipsychotics, BIS-guidance and dexmedetomidine treatment can successfully reduce the incidence of postoperative delirium in elderly patients undergoing elective, non-cardiac surgery. However, present studies are heterogeneous and high-quality studies are scarce. Future studies should add these preventive methods to already existing multimodal and multidisciplinary interventions to tackle as many precipitating factors as possible, starting in the pre-admission period.

Introduction

Delirium is a common postoperative complication in the elderly, often caused by multiple factors. It is defined as an acute neuropsychiatric disorder characterized by fluctuating disturbances in attention, awareness, and cognition and can be divided into three different subtypes; hyperactive, hypoactive or mixed.[1-3] The hypoactive form, present in over 40% of delirium cases, is estimated to be recognized in 20-50% of cases and is often under-diagnosed.[4-6]

Frail patients are vulnerable due to predisposing risk factors. These risk factors, together with provoking triggers (i.e. precipitating risk factors), make patients susceptible for developing delirium.[7, 8] Previous studies on delirium pointed out old age, cognitive or functional impairment, number of comorbidities, history of falls, and sensory deprivation as important predisposing factors.[3, 8-13] Important precipitating factors are polypharmacy, malnutrition, pain, the use of urinary catheters, ICU admission, length of hospital stay (LOS), blood loss, preoperative anaemia, and type of surgery.[8, 14-18]

Postoperative delirium occurs in 17-61% of major surgical procedures.[12, 19, 20] It may be associated with cognitive decline, prolonged LOS, decreased functional independence, and increased risk of dementia, caregiver burden, healthcare costs, morbidity and mortality.[3, 21-28] Therefore, delirium is a possibly disastrous condition and is both a huge burden on a patient's health and on the healthcare system in general.

When delirium occurs, treatments or interventions have little effect on severity, duration or likelihood of recurrence.[29-32] However, before its onset, delirium is assumed to be preventable in 30 to 40% of cases,[33] which emphasizes the importance of attention for primary prevention.[29, 30] This can be achieved by interventions that tackle important risk factors, such as providing adequate pain management, hearing or visual aid, sleep enhancement, exercise training or dietary advice.[9, 34]

Extensive research on reducing the incidence of delirium has been conducted using both pharmacological and non-pharmacological preventive measures in the acute setting and in patients undergoing cardiac surgery.[35-38] The importance of these studies is exemplified by a recent study which showed an independent association between postoperative delirium and major adverse cardiac events.[39]

Several preoperative, perioperative and postoperative unimodal and multimodal approaches have been tested, trying to alter various components most likely to provoke a delirium.[40] These efforts were heterogeneous and often involved relatively small populations. Irrefutable evidence of a successful preventive method has yet to be found.[41-43] This review provides an overview of interventions in elderly hospitalized patients in need of elective surgery without planned intensive care unit admission.

The aim of this study was to collate, evaluate and pool results of the effectiveness of primary preventive methods on the incidence of delirium in elderly patients (≥65 years), planned for elective surgery.

Methods

Data Sources and Searches

PubMed (Medline OvidSP), Embase, Cochrane Centre and Web of Science were systematically searched for relevant studies in March 2018 by a medical information specialist. Our detailed search strategy was added as supplementary material to the original manuscript, which can be found online. Uniqueness of the individual articles was ensured through deduplication. Reference lists were manually screened for additional eligible articles.

Study selection

Randomized controlled trials (RCT's) and (un)controlled before-and-after studies, with focus on prevention of postoperative delirium in older surgical patients were selected.

Selected studies were screened for the relevant inclusion criteria: patients undergoing elective surgery, study populations with a mean age ≥65, and studies with prevention of delirium as a goal. Delirium incidence, duration and/or severity were used as primary and secondary outcomes. Only articles with their full text available in English were selected. No date limit was set.

Studies concerning postoperative planned ICU admission, cardiac surgery, head or neck surgery, acute surgical intervention, unimodal nurses' training, and pilot studies were excluded.

Data extraction

Two reviewers (TLJ and ARA) independently evaluated titles and abstracts on eligibility for this review. When no decision could be made on bases of title and abstract, full texts were screened. Disagreement was resolved by consensus.

The following study characteristics were independently extracted by two reviewers: number of patients, surgical procedure, incidence, duration and severity of delirium, delirium assessor and type of assessment used, type, timing and effects of intervention, study design, power analysis, inclusion of cognitively impaired patients, inclusion of preoperative delirium, study population, baseline patient characteristics (age, gender, burden of comorbidity), primary and secondary outcomes, blinding of patients and caregivers, and duration of follow-up.

Quality assessment

Risk of bias was scored using the Cochrane Risk of Bias tool[44] and graphically presented using Review Manager 5.3.[45] Studies were scored as to have an unclear, low or high risk of bias.

Two reviewers (TLJ and ARA) assessed the quality independently. Any disagreements were resolved by consensus, or in case of persistent disagreement via querying a third author.

Statistical analysis

Review Manager was used to present the data from all studies graphically, to perform a meta-analysis when possible and to perform and standardise the risk of bias assessment.[45]

A meta–analysis was performed when two or more articles presented results for the same comparison and similar intervention techniques to prevent delirium (clinically homogeneous groups). Pooled risk ratio (RR) with a 95% confidence interval (CI) was calculated for the incidence of delirium (dichotomous outcome) using random–effects methods. The Mantel-Haenszel test was used. Studies in the pooled analyses were tested for heterogeneity using inconsistency I^2, where a cut-off of 60% was considered methodically relevant.
The p-values that are presented in this review are the ones calculated for between-group differences as presented by the authors in the original studies. A p-value of < 0.05 (two-tailed) was considered statistically significant.

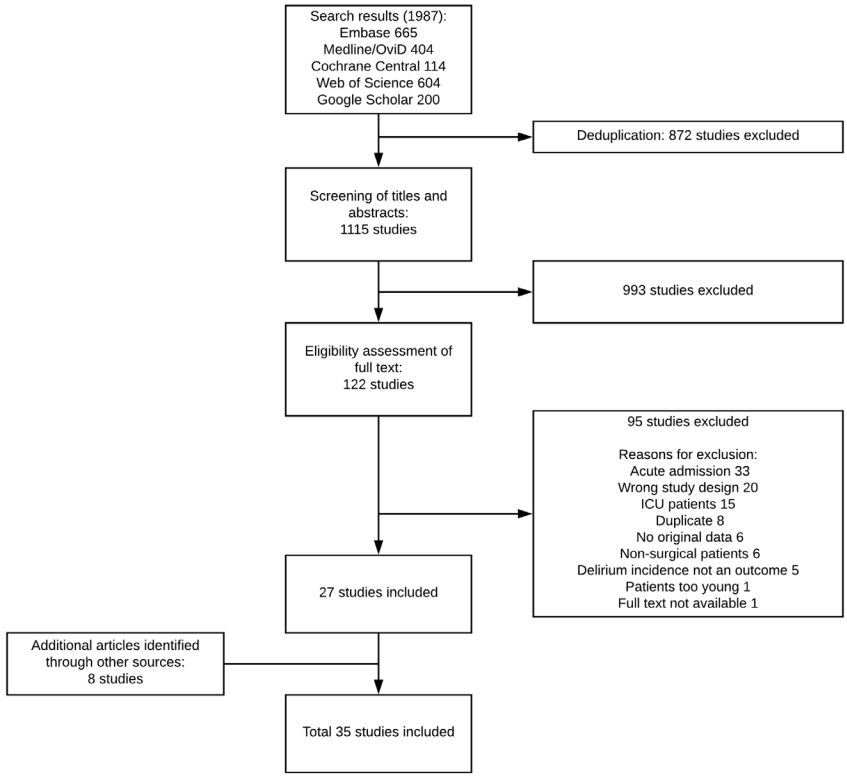
This manuscript was reported using the checklist provided in the PRISMA Statement.[46]

Results

Search

All databases provided a combined total of 1987 articles, of which 872 studies were removed following deduplication. All titles and abstracts of the remaining articles were screened for relevance, after which 122 studies remained. After screening of full texts, another 95 studies were excluded. Main reasons for exclusion were: acute care patients, ICU patients, study design, non-surgical patients or delirium was not an outcome. Eight additional articles were handpicked by screening references of systematic reviews on delirium prevention which were found in the initial search.[47-54] In total, 35 studies were included in this systematic review. A complete overview of search results and study selection are presented in Figure 2.1, which is a flowchart designed in accordance with the PRISMA statement.[46]

Figure 2.1. PRISMA flowchart



Quality assessment – Risk of bias

An overview of the 'risk of bias' assessment is presented in Figure 2.2. Figure 2.2 presents a graphic summary of the assessment. Considerations on the risk of bias were added to the original manuscript and can be found online as a supplementary table.

Eight studies were considered as to have an overall low risk of bias.[55-62] Six of these studies were graded low risk for all types of bias.[55-60] Only the risk of selective reporting was unclear in the study by Kalisvaart et al., since they did not register their research in advance.[61] The same applies for the study by Beaussier et al., with an additional unclear risk of detection bias.[62] All studies with focus on reducing postoperative pain were among these eight low-risk studies.

All before-and-after studies were rated as high overall risk of bias due to the design of their research, as no blinding of patients, caregivers and outcome assessors, no randomization, and no allocation concealment were possible.[63-66]

The study by McCaffrey et al. was graded high risk of selection bias.[67] They used folded slips of paper, which could be manipulated easily. Two studies were rated as high risk for allocation concealment because the intervention and control groups were treated at different locations.[53, 68] Fifteen studies were graded high risk of performance bias,[47, 52, 54, 63-66, 69-76] thirteen of which because of lack of blinding of caregiver, patient or both due to the nature of their intervention. A total of fifteen studies lacked reporting of one of two types of blinding bias in their study, therefore these studies were rated as having an unclear risk.[47, 48, 50-52, 54, 62, 67, 68, 73, 77-81]

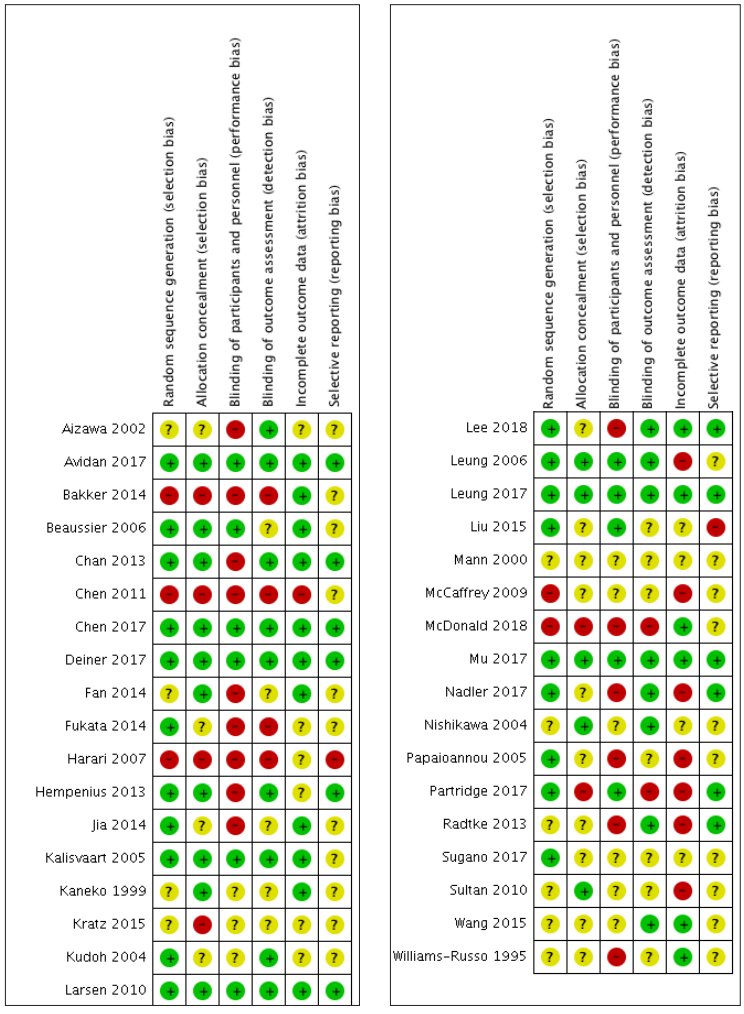
Fourteen of thirty-five studies registered their trials and mentioned trial registration number in their paper.[53, 55-60, 63, 70, 72, 74-76, 78] Remaining studies did not register their trial, did not publish their protocol in advance and reported their results as reported in their methods section.

Patient and study characteristics

A complete overview of patient- and study characteristics was published with the original manuscript and can be found online. Due to its size, this table was not incorporated in the printing of this thesis .

Sample sizes varied from 22 patients to 1155 patients, with nearly 10.000 patients in total. Seven studies included fewer than 100 patients.[50-52, 62, 67, 69, 77] Two studies also included general medicine patients or patients undergoing acute surgery.[61, 63] Because of a separation in results on delirium incidence in general medicine or surgical patients and acute or elective patients, these were still included in this review. The study by Avidan et al. also included patients undergoing cardiac surgery and did not make a separate analysis, however due to the large number of patients (466 patients; 70%) undergoing non-cardiac surgery, this study was also included in this review. We did not include the latter in the pooled analysis, since cardiac surgery is pointed out to be a precipitating factor for postoperative delirium and inclusion in the analysis would give a distorted result.

Figure 2.2. Summary of 'Risk of bias': Review authors' judgements on risk of bias for each study.



Study designs

Thirty-one out of thirty-five included studies were randomized controlled trials, thirteen of which compared an intervention to usual care,[53, 56, 67-73, 75, 76, 79, 80] ten studies compared an intervention to a placebo,[49, 55, 57-62, 74, 77, 78] and seven studies compared different interventions.[47, 48, 50-52, 54, 81] Six of these RCT's were multicenter studies.[55, 57, 60, 71, 72, 79] Four studies were before-and-after studies, all of which compared a multimodal perioperative care plan to usual care in a single center.[63-66]

Comorbidity scoring

APACHE-II,[51] Charlson Comorbidity Index (CCI)[49, 54-56, 59, 64] and ASA score[47, 51, 52, 57, 58, 60, 62, 63, 70, 74, 76, 81] were used to score comorbidities in nineteen studies. Sixteen studies did not use a comorbidity scoring system.[48, 50, 53, 65-69, 71-73, 75, 77-80] Seven of these did show type or number of comorbidities but did not use an evidence-based scoring system.[50, 53, 65, 66, 72, 77, 79] Four studies showed significant differences in baseline comorbidities.[53, 65, 66, 78] Partridge et al. did not provide statistical testing for differences in baseline comorbidities between groups, however cerebrovascular disease and dementia, both important risk factors for the development of delirium, were present more than twice as often in the control group compared with the intervention group.[53]

Cognitive impairment and preoperative delirium

Sixteen studies excluded cognitively impaired patients,[48, 50-52, 57, 58, 61, 62, 64, 68, 70, 73, 74, 76, 80, 81] while only seven studies specifically excluded patients with a preoperative diagnosis of delirium.[47, 55, 60, 61, 63, 68, 80] Because of the elective nature of the procedures, it is assumed that unless indicated otherwise, patients of all remaining studies did not have a delirium prior to surgery.

Period of delirium assessment

Assessment of delirium was done during the full extent of the admission in twelve studies,[50, 53, 56, 61-66, 68, 70, 79] while assessment of postoperative delirium was done for three days or fewer in nine studies.[47, 49, 51, 52, 55, 59, 67, 75, 80]

Delirium assessment method

Eighteen studies used the Confusion Assessment Method (CAM), a method for detecting delirium introduced by Inouye et al. in 1990,[1] as a method of diagnosing delirium.[47-49, 55-63, 66, 68, 70, 74, 75, 78] Nadler et al. and Larsen et al.[56, 75] combined CAM with the DRS-R-98[82] which also includes delirium severity in the test. Two more studies, by Nishikawa et al. and Jia et al., used the DRS and DRS-R-98 to assess delirium respectively.[51, 73] Sultan et al. used the Abbreviated Mental Test 10 questions (AMT-10) to score incidence of postoperative delirium.[80] The NEECHAM Confusion Scale, a screening tool for delirium validated against the DSM-IV criteria,[83, 84] was used in two studies.[67, 71]

Six studies used the fourth version of the DSM to screen for delirium,[61, 69, 72, 76, 79, 81] two studies used the DSM-III criteria,[50, 52] and two studies used criteria from its successor, the DSM-III-R.[58, 77]
Three studies[53, 54, 65] did not specify the method of delirium assessment, however Williams-Russo et al.[54] used the same criteria for positive diagnosis as described in the DSM-III-R, making it a reliable diagnosis. The studies by Partridge et al. and Harari et al. did not use a validated tool for diagnosing delirium.[52, 64] To decrease the risk of bias, both were excluded from the pooled analysis.

Delirium prevention interventions and individual outcomes

Interventions to prevent postoperative delirium can be divided into several different categories. Firstly, in pharmacological (N=20)[47, 48, 50-52, 54, 55, 57-62, 69, 71, 74, 77-80] and non-pharmacological interventions (N=15),[49, 53, 56, 63-68, 70, 72, 73, 75, 76, 81] secondly in single-component (N=26)[47-52, 54, 55, 57-62, 67, 69-71, 74-81] and multicomponent (N=9)[53, 56, 63-66, 68, 72, 73] interventions, and thirdly according to timing of intervention. For this review, the third option was chosen. Interventions were divided into preoperative (N=2),[53, 80] intraoperative (N=13),[4, 8, 49, 51, 52, 54, 55, 57, 62, 70, 74, 76, 78, 81] postoperative (N=7)[56, 60, 64, 67, 69, 71, 77] or perioperative (N=13),[47, 50, 58, 59, 61, 63, 65, 66, 68, 72, 73, 75, 79] of which the latter is the combination of the first three. Perioperative care is defined as all care concerning initial diagnosis, from preoperative outpatient clinic visit, to postoperative follow-up visits.

Preoperative

A study by Sultan et al. used a single-component approach by implementing a preoperative pharmacological intervention.[80] Patients received placebo, melatonin 5 mg, midazolam 7.5 mg, or clonidine 100 mcg during the evening before surgery and another dose ninety minutes preoperatively. The only intervention that was able to significantly reduce the incidence of delirium was administering 5 mg of melatonin (9.4% vs. 32.7%; p=0.003).

In a second study using a preoperative approach, Partridge et al. compared preoperative comprehensive geriatric assessment (CGA) of patients by a multidisciplinary team to usual care.[53] The CGA is a tool, performed prior to admission, to identify risk factors of frailty in order to prevent postoperative adverse outcomes and optimise patients' overall health by using a multimodal approach.[85, 86] Partridge et al. assessed for problems with cognition, tested for anaemia, and evaluated cardiac condition.[52] The CGA also included referral to additional caregivers, medication review and advice to patients and ward teams for the postoperative period.[53] Incidence of delirium in this CGA group was significantly less in the intervention group compared with the control group (10.6% vs 24.2%, p=0.018).

Intraoperative

Reducing postoperative pain, one of the precipitating risk factors for delirium, was the main focus of two studies that implemented a single-component pharmacological prevention.[55, 62] Beaussier et al. compared the administration of 300 mcg intrathecal morphine immediately prior to surgery combined with postoperative patient-controlled intravenous morphine (PCA) to PCA alone.[62] They were not able to show a significant difference between groups (p-value not specified). Avidan et al. divided patients into three groups: the first group received an injection of 0.5 mg of ketamine after induction of anaesthesia and before surgical incision, the second group received 1.0 mg of ketamine at the same time and the third group received a saline injection.[55] None of the intervention significantly reduced the incidence, severity or duration of delirium and none of the interventions demonstrated any differences between groups (p=0.80).

Three studies compared infusion of various amounts of dexmedetomidine with an equal amount of saline infusion.[57, 74, 78] Dexmedetomidine is a highly selective α2-adrenoceptor agonist, which has sedative, amnestic, sympatholytic, and analgesic effects.[87] Deiner et al. infused 0.5 μg/kg/h of dexmedetomidine during surgery and for up to two hours in the recovery room.[57] By doing so, they were unable to significantly lower the incidence of delirium when compared with the saline group (12.2% vs 11.4%; p=0.94), or to significantly decrease the severity of delirium. Lee et al. compared three groups; dexmedetomidine 1 μg/kg bolus followed by 0.2-0.7 μg/kg/h infusion during surgery, dexmedetomidine 1 μg/kg bolus 15 minutes before the end of surgery, and an equivalent saline bolus 15 minutes before the end of surgery.[74] Delirium incidence in the first group was significantly lower compared to the other two groups (9.5% vs 18.4% and 24.8%; p=0.017) and duration of delirium was shorter in both intervention groups (p=0.04). Liu et al. compared infusion of dexmedetomidine to saline infusion in cognitively impaired and in 'normal' patients. In both groups, infusion of 0.2–0.4 μg/kg/h dexmedetomidine during surgery significantly decreased the incidence of postoperative delirium (p<0.05).[78]

Another intraoperative approach was tested in two studies, in which they attempted to control the depth of anaesthesia through the use of BIS-guidance.[70, 76] Both studies successfully reduced the incidence of delirium. The study by Radtke et al. terminated early due to limited funding, however they were still able to show a significant reduction (16.5% vs 21.4%, p=0.036).[76] Chan et al. reduced the incidence of delirium from 24.1% to 15.6% by adding BIS-guidance to their anaesthesia (p=0.01).[70]

Two studies tried to reduce postoperative delirium by changing ventilation.[49, 81] Leung et al. mechanically ventilated patients in the intervention group using N2O and O2, while the control group only received O2. They were not able to reduce the incidence of delirium (41.9% vs 43.8%, p=0.78).[49] In contrast, Wang et al. were able to significantly reduce the incidence of delirium through the implementation of mechanical ventilation with varying tidal volumes instead of mechanically ventilating patients conventionally (16.5% vs 28.9%, p=0.036).[81]

Changing method of anaesthesia was hypothesized to decrease the incidence of delirium in four studies.[48, 51, 52, 54] Both groups in the study by Kudoh et al., received intravenous propofol.[48] In the first group, bupivacaine spinal anaesthesia was added and patients breathed spontaneously with a laryngeal mask airway. The second group received additional anaesthesia through intravenous fentanyl and was mechanically ventilated via endotracheal tube. Delirium incidence was reduced in favor of the first group (5.3% vs 16.0%, p=0.03). Nishikawa et al. compared sevoflurane with propofol for induction and maintenance of general anaesthesia.[51] Even though none of the patients in the sevoflurane group developed delirium, compared to 16% in the propofol group, there was no statistically significant difference due to the relatively small sample size of the groups. Severity of delirium was significantly lower in the sevoflurane group compared to the propofol group (p=0.002). Papaioannou et al. and Williams-Russo et al. investigated the effect of general versus regional anaesthesia on postoperative delirium.[52, 54] Both studies were not able to show a significant result in favor of either of the two types of anaesthesia (21.4% vs 15.8% and 11.9% vs 9.4% respectively).

Postoperative

Kaneko et al. administered 2.5 mg intravenous haloperidol daily for three consecutive days to the intervention group, through which they showed a significant decrease in postoperative delirium incidence (10.5% vs 32.5%, p<0.05), severity and duration (no numbers given) compared to a group receiving a placebo.[77] Fukata et al. administered twice this dose, 5 mg intravenous haloperidol, daily for five consecutive days to their intervention group and compared this to usual care.[71] More people in the intervention group developed postoperative delirium, although this result was deemed not to be significant (42.4% vs 33.3%, p=0.309). No significant effect was found on severity (no p-value) and duration of delirium (p=0.356). Both studies involved small populations.

Mu et al. successfully decreased delirium incidence by reducing postoperative pain (6.2% vs 11%, p=0.031).[60] They provided patients in the intervention group with 40 mg of parecoxib (a COX-inhibitor) dissolved in saline every twelve hours for three days and compared this to the control group who received regular saline.

In another postoperative intervention study, Aizawa et al. successfully lowered delirium incidence from 35% to 5% (p=0.023) by influencing the sleep-wake cycle and providing patients with injections of diazepam (1dd 0.1mg/kg), flunitrazepam (0.04 mg/kg), and pethidine (1 mg/kg) for three nights following surgery.[69] In both groups, only 20 patients were included.

Music therapy for four times a day for an hour significantly increased NEECHAM scores and reduced postoperative confusion rates in a study by McCaffrey et al. (p=0.014).[67]

The final two postoperative studies, both performed by Chen et al., modified the Hospital Elder Life Program (HELP)[88] by adding a postoperative component to improve the perioperative care program.[56, 64] They added three standardised protocols in patient care on immediate postoperative return to the surgical ward. They focused on orientation, oral and nutritional assistance and early mobilization, integrating this into their perioperative patient management. In their first study in 2011, they managed to reduce the incidence of delirium to zero in their intervention group.[64] In both studies, Chen et al. were able to significantly reduce the incidence of delirium (0% vs 16.7%; p<0.001 and 6.6% vs 15.1%; p=0.008).

Perioperative

Kalisvaart et al. provided the intervention group with 0.5 mg oral haloperidol three times a day, starting preoperatively and continuing until the third postoperative day.[61] By doing so, they were not able to reduce the incidence of delirium (p=0.435). However, severity and duration decreased significantly (p<0.001 for both outcomes). In contrast, Larsen et al. were able to significantly reduce the incidence of delirium by administering 5 mg of oral olanzapine right before and after surgery to their intervention group (14.3% vs 40.2%, p<0.001).[58] In their intervention group however, delirium was more severe (p=0.02) and lasted longer (p=0.02).

Leung et al. and Mann et al. were unable to significantly lower the incidence of delirium by reducing postoperative pain. Leung et al. compared the use of 3dd 300 mg gabapentin (an anti-epileptic) the day before surgery until three days after surgery with a placebo (24.0% vs 20.8%, p=0.30).[59] Mann et al. compared combined epidural analgesia and general anaesthesia followed by postoperative patient-controlled epidural analgesia, with general anaesthesia followed by patient-controlled analgesia with intravenous morphine (24% vs. 26%, no p-value was given).[50]

Presence of obstructive sleep apnea is independently associated with the occurrence of delirium.[89] Therefore, Nadler et al. studied the effects of obstructive sleep apnea on delirium and compared perioperative continuous positive airway pressure (CPAP) with routine care.[75] They did not show a decrease in postoperative delirium (21% vs 16%, p=0.53) or in its severity.

In a study by Fan et al. restrictive blood transfusion (Hb < 8 g/dL) was compared with liberal blood transfusion (Hb <10 g/dL).[47] They found no significant difference between the two protocols (21.3% vs 23.9%, p=0.727).

The focus of the study by Sugano et al. was trying to influence the sleep-wake cycle by providing the intervention group with 2.5 mg yokukansan (a traditional Japanese herbal medicine), three times a day from seven days prior to surgery to four days post-surgery.[79] They were also unable to show a significant decrease in delirium (6.5% vs 9.7%, p=0.471).

Six studies investigated a non-pharmacological approach to decrease incidence of postoperative delirium by implementing a multimodal intervention program, or perioperative care pathway.[63, 65, 66, 68, 72, 73] They tried to alter multiple components during both preoperative and postoperative care to prevent postoperative delirium. The number of components influenced varied in each study. These are discussed in detail below.

Perioperative multicomponent interventions

The CareWell in Hospital program (CWH) was designed by Bakker et al.[63] and developed in line with HELP,[88] and consists of two main concepts which were applied during admission: improving patient-centered care by proactive and intensive support and increasing awareness and competency of personnel providing geriatric care. A first screening by a nurse, a second screening by a geriatric nurse, medication review, a CareWell plan, follow-up during admission, collateral history assessment, a CGA, a multidisciplinary meeting, stimulation of cognitive and physical activities by trained volunteers, and education of nurses and physicians were the components of this program. In this before-after study, there was no significant difference in delirium incidence in the group receiving the CWH program and the control group (12.4% vs 13.3%; p=0.983). Results may however have been influenced by the significantly bigger number of ASA III and IV patients in the intervention group.

The team of McDonald et al. developed The Perioperative Optimisation of Senior Health (POSH) program.[66] They involved patients and their families and focused specifically on cognition, medication, comorbidities, mobility, functional status, nutrition, hydration, pain, and advanced care

planning. Patients were assessed before admission in a Geriatric Evaluation and Treatment Clinic for multidisciplinary preoperative evaluation and care coordination. Due to this increased attention and focus, instead of reducing the incidence of delirium, they found a much larger percentage of patients with delirium in the intervention group (28.4% vs 5.6%; p<0.001).

Hempenius et al. designed the Liaison Intervention in Frail Elderly (LIFE), consisting of preoperative assessment and planning of preventive measures by a geriatric team (CGA) and monitoring during hospital stay using several checklists, focusing on orientation, medication, comorbidities, sensory impairment, nutrition, mobility, anxiety, pain, sleep, defecation, incontinence, infection, depression, and cognitive, social and instrumental functioning.[72] LIFE was not able to significantly reduce incidence (9.4% vs 14.3%, OR 0.29-1.35) or severity of delirium (p=0.23).

Kratz et al. focused their intervention, implemented by a geriatric liaison nurse during admission, on 6 components: early mobilization, improvement of sensory stimulation, fluid and nutritional intake and sleep, cognitive activation, and validation therapy.[68] Through the optimisation of these components, Kratz et al. successfully reduced the incidence of delirium (4.9% vs 20.8%, p=0.01) compared to usual care.

The perioperative care pathway developed by Jia et al. significantly reduced the incidence of delirium by implementing a fast-track protocol during admission, focusing on preoperative preparation, anaesthesia, postoperative pain control, and postoperative management of diet, urinary catheter and mobilization (3.4% vs 12.9%; p=0.008).[73]

Harari et al. developed the 'POPS 'intervention, which can be divided into three categories:
Preoperative assessment and education of patients before admission, education of staff on postoperative interventions and follow-up home-based therapy. Patients were preoperatively assessed by a geriatrician, geriatric nurse, occupational therapist, physiotherapist, and social worker. Patients were educated in optimising postoperative recovery by giving them preoperative home exercises, good nutrition, relaxation techniques, and advice on pain management. Staff were educated in early detection and treatment of medical complications, early mobilization, pain management, bowel-bladder function, nutrition, and discharge planning. After discharge, follow-up home-based therapy was offered to those in need.[65] The implementation of this intervention successfully reduced the incidence of delirium (5.6% vs 18.5%; p=0.036).

Overall outcomes and pooled analyses

Delirium incidence

A total of nineteen out of the thirty-five included studies showed a significantly lower incidence of delirium in the intervention group compared to the control group.[48, 53, 56, 58, 60, 64-70, 73, 74, 76-78, 80, 81] In the study by Sultan et al.,[80] the postoperative delirium incidence was only significantly reduced in the melatonin group compared to the usual care group.

Delirium severity

Nine studies investigated the effect of their interventions on the severity of postoperative delirium.[51, 55, 57, 58, 61, 71, 72, 75, 77] Three studies showed a significant reduction in the severity of delirium following implementation of their intervention,[51, 61, 77] although Kaneko et al.[77] did not support this claim with numbers. In the study by Larsen et al.[58] on the other hand, a significantly higher severity of delirium was observed in the intervention group. The five remaining studies did not show any differences between the two groups.[55, 57, 71, 72, 75]

Delirium duration

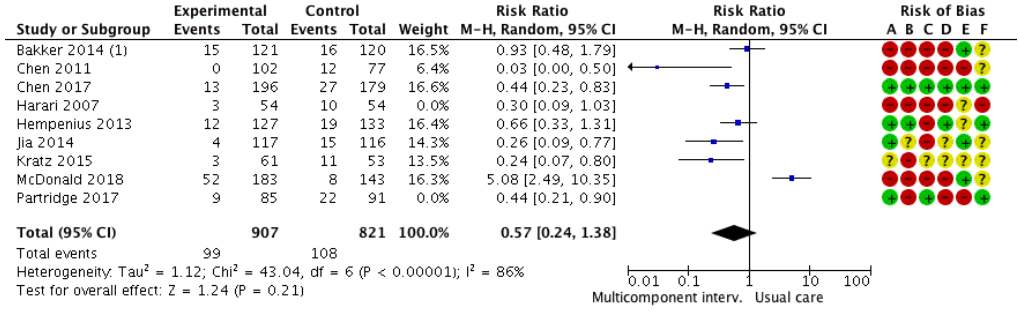
Six studies examined the effect of their interventions on the duration of postoperative delirium.[55, 58, 61, 71, 74, 77] A significantly reduced length of delirium was observed in the intervention group in three of these studies, although Kaneko et al. again did not support this claim with numbers.[61, 74, 77] Olanzapine administration significantly increased the observed length of delirium.[58] The remaining two studies did not show significant differences between either of the groups.[55, 71]

A complete overview of numbers on delirium incidence, severity and duration is shown in Table 2.1, which was not printed in this thesis due to its size and can be found online.

Pooled analyses of preventive methods to reduce the incidence of delirium

Pooled analyses were performed on 7 categories of interventions: multicomponent interventions (N=7),[56, 63, 64, 66, 68, 72, 73] antipsychotics (N=4),[58, 61, 71, 77] postoperative pain management (N=3),[59, 60, 62] sleep-wake cycle (N=3),[69, 79, 80] dexmedetomidine (N=3),[57, 74, 78] general vs. regional anaesthesia (N=2),[52, 54] and BIS-guidance (N=2).[70, 76] The study by Mann et al. was excluded from the pooled analysis, since they did not compare their intervention to usual care.[50] Pooled analyses, in-study comparisons and the results of these comparisons are shown in Figures 2.3-2.9.

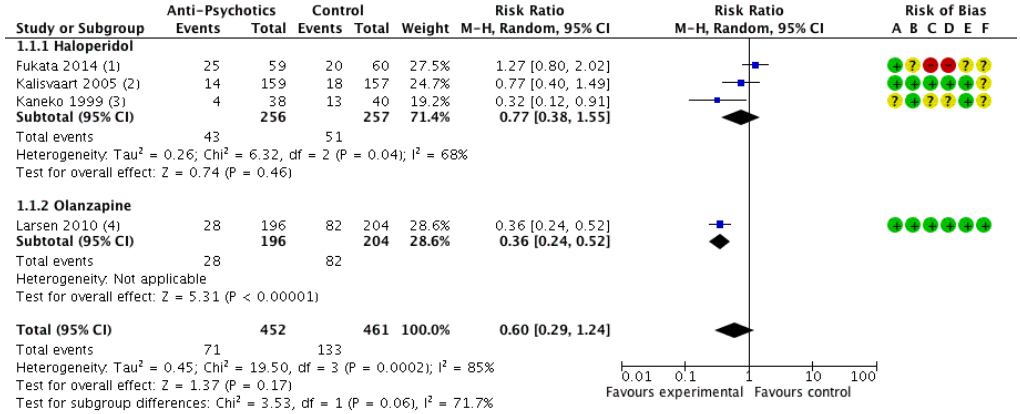
Figure 2.3: Forest plot 1. Multicomponent interventions.



Footnotes
(1) All studies: Multicomponent intervention vs usual care

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel...
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

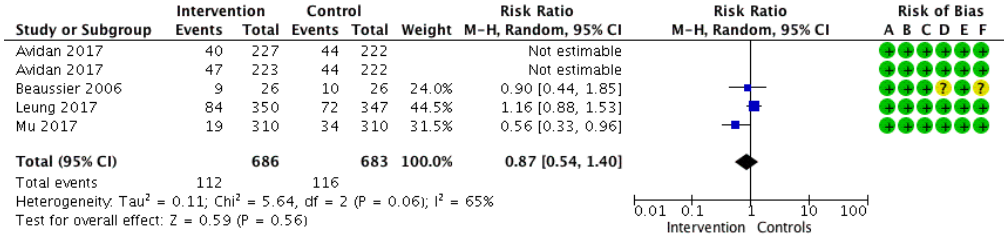
Figure 2.4: Forest plot 2. Antipsychotics.



Footnotes
(1) 5 mg haloperidol vs usual care (5 days)
(2) 3dd 0.5 mg haloperidol vs placebo (4 days).
(3) 2.5 mg haloperidol vs placebo (3 days)
(4) 5 mg olanzapine vs placebo (2x)

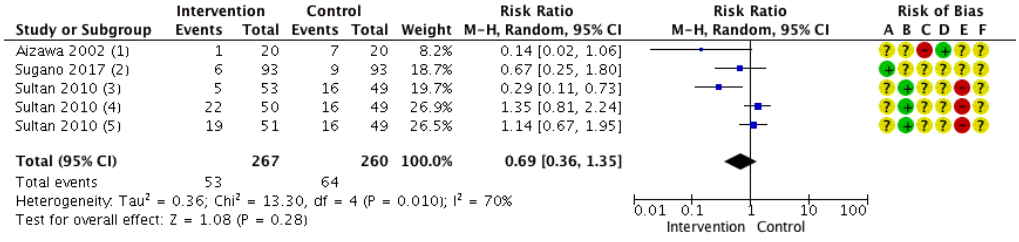
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance...
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

Figure 2.5: Forest plot 3. Postoperative pain management.



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)

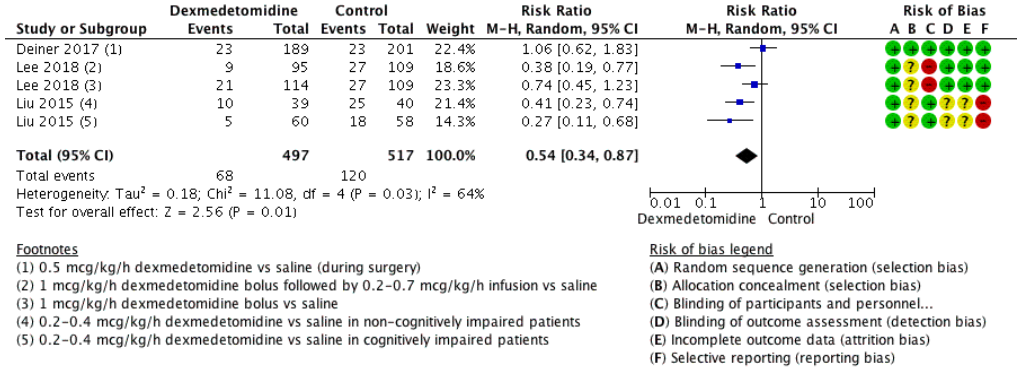
Figure 2.6: Forest plot 4. Sleep-wake cycle.



