Welcome to the Stone Age: minimally invasive treatments for urolithiasis

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Welcome to the **Stone Age**

Minimally invasive treatments for urolithiasis

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Welcome to the stone age. Minimally invasive treatments for urolithiasis

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Welcome to the stone age
Minimally invasive treatments for urolithiasis

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Voor mijn ouders

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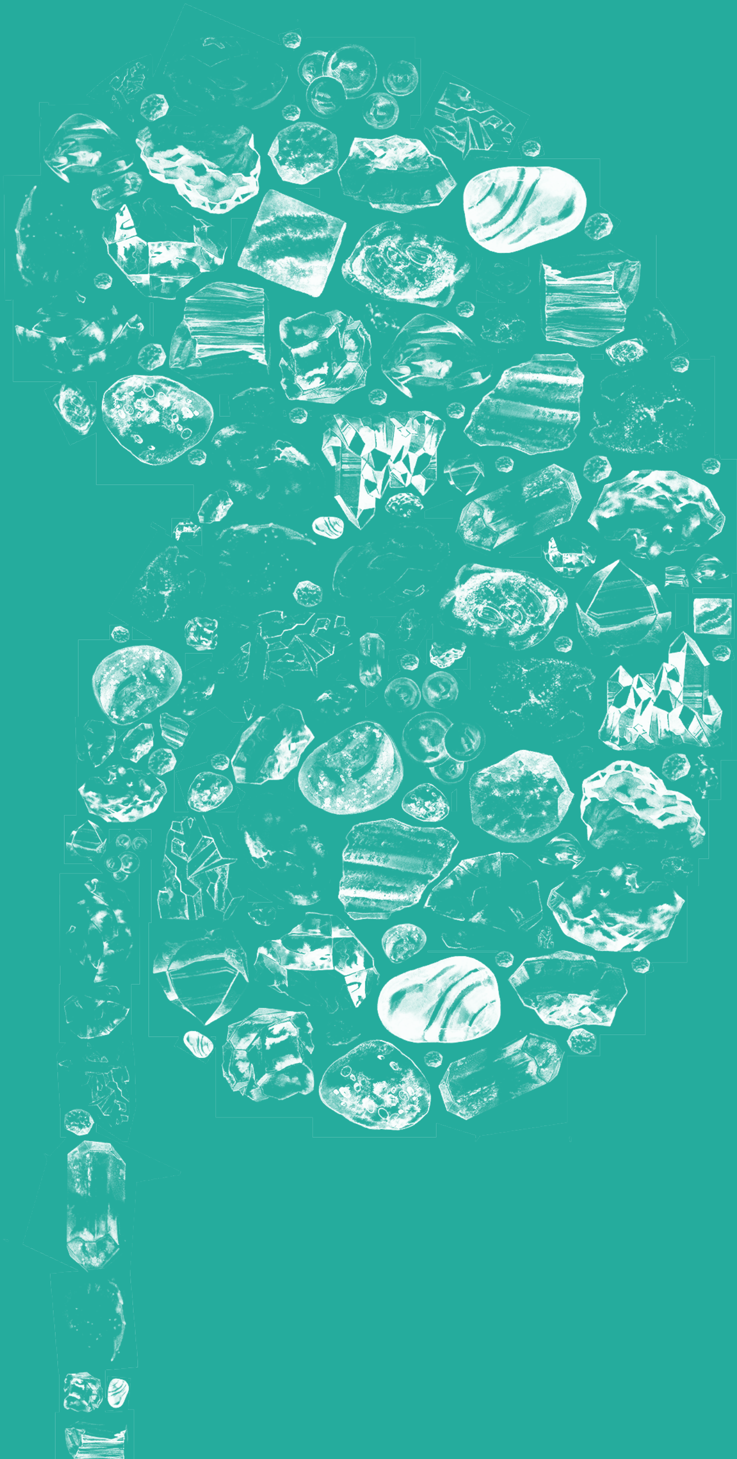

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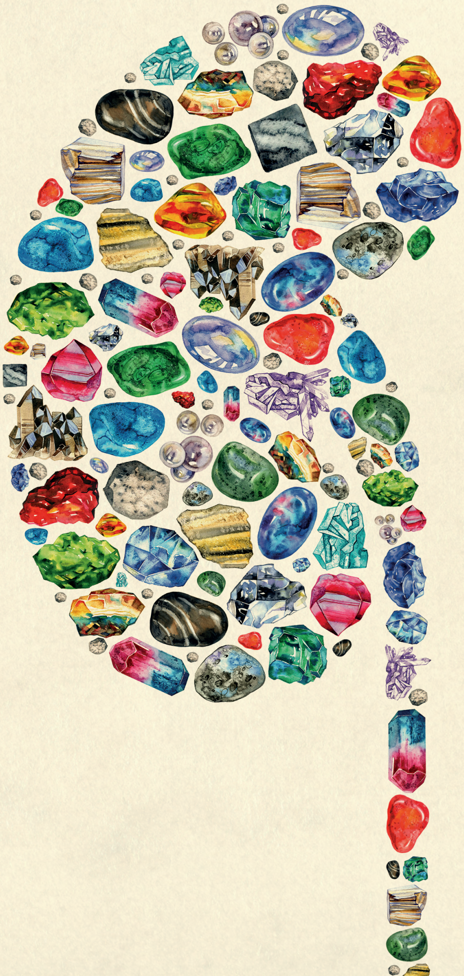