Footnotes
(1) 1dd 0.1mg/kg diazepam, 0.04mg/kg flunitrazepam, 1mg/kg pethidine vs usual care
(2) 3dd 2.5 mg yokukansan vs usual care (12 days)
(3) 5 mg melatonin vs placebo (2x)
(4) 7.5 mg midazolam vs placebo (2x)
(5) 100 mcg clonidine vs placebo (2x)

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel...
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)

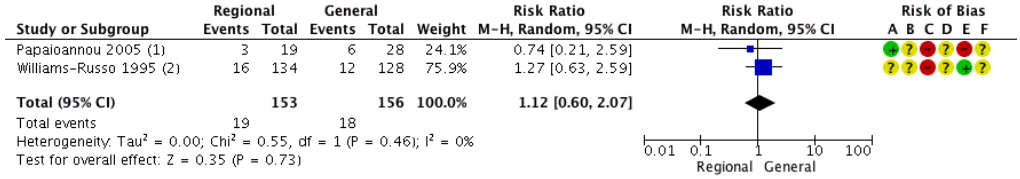
Figure 2.7: Forest plot 5. Dexmedetomidine treatment.



Footnotes
(1) 0.5 mcg/kg/h dexmedetomidine vs saline (during surgery)
(2) 1 mcg/kg/h dexmedetomidine bolus followed by 0.2-0.7 mcg/kg/h infusion vs saline
(3) 1 mcg/kg/h dexmedetomidine bolus vs saline
(4) 0.2-0.4 mcg/kg/h dexmedetomidine vs saline in non-cognitively impaired patients
(5) 0.2-0.4 mcg/kg/h dexmedetomidine vs saline in cognitively impaired patients

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel...
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)

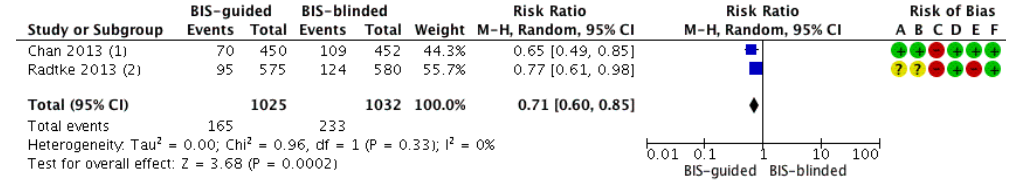
Figure 2.8: Forest plot 6. Type of anaesthesia.



Footnotes
(1) Regional anaesthesia vs general anaesthesia
(2) Regional anaesthesia vs general anaesthesia

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel...
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)

Figure 2.9: Forest plot 7. BIS-guidance.



Footnotes
(1) BIS-guided anaesthesia vs BIS-blinded anaesthesia
(2) BIS-guided anaesthesia vs BIS-blinded anaesthesia

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel...
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)

Analyses showed significant results in favour of dexmedetomidine treatment (RR 0.58 [0.45 – 0.76]; 95% CI) and BIS-guided anaesthesia (RR 0.71 [0.60 – 0.85]; 95% CI). Pooled analyses did not show a significant reduction in the incidence of delirium for multicomponent interventions (RR 0.57 [0.24 – 1.38]; 95% confidence interval), the use of antipsychotics (RR 0.60 [0.29 – 1.24]; 95% confidence interval), postoperative pain management (RR 0.87 [0.54 – 1.40]; 95% confidence interval), sleep-wake cycle improvement (RR 0.69 [0.36 – 1.35]; 95% confidence interval) or in type of anaesthesia (RR 1.12 [0.60 – 2.07]; 95% confidence interval).

Results of these pooled analyses should be interpreted with caution, due to the heterogeneity of the included studies. Sensitivity analyses were therefore performed.

Sensitivity analyses

Sensitivity analyses were performed to check for changes in significance. Different outcomes in favor of the interventions were then observed for multicomponent interventions and the use of antipsychotics. For multicomponent interventions, when leaving out the before-and-after studies with a high risk of bias (Bakker, Chen 2011, McDonald and Kratz), a significant decrease in the incidence of delirium was observed for these interventions when compared to usual care (RR 0.47 [0.31 – 0.74]; 95% confidence interval). For antipsychotics, when leaving out the study with a relatively high risk of bias (Fukata), results shift to a significant decrease of delirium incidence in favor of the use of anti-psychotics (RR 0.45 [0.26 - 0.77]; 95% confidence interval). For all other pooled analyses, sensitivity analyses did not alter outcomes."

Discussion

Prevention of delirium in the older surgical patient is essential as postoperative delirium is an important healthcare issue. This study aimed to describe and pool results of interventions with a focus on preventing postoperative delirium in elderly surgical patients, electively planned for non-cardiac surgery without planned postoperative ICU admission.

Summary and interpretation of results

The pooled analysis on all studies implementing multicomponent interventions shows that these are unable to successfully lower the incidence of delirium. However, McDonald et al. started the POSH program in order to improve perioperative care and prevent adverse postsurgical outcomes.[66] Contrary to their desired effect, their program led to a significant increase in delirium. They concluded that their results were an expected consequence of improved screening. None of the other studies showed a similar effect of improved screening for delirium, therefore diagnostics and screening before intervention may have been inadequate prior to implementation of this program. Their program did extremely well in increasing awareness, and with that, in diagnosing delirium. However, as a preventive method, it was proven unsuccessful. McDonald et al. also reported the lowest percentage of delirium incidence in their control group, which also supports this theory. The authors believe that this deviant result causes a distorted outcome. Without this study, multicomponent intervention would have given a significant reduction of delirium (RR 0.44 [0.25 – 0.78]; 95% CI, not shown in a figure). Risk of bias was relatively high due to the number of before-and-after studies that implemented multicomponent interventions. On the basis of sensitivity analysis, by removing these high risk studies from the pooled analysis, significant results in favor of multicomponent interventions compared to usual care were observed.

The pooled results do not support the use of antipsychotics in the prevention of delirium, however based on the sensitivity analysis antipsychotics can successfully prevent delirium. Larsen et al.,[58] the only study investigating the effect of olanzapine, showed a significant reduction in the incidence of delirium. However, they reported negative effects on duration and severity of delirium. In contrast, the administration of haloperidol did not significantly reduce the incidence of delirium but did have advantageous effects on both severity and duration. These contradictory effects might best be explained by the bigger anticholinergic effects of olanzapine, caused by its high affinity to the muscarinic cholinergic receptor. In contrast, haloperidol has a negligible affinity for this receptor. All studies investigating the effects of antipsychotics were heterogeneous in terms of type of antipsychotic, route of administration and dosage. Overall, the risk of bias in these studies was deemed to be relatively low.

Studies on the prevention of postoperative pain are well set-up, all of them scoring low in our quality assessment. Unfortunately, they were not able to show a significant effect on the incidence of delirium. All of these studies used different analgesic medication, of which only the use of parecoxib seemed to lower the incidence of delirium.[60] A similar effect of parecoxib use was seen in patients with femoral head fractures in a study by Li et al. in 2013.[90]

The three studies investigating interventions to improve sleep-wake cycle lacked clear reporting of their methods, which made the risk of bias unclear. Pooled analysis did not show a significant decrease of delirium. Sultan et al. investigated three types of medication, of which only melatonin seemed to have a favorable effect on delirium incidence.[80] This is in line with an earlier published report by Al-Aama et al.,[91] which supports the use of melatonin in non-surgical patients. In elderly patients with hip fractures however, melatonin was not able to reduce the incidence of delirium.[92]

The pooled analysis on studies using dexmedetomidine to prevent delirium showed a significant reduction in favor of this intervention. The study by Deiner et al. was rated as to have a low risk of bias, but was the only study that did not show a statistically significant result.[57] A 2015 review concluded that dexmedetomidine was an effective method to prevent delirium when compared to propofol or benzodiazepines in surgical patients.[93] Two studies in cardiac patients showed promising results of the drug's effects on postoperative delirium,[94, 95] however opposing results were published by yet another study.[96] Yet another study was able to show a significant reduction of delirium incidence in non-cardiac ICU patients.[97] Dexmedetomidine is a drug with potential beneficial effects; however, more extensive research using a larger sample is needed to identify patients who might benefit most from this treatment.

Two of the studies included in this review compared regional with general anaesthesia, but neither study was able to show a significant outcome in favor of any of the two. These results are in accordance with a study on vascular surgical patients by Ellard et al.[98] and two systematic reviews, performed by Mason et al.[99] in 2013 and O'Donnel et al.[100] in 2018.

Controlling the depth of anaesthesia using BIS-guided anaesthesia seems to have an advantage over BIS-blinded anaesthesia. Both studies and pooled analysis showed a significant reduction in postoperative delirium incidence after BIS-guided anaesthesia. They both included approximately a thousand patients, which strengthens their results, although only the study by Chan et al.[70] was rated as having a low risk of bias.

The seven other studies identified for this review could not be used for meta-analysis, since the interventions used in these studies have only been done in a single trial.[47-51, 67, 75] The sample sizes are low and the quality of the evidence is often poor. The studies by Kudoh et al. and McCaffrey et al. showed a significant result in favor of their interventions, although the quality of the latter was poor and scored a high risk of bias.[48, 67]

An extensive review by Siddiqi et al. in 2016 showed similar results in favor of multicomponent interventions and BIS-guided anaesthesia.[101] They did not include studies examining the effects of dexmedetomidine on delirium incidence. Another review by Zhang et al. in 2013 did examine the effects of dexmedetomidine and concluded that dexmedetomidine sedation, the use of antipsychotics and implementation of multicomponent interventions could potentially prevent postoperative delirium.[102] These findings are in line with this systematic review and meta-analysis. Contrary to this study however, pilot studies and studies involving non-surgical patients, cardiac patients and patients acutely admitted to the hospital were all included in both systematic reviews.

Recommendations

The authors believe that due to the multifactorial etiology of delirium, multicomponent, perioperative and multidisciplinary interventions should be implemented to prevent patients from developing delirium. In the United Kingdom, implementation of multimodal approaches is already recommended in the existing NICE guidelines on how to recognize, prevent and treat delirium.[103] Most of these interventions are performed during admission, focusing on improvement of orientation, mobilization, nutritional status, senses and sleep, on decreased medication use, pain and anxiety, and on stimulation of activities. By adding new components to these efforts and combining them with prophylactic antipsychotics, fast-track protocols, BIS-guided anaesthesia and the use of dexmedetomidine, even more successful multicomponent perioperative care pathways may possibly be created to ensure an additional decrease of postoperative delirium and other complications.

Using these methods, both the preoperative and postoperative period are covered. This leaves open a possibility for interventions during the pre-admission period to further optimise patients prior to surgery, especially since incidence rates of up to 25% are still observed in the intervention groups. These interventions should be customized and tailor-made to tackle specific (precipitating) factors of frailty for each patient individually. Especially in elective surgery, integration of preoperative optimisation into the perioperative management of patients may be able to further reduce delirium in elderly surgical patients, a theory also suggested by a recent study on elective cardiac surgery.[104] In addition, this 'prehabilitation' might be able to reduce other adverse postoperative outcomes.[105]

Since previous studies are heterogeneous and lack high quality results, special attention should go to improving these factors. Severity and duration of delirium and quality of life should be considered as additional outcome factors, because although implementation of an intervention might not necessarily reduce the incidence of this still often encountered and significant condition, it might reduce the burden on the patient as well as the burden on the healthcare system.

Limitations

Studies on the prevention of delirium have been conducted for almost twenty years, with an increase in attention in recent years. These studies show little uniformity, which leads to the conclusion that a successful preventive method has yet to be found. Studies on the prevention are heterogeneous, have varying (often small) sample sizes or have an unclear or high risk of bias. On exploring heterogeneity using χ^2 and inconsistency (I^2), as shown in Figures 2.3-2.9, considerable heterogeneity was found for pooled analyses on multicomponent interventions, antipsychotics, postoperative pain management, sleep-wake cycle and dexmedetomidine. As a consequence of the heterogeneity in the investigated studies included in this review, a great variance in incidence rates of delirium was found (5.6% to 62.5%).

Twenty-eight studies did not specifically exclude patients with preoperative delirium, which is a significant weakness of these studies. Since prevention of delirium, and not treatment, was the focus of these studies, these patients should have been excluded from analyses in the included studies. However, as mentioned earlier, because of the elective nature of the procedures, it is likely that patients in these studies did not have a delirium prior to surgery.

Another limitation in several of our reviewed studies was that the number of days over which delirium was assessed was less than one week in half of the studies, some of which only assessed for delirium in the first two days after surgery. The average time to onset of postoperative delirium is 2.1 +/- 0.9 days,[106] which is why a two-day follow-up is considered insufficient to assess for postoperative delirium fairly.

Conclusions

Multicomponent interventions, the use of antipsychotics, BIS-guided anaesthesia and administration of dexmedetomidine during anaesthesia can successfully reduce the incidence of delirium. By adding these interventions to already existing multicomponent and multidisciplinary approaches, the incidence of delirium might be reduced even further. Additionally, other adverse postoperative outcomes could potentially be prevented by combining these approaches. In order to obtain possible additional benefits, interventions to tackle precipitating risk factors should be supplemented to interventions that are proven successful. In elective surgical patients, a potential for reducing the incidence of postoperative delirium lies in the pre-admission phase. Multimodal prehabilitation pathways should therefore be considered for investigation.

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CHAPTER 3

A multicomponent prehabilitation pathway to reduce the incidence of delirium in elderly patients in need of major abdominal surgery: study protocol for a before-and-after study.

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Abstract

Introduction

Due to the increase in older patients who undergo major abdominal surgery there is a subsequent increase in postoperative complications, healthcare costs and mortality rates. Delirium is a frequent and severe complication in the 'frail' elderly patient. Different preoperative approaches have been suggested to decrease the incidence of delirium by improving patients' baseline health. Studies implementing these approaches are often heterogeneous, have a small sample and do not provide high-quality evience or successful strategies. The aim of this study is to prevent postoperative delirium and other complications by implementing a unique multicomponent and multidisciplinary prehabilitation program.

Methods

This is a single-center uncontrolled before-and-after study. Patients aged ≥70 years in need of surgery for colorectal cancer or an abdominal aortic aneurysm are considered eligible. Baseline characteristics (such as factors of frailty, physical condition and nutritional state) are collected prospectively. During five weeks prior to surgery, patients will follow a prehabilitation program to optimise overall health, which includes home-based exercises, dietary advice and intravenous iron infusion in case of anaemia. In case of frailty, a geriatrician will perform a comprehensive geriatric assessment and provide additional preoperative interventions when deemed necessary. The primary outcome is incidence of delirium. Secondary outcomes are length of hospital stay, complication rate, institutionalisation, 30-day, 6- and 12-month mortality, mental health and quality of life. Results will be compared to a retrospective control group, meeting the same inclusion and exclusion criteria, operated on between January 2013 and October 2015. Inclusion of the prehabilitation cohort started in November 2015; data collection is ongoing.

Discussion

This is the first study to investigate the effect of prehabilitation on postoperative delirium. The aim is to provide evidence, based on a large sample size, for a standardised multicomponent strategy to improve patients' preoperative physical and nutritional status in order to prevent postoperative delirium and other complications. A multimodal intervention was implemented, combining physical, nutritional, mental and hematinic optimisation. This research involves a large cohort, including patients most at risk for postoperative adverse outcomes.

Introduction

The world's population is aging, which subsequently leads to an increase in age-related diseases and conditions. Two major age-related diseases are colorectal carcinoma (CRC) and abdominal aortic aneurysm (AAA), which account for a large percentage of complications and prolonged length of hospital stay.[1] CRC is the third most frequent oncologic disease in the world in both men and women,[2-4] with over 50% of patients being older than 70. People between 70 and 74 years old are most frequently diagnosed with CRC.[3] The cornerstone for treating CRC remains laparoscopic or open surgery.[5] Prevalence of AAA increases with age and ranges from 1.3% in women to between 4% and 7.7% in men over 65 years, with men having a six-fold greater risk.[6] AAA can be surgically treated via either open or endovascular aortic repair.

Up to 30% of patients undergoing major abdominal surgery and up to 35% of patients in CRC surgery develop postoperative complications.[7, 8] Old age increases the risk of complications and unplanned readmissions, which in turn lead to a longer hospital stays, higher mortality rates and a decrease in quality of life.[8, 9]

Physical resilience decreases with age, while frailty increases.[10] Frailty is defined as a state of increased vulnerability which compromises the ability to cope with the physical stress associated with surgery and other acute stressors.[11] Incidence rates of frailty have been described of up to 43% in the population of CRC patients.[12] These frail patients have a four times greater risk of major postoperative complications,[13] with longer hospital stay and higher 30-day readmission rates after both colorectal surgery and abdominal aortic repair.[14, 15] Delirium is a frequent postoperative complication in the frail elderly population, with incidence rates described of 25% after major elective surgery and up to 50% after high-risk procedures.[16, 17]

Advances such as minimally invasive surgery, protocols to prevent surgical site infection and fast-track protocols have decreased the impact of surgically induced trauma and the number and severity of postoperative complications. Despite these advances, incidence rates of delirium remain high.[18-22] Many short- and longterm complications are still observed and occur in older patients especially, with even worse outcomes in the frail.[23-25] Several preoperative programs have been suggested to tackle factors of frailty and further reduce postoperative complications such as delirium in the elderly population. Some programs specifically aimed to prevent delirium, since delirium is independently associated with serious adverse outcomes such as functional decline, cognitive decline, increased length of hospital- and ICU stay, institutionalisation, increase of healthcare costs and increased mortality rates.[24, 26]

Primary prevention is the most effective strategy to prevent delirium and delirium-associated complications,[27] with favourable outcomes after multicomponent (non-pharmacological) interventions, as concluded by two systematic reviews and meta-analyses.[28, 29]

Although of questionable quality, different pharmacological and non-pharmacological preoperative preventive approaches have been trying to further reduce the incidence of postoperative delirium

during admission. Pharmacologic interventions proved unsuccessful and the quality of current evidence for improvement with non-pharmacological approaches was labeled moderate.[28]

Over the past few years, different studies have suggested 'prehabilitation' programs to reduce postoperative complications. Prehabilitation is a preparatory intervention, prior to admission, which aims to optimise a patient's physiologic reserves in anticipation of a forthcoming physiological stressor and to minimise peri- and postoperative adverse events.[7] Uni-, bi- and trimodal approaches have been investigated to tackle factors of frailty and to reduce postoperative complications in both CRC and AAA patients.[7, 28-40] The main focus of these approaches was to improve muscle strength and cardiopulmonary condition, and to treat undernourishment and psychological problems, often with functional capacity as a primary outcome. The studies that were performed were heterogeneous in composition and factors they tried to influence,[37] which makes it impossible to pool results and provide high-quality evidence. Therefore, two recent systematic reviews concluded that there currently is no clear evidence showing that improved preoperative fitness will translate into a decrease in postoperative complications.[7, 39]

Previous prehabilitation trials often involved a small number of patients that underwent the prehabilitation program, not exceeding 75 patients. These trials did not focus on older patients specifically, with a mean age often below 70. Few studies used health-related quality of life as primary or secondary outcome and none of these studies focused specifically on preventing postoperative delirium.[37]

Up to 75% of patients with CRC suffer from iron-deficiency anaemia. Even mild anaemia may lead to impaired functional capacity or postoperative delirium;[24, 40, 41] yet haematinic optimisation is often not included in multicomponent prehabilitation pathways.[42] Patients receiving perioperative red blood cell transfusions because of this anaemia have an increased risk of adverse clinical outcomes, including increased delirium and mortality rates.[43, 44] It is therefore important to optimise haemoglobin levels before surgery and prevent the need for this transfusion.

The aim of this study is to reduce the incidence of delirium by implementing a unique combined pharmacological and non-pharmacological multidisciplinary program in order to optimise overall fitness in the older patients before CRC resection or AAA repair. By implementing this preoperative program, combined with the above-mentioned SSI and ERAS protocols, the primary goal is to reduce the incidence of postoperative delirium. Secondary goals are to reduce other postoperative complications, shorten hospital stay, prevent unplanned ICU admission, reduce mortality rates and improve prehabilitated patients' quality of life postoperatively. If reduction of delirium incidence proves successful, a health-economic analysis will be performed to assess cost-effectiveness. If subsequent results prove (cost-) effective, nationwide implementation is the objective.

Methods

Design and setting of the study

This protocol describes a single-centre uncontrolled before-and-after study with an per-protocol design. A unique multidisciplinary care pathway is designed, starting at the 70PLUS outpatient clinic of the department of surgery of the Amphia hospital Breda, a tertiary teaching hospital in the Netherlands. Table 3.1 provides an overview of the complete study period, from inclusion to 12 months follow-up.

Patients Characteristics and recruitment

All patients aged 70 and older who are scheduled to undergo elective abdominal surgery in case of CRC or AAA at the Amphia hospital are assessed for eligibility. They will undergo robot-assisted laparoscopic resection, laparoscopic resection or open removal of the colorectal tumor, or EVAR or open aortic repair of their AAA.

Patients are considered ineligible if acute hospitalization or acute surgery is needed (necessity established by the gastroenterologist, gastrointestinal surgeon or vascular surgeon), if they had surgery within six months prior to diagnosis or if surgery is planned within 2 weeks of the multidisciplinary meeting.

Eligibility for participation is established at the multidisciplinary meetings for colorectal cancer and for vascular surgery. After this establishment, patients are invited to participate by the gastroenterologist or the vascular surgeon. If preoperative chemotherapy, radiotherapy or chemoradiation is indicated, patients are included in the study when the indication for surgery is made, prior to these neoadjuvant therapies. Patients receive oral and written information about the study. If patients agree to participate, they are invited by the primary investigator to visit the 70PLUS outpatient clinic. Written informed consent will be obtained from all study participants during this visit. Due to the design of the study and the electronic patient file, it is not possible to blind participants, investigators, care providers, or outcome assessors in this study.

Table 3.1. Complete overview of the study period.

		Study period								
		Eligibility assessment		Trial enrollment	70PLUS out patient clinic	Admission	Discharge	Discharge + 2 weeks	6-months follow-up	12-months follow-up
Time point		Pathology result/ CTA	Multidisciplinary meeting	T0 – Informed consent obtained	T1	T2	T3	T3.5	T4	T5
Assessments										
Laboratory testing					X	X	X			
Nurse practitioner or investigator	Baseline patient characteristics				X					
	Factors of frailty				X					
	MMSE				X		X		X	X
	CCI and ASA				X					
	P-POSSUM				X					
	ISAR-HP				X				X	X
	PARKER				X				X	X
	SNAQ				X					
	KATZ-ADL				X				X	X
	Caregiver burden				X			X	X	X
	CESD-16				X			X	X	X
	WHOQOL-BREF				X			X	X	X
Physiotherapist	10MWT				X					
	TCST				X					
	TUG				X				X	X
	MIP				X					
	Handforce				X					

Dietician	MNA-SF	Indications for referral to dietician: Unintentional weight loss Loss of appetite BMI < 22 Undernourishment	X					
	BMI		X				X	X
	SNAQ		X					
Geriatrician	Complete geriatric assessment	Indications for referral to geriatrician: Delirium in history MMSE ≤ 24 TUG ≥ 12.6 seconds Polypharmacy	X					
Interventions								
Laboratory testing / Intravenous iron suppletion	All patients	Single dose of 1000 mg Ferric carboxymaltose (Ferinject®) at day care when indicated: Hb level males < 8,1 mmol/L Hb level females <7,4 mmol/L	X					
Physio-therapist	All patients	30 minutes of daily walking or cycling 5 exercises to improve leg muscle strength 2x15 minutes respiratory muscle exercise Transfer training when indicated (getting out of bed)	X					
Dietician	Malnourished patients / MNA-SF <12	Dietary advice on required protein and calorie intake. Proteins: 1.2 gram/kg bodyweight (BMI<30) Calories: WHO formula for basal need + 30% . Supplements are provided when required protein and calorie intake is not met after dietary advice.	X					
Geriatrician	Frail patients	Non-pharmacological interventions to reduce risk of delirium. Pharmacological interventions (prophylaxis).	X					

Time from pathology result to multidisciplinary meeting: <1 week. Time from multidisciplinary meeting to T0: <1 week. Time from T0 to T1: <1 week. Time from T1 to admission: 10 days to 5 weeks.

MMSE: Mini-Mental State Examination; CCI: Charlson Comorbidity Index; ASA: American Society of Anaesthesiology; P-POSSUM: Portsmouth Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity; ISAR-HP. Identification of Seniors At Risk – Hospitalized Patients; CES-D16: Centre for Epidemiological Studies – Depression 16 questions; WHOQOL-BREF: World Health Organisation Quality of Life – BREF; 10MWT: 10-meter Walk Test; TCST: Timed Chair Stand Test; TUG: Timed-up and Go Test; MIP. Maximum Inspiratory Pressure; MNA-SF: Mini Nutritional Assessment – Short Form; BMI: Body Mass Index; SNAQ: Short Nutritional Assessment Questionnaire

The 70PLUS outpatient clinic

All patients will visit a trained nurse practitioner and a physical therapist at the 70PLUS outpatient clinic. A dietician and a geriatrician will be consulted in case of undernourishment or frailty respectively. Each visit to the healthcare providers takes approximately one hour. The visit to a geriatrician is planned on a separate day because of the burden of a four-hour visit.

In the optimal situation, patients have five weeks prior to surgery to optimise their overall fitness, starting from the moment they visit the 70PLUS outpatient clinic. Patients in need of neoadjuvant treatment will have a longer optimisation period, however this advantage will likely be nullified by the burden of these treatments. Patients are invited to visit the outpatient clinic when indication for surgery is made. Time of surgery is based on the surgical program and physical complaints of the patient at that moment.

The nurse practitioner screens for frailty and determines the need for consulting the other physicians. Indications for consulting these physicians are described in Table 3.1. The following baseline patient characteristics are assessed: age, gender, surgical and general medical history, comorbidities, use of medication, intoxications, social economic status and schooling, body mass index, home situation (need for home care, institutionalisation and social environment), functional dependency (Parker score and Identification of Seniors At Risk – Hospitalized Patients (ISAR-HP) score), psychological history and burden of comorbidity (the American Society of Anesthesiologist (ASA) score, Portsmouth Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (P-POSSUM score) and the Charlson comorbidity index (CCI)).[45-48]

Frailty is screened for by collecting information on visual or hearing impairment, sleep rhythm, feeding impairment, dehydration and fall risk. Additional information on frailty is acquired by performing the following questionnaires: the delirium screening checklist, the Groningen frailty score, the KATZ-Activities of Daily Living score (for assessment of functional dependency and mobility) and the Short Nutritional Assessment Questionnaire (SNAQ) (for assessment of nutritional status).[49-51]

A district nurse assesses the need for additional homecare postoperatively for each patient. This assessment will be applied for by the nurse practitioner for all patients who commit to this pathway, in order to shorten the length of hospital stay.

Physiotherapist visit and assessment of physical condition

At initial assessment, the physiotherapists measure the patients' cardiopulmonary condition, overall strength and frailty.

Gait, stability and speed are assessed by the Timed Up and Go (TUG) test and the 10-meter walking test. These tests are validated and widely used in elderly patients. A cutoff of 12.6 seconds is used to define frailty. If considered frail, a geriatrician is consulted. TUG has been found to be superior to ASA-score in identifying oncogeriatric patients who might benefit from a prehabilitation program.[52-54] The timed-chair-stand test is used to assess lower extremity strength, specifically vertical movement and hip muscle strength.[55]

Strength of diaphragm and inspiratory muscles is assessed by measuring the maximum inspiratory pressure (MIP) during 1.5 seconds, using MicroRPM™. Training of inspiratory muscles successfully reduces length of hospital stay and postoperative pulmonary complications.[56]

Strength of both hands is tested using Hydraulic Hand dynamometer, JAMAR™. Poor handgrip strength is associated with a decline in activities of daily living and cognition in the elderly.[57]

In order to lower the burden for patients, lower the healthcare costs and increase compliance, the prehabilitation program has a large home-based component. All patients receive personalised exercises to preserve or improve their overall fitness and strength at home, unsupervised. These exercises have to be performed daily. The aim of these exercises is to increase respiratory muscle strength using the Threshold inspiratory muscle trainer®, and to improve overall fitness by endurance training, which consists of daily walking or cycling for 30 consecutive minutes. Patients receive specific transfer exercises and specific exercises to increase muscle strength in both legs and arms. All exercises are individualised to each patient's capabilities, as not every patient has the same baseline motivation or fitness.

Patients are asked to keep a diary with a record of their daily activities to assess compliance with the prehabilitation program. A cut-off value of 75% or more was considered compliant with the training program.

Dietician consultation and nutritional assessment

Nutrition is quantified using the body mass index (BMI), the Mini Nutritional Assessment score short form (MNA-SF) and the SNAQ-score.[51, 58] Laboratory research assesses blood levels of folic acid, vitamins B and D, lipid-spectrum and pre-albumin. Indications for consulting the dietician are described in Table 3.1. Based on the hospital's protocol for patients who will undergo major abdominal surgery, the dietician provides supplemental protein drinks and dietary advice if needed.

Cognition and mental health assessment

The patient is labeled frail, or at increased risk of developing delirium, if any form of cognitive impairment has previously been diagnosed. Cognition is examined using the Mini-Mental State Examination (MMSE), a standardised questionnaire designed specifically for this purpose.[59] The MMSE has a sensitivity of up to 97% and specificity of up to 70%, when adjusted for educational level.[60] A score below 24 or 26 points, depending on education level, is also considered an indication of frailty. In these increased-risk cases (see Table 3.1), the geriatrician will perform a complete geriatric assessment (CGA).[61, 62]

The CGA is an effective method to identify patients with increased risk for postoperative complications.[61-64] In the CGA, a geriatrician will assess if additional preventive intervention is necessary (e.g. prescribing prophylactic haloperidol, critically reviewing medication, and providing advice on non-pharmacologic prevention of infection, falls, pain, anxiety and dehydration).

Prophylactic haloperidol was prescribed to be given during admission to cognitively impaired patients and patients with delirium in medical history. The CGA is effective in improving mortality rates after 36 months of follow-up, improving functional independence and physical function and in decreasing rates of institutionalisation.[65]

Depression is screened for by using the CESD-16 questionnaire, which is a shortened version of the CESD-20.[66, 67] Caregiver burden will be assessed by using the caregiver strain index questionnaire.[68]

Quality of life is assessed using the WHOQOL-BREF. This is a shorter version of the WHOQOL-100, a questionnaire introduced by the World Health Organization. This questionnaire does not assess the physical capabilities of a patient, but assesses the patient's opinion of having or not having these capabilities. This way, it provides a better display of a patient's quality of life compared to questionnaires such as the SF-36, which shows a patient's functional capacity.[69, 70]

Biochemistry

Blood is collected from patients at or just before their first visit to the outpatient clinic. The following concentrations are determined via laboratory research: haemoglobin, hematocrit, leukocytes, thrombocytes, MCV, erythrocytes, INR, CRP, sodium, potassium, chloride, urea, creatinine, GFR, pre-albumin, ASAT, ALAT, cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, iron, transferrin, ferritin, folic acid, vitamin B12, 25-OH-Vitamin D and CEA.

Anaemic patients (haemoglobin level of < 7.4 mmol/L (<120 g/L) for women and < 8.1 mmol/L for men (< 130 g/L)) receive a single dose of 1000 mg ferric carboxymaltose (Ferinject®) preoperatively to increase haemoglobin levels.[71-73] This is a fast and safe way of correcting preoperative haemoglobin levels in patients suffering from iron deficiency anaemia.[74]

Blood collection and laboratory research will be repeated at admission (preoperative) and at the day of discharge (postoperative).

Table 3.1 provides a complete overview of cooperating physicians, indications for consulting these physicians, and actions and questionnaires performed by these physicians.

Admission

For both the control group and the intervention group, standard preventive measures for delirium will be taken during admission according to the HELP guidelines and postoperative patient care will be provided according to ERAS protocols.[75]

Follow up

Patients will be asked to visit the outpatient clinic at six and twelve months after discharge. These visits will last no longer than 20 minutes. The WHOQoL-BREF, CESD-16, MMSE, TUG, BMI, KATZ-ADL, PARKER and ISAR-HP are scored. Emergency department visits, readmission since initial discharge and deaths during follow-up will be registered. When trial participation is discontinued postoperatively, follow-up data on complications, readmissions, institutionalisation and mortality will be acquired through retrospective chart review.

Study outcomes

The primary study outcome is the incidence of delirium. Delirium will be screened for with the Delirium Observational Screening Score (DOSS), using the shortened version which consists of 13 items.[76] The DOSS is scored three times every day. A delirium is likely if the patient has a DOSS of ≥3. If delirium is suspected, a geriatrician will confirm the diagnosis using the DSM-5 criteria and the confusion assessment method (CAM).[77,78]

The secondary outcomes are postoperative length of hospital stay, ICU admission, readmissions, institutionalisation, mortality within one year after surgery, and quality of life. Number and severity of postoperative complications during hospital stay and follow-up will be assessed and scored according to the Clavien-Dindo classification.[79-80]

All other factors of frailty, that are mentioned in the sections above, will be evaluated and analysed to confirm association with the incidence of delirium.

Statistical analysis

The sample size was calculated based on data from a previous study.[24] Based on the analysis of 232 patients with AAA or CRC, this study found a delirium incidence of 15%. A 50-50 trial needs 550 patients, or 275 patients per study arm, to reduce the incidence of delirium to 7.5%. These calculations are based on a power of 80% with a 5% two–sided significance level.

Starting in November 2015, the aim is to include 275 patients in the prospective study, which is feasible during approximately 4.0 years of accrual, including follow-up. These patients will be compared to a group of patients treated between January 2013 and October 2015 at the Amphia Hospital Breda, The Netherlands. This group is formed by applying the same inclusion and exclusion criteria as are used to include patients prospectively, they were given the same perioperative care as given to the prehabilitation group, but they did not partake in any prehabilitation program. All baseline characteristics and postoperative outcomes mentioned in previous sections for the control group will be acquired through retrospective chart review, however due to the design of this research it is likely that not all these characteristics have been documented. Data acquired during the six- and twelve months follow-up visits have not been collected for the control group and will only be used for analyses on the prehabilitation group. For example, blood levels cannot be determined through retrospective chart review, however functional dependency can be acquired. The ratio of open versus minimally invasive surgery is expected to be the same in both groups, since conditions and indications for minimally invasive procedures did not change over study time.

Descriptive statistics will be used for presenting baseline characteristics. Differences in these characteristics between the control group and the prehabilitation group will be tested for statistical significance by using Student t-test or Mann-Whitney U test for continuous variables and Pearson chi-squared test or Fisher's Exact test for categorical variables, depending on normality. A subgroup analysis will be performed per diagnosis to test for differences between the groups in the primary and secondary outcomes.

Primary analysis for incidence of delirium will be done by creating a logistic regression model with adjustment for age, history of delirium, ASA ≥3 and diagnosis (AAA or CRC), important prognostic covariates found in previous research.[24] Secondary outcomes will likewise be adjusted for these covariates, however history of delirium will be replaced with type of surgery (open or minimally invasive).[81] Mixed linear modeling will be applied for measurements over time during follow up. Missing retrospective data will not be multiply imputed.

All data will be gathered in the Amphia Hospital Breda, the Netherlands, using the electronic patient file 'Hyperspace Version IU4 (Epic, Inc., Verona, WI)'.

Statistical analysis will be performed with IBM SPSS statistics software (SPSS Inc., Chicago, Illinois, USA). A two-sided p-value of < 0.05 will be considered statistically significant. Data collection is still ongoing. This article was has been reported by making use of the SPIRIT guidelines.[82]

Patient and public involvement

Patients were not involved in the design of this study, selection of outcome measures, development of research question, and in the recruitment to and conduct of this study. The burden of the intervention will be assessed during follow-up. A brief summary of the results will be made available in Dutch or English to all patients on request.

Discussion

This new and unique program is a multicomponent and multidisciplinary approach which aimed to optimise older patients in need of major abdominal surgery. The objective of this prehabilitation program is to decrease the incidence of delirium by tackling factors of frailty and by optimising overall fitness, nutritional status, mental status and anaemia at the same time.

Dutch (SONCOS) guidelines for colorectal cancer suggest an optimal time of six weeks from diagnostic pathology results to surgery.[83] The time between the pathology result and the multidisciplinary meeting (MDM) and between the MDM and the 70PLUS outpatient clinic visit is no more than a week, leaving an ideal optimisation period of approximately four to five weeks. Patients with obstruction or pain will be operated on as soon as possible, thus are not able to finish the entire prehabilitation period. There are no such guidelines for AAA surgery, meaning that this patient group should be able to complete the full five weeks of prehabilitation.

The combination of AAA and CRC was chosen for this study, even though they are different diseases with their own aetiology. Both conditions are a heavy burden on a patient's fitness and are major diseases for which abdominal surgery is required. This combination is justifiable because both diseases have similar surgical risk factors and factors of frailty that increase the risk for a delirium.

Patients are asked to perform unsupervised physical exercises at home, which may affect compliance rates because there is no extrinsic motivator. By giving patients tailor-made exercises and by reducing the number of extra hospital visits, better compliance is to be expected.[36]

The awareness for delirium in older surgical patients has increased in postoperative care, which may cause a relative increase in delirium cases over time. It is expected that the prehabilitation program will cancel out this effect.

Strengths and limitations

Compared to other prehabilitation studies, this study aims to include a large prospective and retrospective patient cohort and focusses solely on patients that are over 70 years of age. A multimodal approach was implemented, combining both pharmacological and non-pharmacological interventions, involving physical fitness, nutritional status and haemoglobin levels. Previous studies often implemented a single intervention, within a small sample and mean age below 70.[30, 31, 34-37] Physical resilience starts to decrease with increasing age. This in turn increases the need for prehabilitation, which emphasizes the importance of prehabilitation in the elderly.

Due to logistic reasons, not all patients can be visited at admission. Timing of admission makes it impossible to verify improvements in overall fitness, pulmonary muscle strength or the effectiveness of the physical interventions in all patients. In the end, the focus of this research is to prevent delirium and other postoperative adverse events, making quantifying the progress made by the

program less relevant. This was therefore not included in this study. Previous studies have proven similar programs to be able to make a significant improvement in functional capacity.[37]

The design of this study makes the risk of bias fairly high. Due to the before-and-after setting, randomization and blinding of patients and caregivers is impossible. Bias may also occur because surgical procedures have changed over time, although no significant differences are expected due to the consecutive timing of both cohorts.

This study has a single-center design, which may limit generalisability of the study. However, the way this intervention is set-up makes it possible to implement it in other centers as well.

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CHAPTER 4

Multimodal prehabilitation to reduce the incidence of delirium and other adverse events in elderly patients undergoing elective major abdominal surgery: an uncontrolled before-and-after study.

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Abstract

Introduction

Delirium is a common and serious complication in older patients undergoing major abdominal surgery and has significant adverse outcomes as a result. Successful strategies or therapies to reduce the incidence of delirium are scarce. The objective of this study was to assess the role of prehabilitation in reducing the incidence of delirium in older patients.

Methods

A single-centre uncontrolled before-and-after study was conducted, including patients aged 70 years or older who underwent elective abdominal surgery for colorectal carcinoma or an abdominal aortic aneurysm between January 2013 and October 2015 (control group) and between November 2015 and June 2018 (prehabilitation group). The prehabilitation group received interventions to improve patients' physical health, nutritional status, factors of frailty and preoperative anaemia prior to surgery. The primary outcome was the incidence of delirium, diagnosed with the DSM-5 criteria or the confusion assessment method. Secondary outcomes were additional complications, length of stay, unplanned ICU admission, length of ICU stay, readmission rate, institutionalisation, and in-hospital or 30-day mortality.

Results

A total of 360 control patients and 267 prehabilitation patients were included in the final analysis. The mean number of prehabilitation days was 39 days. The prehabilitation group had a higher burden of comorbidities and was more physically and visually impaired at baseline. At adjusted logistic regression analysis, delirium incidence was reduced significantly from 11.7 to 8.2% (OR 0.56; 95% CI 0.32 – 0.98; P=0.043). No statistically significant effects were seen on secondary outcomes.

Conclusion

The current prehabilitation program is feasible and safe, and can reduce delirium incidence in older patients undergoing elective major abdominal surgery. This program merits further evaluation.

Introduction

Our society is ageing progressively. The number of people in the world above 60 years old is expected to more than double in the next 35 years.[1] Incidence rates of common age-related diseases that require surgery, such as colorectal carcinoma (CRC) and abdominal aortic aneurysm (AAA), are likely to undergo a similar increase.[2, 3] Older people undergoing surgery for these conditions have an increased risk of postoperative complications and mortality.[4, 5] Roughly 30% of the patients that undergo a colorectal resection suffer postoperative complications,[6] which in turn leads to subsequent adverse outcomes and a decrease in quality of life in these patients.[7, 8]

A person's physical resilience decreases with progressive ageing, while frailty increases.[9] Up to forty-three percent of colorectal cancer patients can be considered frail,[10] which makes them likely to be unable to withstand the physical stress associated with surgery.[11] The risk for morbidity, mortality and institutionalisation is increased over four times in these patients.[12, 13] A recent meta-analysis showed an independent relationship between frailty and delirium. Delirium is a common and serious postoperative complication in older surgical patients.[14]

Despite advances in techniques such as minimally invasive surgery and enhanced recovery after surgery (ERAS) protocols, recent incidence rates of postoperative delirium vary from 4-35% in CRC patients[15-21] and from 13-29% in AAA patients.[15, 22, 23] Delirium is a major complication that may lead to a prolonged hospital stay (LOS), increased healthcare costs, institutionalisation, decreased quality of life and increased morbidity and mortality.[14, 15, 21, 24-27]

Delirium is defined as a neuropsychiatric disorder, caused by a combination of predisposing and precipitating risk factors. Baseline vulnerability is set by predisposing risk factors, such as old age, frailty, comorbidities and functional, cognitive and sensory impairment.[24, 28, 29] An additional risk for delirium is added by precipitating risk factors, such as nutritional impairment, polypharmacy, anaemia, pain, and type of surgery.[24, 28, 29] Patients with higher baseline vulnerability need fewer precipitating factors to develop a delirium.

A recent meta-analysis concluded that there was strong evidence for multicomponent interventions to prevent delirium in hospitalised non-ICU patients.[30] The multifactorial aetiology of delirium is exemplified by the evidence that delirium incidence in elderly patients can be reduced by optimising multiple precipitating risk factors at once.[30, 31] Examples of such efforts, implemented during admission, are the Hospital Elder Life Program (HELP) and the NICE guidelines.[31, 32]

To further reduce the number of postoperative adverse events, prehabilitation programs were investigated in recent studies. Prehabilitation is the optimisation of patients' physical, nutritional and psychological health prior to admission, in order to withstand the stress caused by surgery and prevent postoperative adverse events.[33] Recent reviews on prehabilitation programs did not reach a consensus on efficacy and labelled the quality of the majority of these studies as poor.[34-37] Studies implementing these programs are heterogeneous and focused mainly on CRC patients, while only two studies focused on patients undergoing vascular surgery.[35, 37]

In the case of elective surgery, an additional preventive effect on delirium might be achieved by adding such a prehabilitation program to already existing ERAS protocols and multicomponent intervention programs. That way, elements of frailty, poor preoperative fitness and malnutrition can be identified and tackled even in the pre-admission period. The aim of this study was to reduce the incidence of delirium and other postoperative adverse events by prehabilitating CRC and AAA patients prior to surgery. The focus of this prehabilitation program is to optimise patients' physical health and nutritional status, to tackle factors of frailty and to correct preoperative anaemia prior to admission.

Methods

Study design, setting and participants

This study is a single-center, uncontrolled before-and-after study, conducted in the Amphia hospital in Breda, the Netherlands. Patients aged 70 or older who underwent elective abdominal surgery for CRC or AAA were included.

Past studies on delirium have likewise used a combination of diseases in their trials.[27, 38, 39] CRC and AAA were chosen for this trial because they are common conditions in older patients and require major abdominal surgery, with relatively high numbers of postoperative complications.

Patients were considered ineligible when acute hospitalisation or surgery was required, when they had surgery six months prior to diagnosis or when surgery was planned within 2 weeks of the multidisciplinary meeting. The control group consisted of a historical population meeting the same inclusion and exclusion criteria as the prehabilitation group and underwent surgery between January 2013 and October 2015. The prehabilitation group was formed by patients who followed the prehabilitation program and were operated on between November 2015 and June 2018. Eligibility was assessed and optimal treatment was determined during colorectal and vascular multidisciplinary meetings. Treatment options for CRC patients were (robot-assisted) laparoscopic or open tumour resection. For AAA patients, options were open or (fenestrated) endovascular aortic repair. Written informed consent was obtained during trial enrolment, before the first outpatient clinic visit.

A multidisciplinary care pathway was designed, as an addition to already existing care interventions, to optimise patients' physical and nutritional health and factors of frailty prior to admission. All prospective patients followed this prehabilitation pathway for an optimal period of 5 weeks prior to surgery. The control group was not prehabilitated. For both patient groups, preventive measures for delirium were taken during admission according to the HELP guidelines[31] and postoperative patient care was provided according to ERAS protocols. Randomisation and blinding of the persons involved in this research was not possible due to its design. The study design and methods have been described in detail previously.[40] An overview of the complete study period and design is presented in Table 3.1. This trial has been previously registered in the Dutch Trial Registration, with trial number NTR5932. Initially, the medical ethical committee decided registration of this trial was not required. However, following guidelines of good clinical practice, this trial was retrospectively registered six months after commencement of the trial.

Intervention

During the outpatient clinic visit, a nurse practitioner and a physiotherapist performed a complete assessment of patients' basic health, fitness and factors of frailty. A dietician was consulted in case of undernourishment, decreased appetite or unintentional weight loss. A complete overview of the interventions that were performed has previously been published.[40]

A trained nurse practitioner collected baseline characteristics and screened for factors of frailty. Delirium risk was assessed by collecting information on cognitive impairment, sensory impairment, functional dependency, and burden of comorbidity (using Charlson Comorbidity Index (CCI) and American Society of Anesthesiologists (ASA) score).[41, 42] KATZ-ADL and SNAQ were scored to objectively assess physical dependence and nutritional impairment respectively.[43, 44] In case of a patient being a smoker, the nurse practitioner emphasized the importance of smoking cessation.

A physiotherapist provided patients with home-based personalised exercise programs, depending on a patient's capabilities, to increase respiratory muscle strength, muscle strength of both legs and overall fitness. These exercises consisted of aerobic training, resistance training and respiratory muscle training. To prevent an even further increase of the physical and mental burden of this research on the patient, improvements in fitness were not quantified preoperatively during admission. However, previous research has shown evidence of improvement in functional capacity when patients performed similar, unsupervised home-based exercises.[35] Patients were asked to keep a diary with a record of their daily activities to assess compliance with the prehabilitation program. When the diary was not kept, data on compliance was obtained through telephone contact. Patients were considered non-compliant when compliance could not be assessed or when patients performed less than 75% of provided exercises.

A dietician objectively quantified nutritional status using body mass index, blood levels of pre-albumin and vitamins B and D, and the mini nutritional assessment short form (MNA-SF).[45] Patients were given dietary instructions based on a minimum daily protein intake of 1.2 grams per kilogram bodyweight and a caloric intake of a patient's basal need plus 30%. Supplemental protein drinks were provided when daily intake was not sufficient.

If indicated, patients subsequently visited a geriatrician, who performed a Complete Geriatric Assessment.[46] The geriatrician assessed the need for supplementary interventions to prevent delirium during admission and provided the surgical wards with advice on which additional preventive measures to use (e.g. prescribing prophylactic haloperidol, critically reviewing medication, and providing advice regarding prevention of infection, falls, pain, anxiety and dehydration).

Anaemic patients (haemoglobin level of < 7.4 mmol/L(<120 g/L) for women and < 8.1 mmol/L for men (<130 g/L)) received an intravenous iron injection during admission at daycare to increase preoperative haemoglobin levels.[47]

Outcomes

The primary outcome was incidence of delirium. Ward nurses screened for delirium during regular rounds using the delirium observation screening scale.[48, 49] This scale is a validated and easy-to-use delirium screening tool for nurses with a sensitivity of 94% and a specificity of 78%.[50] When delirium was suspected, a geriatrician was consulted to confirm the diagnosis using the DSM-5 criteria or the Confusion Assessment Method.[51, 52] Secondary outcomes were length of hospital stay (LOS), unplanned ICU admission, length of ICU stay, readmission rate, additional in-hospital complications, discharge disposition, and in-hospital or 30-day mortality.

Statistical analysis

The sample size was calculated based on data from a previous study.[15] Based on this analysis, a 50-50 trial needed 550 patients, or 275 patients per study arm, to gain an absolute risk reduction of the incidence of delirium of 7.5%. These calculations are based on a power of 80% with a 5% two-sided significance level.

Dichotomous variables were presented as frequencies with percentages and continuous variables as medians with interquartile range. Differences in these characteristics were tested for statistical significance by using Pearson chi-squared test or Fisher's Exact test and Student t-test or Mann-Whitney U test respectively, depending on the distribution of the data.

Unadjusted and adjusted regression analyses were performed to calculate odds ratios (OR) and 95% confidence intervals (CI) for the primary and secondary outcomes. In the multivariate regression analysis, the primary outcome was adjusted for important predisposing covariates (age, history of delirium and ASA ≥3), as found in earlier research.[15] For our secondary outcomes, history of delirium was replaced with type of surgery (EVAR, open AAA, laparoscopic or open CRC) as covariate for the multivariate regression analysis.[53, 54] Linear regression analysis and logistic regression analysis were performed in case of continuous and dichotomous outcome variables respectively.

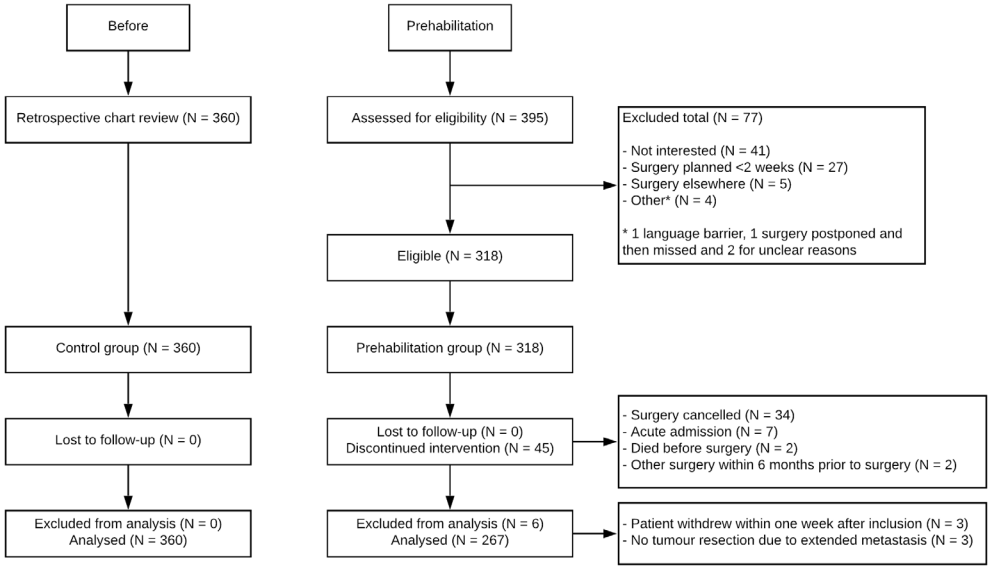
All data were gathered using the electronic patient file 'Hyperspace Version IU4 (Epic, Inc., Verona, WI)'. Data for the control group was prospectively stored in the electronic patient files and retrospectively obtained. Statistical analyses were performed using IBM SPSS statistics software (SPSS Inc., Chicago, Illinois, USA) and 'R' statistical software version 3.5.1 (The R Project for Statistical Computing) with the 'forest plot' package. A two-sided p-value < 0.05 was considered statistically significant. Missing data was not imputed.

This article has been reported according to the CONSORT guidelines.[55]

Results

For the control group, 360 patients were considered eligible. In our prehabilitation group, 395 prospective patients were assessed for eligibility. A total of seventy-seven patients were excluded, mostly due to not being interested or early planning of surgery. Of the 318 eligible patients that entered the prehabilitation program and were seen in the outpatient clinic, 45 patients discontinued intervention and 6 were excluded from further analysis, leaving a total of 267 patients who were included in the final analysis. Two patients died before surgery, one due to respiratory failure and one due to a cerebral infarction. Figure 4.1 shows a diagram with a complete overview of eligibility, patient allocation and attrition.[55]

Figure 4.1. Flow diagram



The mean number of prehabilitation days, the number of days from the outpatient clinic visit to surgery, was 39 days (95% CI; 35 – 43 days). The time between the multidisciplinary meeting and surgery was less than 14 days in four patients.

Patient characteristics

Table 4.1 presents full sample baseline characteristics and baseline characteristics per diagnosis of both the control group and the prehabilitation group. A complete overview of baseline comorbidities was added to the original version of this paper and can be found online (Supplementary Table 2). Significantly more patients in the prehabilitation group had a higher burden of comorbidity and were physically and visually impaired. Intravenous iron was given to 103 anaemic patients, of which 84.5% were CRC patients.

Table 4.1. Full sample baseline characteristics and baseline characteristics per diagnosis in control group and prehabilitation group

	Control group		Prehabilitation group				
	AAA N = 73 (20.3%)	CRC N = 287 (79.7%)	AAA N = 70 (26.2%)	CRC N = 197 (73.8%)	Controls N = 360 (%)	Prehabilitation N = 267 (%)	p-value[a]
Age, median (IQR)	75 (72-80)	76 (73-80)	76.5 (72-80)	77 (74-81.5)	76 (73-80)	77 (73-81)	0.15
Male gender	63 (86.3)	162 (56.4)	59 (84.3)	114 (57.9)	225 (62.5)	173 (64.8)	0.56
(Burden of) comorbidities							
Cognitive impairment	3 (4.1)	22 (7.7)	1 (1.4)	18 (9.1)	25 (6.9)	19 (7.1)	0.93
History of delirium	2 (2.7)	17 (5.9)	5 (7.1)	12 (6.1)	19 (5.3)	17 (6.4)	0.56
CCI[b] ≥ 7	18 (24.7)	95 (33.1)	27 (38.6)	83 (42.1)	113 (31.4)	110 (41.2)	0,011
ASA[b] score ≥ 3	47 (64.4)	101 (35.2)	51 (72.9)	98 (49.7)	148 (41.1)	149 (55.8)	<0.001
Physical impairment							
KATZ-ADL score ≤5	6 (8.2)	41 (14.3)	13 (18.6)	46 (23.4)	47 (13.1)	59 (22.1)	0.003
Nutritional statusc							
SNAQ score ≥ 3	6 (8.2)	71 (24.7)	4 (5.7)	42 (21.3)	77 (21.4)	46 (17.2)	0.20
Intoxications							
Daily alcohol use[c]	27 (37.0)	109 (38.0)	26 (37.1)	82 (41.6)	136 (37.8)	108 (40.4)	0.50
Active smoker[d]	22 (31.4)	35 (12.5)	19 (27.1)	25 (12.7)	57 (16.2)	44 (16.5)	0.94
Sensory impairment							
Visual impairment	16 (21.9)	80 (27.9)	27 (38.6)	80 (40.6)	96 (26.7)	107 (40.1)	<0.001
Hearing impairment	24 (32.9)	88 (30.7)	25 (35.7)	62 (31.5)	112 (31.1)	87 (32.6)	0.70
Surgery							
Open surgery	27 (37.0)	88 (30.7)	18 (25.7)	23 (11.7)	115 (31.9)	41 (15.4)	<0.001
Minimally invasive surgery	46 (63.0)	199 (69.3)	52 (74.3)	174 (88.3)	245 (68.1)	226 (84.6)	

a: Calculated for full samples of control versus prehabilitation

b: CCI: Charlson Comorbidity Index; ASA: American Society of Anesthesiologists

c: <3% of retrospective data missing

d: <10% of retrospective data missing;

Compliance

The overall compliance to the prehabilitation program was 73.9%. Muscle-strength exercises were performed according to protocol by 74.2% of all patients. For daily walking and breathing exercises, rates were 75.7% and 71.9% respectively.

Outcomes

The short-term postsurgical outcomes are presented in Table 4.2. Unadjusted and adjusted odds ratios (OR) with 95% confidence intervals for primary and secondary outcomes are presented in Table 4.3. Incidence of delirium was decreased by almost a third, from 11.7% to 8.2% (p=0.16). After adjustment for important prognostic confounders, the prehabilitation program significantly reduced incidence of delirium, with an OR of 0.56 (95% CI 0.32 – 0.98; p=0.043). Significantly more serious complications (Clavien-Dindo III-V) were present in the prehabilitation group (14.2% vs 8.9%; p=0.036), mostly attributable to anastomotic leakages in CRC patients (7.1% in the prehabilitation group versus 2.8% in control group; p=0.025). These complications led to a significantly higher mortality rate in this same group of patients (p=0.034). After adjusted regression analysis however, the prehabilitation program had no significant effects on all other postsurgical outcomes. Short-term outcomes per diagnosis were added as a supplement to the original version of this paper and can be found online (Supplementary Table 3).

Table 4.2. Postsurgical outcomes of control group versus prehabilitation group in all patients

	Total N=627 (%)	Control N=360 (%)	Prehabilitation N=267 (%)	p-value
Delirium				
Incidence of delirium	64 (10.2)	42 (11.7)	22 (8.2)	0.16
Duration of delirium in days, median (IQR)	3 (2 – 5.75)	3 (2 – 6.5)	3 (1 – 4)	0.39
Complications				
Any complication other than delirium	242 (38.6)	133 (36.9)	109 (40.8)	0.32
Clavien-Dindo I-II	172 (27.4)	101 (28.1)	71 (27.4)	0.69
Clavien-Dindo III-V	70 (11.2)	32 (8.9)	38 (14.2)	0.036
Length of stay				
Length of hospital stay in days, median (IQR)	6 (4 – 10)	7 (5 – 10)	6 (4 – 10)	0.003
Unplanned ICU admission	57 (9.1)	27 (7.5)	30 (11.2)	0.11
ICU length of stay in days, median (IQR)	3 (1 – 7)	2 (1 – 7)	4 (2 – 7)	0.23
Readmission				
30-day readmission	44 (7.0)	22 (6.1)	22 (8.4)	0.28
Mortality				
During admission	20 (3.2)	9 (2.5)	11 (4.1)	0.25
30-day mortality	17 (2.7)	7 (1.9)	10 (3.7)	0.17
Discharge dislocation				
Discharge to new location	50 (8.0)	24 (6.7)	26 (9.9)	0.14
Discharge home with care	168 (26.8)	96 (26.7)	72 (27.4)	0.66
Discharge home without care	382 (60.9)	226 (62.8)	156 (58.4)	
Discharge to nursing home	57 (9.1)	29 (8.1)	28 (10.6)	0.26

Table 4.3. Unadjusted and adjusted regression analysis on postsurgical outcomes: Controls (N=360) versus prehabilitation (N=267)

	Unadjusted effects Odds Ratio (95% CI)	Adjusted effects Odds Ratio (95% CI)	p-value
Primary outcome			
Incidence of delirium	0.68 (0.40 – 1.17)	0.56 (0.32 – 0.98)[a]	0.043
Secondary outcomes			
Any complication	1.09 (0.79 – 1.50)	1.12 (0.80 – 1.57)[b]	0.52
Unplanned ICU admission	1.56 (0.90 – 2.70)	1.54 (0.86 – 2.75)[b]	0.14
30-day readmission	1.41 (0.76 – 2.60)	1.42 (0.75 – 2.68)[b]	0.29
Mortality (admission or <30 days postoperative)	1.84 (0.76 – 4.42)	1.50 (0.61 – 3.72)[b]	0.38
Discharge to new living situation	1.54 (0.86 – 2.75)	1.57 (0.84 – 2.96)[b]	0.16
	Unadjusted effects	**Adjusted effects**	
	Coefficient (95% CI)	**Coefficient (95% CI)**	
Secondary outcomes			
Length of hospital stay in days, B-coefficient (95% CI)	-1.3 (-3.1 – 0.57)	- 0.89 (-2.7 – 0.99)[b]	0.35
ICU length of stay in days, B-coefficient (95% CI)	-4.4 (-14.5 – 5.8)	- 5.7 (-16.6 – 5.3)[b]	0.30

a: Corrected for: Age, history of delirium, ASA ≥3 and diagnosis, based on previous research

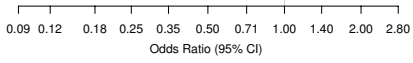
b: Corrected for: Age, ASA ≥3, type of surgery and diagnosis

A subgroup analyses for the effect of the prehabilitation program on incidence of delirium is shown in Figure 4.2. This subgroup analysis was performed as an exploratory analysis and results are to be interpreted with caution. A significant decrease in the incidence of delirium was seen for physically impaired patients (OR 0.30; 95% CI 0.11 – 0.88) and in 80 to 84 year old patients (OR 0.28; 95% CI 0.09 – 0.89).

Figure 4.2. Subgroup analysis on the incidence of delirium

(A) Odds ratios presented are unadjusted.

Subgroup		No. of patients	Controls	Prehabilitation	Odds Ratio	95% CI
			% of patients who met primary endpoint			
All patients		627	11.7	8.2	0.68	0.40–1.17
Age Group	70–74	220	7.9	6.5	0.81	0.28–2.30
	75–79	211	8.4	8.8	1.05	0.39–2.82
	80–84	138	19.2	6.2	0.28	0.09–0.89
	85 or older	58	24.1	17.2	0.65	0.18–2.37
Gender	Male	398	12.9	8.7	0.64	0.33–1.24
	Female	229	9.6	7.4	0.76	0.28–1.97
Pathology	AAA	143	9.6	5.7	0.57	0.16–2.04
	CRC	484	12.2	9.1	0.72	0.40–1.32
Surgery Type	Open	156	18.3	9.8	0.48	0.16–1.50
	Minimally invasive	471	8.6	8.0	0.92	0.48–1.78
CCI	≥ 7	223	17.7	11.8	0.62	0.29–1.32
	< 7	404	8.9	5.7	0.62	0.28–1.39
ASA Class	≥ 3	297	19.6	10.1	0.46	0.23–0.90
	< 3	330	6.1	5.9	0.97	0.37–2.49
KATZ–ADL	< 6 points	107	27.1	10.2	0.30	0.11–0.88
	6 points	520	9.3	7.7	0.81	0.43–1.54
SNAQ score	< 3	504	9.2	7.7	0.82	0.44–1.56
	≥ 3	123	20.8	10.9	0.46	0.16–1.37
Impairment	Visual impairment	203	17.7	9.3	0.48	0.21–1.10
	Proper eyesight	424	9.5	7.5	0.78	0.38–1.59
	Hearing impairment	199	17.0	9.2	0.50	0.21–1.19
	Proper hearing	428	9.3	7.8	0.83	0.41–1.65



Discussion

The incidence of delirium in older patients undergoing elective surgery for CRC or AAA can be reduced by implementing a multimodal prehabilitation program. Although prehabilitation has previously been investigated in other surgical areas, this study is the first to specifically investigate the role of prehabilitation in reducing the incidence of delirium after major abdominal surgery. Patients were preoperatively assessed for frailty, physical dependence, malnourishment, cognitive impairment and other factors that increase the chance of developing a postoperative delirium and were given home-based training exercises, dietary advice and nutritional support, and intravenous iron injections in case of anaemia.

Implementation of the prehabilitation program decrease the incidence of delirium with almost a third, which makes prehabilitation a valuable addition to already existing delirium prevention protocols. This additional advantage can be achieved by a program with a relatively low burden for the patient and at relatively low costs, since exercises are home-based and the number of extra visits to the hospital is kept relatively low.

The significant decrease in the incidence of delirium without any effect on all other postoperative outcomes may be explained by delirium's multifactorial aetiology. The prehabilitation program aimed for a cumulative effect by tackling multiple risk factors for delirium at once. This effect of the combined interventions was not able to decrease the number of other postoperative outcomes, possibly due to a bigger association with risk factors that cannot be improved through prehabilitation (e.g. type of surgery and intraoperative factors). This is in line with the first systematic reviews on the effectiveness of multimodal prehabilitation in colorectal cancer patients. These concluded that multimodal prehabilitation studies that included physical exercises, nutritional interventions and anxiety reduction were not able to reduce the number of postoperative complications or length of hospital stay.[35, 56, 57] One of these reviews showed two unimodal programs on prehabiliation in colorectal cancer patients that did improve these clinical outcomes, one involving supervised high-intensity exercise training[58] and one involving preoperative nutritional support.[59] It also showed a unimodal program involving supervised exercise training for AAA patients that did improve these clinical outcomes.[60] The final conclusion of this review however, in line with above-mentioned reviews, was that there was insufficient data to recommend routine clinical implementation of either unimodal or multimodal prehabilitation programs due to substantial heterogeneity.[37]

The current study showed an increase in severe complications in CRC patients, which the authors feel can unlikely be attributed to the prehabilitation program. This effect on complications may be explained by the bigger number of physically impaired patients and the higher burden of comorbidity that was found in the prehabilitation group, since this effect was nullified after correction. In contrast, the lower rate of open surgery might have compensated for these factors.

The compliance rate in the current study was almost 75%, which was just a little lower than the highest compliance rates of unsupervised exercises in other studies.[35, 56, 57] Supervised exercise programs reach a compliance rate of almost 100%; however, this does not result in better postoperative

outcomes.[35, 56, 57] The authors hypothesised that fewer people would refuse to participate in the program due to the home-based setting of the program and expected the compliance rate to be higher due to a lower patient burden. The main reasons patients provided for non-compliance were that their physical condition was good enough, that exercises were too time-consuming or that they just did not feel like exercising.

The mean length of prehabilitation was just over five weeks, comparable to past prehabilitation studies.[35, 56, 57] A bigger timeframe to prehabilitate patients may improve results. However, quality guidelines state that the time from diagnosis to surgery may not exceed six weeks.[61] In contrast to these guidelines, two recent studies suggest that there is no association between treatment delay and rates of reoperation and mortality.[52, 63] Future studies could therefore try to achieve better results by extending the prehabilitation period.

The sample sizes of previous studies that investigated the effect of a prehabilitation program were relatively small, often not exceeding 100 patients in total. These studies often involved much younger patients, with mean ages not exceeding 70.[35, 56, 57] The design of this research enabled us to include a much larger group of patients. This study only included patients of 70 years and older in the prehabilitation program, sinces improving postoperative outcomes is especially important in patients who are most at risk of adverse outcomes.[13] Moreover, these patients are most likely to achieve meaningful improvement of their physical condition.[64]

Limitations

The risk of bias in this study was relatively high. Randomisation, allocation concealment and blinding were not possible due to the design of this study. The outcome assessors were unaware of trial participation and used the same standardised method for diagnosing delirium as used in non-study patients. However, the electronic patient file does show a patients' enrollment in medical research. The outcome assessors were aware of the intervention that was introduced and could therefore have been aware of a patient being included in the study, making this an important potential source of bias. The risk of bias was partially compensated by performing this trial in a single center, by letting the retrospective period connect directly to the prospective period and by letting the same group of surgeons and hospital staff provide patient care. No significant changes have been made in diagnostic method or treatment protocols during the time of this research. Additionally, by applying the same set of inclusion and exclusion criteria to the control group and the prehabilitation group, similar groups were expected. Despite these similarities in care, by using an uncontrolled design and not using a concurrent control group, this still remains a potential source of bias.

Another limitation of this study is including both CRC and AAA in the current study. While both conditions can be and have been used together in the definition of major abdominal surgery, they are fairly different. To illustrate: surgery for these diseases is carried out by surgeons from different disciplines (i.e. colorectal and vascular surgeons).

Finally, prehabilitation is limited by the fact that those that partake in the programs are generally more motivated (and possibly fitter) than those who do not.

Future research

Based on the experience from this study and feedback from patients, the biggest challenge for future prehabilitation programs is adequately providing patients with information. Providing patients with sufficient and understandable information, emphasizing the importance of prehabilitation and providing patients with custom-made exercises fitting an individual patient's needs are all crucial factors for a better compliance. Patient and caregiver should together engineer a tailored program through shared decision making and thereby increase compliance and, hopefully, decease postoperative adverse events. Results of this study can aid in accomplishing a better understanding of the importance of prehabilitation.

Imperative in developing successful prehabilitation programs is better stratification and identification of patients who are most at risk for developing postoperative complications. Specific risk factors of frailty that are most likely to improve through prehabilitation should be identified and tackled per patient individually, in order to create a program specifically helpful for that individual patient.

It is advisable for future research investigating this or new prehabilitation programs to assess the effectiveness of the program by building in measurements to assess improvements in the different components of the program.

The results of this study are promising, but do not provide conclusive evidence due to flaws in the design of this study. Future studies should use a higher quality study design, for example a controlled before-and-after study or a (cluster) randomized controlled trial.

Conclusions

The incidence of postoperative delirium in older patients undergoing elective major abdominal surgery can be reduced by implementing a prehabilitation program which focuses on optimizing patients' fitness and nutritional status, and tackling factors of frailty and anaemia. Reducing delirium in these patients is feasible and safe with an easy-to-perform program. This program did not reduce LOS, the number and length of unplanned ICU admissions, and rates of other postoperative complications, readmissions, institutionalisation and short-term mortality.

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CHAPTER 5

Long-term outcomes of major abdominal surgery and postoperative delirium after multimodal prehabilitation of older patients

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Abstract

Introduction

The long-term outcomes of delirium after surgery in multimodally prehabilitated patients are largely unknown. We conducted this study to assess the effects of prehabilitation on 1-year mortality and of postoperative delirium on 1-year mortality and functional outcomes.

Methods

The subjects of this study were patients aged ≥70 years who underwent elective surgery for abdominal aortic aneurysm (AAA) or colorectal cancer (CRC) between January 2013 and June 2018. A prehabilitation program was implemented in November 2015, which aimed to optimise physical health, nutritional status, factors of frailty and preoperative anaemia prior to surgery. The outcomes that were assessed were: (i) mortality after 6 and 12 months compared between the two treatment groups; and (ii) mortality and functional outcomes compared between patients with and those without delirium.

Results

There were 627 patients (controls n=360, prehabilitation n=267) included in this study. Prehabilitation did not reduce mortality after 1 year (HR 1.31 [95% CI 0.75 – 2.30]; p=0.34). Delirium was significantly associated with 1-year mortality (HR 4.36 [95% CI 2.45 – 7.75]; p<0.001) and with worse functional outcomes after 6 and 12 months (KATZ ADL p=0.013 and p=0.004; TUG test p=0.041 and p=0.011 respectively).

Conclusions

The prehabilitation program did not reduce 1-year mortality. Delirium and the burden of comorbidity are both independently associated with an increased risk of 1-year mortality and delirium is associated with worse functional outcomes.

Introduction

There is an ever-increasing need for new interventions to prevent postoperative complications, especially as more opportunities arise for older patients to undergo surgical procedures with advances in surgical protocols and less invasive techniques. Consequently, the number of postoperative complications is likely to increase because these older patients are twice as susceptible to complications as younger patients.[1, 2] Delirium is the most common of these complications, with up to 1 in 4 older surgical patients suffering delirium after elective major abdominal surgery for colorectal cancer (CRC) or an abdominal aortic aneurysm (AAA).[3-5] Although its pathophysiology is still not completely understood, it is well accepted that delirium has a multifactorial aetiology and is a reflection of depleted reserves resulting from an accumulation of precipitating insults in already vulnerable patients. This baseline vulnerability, or 'frailty', is caused by the loss of physiological reserve and adaptability caused by multiple small physiological deficits.[6, 7] This baseline vulnerability places patients at increased risk of postoperative adverse events.[7-9] Even in the absence of postoperative complications, major surgery reduces functional capacity by up to 40%.[10] This makes surgery both an important precipitator to delirium as well as a factor that lowers baseline vulnerability.

There is a growing interest in using the period from diagnosis to surgery to prevent postoperative complications and decrease mortality rates in patients undergoing abdominal surgery. Prehabilitation aims to optimise a patient's baseline health and functional capacity, in order to alleviate the impact of an incoming stressor prior to surgery. It may focus on a single physical, nutritional, or haematinic component. Since all these factors are independently related to the risk of postoperative complications, multimodal prehabilitation programs have been developed to optimise multiple components at once.[11, 12] Two recent studies on patients undergoing elective AAA repair and major abdominal surgery showed a decrease in postoperative complications in prehabilitated patients.[13, 14] Moreover, a meta-analysis of pooled data from 15 prehabilitation studies was able to show a significant reduction in overall and pulmonary morbidity in patients undergoing elective major abdominal surgery.[15] A multimodal prehabilitation study to prevent postoperative delirium in older patients after elective major abdominal surgery, conducted by this research group, significantly reduced the incidence of delirium.[16] However, no prehabilitation programs have yet been able to improve long-term postoperative outcomes such as mortality or functional outcome. For this reason, we aimed to compare the 1-year outcomes after major abdominal surgery of patients who followed a prehabilitation program with patients who did not. We also investigated the effect of postoperative delirium on long-term mortality and functional outcomes.

Methods

Study design, setting, and participants

A single-centre, uncontrolled before-and-after study was conducted in the Amphia hospital, a tertiary teaching hospital in Breda, the Netherlands. All patients aged 70 years or older who were scheduled to undergo elective abdominal surgery for AAA or for CRC with curative intent were assessed for possible inclusion. Patients who were admitted for an acute event, those who needed emergency surgery, those who had undergone surgery in the 6 months prior to admission, and those whose surgery was planned within 2 weeks of the multidisciplinary meeting were excluded.

A control group, meeting the same inclusion and exclusion criteria as the intervention group, consisted of patients who underwent surgery between January 2013 and October 2015. The intervention group followed a prehabilitation program and underwent surgery between November 2015 and June 2018. Eligibility and preferred treatment were assessed during colorectal and vascular multidisciplinary meetings. The planned surgical procedures were open or (robot-assisted) laparoscopic removal of the colorectal tumour, or open or (fenestrated) endovascular aortic repair. If considered eligible, written informed consent was obtained during trial enrolment, before the first outpatient clinic visit.

The intervention group followed a multidisciplinary prehabilitation program, ideally for 5 weeks prior to admission, to optimise the patients' physical and nutritional health, haemoglobin levels, and factors of frailty. During admission, both groups received the same standard perioperative delirium prevention measures in accordance with the hospital elder life program[17] and postoperative care in accordance with 'enhanced recovery after surgery' protocols.[18] Randomisation or blinding of the persons involved in this research was impossible because of the design of this study. As the study design, methods, assessments, interventions, and short-term outcomes have been reported in previous publications, they are not described in detail here.[16, 19] This trial was registered retrospectively in the Dutch Trial Registration (Trial number NTR5932).

Intervention

At their first outpatient clinic visit, patients saw a nurse practitioner and a physiotherapist, who assessed their basic health, fitness, and factors of frailty. Indications for referral to a dietician or a geriatrician were assessed by the nurse practitioner. A dietician was consulted if there was undernourishment, decreased appetite, or unintentional weight loss, and the patient was referred to a geriatrician in case of cognitive impairment (MMSE ≤ 24), a history of delirium, a Timed Up and Go (TUG) test of ≥12.6 seconds, or polypharmacy. Anaemic patients (haemoglobin level of < 7.4 mmol/L (<120 g/L) for women and < 8.1 mmol/L for men (<130 g/L)) were given intravenous iron injections.