General introduction and outline of the thesis

INTRODUCTION

This thesis

Kidney stones cause a high burden for health care economy due to their high risk of recurrence and the cost of hospitalization and surgery[1]. Awaiting spontaneous passage of ureteral stones is very often associated with a lot of pain, absence from work and healthcare interference as a consequence. Mortality in urolithiasis however is rare and patient care focuses on treatment of stones rather than prevention.

The main focus of this thesis is on pain management and treatments of urolithiasis. Research on urolithiasis is less common than oncologic subjects in the urologic field, probably for a significant part explained due to a lack of sponsoring. However, the patient with urolithiasis accounts for a large percentage of the urologists' work and complications occur regularly. Many research questions are still unanswered. Some therapeutic regimens have already been used for years, although scientific evidence is missing.

The aim of this thesis is to improve our knowledge, our practice and our standards when treating urolithiasis. The studies in this thesis have taken place in the region of Leiden and The Hague between 2011 and 2020.

History of stone surgery

In the beginning of the 20th Century, the anatomist Elliott Smith, discovered a calculus in the pelvis of a mummy taken from an Egyptian tomb[2]. This stone, dating from 4800 BC had a uric acid nucleus and encrustation of calcium oxalate and ammonium magnesium phosphate. It was probably a bladder stone.

Bladder stones were a common disease in history. Ancient physicians already knew that removing stones required special skills. Hippocrates even warned in his oath: "I will not cut for stone, even for patients in whom the disease is manifest. I will leave this operation to be performed by practitioners, specialists in this art" [3]. The profession of the lithotomist was born.

The first surgical approaches were described in De Re Medicina, written in the year 20 Anno Domini (AD) and required 2 main surgical instruments; a knife and a hook[4]. During the described procedure, the bladder was reached through the perineum. The patient was held in the jack knife position that is still used for the transurethral surgical approach. A finger of the left hand was placed in the rectum to push the stone against the perineum and a deep incision from perineum towards the bladder was made. The stone was pushed out with the finger of the left hand in the rectum. If that was not successful, the hook was used to pull out the stone. Afterwards the wound was dressed with oil and wool. It must have been a very unpleasant procedure, since anesthesia had not been invented.

This procedure was performed for centuries. Many patients suffered incontinence, fistulas, abscesses and 50% of the patients died.

A drawing of a famous episode from 1475, illustrated the vivisection of a man with symptoms of urolithiasis. He was a member of an archers' company in Meudon who had committed a crime and was sentenced to death. The physicians and surgeons of Paris wanted more knowledge of common diseases, including urolithiasis. They sent a petition to Louis XI. The criminal was offered a stay of execution if he agreed to be anatomized alive. The archer survived the procedure.

Earliest operation for the stone, performed in presence of king Louis, by Germain Colot in the cemetary of St Severin, January 1474. Lithograph by A. Rivoulon, 1851.

Other approaches became more common in the 16th century. The first suprapubic cystotomy for the removal of bladder stones was carried out by Franco, a surgeon in Lausanne, France in 1559. He performed the procedure on a child, who survived his surgery[5].

Interventions on kidney stones were only described years later. The first percutaneous nephrostomy was performed in 1865 by dr. Thomas Hillier from Gloucestershire. He repeatedly tapped the hydronephrotic kidney of a four-year-old boy[6]. During this period improvements were made in instrumentation. The first ureteroscopy was performed by Hugh Hampton Young, an American surgeon and urologist, in 1929[7].

The stone

Kidney stones are formed when urine is supersaturated with stone forming salts. At this point, no more of the salt can be dissolved in the urine. This causes molecules to cluster and form a nucleus, the beginning of a crystal. The most common salts are calcium, oxalate, citrate or phosphate.

There are three theories on how the nucleus could originate.

- The first theory is the nucleus forms by clustering on a foundation of interstitial calcium phosphate following loss of urothelial covering of the renal papilla. This foundation is called Randall's plaque.
- The second theory is that small crystals form in the lumen of a nephron at sites of cell injury. When they attach and grow, they form an intraluminal plug. When this reaches the minor calyx, it may be transported with urine or be retained in the kidney.
- The last theory is that free particle formation occurs when the nucleus forms in the renal pelvis by supersaturation of urine[8].

Most nuclei or "mini-stones" are asymptomatic and pass with the urine. Retaining a nucleus or small crystal and exposing it to urine, causes encrustation. An aggregate of these crystals together with an organic matrix (e.g. certain lipids and proteins), form the basis of a kidney stone [9,10]. Supersaturation of urine and crystal formation is influenced by low volume of urine, urinary pH, metabolic diseases, infection and the use of certain medication. Depending on these influencing factors and genetics, other types of stones might form as well. Compositions of phosphate, uric acid, struvite and cystine are seen in daily practice[11]. Knowledge of stone composition may help in analyzing metabolic disorders or prevention. Uric acid stones for instance can be treated by dissolution using alkalinizing of urine. In this case a surgical procedure could be avoided.

Epidemiology

Urolithiasis is highly prevalent and growing in incidence. The increase is related to dietary factors and obesity. However, improvement of detection methods has also resulted in a growing number of patients. The difference in prevalence is determined by various factors. Geography and social health determine fluid intake, climate, diet and occupation. Prevalence among men is higher than it is in women, although the gender gap is narrowing. Also, age influences the likelihood of stone formation, with peaks in the fourth to sixth decades of life.

Prevalence reported in literature is as high as 20% in men in Saudi Arabia and as low as 3% in Icelandic women[12]. The prevalence of urolithiasis in developing countries is probably underestimated. One study reported that urolithiasis was diagnosed with ultrasound in 3% of asymptomatic patients[13].

In children urolithiasis is diagnosed less frequently. Historically, urinary tract anomalies were a major cause for urolithiasis in the pediatric population, but better diagnosis and treatment have decreased this as a factor[14]. An underlying metabolic disorder is the most common cause nowadays, sometimes associated with a urinary tract infection.

Pathophysiology of renal colic

An obstructing ureteral stone is known to cause excruciating pain in waves. We do not fully understand the exact mechanism that causes pain in renal colic. What we do know is that the obstruction of a stone may cause an increased intraluminal pressure in the collecting system. Because of this, the tissue is stretched and the nerve endings in the wall of the system (lamina propria) are stimulated. The smooth muscle in the wall of the ureter will contract as a reaction to move the stone. When the muscles of the ureteric wall are unable to move the stone because it is fixed in one position, they develop a spasm. As a result of spasm, lactic acid is produced which subsequently stimulates the A and C fibers and afferent impulses are sent to the spinal cord. Pain is the result. Local irritation, edema and inflammation are contributing factors for pain as well[10].

We do not fully understand why patients with stones in the urinary tract and hydronephrosis, are sometimes free of pain as well. In some cases, particularly when the stone is at the uretero-vesical junction, urinary symptoms predominate, such as frequency and urgency.

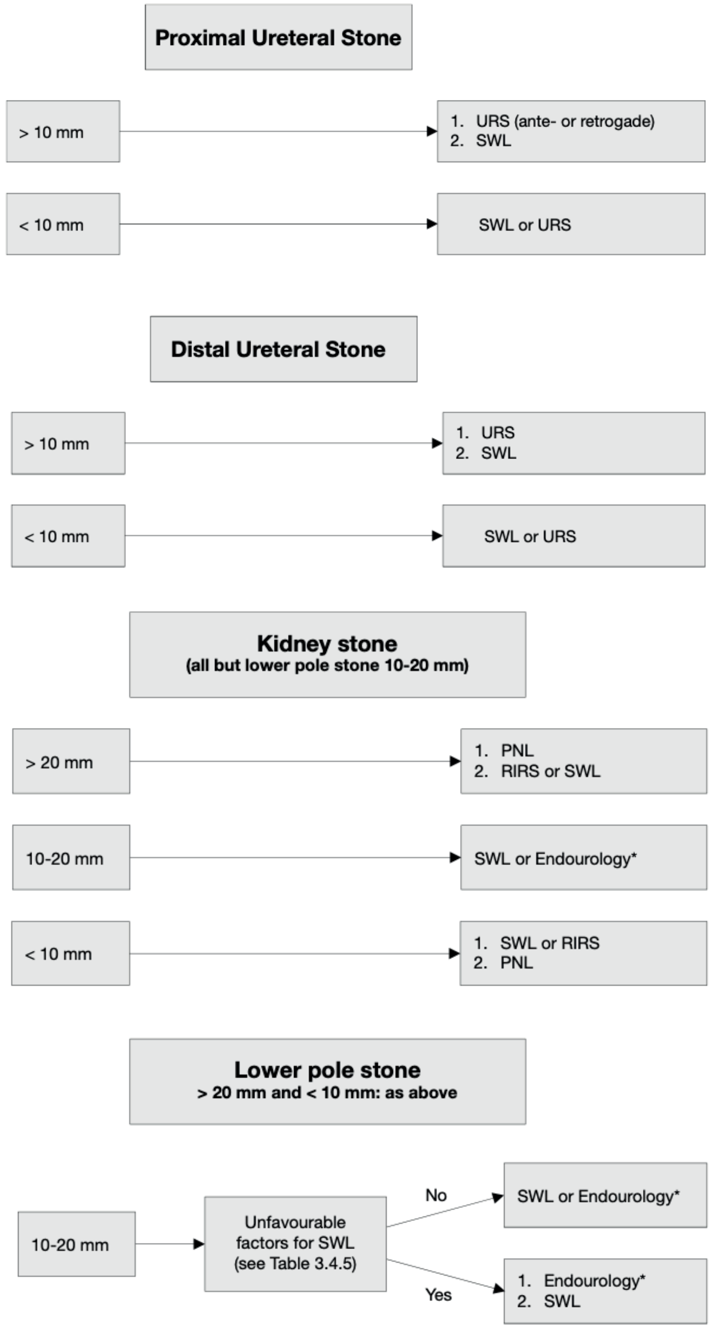

FIGURE 1. Treatment algorithm for ureteral and kidney stones if indicated. Source; EAU guideline urolithiasis 2019

Current practice

Treatment of urolithiasis is mostly started with conservative management using analgesics and supportive management to allow the stone to pass spontaneously. A different approach is used when a stone does not pass spontaneously, or causes pain or when renal function or clinical condition is impaired.