A trained nurse practitioner collected baseline characteristics (age, gender and comorbidities) and screened for factors of frailty. The risk factors for delirium that were assessed were cognitive impairment, history of delirium, sensory impairment, functional dependency, and burden of comorbidity (using Charlson Comorbidity Index (CCI).[20] Physical dependency was scored using the KATZ-ADL score.[21] Nutritional status was assessed using the SNAQ score.[22] The importance of smoking cessation was emphasized to those patients who smoked. A physiotherapist assessed

physical fitness by performing the TUG test.[23, 24] Patients were provided with unsupervised, home-based personalised resistance and endurance exercises, depending on a patient's physical capabilities. The focus of these exercises was to increase inspiratory muscle strength, the strength of both legs, and overall fitness. Patients were instructed to perform these exercises three times a week and to go for a daily 30-minute walk. Improvements in fitness were not assessed prior to surgery, although previous research provides evidence that an improvement in fitness can be achieved by performing similar home-based exercises.[25]

A dietician assessed nutritional status using the mini nutritional assessment – short form (MNA-SF)[26] and by measuring body mass index and blood levels of pre-albumin and vitamin B and D. Patients were given dietary advice to assure they met the minimum required daily intake of 1.2 grams per kilogram bodyweight of proteins and a caloric intake of a patient's basal need plus 30%. Patients were given vitamins in case of depletion and supplemental protein drinks when their daily protein intake was not sufficient. A geriatrician performed a Complete Geriatric Assessment (CGA) when indicated. The CGA is a multidimensional and multidisciplinary intervention to identify frail patients and to reduce the number of risk factors of adverse postoperative outcomes. Supplementary interventions to prevent delirium during admission were provided and advice was given on additional preventive measures, such as prescribing prophylactic haloperidol, critically reviewing medication, and providing advice regarding prevention of infection, falls, pain, anxiety and dehydration.[27, 28]

Delirium

Ward nurses screened for delirium at least twice a day during regular ward rounds, using the delirium observation screening scale,[29, 30] a validated and easy-to-use delirium screening tool for nurses. It has a sensitivity of 94% and a specificity of 78%.[31] When delirium was suspected during admission, a geriatrician was consulted, who confirmed the diagnosis using the DSM-5 criteria or the Confusion Assessment Method.[32, 33]

Outcomes

The primary outcome was mortality after 6 and 12 months, which was compared between the control group and the prehabilitation group for all patients and according to diagnosis, and between patients with and without a delirium. Data on mortality for use in survival analyses were retrieved or confirmed using the CompeT&T national database. Secondary outcomes were functional outcomes after delirium and were assessed using the KATZ-ADL score and the TUG test. The functional outcomes were assessed for prehabilitated patients only and were recorded at baseline and after 6- and 12-months follow-up.

Statistical analysis

Dichotomous variables are presented as frequencies with percentages and continuous variables are presented as medians with interquartile range. Differences in these characteristics were tested for significance by using the Pearson chi-squared test or Fisher's Exact test and Mann-Whitney U test respectively. Between-group differences at follow-up time points were analysed using analyses of covariance (ANCOVA), adjusting the outcomes differences for differences at baseline, age, CCI, physical impairment, diagnosis, and type of surgery. A two-sided p-value <0.05 was considered

statistically significant. A cox proportional hazard model was created to assess the effects of the prehabilitation program and of delirium on overall mortality. The model adjusted for age, CCI, physical impairment, diagnosis and type of surgery. Outcomes are presented as hazard ratios (HR) with 95% confidence intervals (95% CI).

Linear mixed modelling was performed to examine the differences in median KATZ-ADL score and the TUG test at 6- and 12-months post-surgery compared with baseline for patients with and patients without delirium. An unstructured covariance matrix was used to model the residual (co)variances of the repeated measurements. Analyses were adjusted for age, CCI, diagnosis and type of surgery. Tests for differences between the mean scores at baseline and each of the time points during follow-up were derived directly from the mixed model by making use of the custom hypothesis test command in the SPSS syntax. Because the baseline score was compared to scores at two separate time points, the statistical significance for these tests was set at p=0.025 (p=0.05 / 2 tests) to correct for multiple comparisons. Between-group differences at follow-up time points were analysed using analyses of covariance (ANCOVA), adjusting the outcomes differences for differences at baseline, age, CCI, diagnosis and type of surgery.

All data were gathered and stored prospectively using the electronic patient file 'Hyperspace Version IU4 (Epic Inc., Verona, WI)'. Data for the control group was collected retrospectively from these patient files. Statistical analyses were performed using IBM SPSS statistics software version 26.0 (SPSS Inc., Chicago, Illinois, USA). Missing data was not imputed. The Medical Ethical Research Committee of Rotterdam, Maasstad Hospital (TWOR) approved the research protocol, ID number NL55694.101.15, in June 2016. This article has been reported in accordance with the CONSORT guidelines.[34]

Results

Figure 5.1 presents a flow diagram with eligibility, exclusions, losses to follow-up, discontinued interventions, and the final numbers of patients in the prehabilitation group and the control group. The records of 360 patients were reviewed and these patients were included retrospectively. In the prospective prehabilitation group, eligibility was assessed for 395 patients. Seventy-seven patients were excluded and intervention was discontinued for 45 patients, for reasons listed in Figure 5.1. Six more patients were excluded from the final analysis, leaving a total of 267 patients who were prospectively included in this study. For the primary outcome, no patients were lost to follow-up due to the retrieval of information from a national database. Adherence to the program was 73.9%.[16]

Figure 5.1. Flow diagram

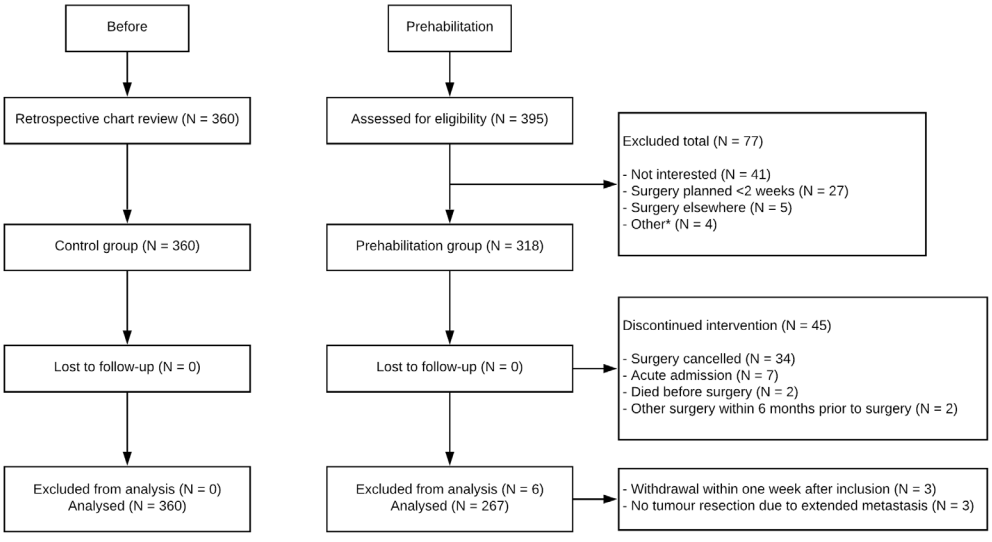

Table 5.1 summarizes the baseline characteristics for both groups. Prehabilitated patients had a higher burden of comorbidity (CCI ≥ 7 41% vs 31%, p=0.011) and were more often physically impaired (22% vs 13%; p=0.004). Significantly more open procedures were performed in the control group (32% vs 15%; p<0.001). Open surgery was performed in 156 patients in total (45 patients open AAA repair and 111 patients open CRC resection). Minimally invasive surgery was performed in 484 patients (EVAR in 98 patients and laparoscopic CRC resection in 373). There were no significant differences in tumour location, location of AAA, rates of preoperative therapy, or rates of adjuvant treatment.

Table 5.1. Full sample baseline characteristics of the control group and the prehabilitation group

	Control group N = 360 (%)	Prehabilitation group N = 267 (%)	p-value
Age, median (IQR)	76 (73 – 80)	77 (73 – 81)	0.15
Male gender	225 (63)	173 (65)	0.56
(Burden of) comorbidities			
CCI ≥ 7	113 (31)	110 (41)	0.011
Impairments			
Physical (KATZ-ADL ≤5)	48 (13)	59 (22)	0.004
Nutritional (SNAQ ≥ 3)	77 (21)	46 (17)	0.20
Cognitive impairment	25 (6.9)	19 (7.1)	0.93
Diagnosis and location of tumour/AAA			
Colorectal cancer	287 (80)	197 (74)	0.18
Ascending colon	114 (40)	73 (37)	
Transverse colon	11 (3.8)	19 (9.6)	
Descending colon	16 (5.6)	13 (6.6)	
Sigmoid	56 (20)	33 (17)	
Rectum	94 (33)	60 (30)	
Appendix	0 (0)	1 (0.5)	
Double tumour	3 (1.0)	1 (0.5)	0.65
Abdominal aortic aneurysm	73 (20)	70 (26)	0.53
Infrarenal	69 (95)	64 (91)	
Juxtarenal	4 (5.5)	6 (8.6)	
Synchronous metastasis	8 (2.8)	6 (3.0)	0.87
Preoperative therapy			
Preoperative radiotherapy	23 (8.0)	15 (7.6)	0.35
Preoperative chemotherapy	3 (1.0)	2 (1.0)	
Preoperative chemoradiation	10 (3.5)	14 (7.1)	

Surgery			
Open surgery total	115 (32)	41 (15)	<0.001
Minimally invasive surgery total	245 (68)	226 (85)	
Open AAA surgery	27 (37)	18 (26)	0.15
Endovascular surgery	46 (63)	52 (74)	
Open CRC surgery	88 (31)	23 (12)	<0.001
Minimally invasive CRC surgery	199 (69)	174 (88)	
Adjuvant therapy			
Adjuvant chemotherapy	54 (19)	29 (15)	0.24

CCI: Charlson Comorbidity Index; KATZ-ADL: KATZ Activities of Daily Living; SNAQ: Short Nutritional Assessment Questionnaire

Table 5.2 shows the cumulative mortality rates for all the patients and for each diagnosis for both the control and prehabilitation groups at each time point. Of the 627 patients included in this study, 57 (9.1%) died within 1 year of surgery. The mortality rates after 6 and 12 months were 5.3% and 8.1% chronologically for the control group and 7.9% and 11% chronologically for the prehabilitation group. No significant changes were observed between treatment groups at any time point or for CRC or AAA patients specifically.

Table 5.2. Mortality rates of the control group versus the prehabilitation group for all patients and according to diagnosis

	Total*		CRC†		AAA†	
	Control N = 360 (57%)	Prehabilitation N = 267 (43%)	Control N = 287 (59%)	Prehabilitation N = 197 (41%)	Control N = 73 (51%)	Prehabilitation N = 70 (49%)
Mortality						
6-month	19 (5.3)	21 (7.9)	12 (4.2)	14 (7.1)	7 (9.6)	7 (10.0)
12-month	29 (8.1)	28 (10.5)	20 (7.0)	21 (10.7)	9 (12.3)	7 (10.0)

No significant differences were observed between the treatment groups after adjustments ($p<0.05$).

*: Adjusted for age, CCI, physical impairment, diagnosis and type of surgery.

†: Adjusted for age, CCI, physical impairment and type of surgery.

Table 5.3 presents the results of the cox proportional hazard model and Figure 5.2 shows the corresponding survival plot. The adjusted hazard ratio for the prehabilitation group versus the control group was not statistically significant (HR 1.31; 95% CI 0.75 – 2.30; p=0.34). Delirium was significantly associated with 1-year mortality (HR 4.36 [95% CI 2.45 – 7.75]; p<0.001). Of the other covariates, only CCI had a significant hazard ratio of 1.20 (95% CI 1.04 – 1.38; p=0.01). Hazard ratios for age, physical impairment, diagnosis and type of surgery were 1.03 (95% CI 0.98 – 1.09; p=0.20), 1.37 (95% CI 0.74 – 2.54; p=0.32), 1.68 (95% CI 0.92 – 3.06; p=0.092) and 1.48 (95% CI 0.83 – 2.62; p=0.18) respectively.

Table 5.3. Cox proportional hazard analysis of factors associated with 1-year mortality

					95% CI for Hazard Ratio	
Variable	Coefficient	Standard Error	p-value	Hazard Ratio	Lower	Upper
Prehabilitation	0.27	0.29	0.34	1.31	0.75	2.30
Delirium	1.47	0.29	<0.001	4.36	2.45	7.75
Age	0.034	0.026	0.20	1.03	0.98	1.09
Charlson Comorbidity Index	0.18	0.071	0.01	1.20	1.04	1.38
Physical impairment	0.32	0.32	0.32	1.37	0.74	2.54
Diagnosis	0.52	0.31	0.092	1.68	0.92	3.06
Type of surgery	0.39	0.29	0.18	1.48	0.83	2.62

Significance of model: chi-square = 41.175; df = 7; p<0.001

The model adjusted for age, CCI, physical impairment, diagnosis and type of surgery.

Figure 5.2 Survival plots for the prehabilitation and control group

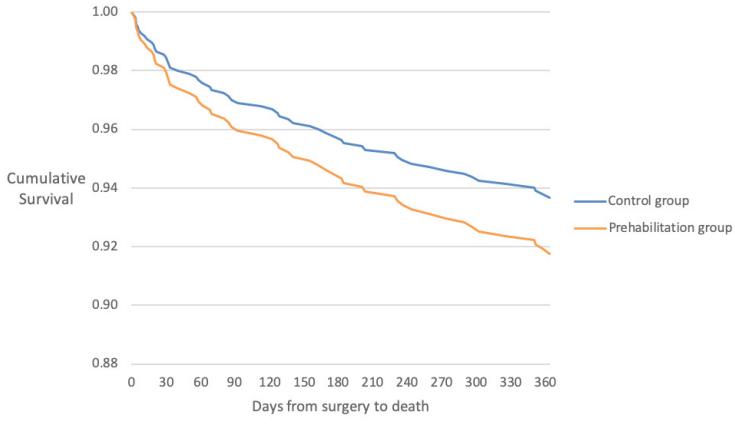

Table 5.4 shows the effect of delirium on mortality. For all three groups; namely, the control group, the prehabilitation group, and all patients, the mortality rates at all time points were significantly higher for patients who suffered delirium compared to those that did not (control group and all patients: p<0.001 for both time points; prehabilitation group: p<0.001 and p=0.003 for both time points in chronological order). A separate analysis per diagnosis was added as a supplementary table to the original version of this manuscript and can be found online.

Table 5.4. Mortality rates of patients with versus those without delirium in both groups and overall

	Delirium			No delirium		
	Controls N = 42 (%)	Prehabilitation N = 22 (%)	Total N = 64 (%)	Controls N = 318 (%)	Prehabilitation N = 245 (%)	Total N = 563 (%)
Mortality						
Within 6 months	10 (24)	7 (32)	17 (27)	9 (2.8)†	14 (5.7)‡	23 (4.1)*
Within 12 months	11 (26)	7 (32)	18 (28)	18 (5.7)†	21 (8.6)‡	39 (6.9)*

Analyses were adjusted for age, CCI, physical impairment, diagnosis and type of surgery.

*: Significant difference between all patients with and without delirium (p<0.05).

†: Significant difference between control groups (delirium vs no delirium; p<0.05).

‡: Significant difference between prehabilitation groups (delirium vs no delirium; p<0.05).

Table 5.5 shows the effects of delirium on the functional outcomes. The delirium group scored significantly worse on physical functioning after 6 and 12 months compared to baseline (p=0.023 and p=0.004, respectively). They also had worse physical functioning at those time points compared to patients without delirium (6 vs 6, p=0.013 and 6 vs 6, p=0.004, respectively), which remained statistically significant after correction for baseline differences (p=0.025 and p=0.006, respectively). Patients with delirium scored significantly worse on the TUG test than those without delirium after 6 and 12 months (9:02 vs 7:50, p=0.041; 7:52 vs 6:27, p=0.011). However, after correction for baseline variables, this only remained statistically significant after 12 months (p=0.055 and p=0.019, respectively). Patients with delirium did not significantly improve their physical fitness over time. For patients without delirium, physical fitness after 6 and 12 months was significantly better than at baseline (7:50 and 6:27 vs 8:38; p<0.001 and p<0.001, respectively).

Table 5.5. Long-term functional outcomes of the prehabilitation group: delirium versus no delirium

	Delirium N = 22	No delirium N = 245
KATZ-ADL score		
Baseline	6 (5 – 6)	6 (6 – 6)
6 months	6 (5 – 6)*	6 (6 – 6)†, ‡
12 months	6 (4 – 6)*	6 (6 – 6)†, ‡
TUG test (seconds)		
Baseline	10:30 (8:06 – 13:01)	8:38 (7:20– 10:13)
6 months	9:02 (8:09 – 11:49)	7:50 (6:01 – 9:26)*, †
12 months	7:52 (6:55 – 10:59)	6:27 (5:23 – 8:16)*, †, ‡

Linear Mixed Modelling adjusted for age, burden of comorbidity, diagnosis and type of surgery

*: Significant difference in patient group between time point and baseline ($p<0.025$)

†: Significant difference between patients with and patients without delirium ($p<0.05$)

‡: Significant difference between patients with and without delirium after correction for baseline variable scores ($p<0.05$)

Discussion

This study found no significant difference in mortality rates at any time point between the prehabilitation group and the control group. Based on the Cox proportional hazard model, prehabilitation did not alter mortality rates. The control group and the prehabilitation group had similar survival rates of 0.94 and 0.92 respectively. However, this study demonstrated a significantly higher 1-year mortality in patients who suffered delirium than in those who did not. As well as an effect on mortality, patients with delirium also suffered worse functional outcomes in the long term. These effects of delirium on long-term outcomes are an important finding of our study.

Few previous prehabilitation studies have incorporated mortality as an outcome.[15, 25, 35, 36] Those that did, were not able to achieve a significant reduction in mortality rates after 90 days or after one year.[37-39] The lack of effect may be explained because healthier patients, who are least in need of preoperative optimisation, were more likely to refuse to participate in or remain adherent to the program. Conversely, in the present study, all consecutive patients were included in the retrospective cohort group. This also demonstrates the methodological weakness of the "before-and-after" design of the study.

Comorbidities significantly affected the risk of mortality in this study, which is in line with a recent systematic review and meta-analysis that demonstrated a 41% increased risk of overall mortality for colorectal cancer patients with even mild to moderate comorbidities. In the current study, a one-point higher CCI score resulted in a 20% bigger risk of mortality within 1 year. Patients who suffered delirium had significantly higher mortality rates than those who did not. Moreover, patients with delirium have a 4.4 times increased risk of mortality within 1 year, which highlights the serious impact of delirium and the need for new effective prevention methods. This prehabilitation program was able to significantly decrease the incidence of delirium. Surprisingly, this decrease did not result in decreased mortality rates, even though delirium is an independent risk factor for mortality. This may be attributed to the small sample size, since this study was initially powered for delirium as outcome. Previous studies have demonstrated this serious consequence of delirium,[40,-42] although a 2018 systematic review and meta-analysis examining the impact of postoperative delirium on mortality after non-cardiac surgery concluded that the quality of most studies was questionable and that those that pre-specified confounders did not find a significant independent association.[43]

Long-term functional outcomes have also been investigated extensively. Studies that focused on these outcomes concluded, in line with the current research, that delirium negatively affects these outcomes. It is associated with a decline in ADL functioning and persistent meaningful impairment of functional recovery for up to 18 months.[42, 44, 45] The delirium group may have been to small to demonstrate a clinically relevant decrease in physical dependency scores. However, scores in patients with delirium did worsen significantly over the course of the investigation and were significantly worse compared to the no delirium group. A similar course was seen for TUG test results: patients with delirium were slower during follow-up than those without delirium, and did not improve significantly in the TUG times. It is notable that all patients were significantly faster

during follow-up. This may be because patients continued to perform the exercises that were given to them after discharge, or because different outcome assessors assessed TUG times at baseline (a physiotherapist) and at 6 and 12 months postoperatively (research assistant). The effects of delirium on long-term functional outcomes may be more extensively investigated by assessing its impact on the quality of life of these patients.

Both low- and high intensity training have been applied in the past to optimise patients preoperatively and to alter the postoperative course. High-intensity training programs struggled with adherence because patients were already 'busy surviving'.[46, 47] Most older patients prefer unsupervised home-based exercise training over supervised training, because of the relation of the latter with frequent hospital visits.[47, 48] Ironically, supervised programs with high intensity interval training (HIIT) and inspiratory muscle training achieve the best results in terms of progress in cardiopulmonary fitness. However, few studies with limited quality of evidence showed a decrease in complications.[25, 35, 48] Information on the importance of prehabilitation programs should improve to convince patients of its benefits. Additionally, interventions should be tailor-made and easily accessible to promote adherence and be customised together with the patient through shared decision making.[47]

Previous prehabilitation studies on patients undergoing major abdominal surgery have included no more than 125 patients.[15] Although the quality of evidence of this study is lacking because it is not a randomised controlled trial, a considerable increase in included patients could be achieved through a before-and-after design. Moreover, it has been demonstrated that prehabilitation programs promote quicker return to baseline functional capacity after surgery.[49] Thus, it may be considered unfair to implement a randomised design and allocate patients to a control group. By initiating a before-and-after trial, this is not an issue.

Limitations

A limitation of this study is the combination of diseases and surgical techniques that were used. While both CRC and AAA can be and have been used together in the definition of major abdominal surgery, they are different. Including both can be justified by the fact that they are frequently observed in older patients, have a high rate of postoperative complications and similar mortality rates,[50, 51] and require surgery as final treatment. However, in this study, we did not aim to compare the postoperative outcomes of colorectal cancer patients with those of AAA patients. Instead, we provided combined mortality rates and mortality rates for both diagnoses separately and made a comparison between the control group and the prehabilitation group (Table 5.2). This is in line with our primary goal to assess the effectiveness of the prehabilitation program in reducing delirium and its related mortality rates. Laparoscopic and endovascular surgery are both considered minimally invasive techniques, although the latter does not involve entering the peritoneal cavity. To decrease the risk of bias, analyses were adjusted for diagnoses and type of surgery.

This study was also limited by the relatively high rate of patients who would not continue visiting the study's outpatient clinic during follow-up. Patients did not want to be reminded of their disease and felt burdened having to come to the hospital more often. Other prehabilitation studies also experience high refusal rates, although many were even higher than in this study.[47] Many patients believe they are in good physical condition to begin with and do not see the benefits of prehabilitation because of misunderstanding the provided information, or are simply already busy surviving.[47] Providing them with sufficient information and evidence may help to reduce this lack of confidence in the effectiveness of these programs. New evidence supporting the use of prehabilitation studies may be used to inform these patients and convince them to partake in a prehabilitation program, even though the physical and emotional burden of their diagnosis weighs on their minds.

Conclusions

This multimodal prehabilitation program, which involved physical and nutritional enhancement, intravenous iron injections, and optimisation of factors of frailty, did not reduce the mortality rates within the first year. Delirium and CCI are both independently associated with an increased risk of 1-year mortality, which again emphasizes the importance of better delirium prevention programs. This is emphasized even more by the the association of delirium with worse functional outcomes after 6 and 12 months. In a previous study conducted by this research group, the incidence of delirium was significantly lower after prehabilitation. The severe consequences of delirium justify offering patients a prehabilitation program prior to major abdominal surgery.

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CHAPTER 6

Intravenous iron in a prehabilitation program for older surgical patients: prospective cohort study

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Abstract

Introduction

Older patients often have iron deficiency anaemia prior to surgery, which can be effectively treated with intravenous iron supplementation (IVIS). Anaemia and blood transfusions are associated with an increased risk of delirium. The aim of this research was to assess the effectiveness and safety of using IVIS in a prehabilitation program which aimed to reduce the incidence of delirium.

Methods

Patients ≥70 years who underwent abdominal surgery between November 2015 and June 2018 were included in this single-centre prospective cohort study. All patients were prehabilitated, however, only anaemic patients received a single dose of 1000 mg intravenous iron (ferric carboxymaltose) to increase preoperative haemoglobin levels (IVIS group). Non-anaemic patients received standard care (SC). The haemoglobin levels (primary outcome) were assessed at the outpatient clinic visit, at admission and at discharge. Secondary outcomes were postoperative delirium, postoperative anaemia, blood transfusion, complications other than delirium and length of hospital stay. All outcomes were compared between the IVIS group and SC group.

Results

Of all patients (n=248), 97 anaemic patients received IVIS (39%). Of the anaemic patients, 50 patients (52%) had iron deficiency. Initial differences in haemoglobin concentrations between the IVIS group and SC group at T1 and T2 (7.2 vs 8.8; $p<0.001$ and 7.4 vs 8.6; $p=0.023$, respectively) were no longer present at discharge (6.6 vs 7.2; $p=0.35$). No statistically significant differences were observed for all secondary outcomes between the IVIS group and the SC group. No infusion-related adverse events occurred.

Conclusions

Adding intravenous iron supplementation to prehabilitation programs is safe and diminishes differences in haemoglobin concentrations at discharge between preoperatively anaemic and non-anaemic patients. Intravenous iron supplementation may be worthwhile as an additional component of prehabilitation programs. Results merit further investigation.

Introduction

Eighteen to sixty-one percent of colorectal cancer (CRC) patients are anaemic prior to surgery.[1-3] The most common causes of preoperative anaemia in CRC patients are iron deficiency as a result of intestinal blood loss or nutritional impairment, and anaemia of chronic diseases.[1, 3, 4] Iron deficiency is present in over 50% of CRC patients.[1, 2] Altered iron recycling due to chronic aortic wall inflammation leads to an increased risk of iron deficiency and subsequent anaemia in patients with an abdominal aortic aneurysm (AAA).[5-7] Anaemia is observed in almost 50% of AAA patients.[8] Anaemic AAA patients have an increased risk for mortality compared with patients without anaemia.[5, 9] Recent studies confirmed the increased risk after endovascular aortic repair but did not provide evidence for an increased risk after open aortic repair.[6-8]

Both CRC and AAA require abdominal surgery as definitive treatment and have been used together in studies on delirium after major abdominal surgery.[10-12] Delirium is the most frequent surgical complication and a common outcome after surgery for both CRC and AAA in older patients.

Preoperative anaemia is associated with an increased risk of delirium,[13-16] other postoperative adverse events and mortality,[1, 17-19] and is predictive of the need of allogenic blood transfusions.[1] In turn, blood transfusions are associated with postoperative delirium[15, 20, 21] and increase the risk of postoperative morbidity and unfavourable oncologic outcomes.[22-24] Previous studies on major abdominal surgery reported that preoperative correction of iron-deficiency anaemia reduces the number of perioperative blood transfusions.[25, 26] Intravenous iron supplementation (IVIS) is proven to be superior to oral supplementation in terms of safety and effectiveness in increasing haemoglobin (Hb) levels[4, 27, 28] and in reducing the need for blood transfusions.[4] However, oral iron therapy remains the usual frontline recommendation for treatment of iron deficiency anaemia. According to Rognoni et al., of all forms of intravenous iron preparations, ferric carboxymaltose may be superior to other intravenous iron supplements.[29]

IVIS has recently been used in our prehabilitation program to prevent postoperative delirium and other adverse events in older patients after major abdominal surgery for CRC and AAA.[10] This program was able to reduce the incidence of postoperative delirium, but did not affect the number of complications, readmissions or short-term mortality, and did not differentiate between patients with iron deficiency anaemia (IDA) and patients with other types of anaemia (OA). The aim of this research was to assess the effectiveness and safety of using IVIS in a prehabilitation program by assessing the changes in Hb and iron parameter measures in anaemic patients who received IVIS. This study also compared the effectiveness of IVIS between patients with IDA and patients with OA in an attempt to differentiate between those groups.

Methods

Study design, setting, and participants

All patients of 70 years or older who were scheduled to undergo elective major abdominal surgery for CRC or an AAA between November 2015 and June 2018 in the Amphia Hospital in Breda were included in this single-centre longitudinal prospective cohort study. Exclusion criteria were: acute hospitalisation, acute surgery, previous surgery in the past six months or surgery planned within two weeks. All patients followed a prehabilitation program which aimed to optimise patients' physical and nutritional health, to reduce factors of frailty and to improve haematinic status in an optimal period of five weeks prior to surgery.[30] The initial goals of this program were to reduce rates of postoperative delirium, complications, readmissions and mortality. A detailed report of the study design and methods has been published previously.[30] The optimisation of the physical and nutritional health status and the optimisation of factors of frailty are beyond the scope of this manuscript and are therefore not elaborated on in detail. In summary: overall fitness, respiratory muscle strength and muscle strength of both legs were trained in a home-based, personalised exercise program; nutritional health status was optimised by providing patients with dietary advice and supplements to maintain a sufficient daily intake; and factors of frailty were screened for by a nurse practitioner and extensively assessed by a geriatrician using the Comprehensive Geriatric Assessment.

Anaemia was defined as an Hb level of < 7.4 mmol/L (<120 g/L) for women and < 8.1 mmol/L (<130 g/L) for men. Iron deficiency anaemia was defined as either absolute (ferritin <30 µg/L) or functional iron deficiency anaemia (transferrin saturation <20% in combination with ferritin <100 µg/L), based on previous literature.[31-33] A higher ferritin cut-off value was used for functional iron deficiency compared to absolute IDA, because ferritin may be elevated due to the acute inflammatory response. All anaemic patients received a single dose of 1000 mg intravenous ferric carboxymaltose preoperatively at day-care to increase Hb levels.[34-36] Patients with factors that possibly affected the Hb levels (i.e. blood transfusion between the first outpatient clinic visit and the surgery, or surgery within ten days of the intravenous iron injection) were excluded from the analysis.

During admission, all patients were managed in accordance with the hospital's standardised infection prevention protocols, delirium prevention protocols and Enhanced Recovery after Surgery protocols.[37, 38]

Baseline characteristics

A trained nurse practitioner collected the following baseline variables during the first outpatient clinic visit: age, gender, cognitive impairment (using the mini-mental state examination), delirium in medical history, burden of comorbidities (using Charlson Comorbidity Index (CCI),[39] physical status (using KATZ-ADL score40) and nutritional status (using SNAQ score[41]). Patients with a KATZ-ADL score below the maximum score of 6 were considered physically impaired. A SNAQ score of ≥2 represents malnourishment.

Biochemical and other haematological variables

Blood was collected from patients during or one day before the first outpatient clinic visit (T1), at admission (T2; 1 day before surgery) and at discharge (T3). Serum concentrations of the following biomarkers were collected: haemoglobin (mmol/L), iron (µmol/L), transferrin (µmol/L), transferrin saturation (%) and ferritin (µg/L). Time from IVIS to admission and data on pre- and postoperative blood transfusion were registered. Anaemic status was recorded at inclusion, admission and discharge.

Delirium

The delirium observation screening score was used by ward nurses to screen for delirium during regular rounds.[42] A geriatrician confirmed the diagnosis of delirium using the DSM-5 criteria or the Confusion Assessment Method (CAM).[43, 44] The CAM is a validated diagnostic tool, specifically designed to accurately identify delirium in patients.

Outcomes

The primary outcomes were the changes in concentrations of Hb, iron, ferritin, transferrin and transferrin saturation over time. The secondary outcomes were postoperative delirium (which was the primary outcome of the prehabilitation program and was significantly reduced in the prehabilitation group[10]), postoperative anaemia, blood transfusion, complications other than delirium and length of hospital stay. All outcomes were compared between the patients receiving IVIS and the patients receiving standard care (SC group). A separate analysis was performed to compare the primary and secondary outcomes between patients with IDA and OA. Adverse events after IVIS were registered.

Statistical analysis

Continuous variables were presented as median with interquartile range and categorical variables as frequencies with percentages. Differences between groups were calculated using the Mann Whitney U test and the chi-squared test respectively. Missing data for the covariates were infrequent and were not imputed. A p-value <0.05 was considered statistically significant.

Between-group differences at specific follow-up time points were analysed using analyses of covariance (ANCOVA), adjusting the differences on the outcome measures for baseline differences in serum concentrations and differences in baseline characteristics.

For all outcome measures, differences between each follow-up measurement and baseline were examined by using linear mixed modelling (LMM) with full information maximum likelihood estimation and tested by making use of a custom hypothesis test in the SPSS syntax. To adjust these tests for multiple comparisons, statistical significance was set at $p=0.025$ ($p=0.05/2$ tests). An unstructured covariance matrix was used to model the error structure of the repeated measurements. The analyses were adjusted for differences in baseline characteristics.

The interaction between change in outcome measures over time and treatment group, and between change in outcome measures over time and type of anaemia were calculated using LMM ($p<0.05$). Adjusted regression analyses were performed to calculate odds ratios (OR) and 95% confidence

intervals (CI) for the secondary outcomes. These outcomes were adjusted for baseline differences. Linear regression analysis and logistic regression analysis were performed in case of continuous and dichotomous outcome variables respectively.

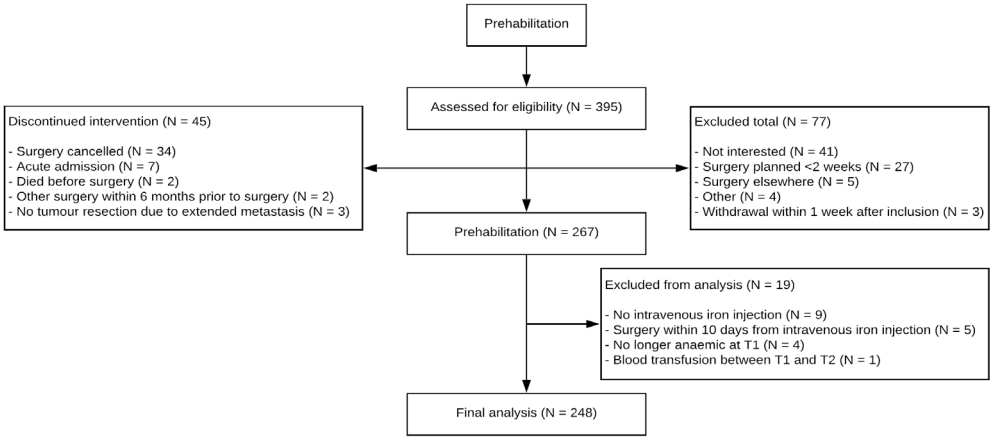
All data were prospectively stored using the electronic patient file 'Hyperspace Version IU4 (Epic, Inc., Verona, WI)' of the Amphia Hospital Breda, the Netherlands. Statistical analysis was performed using IBM SPSS statistics software (SPSS Inc., Chicago, Illinois, USA).

This research project has been registered in the Netherlands Trial Register (NTR5932) and was reported in accordance with the STROBE statement.[45] Informed consent was obtained prior to the first outpatient clinic visit.

Results

Eligibility was assessed in 395 patients (Figure 6.1). One hundred and twenty-two patients were excluded (N=77) or discontinued the intervention (N=45) due to cancelled surgery, acute admission, death or other surgery that had priority. Three more patients withdrew within one week after inclusion and three because their tumour could not be resected due to extended metastasis, leaving 267 patients who were included in this prehabilitation program.

Figure 6.1. Flow diagram



After inclusion in this prehabilitation program, 19 patients were excluded from the final analysis. Four patients received IVIS based on earlier Hb levels and were no longer anaemic during the first outpatient clinic visit. Nine patients did not receive IVIS even though they were anaemic (because of kidney failure (N=2), earlier surgery than initially planned (N=2), personal reasons (N=2) and unclear (N=3)). One patient received a blood transfusion between the first outpatient clinic visit and the surgery, and five patients had surgery within 10 days after IVIS. A total of 248 patients were included for final analysis.

Intravenous iron was administered to 97 anaemic patients (39%). Of these anaemic patients, 50 patients (52%) had anaemia due to iron deficiency. The median time from infusion to admission was 28 days (IQR 19-49 days). The median number of days from surgery to discharge was 5 (IQR 3 – 9 days). No infusion-related adverse events occurred when administering the intravenous iron. No difference in the total amount of perioperative blood loss was observed between the IVIS and SC group (p=0.67).

The baseline characteristics for the full sample and for both treatment groups are presented in Table 6.1. The median Hb level of the full sample at the outpatient clinic visit was 8.2 mmol/L (IQR 7.3 – 8.9). An AAA was diagnosed in 67 patients (27%) and 181 patients (73%) were diagnosed with CRC. Both treatment groups differed significantly in age (p=0.006), CCI (p<0.001), the number of patients diagnosed with each diagnosis (p=0.007), Hb level (p<0.001), and transferrin saturation (p=0.001) at baseline.

Table 6.1. Baseline characteristics for all patients and per treatment group

	Full sample N = 248 (%)	Intravenous ion N = 97 (39%)	Standard care N = 151 (61%)	p-value
Age in years, median (IQR)	76 (73 – 81)	78 (74 – 82)	75 (73 – 80)	0.006
Male gender	161 (65)	59 (61)	102 (68)	0.28
Charlson Comorbidity Index	6.0 (5.0 – 7.0)	7.0 – (5.5 – 8.0)	6.0 (5.0 – 7.0)	<0.001
Diagnosis				0.007
AAA	67 (27)	17 (18)	50 (33)	
CRC	181 (73)	80 (83)	101 (67)	
Surgery				0.198
Open	37 (15)	18 (19)	19 (13)	
Minimally invasive	211 (85)	79 (81)	132 (87)	
Serum concentrations				
Haemoglobin (mmol/L)	8.2 (7.3 – 8.9)	7.2 (6.1 – 7.6)	8.8 (8.4 – 9.2)	<0.001
Ferritin (µg/L)	82 (36 – 175)	58 (28 – 186)	91 (52 – 172)	0.062
Transferrin saturation (%)	20.0 (12.0 – 28.0)	14.0 (8.0 – 22.0)	23.0 (17.0 – 30.0)	0.001

IVIS and SC group – within group differences

Table 6.2 presents the Hb concentrations and iron parameter measures including differences from the baseline levels at the various time points, subdivided in the IVIS group and SC group.