Extracorporeal shock wave lithotripsy (ESWL), ureterorenoscopy (URS) and percutaneous nephrolitholapaxy (PCNL) are the main treatment options.

ESWL, the non-surgical option, is only possible if a stone is relatively small, not located near the ureterovesical junction (UVJ) and when visualization using fluoroscopy or contrast is possible.

URS and PCNL are endourological treatment options and could be combined as well.

Which surgical approach is used depends on many factors, such as stone location, stone size, patient anatomy, hospital logistics and patients' preference. The flow chart in figure 1 points out the treatment algorithm.

THESIS OUTLINE

Part 1; Anatomy and diagnostics

Anatomy of the pyelocaliceal system is studied and described in this first part. Knowledge of the renal anatomy is essential for an endourologist. With adequate information on the pyelocaliceal system it is possible to manage expectations regarding stone passage, surgical approach and instruments needed for endourological treatment.

3D reconstructed CT urography was used to compare the different segments in the kidney in **chapter 2A**. A clockwise system was used to describe the measurements. Results should be taken into account when planning an endourological procedure, to improve access and outcome.

In addition to improving outcomes, prevention of stone formation is also gaining attention. Science on stone formation, intrarenal flow and stone passage will help us understand why one patient will be more affected than the other. In **chapter 2B**, another set of 3D reconstructed CT urography images were used to compare stone forming and non-stone forming kidneys.

Part 2; Treatments evaluated

The aim is to assess current endourological treatments to understand where improvement might be necessary. Transparency and accountability of healthcare providers has recently gained interest. When quality and clinical performance are understood in a disciplined way, it could make a substantial contribution to the value of healthcare and its improvement[15].

Chapter 3 describes the quality of stone treatments with URS and PCNL in 2 main hospitals in The Hague. Success rates, complications and outcome are compared with existing literature.

In **chapter 4** we systematically reviewed the optimal drainage method for obstructive urolithiasis. Practice patterns differ globally and choices are due to experience, availability and logistics. With this review we aim to advice on the best treatment option depending on the patient situation.

Part 3; New insights

Pain is the central subject of this last part. In **chapter 5, 6 and 7** current treatments for urolithiasis are critically researched.

The buscopan study, described in **chapter 5,** was designed to close the gap in literature on the use of butylscopolamine in the treatment against pain in patients with renal colic. This antispasmodic drug is still used daily in hospitals in Belgium and in the Netherlands, however scientific evidence is missing. In a double blind and placebo-controlled randomized clinical trial the effect of butylscopolamine on pain was researched.

Pain during treatment with ESWL is evaluated in **chapter 6**. ESWL is a first step in many cases when treatment for urolithiasis is necessary. The hypothesis is that higher pain scores might impair outcome of ESWL. We investigated the influence of pain and patient comfort on the outcome of ESWL.

Chapter 7 examines indications, success rates and complications of antegrade ureteral stent placement. When drainage of the urinary tract with a ureteral stent is indicated, most of the time the retrograde route is used. In this chapter a retrospective data analysis is performed of the antegrade approach in a large hospital in The Hague.

Part 4; Conclusion

In **chapter 8** this thesis is discussed with a view on future perspectives.

Finally, **chapter 9** summarizes the findings from chapters 2 – 7.

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Part 1

Anatomy & Diagnostics

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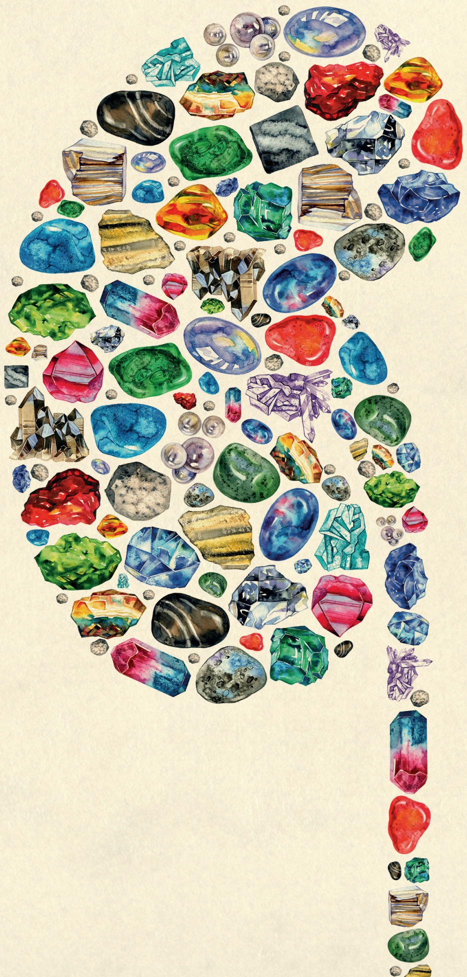