For both the IVIS and the SC group, the concentration of Hb differed significantly between T1 and T2 (p<0.001 for both groups) and between T1 and T3 (IVIS p=0.008 and SC p<0.001).

A significant change in ferritin concentrations was observed at T2 and T3 compared to T1 for both groups (IVIS group: T2: 284 µg/L and T3: 322 µg/L; p<0.001 for both time points; and SC group: T2: -8.0 µg/L; p=0.012 and T3: 113 µg/L; p<0.001 respectively).

Table 6.2. Changes in serum concentrations over time of haemoglobin and iron status measures in patients receiving either treatment

	Intravenous iron N = 97	Change in serum concentration	Standard care N = 151	Change in serum concentration	p-value*
Haemoglobin (mmol/L)ϒ					
Outpatient clinic, T1	7.2 (6.1 – 7.6)	-	8.8 (8.4 – 9.2)	-	<0.001
Admission, T2	7.4 (6.9 – 8.0)	0.5 (0.1 – 1.0)§	8.6 (8.0 – 9.2)	-0.3 (-0.6 – 0.1)§	0.023
Discharge, T3	6.6 (6.0 – 7.0)	-0.4 (-1.0 – 0.4)§	7.2 (6.7 – 8.0)	-1.4 (-1.9 – 1.0)§	0.35
Iron (µmol/L)ϒ					
Outpatient clinic, T1	9.0 (5.8 – 13.0)	-	15.0 (11.0 – 19.0)	-	0.002
Admission, T2	13.0 (9.0 – 16.0)	3.0 (0.0 – 6.3)	14.5 (10.0 – 18.0)	0.0 (-4.0 – 4.0)	0.32
Discharge, T3	6.0 (4.0 – 9.0)	-2.0 (-7.0 – 2.0)§	6.0 (4.0 – 8.0)	-8.0 (-13.0 - -3.0)§	0.65
Ferritin (µg/L)ϒ					
Outpatient clinic, T1	58 (28 – 186)	-	91 (52 – 172)	-	0.27
Admission, T2	350 (163 – 564)	284 (67 – 504)§	83 (45 – 147)	-8.0 (-26.0 – 11.0)§	<0.001
Discharge, T3	440 (236 – 677)	322 (139 – 562)§	192 (118 – 317)	113 (44 – 182)§	<0.001
Transferrin (µmol/L)ϒ					
Outpatient clinic, T1	31.6 (28.6 – 36.1)	-	31.4 (28.5 – 35.2)	-	0.54
Admission, T2	28.2 (24.5 – 31.5)	-5.0 (-7.9 --1.5)§	31.6 (28.6 – 35.5)	-0.3 (-1.7 – 1.7)	<0.001
Discharge, T3	21.6 (18.4 – 24.7)	-10.7 (-14.6 --7.3)§	24.4 (21.1 – 27.8)	-7.8 (-10.8 - -5.0)§	<0.001
Transferrin sat. (%)ϒ					
Outpatient clinic, T1	14 (8.0 – 22)	-	23 (17 – 30)	-	0.001
Admission, T2	22 (16 – 30)	8.0 (0.8 – 14)§	22 (16 – 30)	1.0 (-5.0 – 5.0)	0.051
Discharge, T3	16 (11 – 21)	2.0 (-7.3 – 9.0)	12 (9.0 – 17)	-9.0 (-18 - -1.0)§	0.008

Data are presented as median (IQR) and median difference (IQR).

*: Calculated between treatment groups and adjusted for baseline serum concentration, age, CCI and diagnosis (ANCOVA; p<0.05).

ϒ Significant interaction between treatment group and change in serum concentration over time for this specific laboratory result.

§: Significant difference within group for time point compared to baseline. LMM analyses were adjusted for age, CCI and diagnosis. Significance was set at p<0.025.

In the IVIS group, transferrin saturation was significantly increased at T2 compared to T1 (8.0%; p<0.001), however this difference was no longer significant at T3 (2.0%; p=0.87). In contrast, transferrin saturation did not differ significantly between T2 and T1 for the SC group (1.0%; p=0.84) and was significantly decreased at T3 compared to T1 (-9.0%; p<0.001).

IVIS group versus SC group – between group differences

The IVIS group had a significantly lower Hb concentration at T1 (7.2 vs 8.8 mmol/L; p<0.001) and T2 (7.4 vs 8.6 mmol/L; p=0.023) compared to the SC group. This difference was no longer statistically significant at T3 (6.6 vs 7.2 mmol/L; p=0.35). There was a significant interaction between the change in concentrations of Hb over time and treatment group, in favour of the IVIS group (T2: IVIS 0.5 vs SC -0.3 and T3: IVIS -0.4 vs SC -1.4; p<0.001).

Ferritin concentration did not differ between groups initially (T1; p=0.27), but were significantly higher in the IVIS group at T2 and T3 (p<0.001 for both time points). Similar to Hb concentrations, a significant interaction could be observed between the change in concentrations of ferritin over time and treatment group (p<0.001).

The transferrin saturation of the IVIS group was lower than the SC group at T1 (p=0.001), similar to the SC group at T2 (p=0.051), and higher than the SC group at T3 (p=0.008). A significant interaction between the change in transferrin saturation over time and treatment group could be observed (p<0.001).

The percentage of postoperative delirium did not differ significantly between the IVIS group and the SC group (7.2% vs 9.3%; p=0.56), as shown in Table 6.3. A similar postoperative anaemia rate (92% vs 69%, p=0.96), postoperative blood transfusion rate (14% vs 7.3%, p=0.59), complication rate (40% vs 43%, p=0.73) and length of hospital stay (6 vs 5 days, p=0.35) were observed between both groups.

Table 6.3. Adjusted regression analysis on the secondary outcomes in relation to treatment group

	Intravenous iron N = 97 (%)	Standard care N = 151 (%)	Adjusted effects Odds ratio (95% CI)	p-value*
Postoperative delirium	7 (7.2)	14 (9.3)	1.8 (0.3 – 12)	0.56
Postoperative anaemia	89 (92)	103 (69)	1.0 (0.9 – 1.1)	0.96
Postoperative blood transfusion	14 (14)	11 (7.3)	0.6 (0.1 – 3.6)	0.59
Any complication other than delirium	39 (40)	65 (43)	1.2 (0.4 – 4.0)	0.73
			Adjusted effects Coefficient (95% CI)	
Length of hospital stay, median (IQR)	6 (4 – 8)	5 (4 – 10)	-0.002 (-0.01 – 0.003)	0.35

*Adjusted for age, CCI, diagnosis and preoperative serum haemoglobin concentration.

IDA group versus OA group

Table 6.4 presents the concentrations of Hb and iron parameter measures for all time points, and the differences from baseline, in the IDA group and the OA group. Off all baseline variables, only diagnosis differed significantly between both groups (p=0.011) and was therefore adjusted for in all analyses between these groups.

The Hb concentrations were similar for both groups at T1 (p=0.34), T2 (p=0.74) and T3 (p=0.37). Additionally, no significant interaction could be observed between the change in Hb over time and type of anaemia (p=0.088). The Hb concentration was increased at T2 compared to T1 for both groups (IDA 0.6; p<0.001 and OA 0.3; p<0.001), however it was only decreased at T3 compared to T1 for the OA group (-0.6; p=0.003).

All iron parameter measures differed significantly between the IDA group and the OA group at baseline (p<0.001 for all measures). At T2 and T3, ferritin and transferrin saturation did no longer differ significantly between the IDA group and OA group (ferritin p=0.36 and p=0.16 respectively, transferrin saturation p=0.73 and 0.16 respectively). There was a significant interaction between the change in concentration and type of anaemia for both measurements (ferritin p=0.015; transferrin saturation p<0.001).

No statistically significant differences were observed for all secondary outcomes between patients with IDA and patients with OA (Table 6.5).

Table 6.4. Changes in serum concentrations over time of haemoglobin and iron status measures in patients with baseline iron deficiency anaemia and other types of anaemia

	Iron deficiency anaemia N = 50	Change in serum concentration	Other anaemia N = 47	Change in serum concentration	p-value*
Haemoglobin (mmol/L)Y					
Outpatient clinic, T1	6.7 (6.0 – 7.3)	-	7.3 (6.4 – 7.8)	-	0.34
Admission, T2	7.3 (6.9 – 7.8)	0.6 (0.2 – 1.1)§	7.6 (6.9 – 8.1)	0.3 (0 – 1.0)§	0.74
Discharge, T3	6.5 (6.1 – 7.1)	-0.1 (-0.5 – 0.5)	6.6 (5.8 – 7.0)	-0.6 (-1.3 – 0.2)§	0.37
Iron (µmol/L)Y					
Outpatient clinic, T1	6.0 (4.0 – 8.3)	-	12.5 (10.0 – 17.5)	-	<0.001
Admission, T2	11.0 (9.0–15.0)	5.0 (2.0 – 8.0)§	14.0 (10.0 – 17.0)	0 (-4.0 – 4.0)	0.77
Discharge, T3	7.0 (5.0 – 9.0)	1.0 (-1.5 – 3.5)	5.0 (4.0 – 9.0)	-6.0 (-9.5 - -3.0)§	0.54
Ferritin (µg/L)Y					
Outpatient clinic, T1	29 (18 – 37)	-	196 (104 – 381)	-	<0.001
Admission, T2	349 (164 –522)	321 (157 – 505)§	362 (153 – 813)	228 (-161 – 470)	0.36
Discharge, T3	378 (227 –513)	350 (212 – 479)§	498 (234 – 842)	303 (-22 – 592)§	0.16
Transferrin (µmol/L)Y					
Outpatient clinic, T1	33.4 (29.7–40.0)	-	29.7 (27.3 – 34.4)	-	<0.001
Admission, T2	28.4 (24.2 –32.8)	-7.0 (-9.4 - -3.9)§	27.7 (24.6 – 29.7)	-2.6 (-6.1 – 0.6)§	0.002
Discharge, T3	21.4 (18.1 –24.9)	-13.0 (-15.9 --9.7)§	21.7 (18.6 – 24.5)	-8.0 (-11.6 - -5.8)§	0.003
Transferrin sat. (%)Y					
Outpatient clinic, T1	10 (6 – 14)	-	22 (17 – 26)	-	<0.001
Admission, T2	19 (16 – 27)	9 (5 – 17)§	25 (19 – 33)	3 (-6 – 10)	0.73
Discharge, T3	18 (13 – 21)	8 (3 – 13)§	14 (10 – 21)	-7 (-11 - -1)§	0.16

Data are presented as median (IQR) and median change (IQR).

*: Calculated between treatment groups and adjusted for baseline serum concentration and diagnosis (ANCOVA; p<0.05).

Y Significant interaction between treatment group and change in serum concentration over time for this specific laboratory result.

§: Significant difference within group for time point compared to baseline. LMM analyses were adjusted for diagnosis. Significance was set at p<0.025.

Table 6.5. Adjusted regression analysis on the secondary outcomes in relation to the type of anaemia

	Iron deficiency anaemia N = 50 (%)	Other anaemia N = 47 (%)	Adjusted effects Odds ratio (95% CI)	p-value*
Postoperative delirium	2 (4.0)	5 (11)	0.3 (0.05 – 1.6)	0.16
Postoperative anaemia	48 (96)	41 (87)	3.9 (0.7 – 21)	0.12
Postoperative blood transfusion	5 (10)	9 (19)	0.4 (0.1 – 1.5)	0.19
Any complication other than delirium	18 (36)	21 (45)	0.6 (0.3 – 1.5)	0.33
			Adjusted effects Coefficient (95% CI)	
Length of hospital stay, median (IQR)	6 (5 – 8)	6 (4 – 7)	-0.01 (-0.02 – 0.003)	0.45

*Adjusted for diagnosis and preoperative serum haemoglobin concentration.

Discussion

Preoperative IVIS has been part of our prehabilitation program, which was initially developed to prevent postoperative delirium and other postoperative adverse events in older patients who underwent major abdominal surgery. All anaemic patients received 1 gram of intravenous iron at day-care, at least 10 days and optimally 5 weeks prior to surgery. This study aimed to assess the changes in Hb and iron parameter measures in patients who received IVIS as part of a prehabilitation program and to compare these changes with the changes in patients who received prehabilitation care without IVIS. Additionally, this study assessed the changes in Hb and iron parameter measures in patients with IDA and compared these to the changes in patients with OA.

As to be expected, patients who received IVIS had an increase in Hb levels (+0.5 mmol/L) at admission, compared to the slight decrease in the standard care group (-0.3 mmol/L). Moreover, the difference in Hb levels at the outpatient clinic visit was no longer present at discharge, suggesting effectiveness of the intravenous iron treatment in diminishing differences in Hb concentrations between the FC and SC group. For both groups, Hb levels significantly differed from baseline. Previous studies have reported greater increases in Hb levels after intravenous iron therapy.[1, 31, 46] This may be explained by the use of a fixed time period to assess Hb levels in these studies, while the timing for laboratory testing in the current study depended on time to operation and time to discharge. The study by Khalafallah et al. concluded that postoperative administration of intravenous iron effectively increases Hb levels 4 weeks post-surgery compared to standard care.[31] By administering the intravenous iron at least 4 weeks prior to surgery and allowing patients to prehabilitate for a period of at least 4 weeks, IVIS can be optimally utilised and a bigger effect on the Hb concentration may be expected. This may ultimately lead to better postoperative outcomes.

The change in Hb concentration did not significantly differ between patients with IDA and patients with OA. Moreover, equal Hb concentrations were observed for all time points. Initially, Hb concentrations of both groups were significantly increased at admission compared to baseline. While this led to a similar Hb concentration in the IDA group at discharge compared to baseline, it did not prevent a significant decrease in the OA group in the same timeframe. No significant differences were observed in all secondary outcomes for both the IDA and OA group, although worse rates for these outcomes were expected in the OA group due to 'ineffective' treatment. Overall results suggest a beneficial effect of IVIS in both groups. In the OA group, the beneficial effect may be attributed to functional iron deficiency, which may develop postoperatively due to perioperative blood loss.
The increased ferritin concentration at discharge in the standard care group can be explained by the acute inflammatory response as a result of the surgery. The decreased ferritin at admission in this group supports this theory. The effect of the IVIS on ferritin concentrations is demonstrated by the significantly bigger increase in ferritin concentration in the IVIS group compared to the SC group.

The difference in ferritin concentrations between IDA and OA patients that was present at baseline could no longer be observed at admission and discharge. This finding is in line with a significant difference in change in ferritin concentrations over time. Although both groups had significantly increased concentrations at discharge compared to baseline, the change in ferritin concentration was bigger in the IDA group.

The transferrin saturation in the IVIS group was 14% at admission, significantly lower than in the SC group and indicating iron deficiency. After the intravenous iron supplementation, a significant change from baseline was observed in the IVIS group, resulting in similar transferrin saturation at admission for both groups. Moreover, patients in the IVIS group ended up with higher transferrin saturation than the SC group at discharge, indicating a bigger total iron-binding capacity in the former group.

The transferrin saturation was initially lower in the IDA group than in the OA group, which matches the diagnoses. A significant difference in change in transferrin saturation between groups was observed. Although a significant increase from baseline was observed in the IDA group and a significant decrease from baseline was observed in the OA group, both groups end up with a transferrin saturation at discharge that is indicative of iron deficiency.

All above-mentioned differences between the IVIS group and the SC group, and changes within those groups, led to comparable secondary outcomes. A 2016 study by Calleja et al. demonstrated significantly less blood transfusions in anaemic CRC patients after IVIS, compared with anaemic CRC patients receiving standard care.[47] Moreover, previous studies have demonstrated an association between anaemia and an increased postoperative blood transfusion rate.[18] Although the current data does not support a hard conclusion, combined results may suggest a positive effect of IVIS because no differences were seen between the groups in the current study. No previous studies have investigated the treatment of anaemia with intravenous iron in AAA patients.

The haematinic component of the prehabilitation program may not have contributed to the decreased incidence of delirium,[10] since results of the current study do not present a difference in this outcome between both groups. However, based on previous literature, a higher incidence of delirium can be expected in anaemic patients compared to non-anaemic patients. For this reason, IVIS may have contributed to the positive effect of reducing delirium in the prehabilitation program. A randomised clinical trial should be conducted to test this hypothesis and should only implement a haematinic component in the prehabilitation program. As part of our multimodal prehabilitation program however, by combining preoperative Hb correction with other components of prehabilitation, the haematinic component may have provided a complementary beneficial effect.

Blood transfusions are associated with substantial risks and costs. One in 100 transfusions is followed by a transfusion reaction with subsequent consequences.[48] No adverse events were recorded after IVIS in this study, nor in the study by Khalafallah et al.[31] Although IVIS did not lead to a reduction in the number of postoperative blood transfusions, it is a good alternative for preoperative blood transfusions to correct anaemia since it is well-tolerated and fast,[49] and does not require prior admission to a hospital ward. Moreover, IVIS is cost-saving compared to standard care and other iron supplements.[50, 51] A German study from 2018 concluded that IVIS can potentially save 800 euro per patient.[50]

Limitations

The first part of this study is observational, and limited by the bias caused by providing IVIS only to patients with anaemia and comparing this group to non-anaemic patients who did not receive IVIS. Due to the lack of an important control group, results should be interpreted with caution and conclusions derived from these results should be considered in the light of this important source of bias. The second part, however, makes a comparison between patients with iron deficiency anaemia and other types of anaemia and provides insight into whether IVIS should be given to all anaemic patients in the prehabilitation cohort or only to the ones with low iron status.

The number of patients who were included in the second part of this manuscript was relatively low as a consequence of the study design. As a result, this study may not have been adequately powered to demonstrate differences in the secondary outcomes between patients with IDA and patients with OA.

Finally, the use of the combination of CRC and AAA patients may cause some objections since both conditions are fairly different. However, both diagnoses are common in elderly patients, have high complication rates and are associated with iron deficiency anaemia. Moreover, both conditions have previously been used in studies on delirium prevention.

Conclusions

Adding IVIS to prehabilitation programs is feasible and safe, effectively increases preoperative Hb concentrations and diminishes differences in these concentrations caused by iron deficiency. Ultimately, IVIS results in a loss of difference in postoperative Hb levels between preoperatively anaemic and non-anaemic patients. However, similar incidences of postoperative delirium, other complications and blood transfusions and an equal length of hospital stay were observed, outcomes which are usually adversely affected in an anaemic population. Based on our results, IVIS is a safe alternative for preoperative blood transfusions and may be a worthwhile addition to prehabilitation programs. These results merit further investigation.

Preoperative administration of intravenous iron can effectively increase the preoperative Hb concentration in both patients with IDA and in patients with OA. Despite the significant decrease of the Hb concentration from baseline in the latter group, Hb concentrations were similar for both groups at discharge. In combination with similar rates of all other investigated outcomes, these results suggest that no distinction should be made regarding the cause of anaemia.

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CHAPTER 7

The effects of elective aortic repair, colorectal cancer surgery and subsequent postoperative delirium on long-term quality of life, cognitive functioning and depressive symptoms in older patients

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Abstract

Introduction

This study aimed to demonstrate the impact of elective major abdominal surgery and subsequent postoperative delirium on quality of life (QOL; primary outcome), cognitive functioning and depressive symptoms (secondary outcomes) in older surgical patients.

Methods

A single-centre, longitudinal prospective cohort study was conducted between November 2015 and June 2018, including patients ≥70 years old who underwent surgery for colorectal cancer or an abdominal aortic aneurysm. They were followed-up at discharge and at 6 and 12 months after surgery until June 2019. The QOL was assessed with the World Health Organization Quality of Life-BREF questionnaire (WHOQOL-BREF). Cognitive functioning was measured with the Mini-Mental State Examination (MMSE) and depressive symptoms with the CES-D 16.

Results

In all patients (N=265), physical and psychological health were significantly lower at discharge compared to baseline ($p<0.001$ for both domains). Physical health restored after 6 months, but psychological health remained decreased for the complete study period. Psychological, social and environmental QOL were significantly worse in patients with delirium compared to patients without delirium ($p=0.001$, $p=0.006$ and $p=0.001$ respectively). Cognitive functioning was significantly lower at baseline in patients with delirium compared to those without ($p=0.006$). Patients with delirium had a significantly higher CES-D 16 score compared to those without after 12 months ($p=0.027$).

Conclusion

Physical and psychological QOL were decreased in the early postoperative period. While physical health was restored after 6 and 12 months, psychological health remained impaired. After 12 months, postoperative delirium resulted in worse psychological, social and environmental QOL and more depressive symptoms. Decreased cognitive functioning may be a risk factor for delirium.

Introduction

Population demographics are shifting toward an increasing number of older patients.[1] Consequently, incidence rates of age-related diseases are likely to increase. Colorectal cancer (CRC) and abdominal aortic aneurysm (AAA) are common diseases in older patients.[2-5] Due to improvements in surgical techniques, treatment protocols during admission and cancer treatment, overall morbidity and mortality rates for both CRC and AAA have been decreasing.[4, 6-8]

When morbidity started decreasing and the overall survival increased, new outcome determinants such as quality of life (QOL) have become increasingly important for evaluating the impact of diseases and the effectiveness of treatments. For oncologic surgery patients, a variety of instruments has been developed to assess the physical and emotional impact of cancer and the effectiveness of the treatment on QOL.[9]

Some QOL questionnaires take a functional approach by reporting 'objective' outcomes (physical capabilities and complaints; SF-36, EQ-5D and EORTC QLQ-CR29), while others take an experiential approach by reporting 'subjective' outcomes (feelings about QOL, WHOQOL-100). The WHOQOL-100 questionnaire, and its derivative the WHOQOL-BREF, were developed to assess QOL based on subjective measurements.[10] These questionnaires are specifically designed to be comprehensible, to measure subjective outcomes, to include various facets of QOL and can be used cross-culturally.[10]

The diagnosis of cancer and its treatment affect quality of life and cause symptoms of depression in over 50% of cancer patients.[11, 12] Older patients, hospitalised or institutionalised patients and patients with impaired physical function or cognition are specifically prone to developing depressive symptoms.[13] Moreover, severity of depression is associated with poorer quality of life in older persons.[11, 13, 14] Depression has previously been proven to be a risk factor for delirium, especially in older patients.[15, 16]

Delirium is the most common complication in hospitalised older patients.[17, 18] It may, in turn, lead to depressive symptoms and a decreased quality of life, although studies on its effect on QOL and the association with cognitive decline and depressive symptoms in abdominal surgery patients are scarce.[19, 20] Moreover, studies that did investigate QOL in CRC patients used objective health parameters as patient-reported outcome measures (PROMs), rather than subjective PROMs.[21, 22] Patients with delirium also have an increased risk of (persistent) postoperative cognitive dysfunction and an up to 10-fold increased risk of dementia.[23-25]

This study, therefore, aimed to demonstrate the impact of (i) elective surgery for CRC and AAA and (ii) subsequent postoperative delirium on both short- and long-term QOL (primary outcome), cognition functioning and depressive symptoms (secondary outcomes) in older surgical patients.

Methods

Study design, setting, and participants

A single-centre longitudinal prospective cohort study was conducted, including patients aged 70 years or older who were scheduled to undergo elective surgery for CRC or an AAA between November 2015 and June 2018 in the Amphia hospital in Breda.[26] Eligibility was assessed for all consecutive patients during the study period during multidisciplinary meetings for colorectal cancer and vascular surgery. Patients that were acutely hospitalized or needed acute surgery, and patients who had surgery in the 6 months prior to the outpatient clinic visit were considered ineligible. All patients followed a prehabilitation program in order to optimise overall physical and nutritional health, factors of frailty and haemoglobin levels for an optimal period of 5 weeks prior to surgery, starting from the first outpatient clinic visit. Patients whose surgery was planned within 2 weeks of the multidisciplinary meeting were considered ineffectively prehabilitated and were therefore also considered ineligible. The study design and methods have been extensively reported in a protocol which has previously been published.[26]

During admission, all patients were clinically cared for according to the hospital's standardised infection prevention protocols, Enhanced Recovery After Surgery protocols and delirium prevention protocols.[27-29]

Baseline characteristics

A trained nurse practitioner collected baseline variables during the first outpatient clinic visit. The following baseline characteristics were assessed: age, gender, cognitive impairment, delirium in medical history, burden of comorbidity (using the Charlson Comorbidity Index (CCI)),[30] physical status and nutritional status.

Physical status was assessed using the KATZ-ADL score.[31] Patients with a KATZ-ADL score below the maximum score of 6 were considered physically impaired. Nutritional status was assessed using the SNAQ score.[32] A SNAQ score of ≥2 represents malnourishment.

Delirium

The delirium observation screening (DOS) score was used by ward nurses during regular rounds to screen for delirium three times a day.[33] When delirium was suspected (i.e., a DOS score ≥3), a geriatrician was consulted to confirm the diagnosis using the DSM-5 criteria or the Confusion Assessment Method.[34-36]

Outcomes

The primary outcome was QOL, specified per domain, as assessed with the WHOQOL-BREF.[37] Secondary outcomes were cognitive functioning (assessed with the Mini-Mental State Examination (MMSE)),[38] and depressive symptoms (assessed with the Center for Epidemiologic Studies Depression Scale (CES-D 16)).[39]

Quality of life

QOL was assessed using the World Health Organisation Quality of Life – BREF (WHOQOL-BREF). The WHOQOL-BREF is a 26-item, shortened version of the WHOQOL-100 questionnaire, specifically developed for assessing PROMs in large clinical trials.[37] It was developed by a worldwide collaborative to compare quality of life cross-culturally and focusses on four domains: physical health, psychological health, social relationships and environment; and is rated on a 5-point Likert scale, with a high score indicating a better quality of life.[37, 40] Two final questions assess overall quality of life. The validity and reliability of the WHOQOL-BREF have been extensively investigated in the past.[10, 37, 41] The estimated reliability in the current sample was good (Cronbach's alpha = 0.83). An overview of the contents of the WHOQOL-BREF is added at the end of this chapter as supplementary Table 1. The WHOQOL-BREF questionnaire was added as supplementary material to the original version of this manuscript and can be found online.

Cognitive functioning and depressive symptoms

Cognitive functioning was assessed using the MMSE, a validated scoring instrument to diagnose cognitive impairment with a sensitivity of 0.97.[38, 42] The score ranges from 0 to 30, with a score equal to or lower than 24 indicating cognitive impairment. The MMSE in the current sample had a moderate estimated reliability (Cronbach's alpha = 0.594).

Depressive symptoms were assessed using the CES-D 16 questionnaire. The CES-D 16 is a commonly used 16-item short self-report scale designed to measure depressive symptoms, rated on a 5-point Likert scale and has a sensitivity of 0.87.[39, 43] Questions that were left open were given a score of 1. The estimated reliability of the CES-D 16 questionnaire in the current sample was good (Cronbach's alpha = 0.876).

Follow-up

The WHOQOL-BREF was assessed at baseline (T1; the first outpatient clinic visit), at discharge (T2), after 6 months (T3) and after 1 year (T4). The MMSE and CES-D 16 were assessed at the same time points, with the exception of discharge. All outcomes were compared over time between patients who developed a delirium during admission and those that did not. Additionally, they were compared over time for all patients, and in AAA and CRC patients separately.

Statistical analysis

Continuous variables were presented as mean and standard deviation or median and interquartile range. Categorical variables were presented as frequencies with percentages. A p-value below 0.05 was considered statistically significant. Missing data for the covariates were infrequent and were not imputed.

For all outcome measures, differences between each follow-up measurement and baseline were examined by using linear mixed modelling and tested by making use of a custom hypothesis test in the SPSS syntax. To adjust these tests for multiple comparisons, statistical significance for QOL analyses was set at p=0.0167 (p=0.05/3 tests) and statistical significance for the MMSE and CES-D 16 analyses were set at p=0.025 (p=0.05/2 test). An unstructured covariance matrix was used to

model the error structure of the repeated measurements. Available data was optimally used by using full information maximum likelihood estimation, which is incorporated in the linear mixed modelling analysis. All analyses have been adjusted for the baseline characteristics that differed significantly at baseline.

The interaction between delirium and time was assessed for all outcome measures to test whether patients with delirium differ from patients without delirium in their change on that specific outcome over time ($p<0.05$). Between-group differences at specific follow-up measurements were analysed using analyses of covariance (ANCOVA), adjusting the differences on the outcome measures for differences in scores at baseline and for the baseline characteristics that differed significantly at baseline.

Bivariate correlations between QOL, depressive symptoms and cognition were assessed at baseline using Pearson correlations. To adjust for the high number of statistical tests, $p<0.01$ was considered significant.

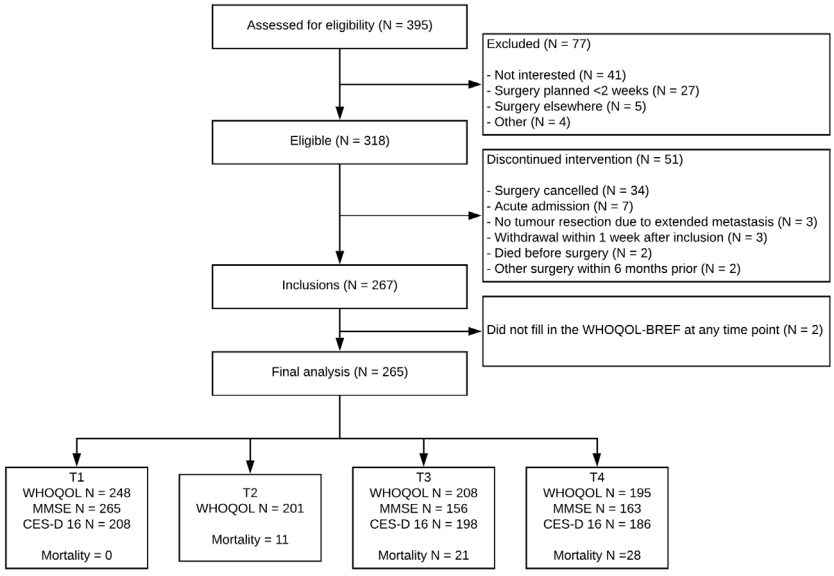
All data were prospectively stored using the electronic patient file 'Hyperspace Version IU4 (Epic, Inc., Verona, WI)' of the Amphia Hospital Breda, the Netherlands. Statistical analyses were performed using IBM SPSS statistics software (SPSS Inc., Chicago, Illinois, USA).

This research project has been retrospectively registered in the Netherlands Trial Register (NTR5932). This manuscript was reported in accordance with the CONSORT guidelines.[44]

Results

Eligibility was assessed in 395 patients. Seventy-seven patients were excluded for reasons shown in Figure 7.1, leaving a total of 318 patients. The intervention was discontinued in 51 patients, in the majority of the cases because surgery was cancelled. Reasons for and numbers of discontinuing the intervention are shown in Figure 7.1. A total of 267 patients were included in this study, of which 265 patients completed the WHOQOL-BREF at any time point and were therefore included in the analysis. The remaining two patients were excluded.

Figure 7.1. Flow diagram



Baseline characteristics and differences in these characteristics between patients with and without delirium are presented in Table 7.1. Differences for these characteristics between diagnoses were added to the original version of this manuscript as a supplement and can be found online (supplementary table 2). Significantly more patients with delirium were cognitively impaired prior to surgery (p=0.035) and had a higher CCI (p=0.03) compared to the patients without delirium. More AAA patients underwent open repair (26% AAA vs 12% CRC), while CRC patients more often underwent minimally invasive surgery (88% CRC vs 74% AAA; p=0.006).

Table 7.1. Full sample baseline characteristics and baseline characteristics for patients with and without delirium

	All patients N = 265	Delirium N = 21 (7.9%)	No delirium N = 244 (92%)
Age, median (IQR)	76 (73 – 81)	78 (74 – 85)	76 (73 – 81)
Male gender	171 (65)	14 (67)	157 (64)
(Burden of) comorbidities			
Cognitive impairment	17 (6.4)	4 (19)	13 (5.3)*
History of delirium	16 (6.0)	3 (14)	13 (5.3)
CCI, median (IQR)	6 (5 – 7)	7 (6 – 10)	6 (5 – 7)*
Physical impairment			
KATZ-ADL score ≤5	59 (22)	6 (29)	53 (22)
Malnourishment			
SNAQ score ≥ 3	45 (17)	5 (24)	40 (16)
Surgery			
Open surgery	41 (16)	4 (19)	37 (15)
Laparoscopic surgery	176 (66)	16 (76)	160 (66)
Endovascular surgery	48 (18)	1 (4.8)	47 (19)

CCI: Charlson comorbidity index; KATZ-ADL: Katz Activities of Daily Living; SNAQ: Short Nutritional Assessment Questionnaire

*: Significant difference between patients with and without delirium ($p<0.05$).

Quality of life after surgery

Table 7.2 presents the QOL domain scores for the entire population and for both diagnoses separately. The QOL in the *social relationships, environment and overall domain* was not affected by the surgery for all patient groups, since no significant differences could be observed between diagnoses or between time points. Additionally, QOL scores in the *physical and psychological health* domains did not differ between both diagnoses after correcting for differences at baseline.

At discharge, *physical health* was significantly decreased compared to baseline in all patient groups (all patients 14.2 vs 15.0, $p<0.001$; CRC 14.3 vs 15.0, $p=0.001$; AAA 14.0 vs 15.1, $p=0.002$). After 6 and 12 months, physical health scores returned to baseline scores.

Table 7.2. Quality of Life for all patients and per diagnosis

	All patients	CRC patients	AAA patients
Physical health			
Baseline	15.0 (2.9)	15.0 (3.0)	15.1 (2.7)
Discharge	14.2 (2.9)[a]	14.3 (2.8)[a]	14.0 (3.1)[a]
6 months	15.2 (2.7)	15.3 (2.7)	15.0 (2.8)
12 months	15.3 (2.8)	15.4 (2.8)	14.9 (2.9)
Psychological health			
Baseline	15.5 (2.3)	15.3 (2.4)	15.8 (1.9)
Discharge	15.0 (2.3)[a]	14.8 (2.4)[a]	15.6 (2.1)
6 months	15.1 (2.4)[a]	15.0 (2.4)	15.3 (2.3)[a]
12 months	15.1 (2.3)[a]	15.1 (2.3)	15.1 (2.5)[a]
Social relationships			
Baseline	15.7 (2.6)	15.7 (2.5)	15.5 (2.6)
Discharge	15.9 (2.5)	15.9 (2.5)	15.8 (2.3)
6 months	15.5 (2.7)	15.5 (2.8)	15.4 (2.6)
12 months	15.3 (3.0)	15.5 (3.0)	14.9 (3.0)
Environment			
Baseline	16.4 (2.1)	16.3 (2.2)	16.5 (1.9)
Discharge	16.2 (2.4)	16.1 (2.3)	16.3 (2.5)
6 months	16.2 (2.3)	16.1 (2.3)	16.3 (2.4)
12 months	16.2 (2.2)	16.2 (2.2)	16.1 (2.2)
Overall			
Baseline	3.6 (0.8)	3.6 (0.8)	3.7 (0.6)
Discharge	3.7 (0.7)	3.7 (0.7)	3.7 (0.7)
6 months	3.7 (0.7)	3.7 (0.7)	3.7 (0.7)
12 months	3.7 (0.8)	3.7 (0.8)	3.7 (0.7)

Data are presented as mean (SD).

a: Significant difference within diagnosis group between time point and baseline (linear mixed modelling, adjusted for gender, cognitive impairment, CCI, SNAQ score and type of surgery; $p<0.0167$).

No significant differences were observed between diagnoses after correction for baseline score, gender, cognitive impairment, CCI, SNAQ score and type of surgery (ANCOVA; $p<0.05$).

No significant interaction was found between time and diagnosis for all QOL domains.

For AAA patients, *psychological health* was significantly decreased after 6 and 12 months compared to baseline (15.3 vs 15.8; p=0.015 and 15.1 vs 15.8; p=0.014). In contrast, a significant decrease in QOL of CRC patients was observed at discharge compared to baseline (14.8 vs 15.3; p<0.001), while this difference was no longer present after 6 and 12 months. In all patients, psychological health was significantly decreased at discharge compared to baseline (15.0 vs 15.5; p<0.001). In contrast to physical health, this difference remained statistically significant after 6 and 12 months (15.1 vs 15.5; p=0.007 and 15.1 vs 15.5; p=0.008).

In each individual domain, no significant interaction was observed between diagnosis and time, suggesting that the change in QOL over time was not affected by the different diagnoses.

Quality of life and delirium

The QOL of patients with and without delirium is presented in Table 7.3. At baseline, patients who developed a delirium had significantly worse QOL scores in the psychological health and overall domain (14.3 vs 15.6; p=0.025 and 3.3 vs 3.7; p=0.045 respectively).
For psychological health, this difference was no longer present at discharge or after 6 months. After 12 months however, a significantly worse QOL score was again observed (12.7 vs 15.3; p=0.001). In the overall domain, no significant differences could be observed between both groups at any of the follow-up time points.

After 12 months, patients who had developed a delirium also had, similar to the *psychological health* domain, significantly worse QOL scores in the *social relationships* (p=0.006), and *environment* domains (p=0.001). Additionally, for patients who developed a delirium, QOL scores in the *social relationships* and *environment* domain were significantly decreased after 12 months compared to baseline (12.7 vs 15.2; p=0.008 and 14.0 vs 15.3; p=0.005 respectively). No significant differences were seen between time points in the other domains for the delirium group.