The anatomy of the renal pyelocaliceal system studied by CTU

The content of this chapter has been published as: The anatomy of the renal pyelocaliceal system studied by CTU. Abdominal Radiology 2019

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ABSTRACT

Introduction & Objectives

Knowledge of the pyelocaliceal system anatomy is essential for safe and successful performance of endourologic procedures. The purpose of this study was to provide a better understanding of the full three-dimensional pyelocaliceal system anatomy.

Methods

Morphometric parameters of the three-dimensional reconstructions of Computed Tomography Intravenous Urography (CTU) scans (n=25 scans) were analysed. Both kidneys were divided in three equal sized segments; upper segment (US), mid segment (MS), lower segment (LS). Infundibular length (IL), infundibular width (IW), number of calyces and the transverse orientation in hours of a clock of each calyx as well as the dimension of the renal pelvis were determined.

Results

The mean upper IL (n=92) was longer than the middle (n=154) and lower IL (n =112) (30.6 ± 7,9 mm vs. 16.4 ± 7.7 mm vs. 16.0 ± 6.0 mm, respectively; P = <.0001). IW was significant smaller in the MS (3.7 ± 1.9 mm), followed by the US (4.6 ± 1.9 mm) and LS (4.9 ± 2.2). No correlation was found between IL and IW (Pearson correlation coefficient = 0.1). US calyces were predominantly orientated lateral (8-10 o'clock: 44.5 %) and medial (2-4 o'clock: 30.5 %), in the MS lateral (8-10 o'clock: 87.6%) and anterolateral in the LS (9-12 o'clock: 67.9%). 74% of the kidneys consisted of 6-8 calyces (mean 7.2 ± 1.4, range 4-10), with the majority of the calyces in the MS (3.1 ± 0.8) followed by the LS (2.24 ± 0.8) and US (1.8 ± 0.7). There were no statistical differences between the right and left kidney in IL (P = 0.112) and number of calyces (P = 0.685).

Conclusion

Anatomical differences between the three segments of the pyelocaliceal system in terms of IL, IW, number of calyces and orientation are seen and should be considered when performing an endourologic procedure.

INTRODUCTION

Urolithiasis is considered to be an important medical problem with an increasing prevalence and incidence in the past years[1]. It affects the functioning of individuals on different levels. Optimisation of treatment will benefit the quality of life and the economic impact of the disease. The exact mechanism of stone formation remains unclear but it has been suggested that, besides metabolic/diet factors, pyelocaliceal anatomic properties may play an important role in the aetiology.

Endourologic procedures, more specifically percutaneous nephrolithotripsy (PCNL) and ureterorenoscopy (URS) are the two main treatment modalities for renal stones. PCNL is the treatment of choice for larger stones (>20 mm in diameter) while URS is the primary treatment modality for smaller/multiple calculi spreading in the different parts of the kidney[2]. Preoperative knowledge of the pyelocaliceal anatomy is fundamental to perform an accurate and safe puncture of the[3,4] calyx when PCNL needs to be performed[5]. Technical improvements of the instrument and its miniaturization have led to an increased use of URS for both renal and ureteral calculi[2]. Although, the flexibility of the URS and its imaging have been improved as well as the techniques used in PCNL, both modalities have their limitations. Intraoperative limitations are beside body habitus, stone size, composition and location, very often caused by the anatomy of the kidney[6,7].

Knowledge of the pyelocaliceal anatomy is essential to make both procedures more reliable and to improve the success rate of stone access and clearance. Controversy still exists on the surgical anatomy of the pyelocaliceal system. The anatomy and presumed function of the kidney and pyelocaliceal system was first described in the early years of science by a Persian philosopher named Avicenna. The technology of injecting liquid rubber into the pyelocaliceal system to create endocast reprints, is introduced in studying anatomy of different structures among which the kidney and its pyelocaliceal system in the 20th century. This technique was able to clarify the internal relationships between the injected cavities but neglected the external relationship to the rest of the body as required for the surgical purpose. It was also prone to errors due to the shrinkage of the rubber after hardening or expansion when creating a higher pressure while injecting[8].

Previous studies suggest that success of endourologic procedures in relationship to the anatomy is mainly limited to the lower pole[7,9-12]. The anatomic parameters of most interest are the angle formed between the main lower infundibulum and the renal pelvis (the infundibulopelvic angle), pelvis surface area, infundibular width and infundibular length[6,9,11,13,14].

The fine knowledge of the anatomy remains the keystone of surgical procedures[15]. The main limitation of previous studies was its 2-dimensional character by performing anatomic measurements on intravenous urography (IVU) [6]. Computed Tomography Urography (CTU) on the contrary makes it possible to measure in three-dimensional reconstructions. CTU has proved to be a useful imaging modality to analyse the intrarenal anatomic properties[10,16].