Physical health and *psychological health* scores were significantly lower at discharge compared to baseline for patients who did not develop a delirium (14.2 vs 15.1; p<0.001 and 15.1 vs 15.6; p<0.001, respectively). This difference in *psychological health* remained present after 6 months (p=0.007), but could no longer be observed after 12 months (p=0.035). For patients without delirium, the initial decrease in the *physical health* domain at discharge could no longer be observed after 6 and 12 months. Additionally, no significant differences were seen between time points in all other domains.

The interaction between delirium and time was statistically significant for the *psychological health* (F(3,204.836)=3.320; p=0.021), *social relationships* (F(3,213.218)=4.289; p=0.006) and *environment* domain (F(3,212.322)=5.847; p=0.001), suggesting that scores on these QOL domains change differently over time for patients with delirium compared to those without.

Table 7.3. Quality of Life in patients with and without delirium

	Delirium		No delirium	
	QOL score	N	QOL score	N
Physical health				
Baseline	13.9 (3.1)	17	15.1 (2.9)	164
Discharge	13.1 (3.8)	10	14.2 (2.8)[a]	136
6 months	14.9 (3.0)	9	15.2 (2.7)	146
12 months	13.9 (2.5)	10	15.4 (2.8)	130
Psychological health*				
Baseline	14.3 (2.8)	17	15.6 (2.2)[b]	164
Discharge	13.7 (2.8)	10	15.1 (2.3)[a]	137
6 months	14.2 (2.7)	9	15.1 (2.4)[a]	147
12 months	12.7 (2.0)	10	15.3 (2.3)[b]	129
Social relationships*				
Baseline	15.2 (3.1)	17	15.7 (2.5)	164
Discharge	15.9 (3.5)	10	15.9 (2.4)	134
6 months	14.8 (3.7)	9	15.5 (2.7)	146
12 months	12.7 (3.6)[a]	10	15.5 (2.9)[b]	130
Environment*				
Baseline	15.3 (2.6)	17	16.4 (2.1)	164
Discharge	15.6 (2.3)	10	16.2 (2.3)	136
6 months	16.3 (2.8)	9	16.2 (2.3)	147
12 months	14.0 (1.8)[a]	10	16.3 (2.2)[b]	130
Overall				
Baseline	3.3 (0.8)	17	3.7 (0.8)[b]	164
Discharge	3.5 (1.0)	10	3.7 (0.7)	137
6 months	3.7 (0.6)	9	3.7 (0.7)	146
12 months	3.3 (0.6)	10	3.7 (0.8)	130

Data are presented as mean (SD).

a: Significant difference within patient group between time point and baseline (linear mixed modelling, adjusted for diagnosis, cognitive impairment and CCI; $p<0.0167$).

b: Significant difference between both groups after correction for baseline score, diagnosis, cognitive impairment and CCI (ANCOVA; $p<0.05$).

*: Significant interaction between time and delirium for the QOL domain.

Cognitive functioning, depressive symptoms and delirium

The interaction between delirium and time failed to reach significance for the cognitive functioning score. A significantly lower cognitive functioning score was observed for patients with delirium at baseline compared to patients without delirium (27 vs 29, p=0.007), as presented in Table 7.4. After 6 months, the cognitive functioning scores of patients who did not develop a delirium were significantly decreased compared to baseline (p=0.001). This decrease remained present after 12 months (p=0.011). Cognitive functioning scores in the delirium group did not differ significantly over time.

Table 7.4. Cognitive functioning and depressive symptoms in patients with and without delirium

	Delirium		No delirium	
	Median (IQR)	N	Median (IQR)	N
MMSE score±				
Baseline	27.0 (25.5 – 29.0)	21	29.0 (27.0 – 29.0)[b]	244
6 months	27.0 (25.3 – 29.0)	8	28.0 (27.0 – 29.0)[a]	148
12 months	26.5 (23.5 – 29.3)	10	28.0 (26.0 – 29.0)[a]	153
CES-D 16¥*				
Baseline	25.0 (17.0 – 29.0)	15	20.0 (17.0 – 26.0)	203
6 months	21.0 (18.0 – 29.5)	9	19.0 (17.0 – 24.0)	194
12 months	26.0 (18.8 – 31.8)	12	19.0 (16.0 – 24.0)[c]	179

Data are presented as median (IQR).

± Corrected for diagnosis and CCI.

¥ Corrected for diagnosis, cognitive impairment and CCI.

*: Significant interaction between time and delirium for the outcome variable.

a: Significant differences within patient group between follow-up time points and baseline (linear mixed modelling, adjusted for diagnosis and CCI; p<0.0167).

b: Significant difference between both patient groups (ANCOVA; p<0.05).

c: Significant difference between both patient groups after additional correction for baseline scores (ANCOVA; p<0.05).

There was a significant interaction between delirium and time for depressive symptom scores (F(2,236.305)=3.498; p=0.032), suggesting that delirium affected the change in depressive symptoms over time. Patients who developed delirium had significantly higher depressive symptoms scores after 12 months compared to the patients who did not develop a delirium (26 vs 19; p=0.027). No significant differences were observed between both groups at baseline or after 6 months, and between time points in either group.

Quality of life, cognitive functioning and depressive symptoms

The correlations between all QOL domains, cognitive functioning and depressive symptoms are presented in Table 7.5. As expected, all QOL domains were significantly correlated with one another. Additionally, depressive symptoms were negatively and strongly correlated with all QOL domains. Cognitive functioning was neither correlated to any of the QOL domains, nor to depressive symptoms.

Table 7.5. Bivariate correlations between QOL, depressive symptoms and cognition

	Physical health	Psycho-logical health	Social relation-ships	Environment	Overall	CES-D 16	MMSE
Physical health	X	X	X	X	X	X	X
Psychological health	0.64*	X	X	X	X	X	X
Social relationships	0.42*	0.54*	X	X	X	X	X
Environment	0.66*	0.69*	0.53*	X	X	X	X
Overall	0.74*	0.65*	0.41*	0.54*	X	X	X
CES-D 16	-0.57*	-0.55*	-0.21*	-0.40*	-0.45*	X	X
MMSE	0.07	0.06	-0.01	0.09	0.03	-0.15	X

* p<0.01

Discussion

The negative effects of delirium on morbidity, mortality, institutionalisation and healthcare costs have been extensively investigated.[25, 45] New treatment outcomes to assess the effectiveness of these treatments, such as QOL, have emerged over time. This study aimed to demonstrate the changes of QOL over time and the effect of delirium on QOL, cognitive functioning, and depressive symptoms in older patients who underwent elective surgery for CRC or AAA.

Not surprisingly, the physical health domain was affected by surgery, resulting in a lower QOL at discharge for all patients as well as for both diagnoses separately. Similar to the current study, a systematic review on health status and QOL measures in older patients with CRC concluded that an immediate decline in QOL after surgery was followed by a quick recovery.[46] Physical QOL was also lower in AAA patients, even though the majority of the aortic repair surgeries are performed endovascularly. This may best be explained by the fact that most AAA patients are asymptomatic prior to elective surgery.

In all patients and in the CRC group specifically, psychological health was significantly decreased at discharge. This difference between diagnoses can most likely be attributed to the mental burden of the diagnosis of cancer. After the initial decrease in QOL in CRC patients and after the tumour was resected, psychological health was restored to baseline values after 6 and 12 months. In contrast, psychological health in AAA patients was significantly decreased after 6 and 12 months. This may possibly be due to a bigger impact of the surgery than the patient initially expected or due to a recovery that takes longer than a patient had hoped, especially since, as mentioned earlier, most elective AAA patients have no physical complaints. In all patients, QOL scores remained unchanged after the initial decrease at discharge and were also lower after 6 and 12 months compared to baseline.

In line with findings for QOL from this study, previous research on health status showed an initial decrease in the early postoperative period for the physical and psychological domains of the SF-36. For the physical health domain, scores did no longer differ significantly after six months when compared to baseline.[47] In contrast to the current study however, psychological health also no longer differed from baseline after 6 months. A possible explanation may be the different questionnaires that were used: the WHOQOL-BREF demonstrates subjective PROMs (QOL) while the SF-36 mainly presents objective PROMs (health status).

Delirium was significantly associated with a change in psychological health over time. For patients without delirium, the psychological QOL was initially decreased at discharge and remained decreased after 6 months. However, it was restored after 12 months. In line with these findings, the psychological health of patients with delirium was significantly lower after 12 months compared to the psychological health of patients without delirium. The QOL of patients with delirium was already lower to begin with, suggesting that the psychological impact of surgery may be outweighed by the impact of other factors that influence pre-surgical quality of life in patients who developed a

delirium after surgery, such as overall frailty, cognitive impairment or burden of comorbidity. This does not apply for patients who did not develop a delirium, which explains the loss of a significant difference between both groups at discharge and after 6 months.

The negative impact of postoperative delirium on long term social relationships and environment is demonstrated by the significantly lower QOL in those domains after 12 months for patients with delirium compared to those without, in combination with the lower QOL after 12 months compared to baseline in patients with delirium specifically. Both domains also had a significant interaction between delirium and QOL scores over time. Previous studies have also concluded that high-quality social contacts and relationships are an important factor in the quality of life of older patients.[48, 49] Delirium affects informal caregivers even more than patients themselves and may lead to feelings of isolation, emotional exhaustion and missing out on life, which in turn may impact the social relationships.[50-52]

At baseline, lower cognitive functioning scores were observed in patients with delirium compared to those without. This difference was no longer present after 6 and 12 months, likely because cognitive functioning scores were significantly decreased during follow-up in patients who did not develop a delirium. Other studies have previously suggested that cognitive impairment is an important risk factor for delirium,[36, 53-56] although different cut-off points for cognitive impairment were used. In the Netherlands, it is uncommon to perform elective surgery in patients who are considered moderately cognitively impaired. Cognitive functioning scores in studies involving a surgical cohort will consequently be higher. In this study, delirium did not affect change in cognitive scores over the course of 12 months. This may not have been a long enough follow-up period to achieve significant results, since previous studies have demonstrated an increased risk for dementia after three to five years.[24, 36, 57] Another explanation may be that the MMSE has limited sensitivity to detect small differences in patients with delirium and that it had a moderate reliability in this study.

Depressive symptoms were negatively associated with all QOL domains, indicating that depressive symptoms not only affect a patient's mental status, but also impact physical health, social relationships, environment and overall quality of life. Previous studies in CRC patients have also demonstrated a negative correlation between depressive symptoms and QOL.[11, 13, 14, 58] No previous studies have investigated the correlation between depressive symptoms and QOL in vascular surgical patients.

A significant interaction between delirium and time was found for depressive symptoms, which resulted in a significant difference between both patient groups after 12 months. In line with these findings, a 2017 systematic review concluded that there is an increased burden of depressive symptoms after delirium.[59] As discussed previously, PROMs have been gaining interest as an outcome measurement, because patients themselves can best describe their physical and mental wellbeing. A wide variety of quality of life questionnaires has been developed, most of which report health status rather than the emotional reflection on this health status. This makes, together with being able to universally compare quality of life between cultures, the WHOQOL-BREF the ideal choice of questionnaire. Additionally, by dividing quality of life in 5 different domains, interventions

can specifically target those domains of quality of life that are affected most. Future studies examining new delirium prevention programs or prehabilitation programs should include quality of life (measured by the WHOQOL-BREF) as an important outcome measure. These prehabilitation programs may incorporate an intervention to prevent the decrease in the psychological health domain that develops during admission, and persists during follow-up, by providing patients with adequate psychological support.[60]

This study emphasizes the not-to-be-underestimated consequences of delirium and the importance of its prevention. It does not only affect 'conventional' outcomes such as length of hospital stay, morbidity and mortality, but it also affects a patient's long-term quality of life and depressive symptoms. Previous meta-analyses recommended multicomponent interventions to prevent delirium.[20, 61] A recent study, conducted by this research group, was able to successfully reduce the incidence of delirium by means of multimodal prehabilitation.[62] New programs may use a similar approach and expand the prehabilitation modalities with psychological support programs to decrease the incidence of delirium even further.

Limitations

A limitation of this study is using the combination of AAA and CRC, even though those conditions are fairly heterogeneous. Additionally, unlike laparoscopic CRC surgery, endovascular aortic repair does not involve entering the peritoneal cavity. This combination was chosen because both are common conditions in older patients and both require surgery as definitive treatment. Past studies on delirium have also used a combination of diseases in their trials.[53-65]

The total number of events in all patients was relatively low (N=21; 7.9%). This is likely attributable to the prehabilitation program, which aimed to lower the incidence of delirium. Consequently, the risk of bias in this study was increased.

This study aimed to make a separate analysis for delirium in both conditions. However, because of the low sample size in the AAA group, results were unreliable for this group due to imprecise effect estimations. Nevertheless, no previously published studies have investigated the effects of delirium on quality of life in vascular surgical patients.

Another limitation is that working with questionnaires in older patients with delirium inevitably leads to non-response bias, even though the importance of these questionnaires was emphasized to the patient and their caregiver. Delirium has a multifactorial aetiology, is often an expression of low baseline vulnerability and precipitated by a variety of stressors. Since delirium is usually present in the more frail patients, it is likely that some patients already felt burdened by their disease and comorbidities and were, therefore, not willing to complete quality of life and depressive symptom questionnaires. Additionally, patients who experience the greatest decline in quality of life are more likely to cancel their follow-up appointments due to already being considerably burdened with a decreased quality of life as it is.

Conclusions

This study is the first to examine the effect of postoperative delirium on subjective quality of life over time in elective colorectal and aortic surgery patients. Overall, both physical and psychological QOL domains are affected by surgery and are decreased at discharge. After 6 months, physical health returned to baseline levels and remained unchanged after 12 months. Psychological health remained affected for the complete study period. Additional psychological support during follow-up should therefore be considered as an addition to current treatment protocols.

Delirium leads to significantly worse psychological, social and environmental QOL after 12 months. These results are an addition to previous outcomes and again emphasize the serious negative outcomes of delirium. The significance of the problem is highlighted by the decrease in patient-reported long-term quality of life, which may be an even more important outcome than the conventional ones. Future studies on delirium prevention should therefore include quality of life as the main outcome measure. If a patient develops a delirium, they may benefit from additional psychological, social and environmental support during follow-up.

Patients who developed a delirium already had worse psychological health and overall QOL, and lower cognitive functioning scores at baseline, suggesting that these variables are indicators of an increased risk of delirium. Future prehabilitation studies on the prevention of delirium may therefore incorporate psychological interventions in their programs and provide special attention to patients with these indicators specifically.

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Supplementary Table 1. WHOQOL-BREF domains

QOL Domain	QOL feature
Physical health	Activities of daily living
	Energy and fatigue
	Sleep and rest
	Pain and discomfort
	Dependent on medication/medical aids
	Work capacity
	Mobility
Psychological health	Positive feelings
	Negative feelings
	Self-esteem
	Bodily image and appearance
	Spirituality, religion and personal beliefs
	Thinking, learning, memory and concentration
Social relationships	Personal relationships
	Social support
	Sexual activity
Environment	Freedom
	Physical safety and security
	Physical environment (pollution, noise, traffic, climate)
	Home environment
	Financial resources
	Opportunities for acquiring new information and skills
	Participation in and opportunities for recreation/leisure activities
	Accessibility and quality of health and social care
	Transportation
Overall	Overall perception of quality of life

CHAPTER 8

Caregiver strain on informal caregivers when providing care for older patients undergoing major abdominal surgery: a longitudinal prospective cohort study

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Abstract

Introduction

Healthcare systems nowadays rely on complementary patient care by informal caregivers. The need for, and burden on, informal caregivers will likely increase in the upcoming years. This study aimed to examine the burden on caregivers when providing care for older patients undergoing major abdominal surgery.

Methods

A single-centre longitudinal cohort study was conducted between November 2015 and June 2018 in the Amphia hospital in Breda, the Netherlands. Patients aged 70 and older undergoing elective surgery for colorectal carcinoma (CRC) or an abdominal aortic aneurysm (AAA) were included in this study. Informal caregiver burden was compared over time using the Caregiver Strain Index (CSI) and was assessed at the outpatient clinic visit, at discharge, two weeks post-discharge and after 6 and 12 months. The effects of patient- and caregiver-related factors on the experienced caregiver strain were examined.

Results

CSI scores of 248 caregivers were significantly increased at discharge (3.5 vs 2.6; $p<0.001$) and two weeks post-discharge (3.3 vs 2.6; $p<0.001$). After 12 months, scores dropped below baseline scores (1.8 vs 2.6; $p=0.012$). The highest strain was observed two weeks post-discharge for AAA patients and at discharge for CRC patients. Older age, physical or cognitive impairment and burden of comorbidity were associated with an increased caregiver strain at baseline. Type of surgery was independently associated with the change in mean CSI scores over time; a bigger change in caregiver burden is observed after open surgery.

Conclusion

In the early postoperative period, perceived caregiver strain was significantly increased. Psychological support for caregivers may be advisable, with timing of this support depending on diagnosis and patient-related factors.

Introduction

Two diseases that are commonly present in older patients are colorectal cancer (CRC) and abdominal aortic aneurysms (AAA). Both conditions require major abdominal surgery and may both have serious impact on a patient's physical and mental well-being, thereby possibly requiring additional help from informal caregivers.

In CRC patients, an additional mental burden is experienced due to the diagnosis of cancer, with possible psychological problems and decreased quality of life as a consequence.[1, 2] The quality of life in cancer patients is highly and significantly correlated with their informal caregivers' quality of life.[3] According to a 2013 Dutch report, 34% of informal caregivers experience overload when providing care for patients who are suffering from psychological problems, compared to 19% of the caregivers of psychologically healthy patients.[4] Providing informal care to cancer patients negatively affects psychological health in over 90% of caregivers and physical health in nearly 10%.[5, 6]

Open or endovascular (minimally invasive) surgical repair of an AAA also has a negative effect on the short-term quality of life and health status of the patient.[7, 8] Only one previous study described the impact of AAA repair on informal caregivers,[9] even though AAA repair is considered major abdominal surgery and has considerable impact on elderly patients and their caregivers.

The number of elderly people diagnosed with above-mentioned diseases is increasing. Due to population ageing, fewer working people have to pay for the costs of sufficient healthcare for the growing elderly population. To reduce these costs, a shift from institutional care to informal- or family care is inescapable.[10] Most healthcare systems, therefore, rely on informal caregivers to play a significant role by providing complementary care.[10]

In the Netherlands, one in three adults (nearly 4.5 million) are informal caregiver and provide any form of short- or long-term care for a spouse, parent, relative, friend, or neighbour.[11] Thanks to these caregivers, both patients' quality of life and participation in society increases and the burden on and costs of the healthcare system decrease.[11] A near 8 billion euro is saved, which otherwise had to be spend on home care services.[4]

It is expected that the number of available informal caregivers per 85-year old person will decrease from 30 in 1975 and 15 in 2015, to 6 in 2040.[12] The demand for and burden on informal caregivers is expected to increase even further due to the ageing of the population, the socialisation and extramuralisation of care and budgetary restrictions in professional care.[4] In the Netherlands in 2017, nearly 10% of these caregivers experience the providing of care as a strain and a serious burden,[11] influencing caregivers' quality of life.

In accordance with the Dutch Work and Care act, caregivers can take a 2-week paid leave to provide care for a family member. After these 2 weeks, caregiving must be combined with a regular job. Five in six caregivers between 18 and 65 years old combine informal caregiving with a regular job.[11]

The well-being of informal caregivers depends on the interplay between stressors (cognitive impairment, functional disability or problem behaviour of a patient), the number of hours of informal caregiving and mediators (formal services, quality of the relationship, emotional support). An imbalance can lead to overload of the caregiver and decreased well-being.[13] The combination of informal caregiving with full-time employment also increases the risk for overload.[14] In the Netherlands, just over half of the labour force works full-time.

The aim of this study was to provide an overview of the subjective caregiver strain as experienced by informal caregivers and to examine possible patient- or caregiver-related factors influencing strain on these informal caregivers when providing informal care for elderly patients undergoing major abdominal surgery for CRC or an AAA.

Methods

Study design, setting and participants

A single-centre longitudinal cohort study was conducted in the Amphia hospital, a large teaching hospital in Breda, the Netherlands. Patients aged 70 years or older undergoing elective surgery for CRC or an AAA between November 2015 and June 2018 were included in this study. Patients were excluded if they were acutely admitted, needed acute surgery, underwent surgery in the 6 months prior to the first outpatient clinic visit, and when surgery was planned within 2 weeks of the outpatient clinic visit. Patients' physical and nutritional health status, factors of frailty and haemoglobin levels were optimised by prehabilitation in the five weeks prior to surgery. Informal caregivers were asked to visit the outpatient clinic together with the patient at each time point, in order to assess the burden experienced by these caregivers when providing care of elderly patients undergoing major abdominal surgery. No specific supporting programmes for informal caregivers were provided by the hospital, however special attention was provided to these caregivers during the first outpatient clinic visit in order to help them prepare for the burden they may experience after discharge. Written informed consent was obtained during trial enrolment, before the first outpatient clinic visit. The prehabilitation protocol has previously been published.[15]

Data collection: Informal caregiver characteristics

Informal caregiving was defined as providing any short- or long-term care to a person in the social network in need of care, complementary to institutional care.

Informal caregiver burden was assessed using the Caregiver Strain Index (CSI).[16] The CSI is a brief and reliable, 13-item dichotomous (yes/no) questionnaire developed by Robinson et al. in 1983 and validated by Post et al. in 2007,[17] designed to measure perceived burden of caregivers when providing care for a patient. The CSI questionnaire in the current sample had a good estimated reliability (Cronbach's alpha = 0.832). It comprises important domains (employment, financial, physical, social and time) and focusses on stressors which can burden the caregiver when providing care to a patient. The questionnaire has a maximum score of 13 points. A score ≥7 represents high strain. Additionally, the relation between caregiver and patient, the age of the caregiver and the distance between a caregiver's residence and the patient's residence were registered.

Informal caregivers were asked to complete the CSI during the first outpatient clinic visit (T1), at discharge (T2), two weeks post-discharge (T3), after six months (T4) and after twelve months (T5). When a patient died, the informal caregiver was no longer asked to complete the CSI.

Data collection: Patient characteristics

The following baseline demographic patient information was assessed: age, gender, cognitive impairment, burden of comorbidities (Charlson Comorbidity Index (CCI)),[18] dependence in activities of daily living (the KATZ-Activities of Daily Living (KATZ-ADL) score),[19] and nutritional health status (Short Nutritional Assessment Questionnaire (SNAQ)).[20] Patients were considered dependent in ADL when the KATZ score was less than six. Patients with a SNAQ score ≥ 3 were considered malnourished. The discharge location (home or in an institution) was registered.

Aims

The primary aim was to assess the caregiver strain across different time points using the CSI and to compare the scores over time. Secondary aims were to examine the influence of: 1) patients' age, 2) dependency in ADL, 3) type of surgery, 4) burden of comorbidity, 5) cognitive impairment and 6) development of delirium, on the perceived caregiver strain.

Statistical analysis

Dichotomous variables were presented as frequencies with percentages. Continuous variables were tested for normality using the Shapiro-Wilk test and presented as medians with interquartile ranges in case of a skewed distribution. Between-group differences for continuous variables were tested for statistical significance using the Mann-Whitney U test. A p-value below 0.05 was considered statistically significant. Missing data for the covariates was infrequent and was not imputed.

Linear mixed modelling was performed to examine the differences in mean CSI score between each time point and baseline for each diagnosis and for the total group. Generalized linear mixed models were used for the dichotomized outcome of having a CSI score of seven or higher. An unstructured covariance matrix was used to model the residual (co)variances of the repeated measurements. Analyses have been adjusted for the following covariates: age, cognitive impairment, dependence in ADL, Charlson Comorbidity Index and type of surgery. Tests for differences between the mean CSI score at baseline and each of the CSI time points during follow-up were derived directly from the mixed model by making use of the custom hypothesis test command in the SPSS syntax. Because the baseline score was compared to scores at four separate time points, the statistical significance for these tests was set at $p = 0.0125$ ($p = 0.05 / 4$ tests) in order to correct for multiple comparisons. Missing data for the CSI scores was handled through full information maximum likelihood estimation, incorporated in the linear mixed modelling analysis.

For the primary outcome measures, Cohen's d effect sizes were computed. An effect size between 0.00 and 0.30 was considered small, between 0.30 and 0.60 was considered medium and above 0.60 was considered a large effect.

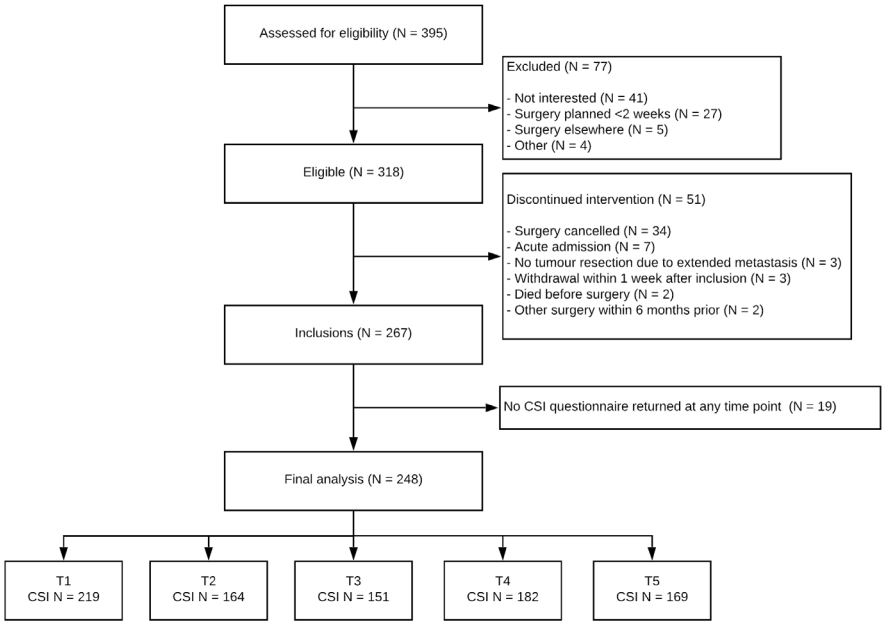
All data were prospectively stored using the electronic patient file 'Hyperspace Version IU4 (Epic, Inc., Verona, WI)' of Amphia Hospital Breda, the Netherlands. Statistical analysis was performed using IBM SPSS statistics software version 24.0 (SPSS Inc., Chicago, Illinois, USA).

This research project has been retrospectively registered in the Netherlands Trial Register (NTR5932).

Results

A flow diagram from eligibility assessment to inclusion to final analysis is shown in Figure 8.1.

Figure 8.1. Flow diagram



Eligibility was assessed in 395 patients. A total of 267 patients underwent elective surgery for CRC or an AAA from November 2015 to June 2018 and were included in this study. Of these, 248 patients (93%) had an informal caregiver who filled in the CSI questionnaire at any time point and were therefore included in this analysis. The remaining 19 patients (7%) responded that they did not have an informal caregiver and returned the questionnaires empty.

Table 8.1. Baseline characteristics of all patients

	AAA N = 64 (26%)	Colorectal cancer N = 184 (74%)	Full sample N = 248 (100%)
Age, median (IQR)	77 (72 – 81)	77 (74 – 82)	77 (73 – 81)
Male gender	53 (83)	108 (59)	161 (65)
Comorbidities			
Charlson Comorbidity Index, median (IQR)	6 (4 – 7)	6 (5 – 7)	6 (5 – 7)
Cognitive impairment	1 (1.6)	17 (9.2)	18 (7.3)
Dependent in ADL/Nutritional impairment			
KATZ-ADL score ≤5	13 (20)	44 (24)	57 (23)
SNAQ score ≥ 3	3 (4.7)	38 (21)	41 (17)
Type of surgery			
Open	14 (22)	22 (12)	36 (15)
Minimally invasive	50 (78)	162 (88)	212 (86)
Discharged home	56 (89)	154 (88)	210 (88)

Sixty-four patients (26%) underwent AAA repair and a colorectal tumour was resected in 184 patients (74%). A complete overview of baseline patient characteristics is presented in Table 8.1.

The median age of all caregivers was 70 years (IQR 54 – 75), as presented in Table 8.2. The majority of informal caregivers provided informal care for their spouse (57%) or for a parent (34%). In this cohort, children were more often involved when a patient was suffering from CRC (36% vs 27%). Less than one in seven patients lived over five kilometers away from the patient and only 11 of 219 caregivers (5%) lived over 20 kilometers away.

Table 8.2. Baseline demographic variables of informal caregivers

	AAA N = 64 (26%)	Colorectal cancer N = 184 (74%)	Full sample N = 248 (100%)
Age, median (IQR)	70 (56 – 74)	70 (53 – 76)	70 (54 – 75)
Relation to patient			
Children	17 (27)	67 (36)	84 (34)
Spouse	42 (66)	100 (54)	142 (57)
Other relative	2 (3.1)	7 (3.8)	9 (3.6)
Friend/Neighbour	0 (0)	4 (2.2)	4 (1.6)
Unknown	3 (4.7)	6 (3.3)	9 (3.6)
Distance to patient			
Living in	41 (64)	104 (57)	145 (59)
0 – 5 km	14 (22)	46 (25)	60 (24)
Over 5 km	5 (7.8)	27 (15)	32 (13)
Unknown	4 (6.3)	7 (3.8)	11 (4.4)

Table 8.3 presents mean CSI scores and the number of informal caregivers with a high burden from T1 to T5. A statistically significant increase was observed in overall CSI score in the early postoperative period (T2 3.5 vs 2.6, p<0.001; Cohen's d 0.339; and T3 3.3 vs 2.6, p<0.001; Cohen's d 0.269). The highest strain was experienced at discharge. After that, after 6- and 12-months post-surgery, CSI scores dropped below the scores at the outpatient clinic visit. This drop reached statistical significance at 12 months (1.8 vs 2.6, p=0.012; Cohen's d 0.283), showing a relief of the burden for the informal caregiver once a patient has been treated for his disease. A similar course is seen for the number of patients experiencing a high strain, according to a CSI score ≥ 7. For AAA patients, the highest perceived strain was observed two weeks after discharge and was significantly higher compared to baseline (3.7 vs 2.1, p=0.004; Cohen's d 0.514), while in CRC patients the highest strain, also significantly higher compared to baseline, was observed at discharge (3.6 vs 2.7, p=0.001; Cohen's d 0.365). In CRC patients, caregiver strain also dropped below baseline after 12 months (1.8 vs 2.7, p=0.011; Cohen's d 0.306).

Table 8.3. Caregiver strain index per time point for all patients and per diagnosis

	Outpatient clinic visit (T1)	Discharge (T2)	Two weeks post-discharge (T3)	6 months post-surgery (T4)	12 months post-surgery (T5)
AAA patients	N = 54	N = 47	N = 39	N = 46	N = 45
CSI, mean (SD)	2.1 (2.0)	3.1 (3.0)[a, d]	3.7 (3.4)[a, d]	1.4 (1.9)[d]	1.7 (2.6)[c]
CSI Score ≥ 7[b]	3 (5.6)	6 (13)	11 (28)	1 (2.2)	3 (6.7)
CRC patients	N = 165	N = 117	N = 112	N = 136	N = 124
CSI, mean (SD)	2.7 (3.0)	3.6 (3.4)[a, d]	3.1 (3.2)[a, c]	2.3 (2.9)[c]	1.8 (2.7)[a, d]
CSI Score ≥ 7	18 (11)	29 (25)[a]	15 (13)	16 (12)	11 (8.9)
All patients	N = 219	N = 164	N = 151	N = 182	N = 169
CSI, mean (SD)	2.6 (2.8)	3.5 (3.3)[a, d]	3.3 (3.2)[a, c]	2.1 (2.7)[c]	1.8 (2.7)[a, c]
CSI Score ≥ 7	21 (9.6)	35 (21)[a]	26 (17)[a]	17 (9.3)	14 (8.3)

a: Significant difference in patient group between time point and outpatient clinic visit (T1; p<0.0125)

b: Linear mixed modelling not possible due to the low number of events

c: Small Cohen's d effect size(<0.30)

d: Medium Cohen's d effect size(0.30-0.60)

The patient- and caregiver-related factors that may influence the experienced informal caregiver strain for caregivers of all patients are presented in Figures 8.2 and 8.3. Tables for these figures, together with tables divided per diagnosis, were added as supplementary material to the original version of this manuscript and can be found online (Appendices A to F).

Figure 8.2. CSI in relation to patients' age and dependency in ADL and type of surgery

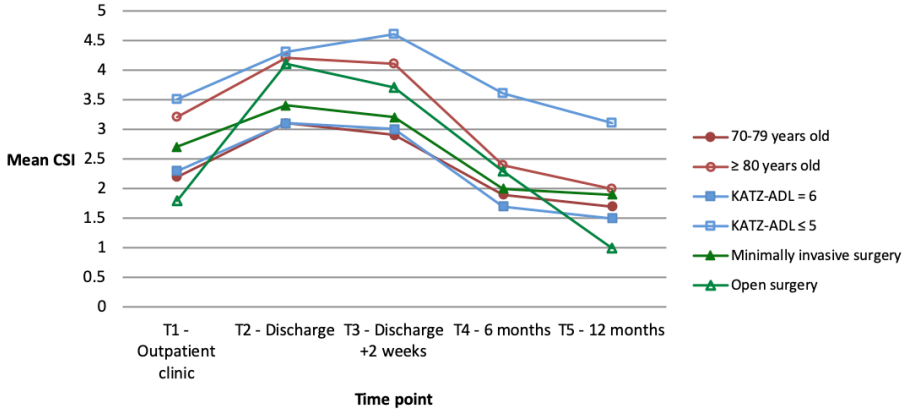
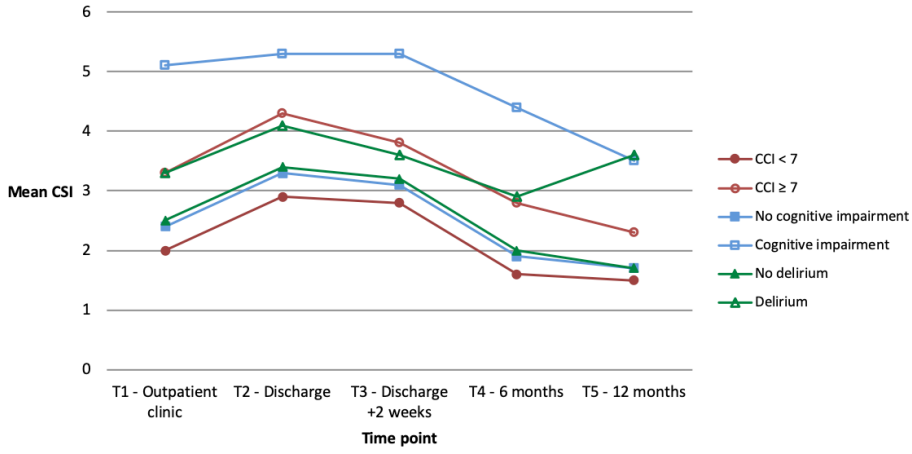


Figure 8.3. CSI in relation to patients' burden of comorbidity, cognitive status and development of delirium



The interaction between T-moment and type of surgery (F(4,189.615)=2.594; p=0.038) reached statistical significance, suggesting that type of surgery affects the change in mean CSI score over time. In contrast, the interactions between T-moment and age group (F(4,178.928)= 1.676; p=0.16), dependency in ADL (F(4,170.941)=1.338; p=0.26), burden of comorbidity (F(4,185.487)=0.148; p=0.96), cognitive impairment (F(4,171.956)=0.406; p=0.80) and delirium (F(4,202.095)=1.165; p=0.33) failed to reach statistical significance.

Figure 8.2. presents the CSI divided by patients' age group, dependency in ADL, and type of surgery. Overall, caregivers of octogenarians (80+) had a higher mean CSI score for all time points compared to those providing care for non-octogenarians, however this difference was only statistically significance at baseline (p=0.016). After 6 and 12 months, mean CSI scores for caregivers of octogenarians decreased significantly compared to baseline (p=0.008 and p=0.002 respectively). For caregivers of 70- to 79-year-olds, the experienced strain was significantly increased at T2 and T3 (p<0.001 for both time points). This difference was no longer present after 6 and 12 months. In CRC patients specifically, the mean CSI was significantly higher in caregivers of octogenarians (80+) at T1 to T3 compared to caregivers of 70-79-year olds (p=0.001, p=0.004 and p=0.050 respectively), but these differences were no longer significant after 6 and 12 months.

No significant differences were observed between follow-up and baseline in CSI scores of caregivers of patients that were dependent in ADL. Compared to caregivers of independent patients, caregivers of dependent patients perceived more strain at baseline (p=0.011), after two weeks (p=0.035), six months (p=0.001) and twelve months (p=0.001). Caregivers of independent patients had significantly higher mean CSI scores at discharge and after two weeks compared to baseline (3.2 and 2.9 vs 2.3; p<0.001 and p=0.001 respectively), and a significantly lower mean CSI score after 12 months (1.5 vs 2.3; p=0.004). After 12 months, caregivers of dependent AAA patients perceived more strain (2.9 vs 1.4; p=0.041).

For caregivers of patients undergoing open AAA repair, a statistically significant increase was seen in mean CSI score at discharge (5.2 vs 1.7; p=0.001) compared to baseline. Scores at discharge and after two weeks were also significantly higher compared to the endovascular repair group (5.2 vs 2.6, p=0.049; and 6.6 vs 2.9, p=0.008 respectively). For all caregivers, the mean CSI scores were significantly increased at discharge and two weeks post-discharge compared to baseline after minimally invasive surgery (p=0.002 and p=0.001 respectively) and at discharge compared to baseline after open surgery (p=0.002) No significant differences were observed between groups.

The CSI in relation to patients' burden of comorbidity, cognitive status, and to the development of delirium is presented in Figure 8.3. The perceived caregiver strain was significantly higher at baseline and at discharge in caregivers of patients who had a high burden of comorbidity compared to those taking care of patients with a low burden of comorbidity (p=0.001 and p=0.005 respectively). Two weeks after discharge, these differences were no longer present. The perceived caregiver burden was significantly higher at discharge and at two weeks after discharge compared to baseline in caregivers of patients with a CCI<7 (p=0.001 for both time points), and at discharge compared to baseline in caregivers of patients with a CCI≥ 7 (p=0.010). Overall, cognitive impairment seemed to influence the perceived caregiver burden, resulting in significantly higher mean CSI scores at baseline (p=0.003), at discharge (p=0.042) and after six months (p=0.015) compared to caregivers of cognitively unimpaired patients. Cognitive impairment did not affect differences in mean CSI score between follow-up and baseline. Caregivers of cognitively unimpaired patients perceived a higher burden at discharge and two weeks post-discharge compared to baseline (p<0.001 for both time points). Mean CSI scores or differences in these scores could not be calculated for caregivers of cognitively impaired AAA patients separately, due to a low number of events.

As with cognitive status, mean CSI scores or differences in these scores could not be calculated for caregivers of AAA patients with and without delirium separately. Caregivers of patients that did and did not develop a delirium during admission had a significantly higher CSI score at discharge and two weeks after discharge compared to baseline (p<0.001 for all time points). Caregivers of patients who did not develop a delirium perceived a significantly lower burden after 12 months (p=0.003), while caregivers of patients with delirium had scores that were similar to baseline.

When performing a sensitivity analysis, caregivers who were lost to follow-up provided care for patients who were more often dependent in ADL (p=0.008). No differences were observed in all other baseline variables.

Discussion

The burden on healthcare systems will increase due to population aging and the subsequent increase in the number of older patients who require additional care. To relieve this burden, these systems rely on informal caregivers to provide complementary care. Due to developments in society, the demand for and burden on informal caregivers are likely to increase. This may lead to overload and decreased quality of life of these caregivers. This study aimed to describe the caregiver strain experienced by informal caregivers when providing care for older patients undergoing elective major abdominal surgery for CRC and AAA, and the factors influencing this strain.

Caregiver strain was highest at discharge and two weeks post-discharge, emphasizing the importance of informing informal caregivers prior to surgery to prepare them for the care situation at home and of offering adequate psychological support for both patient and the patient's informal caregiver during the early postoperative period when desired. Although more research on the clinical significance of differences on the CSI scale is needed, the Cohen's d effect size for all CSI scores at discharge was medium, suggesting that these changes over time may be clinically relevant. This finding is in line with previous studies on caregiver strain on spouses of patients with laryngeal cancer and caregiver strain following orthopaedic surgery, where the highest caregiver strain is observed in caregivers shortly after discharge.[21-23] However, two of these studies did not assess caregiver strain prior to admission. Caregiver strain dropped below preoperative scores after one year in a study by Zadzilka et al., which is in line with this study.[23] In another study assessing strain in caregivers of paediatric surgical patients, a decreased score was seen at three months post-surgery when compared to baseline.[24] However, the overall caregiver strain was higher in this study and all caregivers experienced a high strain (CSI ≥ 7) for the entire study period, most likely due to the paediatric nature of the study.

The experienced caregiver strain was lower after 12 months than at baseline, suggesting that surgery was not only effective in treating the patient, but also in lowering overall caregiver burden.

Compared to previous studies, our study on average showed lower caregiver strain on informal caregivers who provide care for elderly patients with cancer.[25-28] Studies using the CSI to assess caregiver strain for caregivers of patients with neurologic diseases or neurodegenerative disorders also demonstrate a higher caregiver strain.[29, 30] However, none of the above-mentioned studies assessed differences in caregiver strain across several time points. Also, no previous study has investigated the effect of abdominal surgery on the caregiver strain over time. In the current study, no more than a quarter of caregivers experience a high strain when providing care for a patient at any time point.

The strain perceived by caregivers of CRC and AAA patients on average differs less than one point on the 13-item questionnaire. This may lead to the conclusion that the burden of these diseases, their treatments and their impact on a patient lead to comparable strain on caregivers for patients with either disease. A notable difference though, is that perceived caregiver strain for caregivers of AAA patients was highest 2 weeks after discharge, while the highest perceived caregiver strain was

highest at discharge for caregivers of CRC patients (both medium effect sizes). This difference may best be explained by the combination of physical complaints and the psychological impact of the diagnosis of cancer, while an electively treated AAA often does not come with symptoms and may therefore have less impact on a caregivers' mental burden. The timing of offering psychological support to caregivers should therefore be adjusted per diagnosis.

The strain of caregiver of octogenarians, patients that were dependent in ADL, cognitively impaired patients and of patients with a high burden of comorbidity was higher at baseline. In caregivers of these patients, the strain is not increased at discharge or two weeks post-discharge compared to baseline (with the exception of patients with a high burden of comorbidity at discharge), which suggests that the strain on these caregivers is affected more by these patient-related 'risk' factors, rather than the surgery itself. Caregivers of patients with these specific factors should therefore be better informed to prepare them for the upcoming care situation at home. Additionally, they may benefit from additional psychological support during the complete perioperative course, starting at the first outpatient clinic visit, prior to admission. Previous research demonstrated that psychological support as part of prehabilitation programs is also recommended for patients.[31] Current prehabilitation programs may therefore combine psychological support for both patient and caregiver and add this as a component to the program.[15]

In contrast, surgery significantly affects the strain on caregivers of 70-79-year olds, of patients who are independent in ADL, cognitively unimpaired patients and of patients with a lower burden of comorbidity at both discharge and two weeks post-discharge. For caregivers of patients without above-mentioned 'risk' factors, information provision and additional psychological support should focus on the early post-operative period specifically.

Open surgery and minimally invasive surgery affected the changes in caregiver strain over time differently. Healthcare professionals should anticipate to this accordingly (i.e. additional psychological support for caregivers of patients who undergo open surgery may be desirable). It is advisable to offer this support to caregivers of patients with specific factors that may influence strain, as discussed above. In patients undergoing open AAA surgery, where perceived caregiver burden is over twice as high in the early postoperative period, this additional support may be specifically important.

The caregiver strain was higher in patients who were dependent in ADL at all time points, except at discharge. This finding is in line with previous studies which found that informal caregivers who provide assistance with activities of daily living had an increased risk for overload and with that, a higher caregiver burden.[14, 32] An earlier-mentioned study on caregiver strain in caregivers of patients with (orthopaedic) hip fracture surgery also mentioned pre-fracture functional status as an important factor to influence caregiver strain negatively after one year postoperatively.[22]

The relation between caregiver burden and cognitive impairment has been extensively investigated in non-surgical patients in the past.[33] This study is one of the first to show a significant association between cognitive impairment of elderly surgical patients and perceived caregiver burden at

baseline, discharge and after six months. Scores after two weeks and 12 months were also higher but did not reach statistical significance, possibly due to the relatively low number of events. Two surgical studies have investigated this association before; one focussing on hip surgery patients and one on patients with intracranial tumours.[34, 35] In line with current research, the hip surgery study showed an association between both factors.

As mentioned earlier, preparing informal caregivers by providing them with information on the upcoming care situation at home and offering psychological support to caregivers during this period may help to lower the perceived burden. Another possible beneficial intervention may be to include them, if possible and desired, in caregiving during a patient's hospital stay, to prepare them for the upcoming care. They may be considered as partners in the care for older patients.

This research did not focus on characteristics of informal caregivers, even though these are also likely to influence the amount of strain experienced by caregivers. For example, comorbidities of the caregiver, being physically impaired and even gender are factors that may potentially influence a caregivers' burden. Future research may therefore incorporate these factors in their study.

Limitations

The CSI is a self-report questionnaire which focuses on the presence or absence of strain, experienced on different domains of informal caregiving. For each question, caregivers either experience strain, or they don't. By extending the answer scale to 1 to 5, a better experience of strain may possibly be presented, making this test more accurate and reliable. A big advantage of the CSI however, is that it has a very good internal reliability (0.90), test-retest reliability (0.88) and a high level of internal consistency ($\alpha = .90$).[36]

This study may have been underpowered to demonstrate significant effects of investigated factors on the caregiver strain in the informal caregivers of AAA patients. A trend can be observed in these analyses for AAA patients, however results often did not reach statistical significance.

This study is limited by using the combination of CRC and AAA, even though both conditions are fairly different. Including both can be justified by the fact that they have previously been used together in the definition of major abdominal surgery, are common in older patients, have a high rate of postoperative complications and require surgery as final treatment. Moreover, the strain experienced by informal caregivers is comparable for both diagnoses.

Another limitation is the relatively high percentage of attrition found in this study. At T3, only 61 percent of the informal caregivers filled in and returned the CSI questionnaire. Common reasons that were given were: "I don't want to fill in the questionnaire, I'm not a patient.", "This questionnaire does not apply to me or the patient." and "This is a bad questionnaire." Additionally, these types of questionnaires are limited by the relatively high risk of non-response bias. Caregivers of patients who require the most care are the ones most likely not to fill in follow-up questionnaires, especially when patients are considered too sick or weak to visit the outpatient clinic for their follow-up visits. The sensitivity analysis that was performed supports this theory.

This non-response bias may also be an explanation for the lack of significant results when comparing the CSI of caregivers who provided care for patients who developed a delirium and patients that did not. Another explanation may be that the CSI is not sensitive for demonstrating the caregiver burden in patients with delirium. Future studies investigating the burden of caregivers of patients with delirium may therefore use questionnaires that were specifically designed for these patients.[37]

Conclusions

A not-to-be-overlooked burden is experienced by informal caregivers when providing care for older patients who undergo elective surgery for CRC and AAA, especially in the early postoperative period. The highest strain is experienced two weeks post-discharge when providing care for AAA patients and at discharge when providing care for CRC patients. The overall caregiver strain dropped below baseline after one year. The burden on informal caregivers when providing care will increase in the upcoming years. These results emphasize the need for increased awareness for the impact of surgery on informal caregivers and the need for programmes to support these caregivers by preparing them for caregiving after discharge and to provide psychological support when necessary. This support should be timed according to the highest perceived strain per diagnosis.

Type of surgery is independently associated with the change in mean CSI scores over time; a bigger change in caregiver burden is observed after open surgery. The patient factors older age, dependency in activities of daily living, cognitive impairment and a higher burden of comorbidity are associated with a higher caregiver burden at baseline. Caregivers of patients with these factors may therefore benefit from information programmes and psychological support prior to surgery, possibly as a part of prehabilitation programs.

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CHAPTER 9

Risk factors for postoperative delirium after elective major abdominal surgery in elderly patients: a cohort study

Janssen TL, Steyerberg EW, Faes MC, Wijsman JH, Gobardhan PD, Ho GH, van der Laan L.
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Abstract

Introduction

Prehabilitation programs have recently been suggested as potentially being able to lower the incidence of delirium in older patients undergoing major abdominal surgery. For these prehabilitation programs to become successful, it is essential to identify those patients who are most likely to develop a delirium.

Methods

A single-centre cohort study was conducted. Inclusion criteria were: age ≥70 years and scheduled for abdominal surgery for colorectal cancer or an abdominal aortic aneurysm between January 2013 and June 2018. Baseline patient, surgical, anaesthesiological and haematological characteristics were collected. A risk factor analysis was conducted by performing a multivariable logistic regression analysis, with postoperative delirium as primary outcome.

Results

In this study, 627 patients were included, of whom 64 (10%) developed a delirium. Variables that differed significantly between patients with and without delirium were age, burden of comorbidity, renal impairment, hypertension, cognitive impairment, history of delirium, physical and nutritional impairment, open surgery, preoperative anaemia and erythrocyte transfusion. After multivariable logistic regression analysis, risk factors for postoperative delirium after major abdominal surgery were renal impairment (OR 2.2; 95%CI 1.2 – 4.3), cognitive impairment (OR 4.1; 95%CI 1.8 – 9.2), an ASA score ≥ 3 (OR 2.0; 95%CI 1.0 – 3.9), being an active smoker (OR 2.7; 95%CI 1.3 – 5.8), ICU admission (OR 7.1; 95%CI 3.5 – 14.3), erythrocyte transfusion (OR 2.4; 95%CI 1.2 – 4.9) and a diagnosis of colorectal cancer (CRC); (OR 4.0; 95%CI 1.7 – 9.6). Prehabilitation had a protective effect (OR 0.5; 95%CI 0.3 – 0.9).

Conclusion

Postoperative delirium is a frequent complication after major abdominal surgery in older patients, especially in octogenarians and after open procedures. Renal impairment, cognitive impairment, being an active smoker, ICU admission, erythrocyte transfusion and a diagnosis of CRC are important risk factors for the development of delirium. Prehabilitation lowers the risk of developing a delirium.

Introduction

The number of elderly patients in society has increased with 90% over the last 30 years.[1] In the upcoming 35 years, the percentage of older patients is expected to double from 8.5% in 2015 to 17% in 2050.[2] Thanks to advances in anaesthesiologic and surgical techniques, an increasing number of older patients are able to undergo surgery. As a consequence, a similar increase is expected in postoperative delirium, one of the most frequent and severe complications that occur in older surgical patients. Delirium eventually leads to increased healthcare costs and increased rates of institutionalisation, morbidity, and mortality, making it a substantial problem in our society.[3, 4]

Two conditions that require surgery and are commonly present in older patients are colorectal cancer (CRC) and abdominal aortic aneurysm (AAA). Incidence rates of delirium in vascular surgery patients vary from 5% to 39%.[5-7] Even higher incidence rates of up to 51% and a median of 24% are described in studies on colorectal cancer patients, making this a highly relevant healthcare topic.[8]

A sufficient treatment for delirium still has not been identified. Non-pharmacological treatment is the preferred initial treatment since evidence for pharmacological approaches is lacking and pharmacological treatment options are limited. Firstly, the most likely underlying cause of delirium should be treated. After that, treatment consists of tackling important precipitators of delirium, by applying the same non-pharmacological strategies as are used to prevent delirium.[9]

Strategies to prevent delirium, instead of treating it, are still considered the most effective method to decrease the incidence of postoperative delirium. This conclusion was already made by Inouye and colleagues in 1998.[10] Thirty to forty percent of delirium cases is said to be preventable.[11] Evidence from two large systematic reviews suggests that multicomponent non-pharmacological interventions, bispectral index guided anaesthesia and dexmedetomidine treatment can lower the incidence of delirium.[12, 13] Multicomponent interventions that are already widely used, such as the Hospital Elder Life Program (HELP), mainly focus on non-pharmacological interventions at the nursing wards during admission.[14, 15] Its effectiveness on reducing the incidence of delirium has been proven and HELP is now considered as a reference for standard care of older persons.[15] Prehabilitation programs have recently been suggested as a possible addition to already existing programs to reduce the incidence of delirium.[16]

Prehabilitation is the optimisation of a patient's physical, nutritional and mental health in order to withstand the stress associated with surgery. For these prehabilitation programs to become (more) successful, identification of patients who are most likely to develop a delirium, and who are therefore mostly in need of these programs, is essential. Additionally, by doing so, the healthcare burden of these programs can be kept relatively low, which is a big advantage since these programs are costly and labour-intensive. The aim of this study is to identify risk factors for postoperative delirium after elective major abdominal surgery. Future prehabilitation programs may then focus on patients with these risk factors in particular.

Methods

Study design, setting and participants

A single-centre before-and-after study was conducted, including patients aged ≥70 years who underwent elective abdominal surgery for CRC or an AAA between January 2013 and June 2018 in a large, non-university, teaching hospital in Breda, the Netherlands. Exclusion criteria were acute hospitalisation or surgery, and prior surgery within the previous six months. Extensive methods have previously been published.[16] Patients that were scheduled for surgery after November 2015 were prospectively included and followed a prehabilitation pathway in order to optimise overall physical, nutritional and mental health. The 'before' patients were retrospectively included and were not prehabilitated. Data of all included patients were prospectively stored and acquired through medical chart review. To prevent distorted results, baseline characteristics that may have been influenced by the prehabilitation program were reassessed at admission, after the prehabilitation program and prior to surgery.

All patients were clinically cared for according to the hospital's delirium prevention protocols, which are set up in accordance with the Hospital Elder Life Program.[14] Postoperative care of all CRC patients was provided according to Enhanced Recovery After Surgery (ERAS) protocols.

Data collection: Patient characteristics

The following patient characteristics were considered as potential variables influencing the development of delirium and were extracted from patient charts: age, gender, medical history (cardiac, pulmonary and neurologic comorbidities, renal impairment, diabetes mellitus, hypertension, hypercholesterolaemia), burden of comorbidity, prior diagnosis of cognitive impairment, hearing or visual impairment, history of delirium, physical dependency, nutritional status, daily alcohol use and smoking status. Renal impairment was defined as a glomerular filtration rate of <60 mL/min/1.73 m^2. Cognitive impairment was defined as a MMSE score of ≤24.

The burden of comorbidity was scored using the Charlson Comorbidity Index (CCI) and the American Society of Anaesthesiologists (ASA) score.[17, 18] The CCI ascribes points according to age and comorbidities. All included patients are aged ≥70 years, so the minimum CCI score for AAA patients was three. For colorectal cancer patients, the minimum score was five. A cut-off value of CCI ≥7 was used, based on the median CCI score.

Physical dependency was assessed using the KATZ-ADL score.[19] Patients with any score below the maximum score of 6 were considered physically impaired. Nutritional status was assessed using the SNAQ score.[20] A SNAQ score of ≥3 represents malnourishment. The KATZ-ADL score and the SNAQ score of the prehabilitated group were collected after the prehabilitation program, prior to surgery.

Data collection: Haematological, anaesthesiological and surgical data

Preoperative and postoperative blood levels of haemoglobin were tested. Women with haemoglobin levels below 7.4 mmol/L (<120 g/L) and men with levels below 8.1 mmol/L (<130 g/L)) were considered anaemic. The patients requiring blood transfusion were registered.

Data on time and method of anaesthesia were acquired by accessing anaesthesiological patient files. The length of anaesthesia was calculated as the time from intubation to extubation.

Surgeries that were performed were open abdominal aortic aneurysm repair, endovascular abdominal aortic aneurysm repair (EVAR), open colorectal resection, laparoscopic colorectal resection and robot-assisted laparoscopic colorectal resection. The type of surgery was divided into open or minimally invasive.

Delirium assessment and risk factor analysis

The primary outcome was postoperative delirium. Ward nurses screened for delirium during regular rounds using the DOS score.[21] When delirium was suspected, a geriatrician was consulted to confirm the diagnosis using the DSM-5 criteria or the Confusion Assessment Method (CAM).[22, 23] The geriatrician was not made aware of study participation and used the same standardised method for diagnosing delirium as used in non-study patients; however, the electronic patient file does show a patient's enrollment in medical research.

All collected patient, surgical, anaesthesiological and haematological characteristics were considered as potential risk factors for developing delirium.

Statistical analysis

Dichotomous variables were presented as frequencies with percentages and continuous variables were presented as medians with interquartile range. Between-group differences were tested for statistical significance using Pearson's chi-squared test in case of categorical variables and the Mann-Whitney U test in case of continuous variables.

Unadjusted and adjusted regression analyses were performed to calculate odds ratios (OR) and 95% confidence intervals (CI) for the primary outcome. All baseline patient, surgical, anaesthesiological and haematological characteristics with a univariable p-value below 0.20 were selected to simultaneously enter a multivariable logistic regression model. To correct for possible late consequences of the prehabilitation program and to correct for the combination of diagnoses, 'prehabilitation' and 'diagnosis' were inserted as variables into the model. By performing a stepwise backward elimination based on the largest p-value above 0.20, risk factors were eliminated from the model.

Effects of the risk factors were expressed as odds ratios with 95 % confidence intervals (95%CI) and p-values. An effect was considered statistically significant if its p-value dropped below 0.05.

All data will be inserted in the previously published 'Raats' model[24], to validate the model that was created to identify risk factors for delirium based on historic data from a smaller patient group from the Amphia Hospital.

All data were prospectively stored using the electronic patient file 'Hyperspace Version IU4 (Epic, Inc., Verona, WI)' of Amphia Hospital Breda, the Netherlands. Statistical analysis was performed using IBM SPSS statistics software version 24.0 (SPSS Inc., Chicago, Illinois, USA). Missing data were infrequent and not imputed.

This research project has been retrospectively registered in the Netherlands Trial Register (NTR5932).

Results

A total of 627 patients were included in this risk factor analysis, of whom 143 (23%) underwent surgery for an abdominal aortic aneurysm (45 open correction; 32%) and 484 (77%) underwent surgery for a colorectal tumour (111 open resection; 23%). The mean age was 77 years. The incidence of delirium prior to the prehabilitation program was 11.7%, while 8.2% of the patients developed a delirium post-implementation. The overall incidence of postoperative delirium was 10.2%; 7.7% in AAA patients and 11% in CRC patients. The mean length of hospital stay was 9 days. The overall mortality during admission was 3.2% and the overall complication rate was 41%.

Table 9.1. Preoperative variables in relationship to onset of postoperative delirium in all patients

	Delirium N = 64 (%)	No delirium N = 563 (%)	p-value
Age			
Age in years, median (IQR)	79 (74 – 84)	76 (73 – 80)	0.002*
70-79	34 (53.1)	397 (70.5)	0.004
≥80	30 (46.9)	166 (29.5)	
Gender			
Male	44 (68.8)	354 (62.9)	0.36
Comorbidities			
Cardiac	26 (40.6)	224 (39.8)	0.90
Pulmonary	13 (20.3)	138 (24.5)	0.46
Neurologic	24 (37.5)	147 (26.1)	0.053*
Renal impairment	25 (39.1)	105 (18.7)	<0.001*
Diabetes mellitus	18 (28.1)	108 (19.2)	0.091*
Hypertension	45 (70.3)	315 (56.0)	0.028*
Hypercholesterolemia	22 (34.4)	172 (30.6)	0.53
Cognitive impairment	16 (25.0)	28 (5.0)	<0.001*
History of delirium	10 (15.6)	26 (4.6)	0.002*
CCI, median (IQR)	7 (5 – 7)	6 (5 – 7)	0.017
CCI ≥ 7	33 (51.6)	190 (33.7)	0.005*
ASA score ≥ 3	44 (68.8)	253 (44.9)	<0.001*
Physical impairment			
KATZ-ADL score, median (IQR)	6 (5 – 6)	6 (6 – 6)	<0.001
KATZ-ADL score < 6	19 (29.7)	88 (15.6)	0.005*

Nutritional status			
SNAQ score, median (IQR)	1 (0 – 3)	0 (0 – 2)	<0.001
SNAQ score ≥ 3	21 (32.8)	102 (18.1)	0.005*
Intoxications			
Daily alcohol use	19 (29.7)	225 (40.0)	0.11*
Active smoker	15 (24.2)	86 (15.5)	0.078*
Sensory impairment			
Visual impairment	27 (42.2)	176 (31.3)	0.077*
Hearing impairment	27 (42.2)	172 (30.6)	0.058*
Diagnosis			
AAA	11 (17.2)	132 (23.4)	0.26
Colorectal carcinoma	53 (82.8)	431 (76.6)	

* Included in the multivariable logistic regression model

The percentage of octogenarians who developed a delirium was almost twice as high as the percentage of patients between 70 and 79 years old (15% vs 7.9%; p=0.004, Table 9.1). Over one in six patients who were physically or nutritionally impaired developed a delirium during admission. Delirious patients were significantly older (median age 79 vs. 76 years; p=0.002), had a significantly higher comorbidity index (median CCI 7 vs. 6; p=0.017) and were more frequently physically and nutritionally impaired (respectively 30% vs. 16%; p=0.005 and 33% vs. 18%; p=0.005). Individual comorbidities that differed significantly between groups were renal impairment, hypertension, cognitive impairment and history of delirium. The variables with a p-value below 0.20 were selected for inclusion in the logistic regression model.

Surgical, anaesthesiological and haematological variables in relation to the onset of postoperative delirium are presented in Table 9.2. Compared to minimally invasive surgery, nearly twice as many patients who underwent open surgery developed a delirium (8.3% vs 16%; p=0.006). Patients with delirium were also significantly more often anaemic preoperatively (p=0.047) or needed erythrocyte transfusion during or after surgery (p<0.001). Almost 25% of the patients who needed erythrocyte transfusion developed a delirium. Similar to Table 9.1, the variables with a p-value below 0.20 were selected for inclusion in the logistic regression model.

Table 9.2. Surgical, anaesthesiological and haematological variables in relation to onset of postoperative delirium in all patients

	Delirium N = 64 (%)	No delirium N = 563 (%)	p-value
Surgery			
Open surgery	25 (39.1)	131 (23.3)	0.006*
Minimally invasive surgery	39 (60.9)	432 (76.7)	
Anaesthesia and ICU			
Length of anaesthesia	2:30 (1:58 – 3:42)	2:35 (1:54 – 3:41)	0.99
ICU admission	30 (46.9)	69 (12.3)	<0.001*
Haematology			
Preoperative anaemia	33 (51.6)	218 (38.7)	0.047*
Postoperative anaemia†	57 (90.5)	446 (80.4)	0.051*
Erythrocyte transfusion	20 (31.3)	61 (10.8)	<0.001*

* Included in the multivariable logistic regression model

† 9 cases missing

Preoperative variables per diagnosis were added to the original version of this manuscript as supplementary material and can be found online (Appendix 1 and 2). The majority of AAA patients were male. Ten percent of AAA patients between 70 and 79 years old developed a delirium compared to only 2.3 percent of octogenarians. Only 2% of the AAA patients developed a delirium after endovascular repair, in contrast to 20% after open surgery. No AAA patients who developed a delirium have previously been diagnosed with cognitive impairment or with delirium. None of the preoperative variables varied significantly between delirious and non-delirious patients for AAA patients.

Over twice as many CRC patients over 80 years old developed a delirium compared to those aged between 70 and 79 years old (19% vs 7.2%; p<0.001). More than a third of the patients with a history of delirium and 40% of the cognitively impaired patients were diagnosed with delirium. Almost one in five physically impaired CRC patients and one in six nutritionally impaired CRC patients developed a delirium. Median age, Charlson comorbidity index, physical and nutritional impairment, smoking, and visual and hearing impairment significantly differed between delirious and non-delirious CRC patients.

Robot-assisted laparoscopic colorectal resection had the lowest percentage of delirium as a complication in CRC patients (6.3%), while 9.9% of the patients developed a delirium after laparoscopic resection and 14% after open resection. In AAA patients, type of surgery differed significantly between both groups.

Table 9.3. Multivariable logistic regression analysis of risk factors for postoperative delirium

	Coefficient	SE	Odds Ratio (95% Confidence interval)	p-value
Age per 10 years	0.47	0.29	1.6 (0.9 – 2.8)	0.10
Renal impairment	0.80	0.33	2.2 (1.2 – 4.3)	0.017
Cognitive impairment	1.41	0.42	4.1 (1.8 – 9.2)	0.001
ASA ≥ 3	0.70	0.33	2.0 (1.0 – 3.9)	0.037
Active smoker	1.01	0.38	2.7 (1.3 – 5.8)	0.009
ICU admission	1.96	0.36	7.1 (3.5 – 14.3)	<0.001
Erythrocyte transfusion	0.89	0.35	2.4 (1.2 – 4.9)	0.011
Diagnosis of CRC	1.39	0.45	4.0 (1.7 – 9.6)	0.002
Prehabilitation	-0.72	0.33	0.5 (0.3 – 0.9)	0.030

Significance of model: chi-square = 97.43; df = 9; p < 0.001.

Area under the ROC curve: 0.83 (95% CI 0.78 – 0.89).

Positive predictive value 62%; Negative predictive value 92%.

In the adjusted logistic regression analysis, the following variables were successively deleted from the model: neurologic comorbidity, hearing impairment, KATZ<6, type of surgery, daily alcohol consumption, diabetes comorbidity, postoperative anaemia, preoperative anaemia, SNAQ≥3, CCI≥7, visual impairment, hypertension, and delirium in history. Table 9.3 presents the odds ratios and 95%CI of the remaining risk factors after successive deletion based on a p-value below 0.20. Risk factors for postoperative delirium after major abdominal surgery are renal impairment (OR 2.2; 95%CI 1.2 – 4.3), cognitive impairment (OR 4.1; 95%CI 1.8 – 9.2), ASA ≥ 3 (OR 2.0; 95%CI 1.0 – 3.9), being an active smoker (OR 2.7; 95%CI 1.3 – 5.8), ICU admission (OR 7.1; 95%CI 3.5 – 14.3), erythrocyte transfusion (OR 2.4; 95%CI 1.2 – 4.9) and diagnosis of CRC (OR 4.0; 95%CI 1.7 – 9.6). The prehabilitation program has a protective effect on the development of delirium (OR 0.5; 95%CI 0.3 – 0.9).

The current data was inserted in the Raats model, to validate the model that was previously created based on historic data. Table 9.4 presents outcomes after inserting the historic data[24] and the current data into the Raats model. While the risk factors for postoperative delirium remain the same, odds ratios are lower compared to what was previously calculated. Moreover, the area under the ROC curve dropped to 0.68 (95%CI 0.61 – 0.75) when using the same three predictors that were used in the study by Raats et al. The area under the ROC curve for the newly developed model with the current data was 0.83 (95%CI 0.78 – 0.89).

Table 9.4. Comparison between the Raats model* based on historic data and based on current data: Odds ratios and area under the ROC curve

	Historic data* (95% Confidence interval)	Current data (95% Confidence interval)
Age per 10 years	2.0 (1.1 – 3.8)	1.6 (1.0 – 2.6)
Delirium in history	12 (2.7 – 50)	3.0 (1.3 – 6.8)
Katz-ADL score <6	1.7 (0.6 – 4.4)	1.5 (0.8 – 2.8)
ASA score ≥ 3	2.6 (1.1 – 5.9)	2.1 (1.2 – 3.7)
Preoperative anaemia	2.0 (0.8 – 4.8)	1.4 (0.8 – 2.3)
Area under the curve	0.76 (0.66 – 0.85)	0.68 (0.61 – 0.75)

* J.W. Raats, W.A. van Eijsden, R.M. Crolla, E.W. Steyerberg, L. van der Laan. Risk Factors and Outcomes for Postoperative Delirium after Major Surgery in Elderly Patients. PLoS One. 2015; 10(8):e0136071.

Discussion

The aging of the world's population requires new methods to prevent delirium in elderly patients, because a higher age is associated with an increase in delirium, but also in other postoperative adverse events.[25] Identification of specific risk factors that can be addressed in prevention programs is therefore imperative. This research aimed to identify risk factors for postoperative delirium in elderly patients who undergo elective major abdominal surgery. It elaborates on a previously designed prognostic model in a study conducted by Raats et al,[24] wherein higher age, delirium in medical history, and ASA≥3 were proven to be risk factors for postoperative delirium in a similar patient group.

When recalculating the area under the curve of the previous model by inserting the current data, the accuracy of the model dropped from 0.76 to 0.68. The newly created model, created with a larger population, had a much bigger accuracy of 0.83. The risk factors for postoperative delirium identified by this model are renal impairment, cognitive impairment, an ASA score ≥ 3, being an active smoker, ICU admission, erythrocyte transfusion and the diagnosis of CRC. In line with the previous study in this hospital by Raats et al,[24] but also to several meta-analyses conducted in the past,[5-8, 11] a high burden of comorbidity identified by an ASA score of three or more was found to be a risk factor for delirium. Delirium in medical history was no longer found to be a risk factor for delirium in surgical patients, a finding supported by the previously mentioned meta-analyses.

The number of older patients is likely to more than double in the next 35 years according to current projections,[26] making age a specifically important factor. In contrast to previous studies in vascular and gastrointestinal surgery however, age was not identified as an independent risk factor for postoperative delirium.[5-8, 24] Based on currents results in older patients undergoing elective major abdominal surgery, other factors are more relevant when assessing the risk for delirium and the need for prehabilitation. Prior research in CRC patients likewise concluded that age on itself was not a risk factor for postoperative adverse events, in contrast to the burden of comorbidities.[27, 28] In AAA patients, increasing age was associated with a small increase in risk for in-hospital morbidity, however comorbidities are associated with a much greater risk for postoperative complications.[29]

Cognitive impairment is a known risk factor for delirium in general medicine, non-cardiac surgery and vascular surgery patients.[7, 11, 30] Findings of the current study complement these findings by proving that cognitive impairment is also a risk factor for delirium in older patients after major abdominal surgery. Although age is associated with increased risk of cognitive impairment, it is not a risk factor for postoperative delirium on itself. This again exemplifies the importance of taking other comorbidities such as cognitive impairment into account, rather than age, when assessing whether a patient is in need for prehabilitation.

No previous studies have reported active smoking as a risk factor for delirium. History of smoking was previously described to be a risk factor for delirium in vascular surgery patients, however it is unclear whether this variable also included patients that were currently smoking.[5] It is plausible that active smokers who cannot smoke because of admission in the hospital can experience physical

and mental distress, making them more prone to developing a delirium. This finding emphasizes the importance of timely smoking cessation as a part of future prehabilitation programs.

Delirium is a frequent complication in ICU patients, with incidence rates varying widely between studies. Demonstrated by a 2015 systematic review, incidence rates vary from 9% to 91% (with an overall delirium incidence of 32%), depending on the population included per study. Previous studies have also demonstrated the association between ICU admission and delirium in vascular surgery patients. No previous studies have reported ICU admission as a risk factor for delirium in colorectal cancer patients.[5, 31, 32]

In line with two previous studies on risk factors for delirium after gastrointestinal surgery,[8, 33] erythrocyte transfusion was found to be a risk factor for postoperative delirium. This has not been reported before in vascular surgery. Precautions should be taken in future programs to prevent the need of an erythrocyte transfusion as much as possible, for instance by optimising preoperative haemoglobin levels. In CRC patients, where iron deficiency is the most frequent cause of low preoperative haemoglobin levels, intravenous iron injections can successfully increase haemoglobin levels and may therefore be a good addition to prehabilitation programs.[34, 35]

Impaired mobility[11, 36] and visual and hearing impairment[11] have previously been proven to be risk factors for delirium and are all included to be optimised by non-pharmacological approaches in the Hospital Elder Life Program.[15] Since these approaches are standard care in the study hospital, it is of no surprise that these could not be identified as risk factors for delirium in the current study.

Large prospective trials, such as the Dutch DREAM trial and a large meta-analysis based on four large prospective trials, have questioned the long-term benefits of EVAR compared to open correction for AAA since survival rates are comparable between both procedures and EVAR often needs secondary interventions.[37, 38] In this study, significantly less delirium cases were present after EVAR compared to open repair. By significantly reducing the incidence of delirium, EVAR might be more beneficial than described in the past.

Compared to AAA patients, CRC patients have an increased risk of developing delirium. This finding can also be deduced by the incidence rates of delirium in previous cohorts, with higher rates described in CRC patients.[6, 8] Based on the supplementary material, delirium is much more frequent after open aortic repair compared to after endovascular aortic repair. Since the percentage of delirium cases after EVAR is below 2%, prehabilitation of these patients might not be worthwhile.

In recent years, there has been an increasing interest in prehabilitation. Common concerns are the economic and societal costs of these programs. For now, few studies have demonstrated the advantage of prehabilitation programs in terms of conventional outcomes.[39-41] This study however, shows a protective effect of prehabilitation on the development of delirium, in line with a previous study.[42] Since the benefits of these programs are therefore hard to quantify, many of these studies may suffer from difficulties in getting funding. By identifying patients who are most at risk for developing a delirium or other postoperative complications, prehabilitation programs can be made more effective and cost-effective.

Limitations

An important limitation is the inclusion of both AAA and CRC patients for this trial. Both conditions, but also minimally invasive laparoscopic and endovascular procedures, are fairly different. Including this combination can be substantiated by the fact that both conditions are common in the elderly population and require major abdominal surgery. Within this population, postoperative complications are frequent. Previous studies on risk factors for delirium have likewise used a combination of diseases in their trials.[24, 36, 43-45] For example, Gleason et al. included 81% orthopaedic, 13% colon and 6.2% vascular patients in their study, which was published in the JAMA Surgery; Raats et al. included 22% vascular and 78% colon patients; and Schmitt et al. propose to include orthopaedic, vascular and colon patients. As a consequence of combining these conditions, a less accurate identification of risk factors per disease can be achieved and generalisability is limited. If desired, this study may be used as a basis on which future studies can build and separate risk factor analyses for CRC patients and AAA patients may be performed.

Another limitation is the issue of residual confounding, i.e. there remains a confounder for which mitigation by logistic regression is not possible. For example, there may be a beneficial effect on delirium beyond that of laparoscopic or robotic colorectal surgery that cannot be fully accounted for by grouping EVAR under the heading minimally invasive surgery, since EVAR does not involve entering the peritoneal cavity.

By making use of backward elimination based on a p-value of 0.20, after adding the prehabilitation program and the diagnosis as variables, the final model includes 9 variables. Since the number of events in this study was 64, the risk of unstable regression modelling is increased.

Finally, the prehabilitation program which was implemented halfway through the study period is a major confounder. To minimise the impact of this confounder, prehabilitation was added as a variable in the multivariable logistic regression model. By implementing the program, the incidence of delirium was lowered. Therefore, it is likely that there may be some residual confounding here as well.

Future studies

Previous meta-analyses have shown that multicomponent interventions can decrease the incidence of delirium.[12, 13, 46] Multimodal prehabilitation programs may possibly be able to achieve an additional decrease in delirium incidence.[16] For these programs to become more successful, as many risk factors for postoperative delirium as possible should be tackled simultaneously. As discussed above, smoking cessation and intravenous iron injections should be considered as components of new prehabilitation programs.

Future studies on risk factors of delirium should focus on identifying risk factors that can potentially be optimised (i.e. precipitating risk factors), rather than on risk factors that cannot be influenced (i.e. predisposing risk factors). A new study should be set-up, aiming to include more patients and to collect more preoperative precipitating risk factors for delirium. Additionally, these studies should include patients with the highest number of predisposing risk factors. This way, a delirium prediction model may be designed, identifying patients most likely to benefit from prehabilitation programs.