We analysed 25 CTU images and both kidneys were studied separately. Calyces were counted in the upper, middle and lower segments of each kidney. Calyx length in relation to the renal pelvis and its infundibular width as well as their orientation in the transversal plane are studied and measurements were saved in a database for analysis. With this data we expect to demonstrate a relationship between anatomical findings and their possible impact on the surgical procedure and outcome.

METHODS

Study Design & Subjects

The database of the department of radiology of our hospital has been used and CTU scans made between January 2015 and January 2017 have been assessed. The CTU scans without uropathology and complete imaging of both pyelocaliceal systems were selected for further analysis. IRB approval was obtained.

Image Analysis

CTU scans were made using Siemens Somatom definition flash. Patients were given iv contrast fluid 10 minutes before scanning.

All measurements were performed on a 3-dimensional reconstruction, made by Multiplanar Reconstruction / Maximum Intensity Projection (MPR/MIP) functionality in PACS IntelliSpace version 4.4.516.0 (figure 1). Late phase CTUs (+10 min), when the whole pyelocaliceal system was filled with contrast were used for 3D reconstruction.

Each kidney was divided into three equal sized segments. The right and left kidney of the subjects were analysed separately. Every calyx was given a letter according to the alphabet, starting from cranial to caudal segment and from dorsomedial to lateral to medioventral position. Of each calyx, the infundibular length (IL) and corresponding infundibular width (IW) were measured according to the method described by Elbahnasy et al[13]. IL was measured in the middle of the infundibulum in a straight line beginning at the transition from renal pelvis to infundibulum to the most distal point of the corresponding calyx. IW was measured at the narrowest point along the infundibular axis. The mediolateral, anteroposterior and craniocaudal distances of the renal pelvis were determined.

Orientation of the calyces in the transversal plane were registered according to the analogue hour positions, clockwise for the right kidney and anticlockwise for the left kidney. Renal hilum is by definition at the three o'clock position, with the 9, 12 and 6 o'clock positions respectively representing laterally, anteriorly and posteriorly orientated calyces.

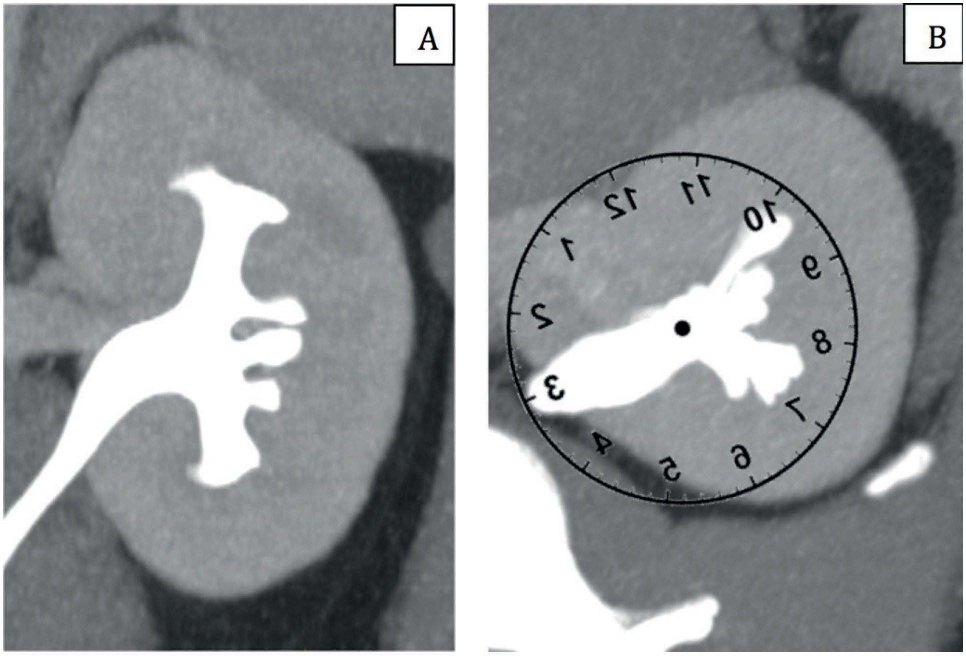

FIGURE 1: 3-dimensional reconstruction of CTU scan. Coronal overview of pyelocaliceal system as generated during this study(Panel A); and transversal sectioning to study the orientation of the calyces (Panel B).

Statistical analysis

Data analysis was performed with SPSS 22.00 (SPSS Inc, Chicago, IL). Normally distributed date is expressed as mean ± SD. Statistical significance between the segments was evaluated using the independent samples T-Test. P values of 0.05 or less were considered to indicate statistical significance for all statistical tests.

RESULTS

A total number of 25 patients (7 male and 18 female) were included. The mean age of our study population was 50.8 ± 12.4 years (range 26-75). Indications for the CTU scan were analysis macro/microscopic haematuria (n=18), (history of) bladder tumour (n=4) and persisting flank pain (n=3). The subjects had no history of surgery in the pyelocaliceal system.