Conclusions

Postoperative delirium is a frequent complication after major abdominal surgery in older patients, especially in octogenarians and after open procedures. Renal and cognitive impairment, an ASA score ≥ 3, being an active smoker, ICU admission, erythrocyte transfusion and the diagnosis of CRC are important risk factors for postoperative delirium after elective major abdominal surgery. Prehabilitation has a protective effect on the development of delirium. When designing new multicomponent prehabilitation programs to decrease the incidence of delirium, studies should focus on patients with these risk factors specifically.

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CHAPTER 10 General discussion

General discussion

Growing older and staying healthy has been the newest challenge of humanity. Throughout history, our goal has always been survival by overcoming the historically most common causes of death: famine, plague and war. The scientific revolution, the industrial revolution, medical research and economic growth have made these causes of death manageable, and therefore increasingly rare. They currently only continue to exist in society because of human choices and political gain.[1]

The success of modern-day medicine prevents us from premature death, by preventing and treating diseases that have been lethal in the past, but are presently no longer lethal.[1] It allows us to grow older, consequently bringing with it new challenges such as overpopulation and age-related diseases. Today's economic and medical successes allow more and more older people to undergo surgical interventions that extent a person's life expectancy, even though this unfortunately does not always result in successful ageing and a happier life.

While surgery in itself aims to extend a person's life-expectancy, complications can be life-threatening and impose a serious risk of death; especially in older patients. Even when a complication does not lead to earlier death, it may seriously impact a patient's quality of life and with that, take away a person's joy in living. Older patients are specifically prone to adverse events after surgery due to physiological and psychological changes that go hand and hand with ageing. These changes resulting from senescence and a progressively sedentary lifestyle may lead to a condition called 'frailty', an age-related state of vulnerability which is characterised by multisystem physiologic decline and makes older patients specifically vulnerable for hospitalisation, complications and mortality.[2] Frailty can be seen as the absence of resilience (i.e. physical and mental capacity to cope with a disease and its treatment)[3] and is the most important predictor of the postoperative course in older surgical patients.[4]

A patient's resilience decreases due to aging. The resilience of cancer patients likewise decreases due to the physiological and psychological changes associated with the diagnosis of cancer,[2] such as cachexia, myopenia and sarcopenia.[5] Sarcopenia is a loss of muscle mass and function and is also a result of normal aging.[6] Moreover, surgery and possible neoadjuvant treatment may lead to a further deterioration of a patient's resilience and overall fitness.[2] Delirium, one of the most frequent complications in older surgical patients, is an expression of this absence of resilience.

Preventing the negative changes associated with the surgical diagnosis, tackling risk factors that are associated with adverse outcomes and improving surgery-related outcomes, prior to surgery, has been gaining interest in the past two decades. These preoperative optimisation, or prehabilitation, studies mainly focus on cancer patients because of the above-mentioned physiological changes that are associated with the disease. Weakened cancer patients are however not the only ones that may benefit from preoperative optimisation. Currently, only few studies focus on the highly important and in-size-increasing group of older patients. A group that is particularly at risk for postoperative delirium due to an age-related decrease in resilience and increased risk of frailty. Prehabilitation may help to increase the physiological reserve in frail patients, to atone for the functional decline

associated with surgery. Our idea is that by increasing patients' resilience, the risk of postoperative delirium may be reduced. This thesis therefore aimed to establish the best possible approach to prevent postoperative delirium, to design and asses the effectiveness of a new prehabilitation program focussing on older surgical patients specifically and to assess the impact of surgery and subsequent delirium in this patient group.

A multicomponent prevention program to prevent postoperative delirium

We conducted a review (chapter 2) to assess the effectiveness of previous interventions to prevent postoperative delirium. The majority of the 35 studies that were included, were able to successfully lower the incidence of delirium. After pooled- and sensitivity analyses, multicomponent interventions, antipsychotics, BIS-guided anaesthesia and dexmedetomidine were able to reduce the incidence of postoperative delirium. Most of these studies implemented their intervention during admission, during surgery or post-surgery, leaving out the pre-admission period in which important optimisation may be achieved. This provided us with an opportunity to fill this gap in delirium prevention by developing a new program. A unique pathway (chapter 3) with a multicomponent, multimodal approach was set up, which focused on tackling multiple important risk factors for delirium at once (i.e. physical- and nutritional impairment, anaemia and frailty). By combining this pre-admission prehabilitation program with multicomponent delirium prevention protocols that were standard care in our hospital, optimal results were expected.

It seems logical that a complication with a multifactorial aetiology such as delirium may be prevented by implementing a program which tackles multiple factors at once. When developing such a new multicomponent delirium prevention program, power calculation based on previous research in our hospital concluded that 275 patients per study arm were needed to demonstrate a possible clinically significant reduction in the incidence of delirium. This significant reduction was achieved by including a total number of 627 patients with both CRC and AAA undergoing either endovascular, laparoscopic and open surgery. For prehabilitation programs to become (more) successful in the future, specific programs should be developed per diagnosis and components should be tailor-made depending on patient-specific risk factors for delirium and other adverse events. A multicomponent personalised approach should be implemented, designed specifically to tackle those components that increase the risk of delirium in a specific patient.

Our program included patients with both major vascular and colorectal pathology, even though both diseases have a different pathophysiology. Moreover, while minimally-invasive surgery for colorectal cancer still involves entering the peritoneal cavity, minimally-invasive surgery for an abdominal aortic aneurysm is performed endovascularly and is therefore even less invasive. Ideally, for methodological strength, both diseases should be investigated separately, especially when focusing on conventional outcomes. However, the main focus of this thesis was (prevention of) delirium. Previous studies on delirium prevention strategies have likewise implemented many combinations of diseases in their research.[7,8] Because of the multifactorial aetiology of delirium, surgery is only one of many factors that increase its risk. Also, by combining both diagnoses and both types of surgery, a large number of patients could be included in this one study. To reduce the risk of bias, we corrected for diagnosis and type of surgery in all the manuscripts that were included in this thesis.

Should all patients be prehabilitated?

It has previously been proven that both diagnoses (i.e. gastrointestinal cancer and abdominal aortic aneurysm) and types of surgery (i.e. open- and minimally invasive surgery) differently affect the risk of delirium. This is confirmed by the results of this thesis: not all these patients should be prehabilitated prior to the planned intervention. Only two percent of the patients who underwent EVAR developed a delirium; compared to a ten times higher delirium rate in patients who underwent open aortic repair. Prehabilitation of the first group may therefore not be worthwhile. Almost one in five patients developed a delirium after open aortic surgery, without a significant difference between the control group and the prehabilitation group. Although the current prehabilitation program did not significantly affect the incidence of delirium after open aortic repair; its incidence and the incidence of other postoperative adverse events warrants further research to prevent these events. Simultaneously, research focusing on new designs of prehabilitation pathways should be stimulated. No other studies have been published that aimed to reduce the number of postoperative complications or delirium in vascular surgery patients by means of prehabilitation.

In contrast to minimally-invasive aortic repair, ten percent of laparoscopic colorectal surgery patients developed a delirium. Fifteen percent of open colorectal surgery patients developed a delirium, which was not significantly different from laparoscopic surgery. Because of the relatively high number of delirium cases after both types of surgery, and because of the above-mentioned physiological changes associated with the diagnosis of cancer, prehabilitation of these patients is advisable.

Haematinic optimisation

Previous studies show a trend in effectiveness of haematinic optimisation; however, quality of these studies is low and results should therefore be interpreted with caution. In line with our study, no significant effects were seen on the rate of blood transfusions,[9] even though haemoglobin levels were successfully increased. Intravenous iron injections do not affect the number of blood transfusions; however, elevated haemoglobin levels may help to eliminate one of many factors (i.e. anaemia) that influences the risk of delirium.

Quality of life

Previous studies on prehabilitation mainly focus on short-term conventional outcomes such as complications, length of hospital stay, readmission rate and short-term mortality. Many of these studies forgot to, or chose not to, incorporate quality of life as outcome in their study. While positive effects can be observed with regard to preoperative fitness and postoperative return to baseline fitness, many studies are not able to demonstrate an advantageous effect on above-mentioned conventional outcomes. This highlights the importance of shifting the focus to quality of life as study outcome.

Those studies that did focus on 'quality of life', actually investigated functional status by using questionnaires on objective quality of life. In contrast, our study is one of the few that actually assessed quality of life by using questionnaires on subjective quality of life. Our studies have demonstrated that physical and psychological quality of life are affected by surgery, but more

importantly, that delirium affects long-term psychological, social and environmental quality of life. Uniquely, we also incorporated questionnaires that examined the effects of surgery and delirium on a patient's environment, specifically: on their informal caregivers. The burden of care on informal caregivers is increased in the early postoperative period. Patients and caregivers of patients who developed a delirium during admission, may therefore benefit from postoperative rehabilitation, which should include psychological support to compensate for the loss in quality of life and the increased burden that is experienced. A medical psychologist should therefore be consulted as part of these perioperative programs, both during prehabilitation and during rehabilitation. Additionally, it may help to support colorectal cancer patients and caregivers during the first follow-up visit after admission, when the results of the pathology report are communicated. Taking the time to psychologically support AAA patients and providing them with extensive information may help to overcome the pre- and postoperative stress caused by the 'ticking time-bomb' that may explode or may have exploded in their body.

Due to the before-and-after setting of our prehabilitation study, no data on quality of life was collected for the patients and informal caregivers of the patients in the 'before' group. A new study, including a control group, on the effect of prehabilitation on patients' quality of life and caregiver burden will have to be conducted. Previous multimodal prehabilitation programs did not demonstrate a better quality of life in prehabilitated patients.[10,11] Some physical and psychological unimodal programs showed promising results; however due to the heterogeneity of studies and questionnaires, results could not be pooled.[10] The quality of life instruments used in future studies should be carefully considered, as many of these tools focus on functional status rather than quality of life. Only few studies have focused on informal caregivers; even though surgery seriously affects the burden on these caregivers. Moreover, the importance of focusing on informal caregivers will only grow due to the likely increase in their numbers in the upcoming years.

Frequently used outcomes on which other prehabilitation programs have a positive effect are all short-term: functional capacity (assessed via cardiopulmonary exercise test or 6-minute walk test), (pulmonary) complications, and length of hospital stay.[12-14] So far, no studies have provided evidence on long-term benefits of prehabilitation (e.g. better overall survival rates; increased quality of life). Common sense would suggest that a faster return to baseline fitness would result in a better short-term and even long-term quality of life, especially in older patients for whom the rehabilitation period is often longer than for younger patients. However, determining quality of life in older patients and in frail patients remains complicated due to the inevitable result of non-response in patients with a lower quality of life and in more frail patients. Adequate information provision of the importance of prehabilitation and of studies on prehabilitation, together with sufficient support provided by the treating surgeon, may help patients to see the importance of participating in and completing such prehabilitation programs.

Compliance and heterogeneity of studies

Randomised controlled trials and feasibility studies on prehabilitation are starting to accumulate. Most of these studies include fewer than 60% of the eligible patients in the final analysis and include less than 125 patients.[12,13] Thanks to the before-and-after setting of our prehabilitation study, over twice as many patients could be included in the final analysis; 84% of the eligible patients. Reasons for exclusion in these other studies are severe comorbidity or inability to complete the program, factors that are frequently observed in older patients. Moreover, patients with these factors are the ones who are most in need of preoperative optimisation. On top of high attrition rates and small populations, compliance rates vary from 16% to 100%, often only achieving high rates of compliance with expensive and time-consuming supervised exercises.[5,9,13] In our study, three in four patients were compliant with the physical exercise program. An explanation may be that older cancer patients are 'already busy surviving' and consider it an extra burden to visit the hospital more frequently, on top of the emotional burden of the diagnosis and its treatment.[15] Paradoxically, older patients are the group that may benefit most from prehabilitation.

Most of the prehabilitation studies were feasibility trials, did not have uniform endpoints and were not adequately powered to determine efficacy of treatment.[9,12,16] Several reviews on prehabilitation therefore cautiously conclude that prehabilitation may be effective, depending on the number and types of modalities that these programs include, supervised or unsupervised training, the type of surgery, the age of the patients that are included, the duration of the program and the primary endpoints. The general consensus is that a multimodal approach is more likely to improve postoperative outcomes compared to unimodal approaches, even though most studies only implemented a unimodal intervention.[9,13] The conclusions of previously published systematic reviews were that prehabilitation studies were too heterogeneous and the quality of the evidence for the investigated interventions is poor.[9,13] Our study can be added to the long list of studies with a unique pathway, focussing on its own unique population. Although our study was methodologically sound, the grade of evidence was compromised due to the risk of bias associated with the before-and-after setting.

High-quality meta-analyses are lacking due to the heterogeneity and low methodologic quality of the studies. Pooled results of the meta-analyses that were published in recent years suggest that prehabilitation may be effective in decreasing the number of short-term pulmonary complications, overall morbidity, and length of hospital stay.[14,16-18] The majority of the patients that were included in the studies included in these meta-analyses were younger than 70 years of age. Moreover, none of these studies focused on prevention of delirium. Above-described results cannot be extrapolated to our study population and therefore, and because of the ageing population, there is still much need for new methods to prevent postoperative adverse events in older patients.

The heterogeneity of studies on prehabilitation is demonstrated by the many different components that these prehabilitation pathways comprise. As discussed above, studies can choose to focus on a single component (i.e. physical optimisation, nutritional support and supplementation, smoking cessation, haematinic optimisation or psychological support), while other studies choose a multimodal approach. Within these separate components, another large variety of options still

remain. Physical optimisation for example, may comprise of aerobic exercises, resistance training or endurance training. Some of the previously published prehabilitation studies allow patients to perform these exercises at home, while other studies require structural visits to a physiotherapist in the hospital. Especially in older patients for whom frequent visits to the hospital may be a burden, the former is most desirable.

Geriatric assessment

Our prehabilitation pathway consisted of physical optimisation, nutritional support, correction of preoperative anaemia and a comprehensive geriatric assessment. These components are in line with the recommended work-up prior to surgery.[4] Analysis and optimisation of medication, determination of cognitive status and fall risk evaluation are all part of the comprehensive geriatric assessment.

In the Netherlands, current guidelines require geriatricians to perform a full geriatric assessment of all geriatric patients that are planned to undergo surgery for colorectal cancer. However, the number of geriatricians does not keep up with the growing number of older patients. As a result, nurse practitioners end up performing a full geriatric screening on these patients, rather than geriatricians themselves. The question remains, and is still not answered directly in this thesis, whether it is necessary to screen all patients of 70 years or older prior to colorectal surgery for cancer. By allowing preoperative screening of patients by a surgical nurse practitioner, the need for a full geriatric screening (i.e. comprehensive geriatric assessment; CGA) can be determined. The workload on geriatricians may be lowered by only offering CGA's to those patients who are most in need of such an assessment. For such a new system to work however, new evidence-based frailty indicators based on large clinical trials are essential. In our prehabilitation program, indicators for referral to a geriatrician were delirium in history, MMSE ≤ 24, TUG ≥ 12.6 seconds and polypharmacy. Of those patients who were not referred to a geriatrician in our study, no one developed a delirium during admission. The Dutch guidelines on geriatric assessment of older colorectal cancer patients should therefore be amended: geriatricians should be consulted preoperatively by the treating specialist when needed, rather than being involved as standard of care.

Prehabilitation and the future of eldercare

In conclusion, prehabilitation of older surgical patients seems promising but is still in its infancy. Faster return to preoperative functioning is desirable in older patients, because a sedentary lifestyle leads to an increased loss of muscle and corresponding physiological changes. Moreover, faster return to preoperative functioning may result in a faster return to preoperative quality of life. Based on a strong rationale, prehabilitation seems to be advantageous. While it effectively decreases a serious complication of surgery (i.e. postoperative delirium), still no hard evidence is available in favour of conventional outcomes.

The perioperative care of older patients is a dynamic process and needs to be reevaluated along the way. The process of delirium prevention, optimisation and fast return to baseline functioning after surgery is continuous and is not limited to the admission period; it begins prior to hospital admission and ends long after discharge. Close interdisciplinary, interprofessional and cross-sectoral collaborations are essential. For optimal care for a growing population of older patients, restructuring and optimisation of perioperative procedural pathways is required.[4]

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CHAPTER 11 Future perspectives

Future perspectives

Since the pathophysiology of delirium is still not fully understood and no evidence exists on the effectiveness of delirium treatment, primary prevention of delirium remains the focus of averting the serious adverse consequences in elderly patients that are associated with the disease. Previous systematic reviews have confirmed the effectiveness of multicomponent interventions (i.e. tackling multiple risk factors for delirium at once). By using the preoperative period, risk factors may be optimised or tackled even before this increased risk becomes clinically relevant. Prehabilitation is therefore a suitable addition to existing delirium prevention programs and should be integrated in hospitals' delirium prevention protocols in the future. Setting up such a program within hospitals requires time, money and thought. For the purpose of aiding physicians in initialising such a program and providing them with direction and guidance, Table 11.1 shows possible considerations before setting up a prehabilitation program. Before these programs can become standard practice, future studies should focus on important concerns that still remain.

Patient selection

Adequate patient selection may be key to the success of new prehabilitation programs. A specific risk profile should be conducted per patient, identifying those who are most at risk for adverse events. Although a wide variety of frailty scores have been developed in the past, none are considered the gold standard for estimating the risk of postoperative adverse outcomes.

Additionally, patients most likely to actually make improvements based on psychological and physical evaluation should be selected for prehabilitation. To set-up these risk profiles and design better prehabilitation programs, future research should focus on identifying factors which increase the risk for delirium and other adverse outcomes, and factors that are potentially optimisable.

Outcome measures

Hitherto, besides a few recent studies of limited quality and a strong rationale in favour of prehabilitation, evidence is lacking for effectiveness of these programs on conventional outcomes. Quality of life is an important outcome measure which has been getting too little attention. Moreover, when it is used, it is often still incorrectly defined. Prehabilitation studies that deemed to use ‘quality of life’ as an outcome factor actually used ‘health status.’ Quality of life is a person's opinion on whether or not they are physically or emotionally able to do things; health status factually describes a person's ability to do things. Especially for older persons, a decrease in health status does not have to lead to a decrease in quality of life. For example, when a person lives in a 1-floor apartment, their quality of life is not directly affected by a sudden inability to climb stairs. Previous studies have demonstrated a positive effect of prehabilitation on functional outcomes and conclude that prehabilitation safeguards a quicker return to baseline physical functioning. Consequently, this may have a positive effect on their quality of life. A health-economic analysis based on quality-adjusted life-years may then likely be able to show a significant cost reduction and prove cost-effectiveness of the treatment.

Technological advances

Patients may benefit from technological advances such as 'wearables', which are becoming increasingly integrated in everyday life. Wearable fitness trackers vary from pedometers, which count the number of steps taken, to smartwatches, which collect data on heart rate and quality of sleep.[1] Direct visual feedback or verbal encouragement, given by a smartwatch for example, can stimulate a person to keep going and can help motivate to perform even better the next time.[1] Moreover, wearables provide excellent data that can be used to improve and optimise prehabilitation programs. This data can be actively used to modify the intensity of the exercise program when a patient's progress starts to stagnate due to the relative decrease in resistance or strength that is needed. They also allow researchers to monitor adherence to the prehabilitation programs, even when the program consists of home-based unsupervised exercises. In turn, the barrier for patients to partake in these programs is lowered. In delirium prevention programs for older patients, apps should be customised with an easier-to-handle interface and possibly fewer complex features. Smartwatches with a single button that can change the displayed information and register data may then be ideal.

Availability and extent of information

One of the most important challenges will be providing patients with sufficient, but more importantly, understandable information. Now that evidence for the positive effects of prehabilitation programs is starting to accumulate, dispersion of information to patients and medical specialists can be invigorated. Information should be customised to the population that will be prehabilitated; which in the case of delirium will be older patients. Especially frail older patients appear to mainly see the difficulties of prehabilitation. Sufficient information provision for family and friends may also help to emphasize the importance of prehabilitation. New tools should therefore be developed to convince patients and their caregivers that tackling risk factors is essential for better postoperative results.

One such a tool is specifically developed for the PREPWELL program in the UK, which focusses on community prehabilitation and wellbeing.[2] On their website, a 2:24 minute video demonstrates the risk factors of adverse outcomes after surgery and the prehabilitation program that tackles these risk factors. It is an easy-to-understand, simple and straightforward animated video that is shown to all patients that are scheduled to undergo major surgery and is a great example of information provision.

Other types of surgical and oncologic treatment

Patients who undergo neoadjuvant cancer treatment may benefit from preoperative optimisation to compensate for the cardiopulmonary toxicity and deterioration of physical reserves as a result of radio- and chemotherapy.[3] These programs may start either before neoadjuvant treatment or after neoadjuvant treatment, but prior to surgery. Previous literature reports that prehabilitation in this patient group is safe and can increase aerobic capacity, however (favourable) results on conventional outcomes have not yet been reported.[4] A few pilot studies, mainly focusing on esophageal and rectal cancer, show promising results.[4, 7] A recent study suggests that the combination of prehabilitation and neoadjuvant chemoradiotherapy may even result in augmented tumour regression.[8]

Most studies have focused on gastrointestinal cancer patients. However, studies on prehabilitation are starting to emerge for other specialties. Examples of these specialties are gynaecology,[9] urology,[10, 11] thoracic surgery[12] and orthopaedics.[13] Results up to now are promising, showing feasible and safe programs. More ground must still be gained; more research is indispensable for future success.

Perioperative care: prehabilitation and rehabilitation

Surgical healthcare has evolved to perioperative medicine and continues even after discharge. In addition to prehabilitation, postoperative rehabilitation may be able to speed up recovery even more. This may in turn lead to the additional benefit of faster return to preoperative quality of life. Adding intensive mental support and encouragement postoperatively may provide a complementary beneficial effect, leading to an even faster return to baseline functioning and quality of life. Future studies should therefore consider to add a postoperative program which focuses on the same factors as the preoperative program.

Promotion of health and prevention of disease

Promotion of health and prevention of disease is a shared responsibility of governments, healthcare professionals and patients. Even without the presence of disease, a patient benefits from a healthier lifestyle, physical exercise and healthy nutrition. Medical devices, platforms or apps may provide additional support to monitor and change health behaviour in the future. With the help of updates and improvements in healthcare legislation, these advancements in digitalisation and process automation may be able to provide support to promote health, prevent disease and achieve better fitness. By doing so, unwanted postsurgical outcomes may be prevented. This may in the future lead to a subsequent reduction in healthcare costs and to easier and more availability of care.

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Table 11.1 Considerations for future prehabilitation studies

Prior to prehabilitation	Patient selection	- Which patients are most in need of prehabilitation? And which patients may benefit most from prehabilitation? - Which inclusion criteria can best select those patients for prehabilitation?
	Outcome measures	- What are the main goals? Better quality of life, faster return to baseline fitness or better conventional outcomes? - Which questionnaire(s) should be used to capture the most relevant aspects of quality of life? - Should a health-economic analysis be included?
	Timeline	- From diagnosis to treatment, what is the maximum allowed delay? - Should all patients be prehabilitated for the same number of days? Or should there be a minimum number of days? - How often should patients go to which modality of the prehabilitation program?
	Availability and extent of information	- How to inform patients and their family or caregivers? - How to achieve optimal adherence? - Should the method of information extension be customised depending on age or level of education?
	Location of prehabilitation and progress monitoring	- How often should a patient's progress be monitored or evaluated? - Where should this progress be monitored? In the hospital? At a physiotherapist near a patient's home? - Should the participating physiotherapists follow a training? Or are they provided with written information/ instructions?
	Feedback	- Should patients receive direct visible feedback by an app or smartwatch? What information should be provided to patients, their caregivers, and family?
Prehabilitation	Physical	- Are all patients given tailor-made, individualized exercises? Or do all patients follow the same program? - What kind of exercises should patients do? High-intensity interval training, resistance training and/or endurance training? Breathing exercises and/or aerobic exercises? - How often do patients need to do these exercises? Multiple times a day? Daily? Multiple times a week? - Where do patients do these exercises? Home-based, hospital-based, clinic-based or both combined?
	Psychological	- At diagnosis, should all patients be offered psychological support?

	Psychological	- Should psychological support also be offered to informal caregivers? - Should patients receive psychological support during follow-up meetings to improve motivation for physical exercises?
	Nutrition	- What questionnaires are used to screen for under- or malnutrition? - Are all patients provided with additional protein to optimise their caloric and protein intake? - What are the criteria for vitamin supplementation or additional protein drinks?
	Haematinic optimisation	- Should intravenous iron be given to all patients? Or only those with iron deficiency anaemia? - Can intravenous iron be administered in day-care, optimally for 4-5 weeks prior to surgery?
	Smoking cessation	- What is the most effective way to inform patients of the importance of smoking cessation? - Are patients actively offered a smoking cessation program? Within the hospital? Or in a clinic?
	Comprehensive Geriatric Assessment	- Should all patients be screened by a geriatrician? - If not, what are the criteria for sending a patient to be screened by a geriatrician?
Admission	Enhanced recovery and complication prevention	- Are protocols available for enhanced recovery after surgery, infection prevention, delirium prevention? - Are these protocols and other protocols that may accelerate recovery and prevent complications adequate and up-to-date?
Post-discharge	Prevention of discharge delay	- What will most likely be the level of care this patient needs after discharge? No additional care, home-care, a nursing home or a medical rehabilitation clinic? - Based on the most-likely level of care that is needed, can arrangements be made prior to admission to secure a discharge location, in order to prevent discharge delay?
	Post-discharge rehabilitation and follow-up	- Are patients offered post-discharge rehabilitation support in order to achieve a faster return to baseline fitness? - Should post-discharge rehabilitation exercises be offered in the hospital or are patients given a letter with instructions for a medical rehabilitation clinic or a physiotherapist near home to continue rehabilitation? - What will be the frequency of follow-up visits?

APPENDICES

Summary

The ageing of the world's population requires new methods to prevent adverse outcomes in older patients after surgery. Delirium is one of the most frequent postoperative complications in this population and is associated with serious consequences such as prolonged hospitalisation, institutionalisation, increased healthcare costs, morbidity and mortality.

The pathophysiology of delirium remains unclear. The syndrome itself seems to be an expression of depleted reserves, which in turn decreases a patient's resilience and makes a patient more frail. This frailty, and with that the risk of delirium, is increased due to an accumulation of predisposing risk factors. A delirium may be triggered due to precipitating risk factors that shift the balance and overflow a patient's resilience.

This thesis aimed I) to identify the most successful delirium prevention methods based on currently available literature, II) to develop a new intervention to prevent postoperative delirium in older surgical patients and to assess the outcomes of this intervention, III) to assess the impact of surgery and subsequent delirium on the quality of life of patients and its strain on caregivers, and IV) to elaborate on these results by providing suggestions for future prehabilitation programs and to identify patients who are most likely in need of these programs.

In Chapter 2, we performed a systematic review and meta-analysis and identified 35 studies on delirium prevention in older surgical patients. Overall, these studies were heterogeneous and lacked good quality. Delirium can be prevented by implementing multicomponent interventions, by using antipsychotics during admission, by controlling the depth of anaesthesia by using bispectral index guidance and by treating patients with dexmedetomidine.

We designed a new multicomponent prehabilitation intervention and presented the study protocol for this uncontrolled before-and-after trial in Chapter 3. The hypothesis of this study was that prehabilitation of patients prior to abdominal surgery for an abdominal aortic aneurysm or colorectal cancer could reduce the incidence of delirium, length of hospital stays, and rates of complications, institutionalisation and mortality.

The short-term and long-term outcomes of the prehabilitation program were presented in Chapters 4 and 5. The study was powered to reduce the incidence of delirium, which it was able to demonstrate. No significant effects were observed on all other outcomes, for all patients, but also per diagnosis. Mortality rates after prehabilitation did not differ in the early postoperative period or after one year. Chapter 5 demonstrated that postoperative delirium increases the risk of 1-year mortality over 4 times and that it is associated with decreased functional outcomes after 6 and 12 months.

In Chapter 6, we investigated the safety and effectiveness of intravenous iron supplementation and demonstrated that it may be worthwhile as an addition to future prehabilitation programs. Intravenous iron supplementation diminishes differences in haemoglobin levels between preoperatively anaemic and non-anaemic patients by effectively increasing low preoperative serum haemoglobin concentrations in anaemic patients, regardless of the type of anaemia.

Current research in medicine has been increasingly focusing on new outcomes when advances of new treatments on conventional outcomes started to stagnate. The quality of the remaining life, rather than the length of it, is the topic that stands out nowadays and was therefore the focus of Chapters 7 and 8. In Chapter 7, we demonstrated the effect of surgery and subsequent delirium on different subparts of quality of life. Psychological health is affected a year after surgery, while physical health is only decreased in the early postoperative period. Delirium resulted in a decreased psychological, social and environmental quality of life after 12 months. It may additionally lead to depressive symptoms. Chapter 8 focused on informal caregivers because of the serious burden that may befall on them. We have demonstrated that it may be helpful to offer psychological support to these caregivers, especially in the early postoperative period. Caregivers may experience an increased burden when providing care for patients, depending on a patient's diagnosis, age, physical and cognitive functioning, and comorbidities. In turn, this may lead to overload in these caregivers.

Chapter 9 demonstrated that renal impairment, cognitive impairment, an ASA score of 3 or higher, being an active smoker, ICU admission, erythrocyte transfusion and a diagnosis of CRC increase the risk of delirium. It additionally showed that delirium is most frequently observed in octogenarians and after open abdominal surgery. These last findings aid future research on selecting patients who may benefit most from prehabilitation and, with that, on which patients to focus specifically.

In the last part of this thesis, Chapters 10 and 11, we discussed the results of the previously described chapters of this thesis in the light of current knowledge and offer recommendations for future research.

Nederlandse samenvatting

Een steeds ouder wordende wereldbevolking vergt nieuwe interventies om postoperatieve complicaties bij oudere patiënten te voorkomen. Delier is een van de meest voorkomende postoperatieve complicaties in deze populatie, met lange opnameduur, institutionalisering, hogere kosten van de gezondheidszorg, morbiditeit en mortaliteit tot gevolg.

De pathofysiologie van delier is nog steeds onduidelijk. Het syndroom zelf lijkt een uiting te zijn van uitgeputte biologische reserves, wat leidt tot een afname van de veerkracht van de gezondheid en een toegenomen kwetsbaarheid van een patiënt. Deze kwetsbaarheid, met daarbij het risico op het ontwikkelen van een delier, wordt veroorzaakt door een opeenstapeling van predisponerende risicofactoren. De combinatie van predisponerende en precipiterende (uitlokkende) factoren kan de schaal van de balans doen kantelen. Als dit de overgebleven veerkracht van een patiënt te boven gaat, kan dit een delier tot gevolg hebben.

Dit proefschrift had als doelen I) het aantonen van de meest succesvolle manier om delier te voorkomen op basis van de huidige literatuur, II) het ontwikkelen van, en het evalueren van de uitkomsten van, een nieuwe interventie om postoperatief delier te voorkomen in de oude chirurgische patiënt, III) het vaststellen van de gevolgen van chirurgie en een eventueel daaropvolgend delier op de kwaliteit van leven van patiënten en hun mantelzorgers, en IV) het identificeren van patiënten die het meest baadt hebben bij prehabilitatie en het geven van adviezen voor toekomstige prehabilitatieprogramma's.

Hoofdstuk 2 is een systematische review en meta-analyse, waarbij 35 studies zijn geïncludeerd die de preventie van delier in de oudere chirurgische patiënt hebben onderzocht. Deze studies waren over het geheel genomen zeer heterogeen en van matige kwaliteit. Delier kan worden voorkomen door interventies te implementeren die bestaan uit meerdere componenten, door het gebruik van antipsychotica tijdens opname, door de diepte van de anaesthesie te controleren middels bispectral guidance en door de behandeling met dexmedetomidine.

Wij hebben een nieuwe interventie ontwikkeld, bestaande uit meerdere componenten, met focus op prehabilitatie. Het studieprotocol van deze ongecontroleerde, voor-na (before-and-after) studie werd gepresenteerd in Hoofdstuk 3. De hypothese van deze studie was dat prehabilitatie van patiënten, voorafgaand aan abdominale chirurgie voor de behandeling van een abdominaal aortaal aneurysma of colorectaal kanker, de incidentie van delier kon verlagen, de opnameduur kon verkorten, het aantal complicaties kon verminderen en institutionalisering en mortaliteit kon voorkomen.

De korte- en lange termijn uitkomsten van dit prehabilitatie programma worden gepresenteerd in respectievelijk Hoofdstuk 4 en 5. De studie was opgezet en slaagde erin om de incidentie van delier significant te verlagen. Op alle overige uitkomstmaten werd geen significant effect gezien, zowel niet voor de groep in zijn geheel, als opgesplitst per diagnose. Op de mortaliteit werden zowel in de vroege postoperatieve fase als na een jaar geen verschillen geobserveerd. Hoofdstuk 5 toonde aan dat postoperatief delier het risico op 1-jaars mortaliteit met een factor 4 vergroot en dat het geassocieerd is met slechtere functionele uitkomsten na 6 en 12 maanden.

In **Hoofdstuk 6** onderzochten we de veiligheid en effectiviteit van intraveneuze ijzersuppletie, waarbij we aantoonden dat het de moeite waard zou kunnen zijn als aanvullend onderdeel van toekomstige prehabilitatie programma's. Intraveneuze ijzersuppletie zorgt ervoor dat de verschillen in haemoglobinewaarden tussen preoperatief anaemische en niet-anaemische patiënten verdwijnt door op effectieve wijze de lage preoperatieve haemoglobinewaarden van de anaemische patiënten te laten toenemen; ongeacht de oorzaak van de anaemie.

Vanaf het moment dat nieuwe behandelingen steeds minder positieve effecten op conventionele uitkomsten lieten zien, begonnen onderzoeken in de geneeskunde zich te focussen op nieuwe uitkomstmaten. De kwaliteit van het resterende leven, in plaats van de lengte ervan, is in de huidige tijd een steeds belangrijkere uitkomst en was daarom de focus van **Hoofdstuk 7 en 8**. De impact van chirurgie en eventueel daaropvolgend delier op verschillende subonderdelen van de kwaliteit van leven werd onderzocht in **Hoofdstuk 7**. De psychologische gezondheid is zelfs een jaar na chirurgie nog aangedaan, terwijl de fysieke gezondheid alleen in de vroege postoperatieve periode is verminderd. Delier kan na 12 maanden leiden tot verminderde psychologische, sociale en omgeving-gerelateerde kwaliteit van leven. Bovendien kan een delier leiden tot meer depressieve symptomen. In **Hoofdstuk 8** focusten wij ons op de vaak ondergesneeuwde mantelzorgers, vanwege de serieuze last die zij op hun bord kunnen krijgen na een operatie of een postoperatief delier van een naaste. Deze mantelzorgers zouden mogelijk baadt kunnen hebben bij psychologische ondersteuning, met name in de vroeg-postoperatieve periode. Afhankelijk van de diagnose, de leeftijd, de fysieke en cognitieve gesteldheid en de comorbiditeiten van een patiënt kunnen mantelzorgers een toegenomen last ervaren bij de verzorging, met overbelasting van de mantelzorger als mogelijk gevolg.

In **Hoofdstuk 9** toonden wij aan dat nierinsufficiëntie, een cognitieve beperking, een ASA score van 3 of hoger, roken, IC-opname, bloedtransfusie en de diagnose van CRC risicofactoren zijn voor het ontwikkelen van een delier. Bovendien liet dit hoofdstuk zien dat delier het meeste voorkomt bij 80+'ers en na open abdominale chirurgie. Deze laatste bevindingen kunnen toekomstig onderzoek helpen in het selecteren van patiënten die het meest baadt hebben bij prehabilitatie en op welke patiënten zij zich dus zouden moeten focussen.

In het laatste deel van dit proefschrift, **Hoofdstuk 10 en 11**, bediscussieer ik de resultaten van de bevindingen in dit proefschrift en zet deze in het licht van de huidige kennis omtrent delier en prehabilitatie. Ik bied daarnaast een handvat voor toekomstig onderzoek.

List of publications

Publications related to this thesis:

Janssen TL, Alberts AR, Hooft L, Mattace-Raso F, Mosk CA, van der Laan L. Prevention of postoperative delirium in elderly patients planned for elective surgery: systematic review and meta-analysis. *Clin Interv Aging. 2019;14:1095-117.*

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About the author

Ties Lukas Janssen was born on 5 June 1990 in Eindhoven, as son of Dianne Breuer en Rick Janssen. He grew up there together with his sister Dieke, who was born when he was 2 years old. In 2008 he graduated from the 'Pleincollege van Maerlant' in Eindhoven and started studying Medicine at the Erasmus University of Rotterdam in 2009. He alternated his attendance at the university with his social life at the Algemene Rotterdamsche Studenten Roeivereniging Skadi. He combined his love for travelling with his research studies and internships, for which he went to South Africa and Surinam. He successfully finished his studies and received his medical degree (MD) in May 2017, after which he started his career as a surgical resident (ANIOS) at the Amphia Hospital in Breda. After having worked as a surgical resident for 5 months, he started off his PhD trajectory under supervision of prof. dr. L. van der Laan with a 14-month fulltime research employment at the Amphia Hospital. After this period, he continued working on his theses and combined this with his work as a surgical resident at the Amphia Hospital in Breda, from August 2020 at the Ikazia Hospital in Rotterdam and from May 2021 at the Elisabeth-TweeSteden Ziekenhuis in Tilburg. From August 2021, Ties started working as an R&D consultant at 'Quin' and as a GP resident at 'Quin Dokters'.

During the period November 2017 – October 2021, he focused on his scientific medical research under the supervision of prof. dr. E.W. Steyerberg and prof. dr. L. van der Laan, resulting in this dissertation.

Ties is living happily in Rotterdam with his girlfriend Lisa Boddé.

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