Infundibular length; IL

The mean upper IL (n=92) was calculated to be 30.6 ± 7,9 mm, while the middle (n=154) and the lower IL (n=112) were measured as 16.4 ± 7.7 mm and 16.0 ± 6.0 mm respectively. The differences between ILs were statistically significant when the upper compared with the middle and the lower segment (P < 0.0001) (table 1). The mean IL in the left pyelocaliceal system was slightly larger than the right one (20.7 ± 9.8 vs 19.1 ± 9.2 mm) (P = 0.112).

Infundibular width; IW

The mean IW was established to 4.6 ± 1.9 mm, 3.7 ± 1.9 mm and 4.9 ± 2.2 in the upper, middle and lower segment, respectively. The middle IW was significant smaller than the upper (P=0.0002) and lower (P <0.0001) segment (table 1). There was no correlation between the IL and IW (Pearson correlation coefficient=0.1).

TABLE 1. Comparison between the upper, middle and lower segment of the pyelocaliceal system.

	Upper Segment (A)	P value (A vs. B)	Middle Segment (B)	P value (B vs. C)	Lower Segment (C)	P value (A vs. C)
N	92		154		112	
IL (mm)	30.6±7.9 (17.0-50.4)	<.0001	16.4±7.7 (2.7-37.9)	0,687	16.0±6.0 (3.2-29.5)	<.0001
IW (mm)	4.6±1.9 (1.5-11.0)	0,0002	3.7±1.9 (1.2-11.0)	<.0001	4.9±2.2 (1.2-10.4)	0,283

Values in cells correspond to the mean ± standard deviation (range). IL: infundibular length IW: infundibular width.

Orientation and the number of the calyces

Figure 2 shows the frequencies of the transverse orientation of the calyces per segment. In the upper segment (n=92) the most common orientation was lateral at 8 o'clock (22.8 %) and medial at 4 o'clock (19,6 %). A posterior orientation at 5, 6 or 7 o'clock was the most frequent in the upper segment (4.3%, 8.7% and 6.5%, respectively) in comparison to the other segments. The orientation of the calyces in the mid segment (n=154) was mostly lateral at 8, 9 and 10 o'clock (26.6%, 26.6%, and 34.4%, respectively). The lower segment orientation (n=112) was predominantly lateral at 8, 9 and 10 o'clock (67.8%) and anterior at 11, 12 and 1 o'clock (25.1%).

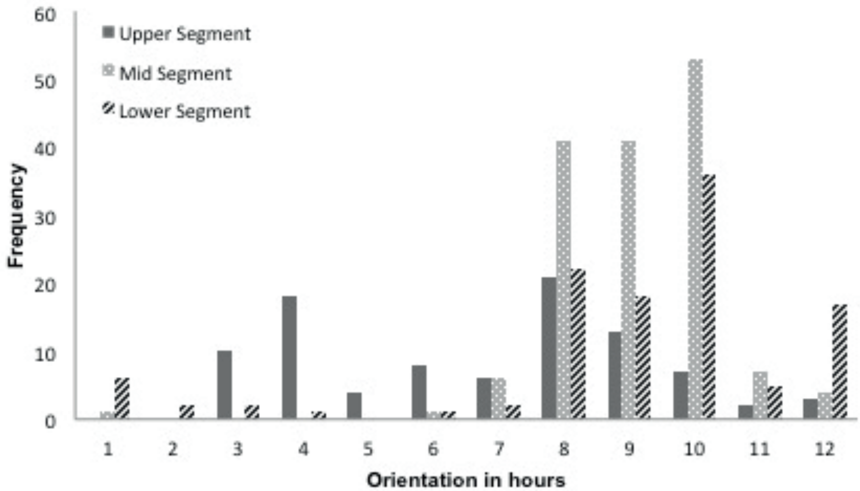

FIGURE 2. Frequency of the transverse calyces orientation in hours per segment

The mean number of calyces per kidney (n=50) was 7.2 ± 1.4 (range 4-10), with 74% (n=12) of the kidneys containing between 6-8 calyces. Divided into the upper, middle and lower segment the number of calyces were 1.8 ± 0.7, 3.1 ± 0.8 and 2.24 ± 0.8 respectively. These differences are all statistically significant as illustrated in table 2.

The US was drained by only 1 calyx in 30% of the cases and 18% in the LS, a single drainage of 1 calyx in the MS was not seen. No significant differences were found in the total number of calyces between (P =0.685) the right and left kidney (figures. 3, 4).

TABLE 2. Number of calyces in the upper, middle and lower segment of the pyelocaliceal system.

	Upper Segment (A)	P value (A vs. B)	Middle Segment (B)	P value (B vs. C)	Lower Segment (C)	P value (A vs. C)
N	50		50		50	
Calyces	1.84±0.65 (1-3)	<0,0001	3.08±0.83 (2-6)	0,0001	2.24±0.85 (1-4)	0,009

Values in cells correspond to the mean ± standard deviation (range).

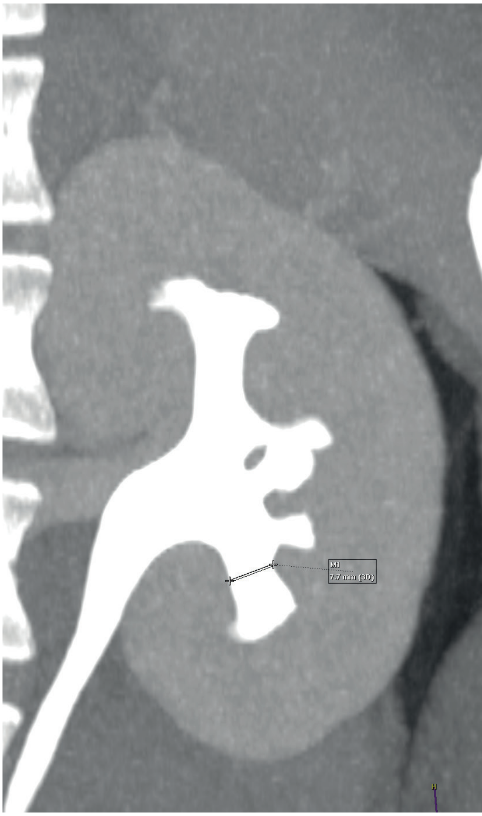

FIGURE 3. Measuring infunfibular width of the lower pole.

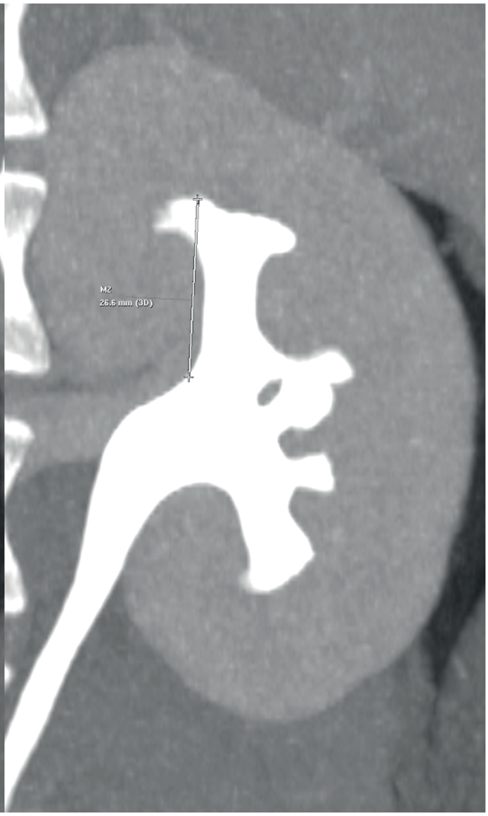

FIGURE 4. Measuring infundibular length of the upper pole.

Morphometric properties of adult renal pelvis

The mean mediolateral dimensions of the renal pelvis were measured to be 19.9 ± 4.6 mm (range 10.6 - 29.2), while the craniocaudal and anteroposterior measured length were 16.6 ± 5.7 mm (range 7.1 – 34.7) and 11.2 ± 3.6 mm (range 5.5 – 18.7) respectively.

DISCUSSION

This study describes the anatomic properties of the pyelocaliceal system and shows significant differences between the three segments of the kidney. MS calyces tends to have short and narrow infundibula, while the US calyces significantly have longer IL when comparing to the other segments. A lateral orientation of the calyces was most frequently found, with almost 90% of the calyces in the MS. The US calyces were mainly orientated laterally and medially (75%) and anterolateral in the lower segment (67.9%).

The anatomy of the pyelocaliceal system

There are different approaches in the description of the anatomy of the kidney and the pyelocaliceal system in particular. Some describe the upper urinary tract (UUT) in relation to urine producing parenchyma, while others published the morphometric aspects of the cast made by polymers injection into the UUT[8]. Over the years different classifications of the pyelocaliceal system have been proposed. In 1998 Sampaio made a pyelocaliceal classification system by using endocasts of the renal collecting system. Sampaio divided the endocasts into four morphological types, the renal midzone drainage was decisive for this subdivision[8]. The majority of these studies described the 2D morphology of calyces using its length, diameter and its angle of drainage into the renal pelvis in order to classify the anatomy into groups. In our opinion the value of this classification is limited due to diversity of the morphology of the pyelocaliceal system.

There are different publications describing the lower pole anatomy in relation to the surgical outcomes. In 1992 Sampaio and Aragão[17] were the first authors, and later in 1998 Elbahnasy[13], to report that some lower pole anatomic features, such as an long IL (>3 cm) [13] and a narrow IW (Sampaio: <4 mm, Elbahnasy: <5mm), negatively affects the stone clearance after shock wave lithotripsies (ESWL). In our study, infundibular length and width was measured according to the Elbahnasy method[5][13]. Our findings were considerably smaller than the mean IL and IW of the lower pole described by Elbahnasy himself. These differences may be due to different patient populations and/or different imaging of the pyelocaliceal system (IVP versus CTU).

We observed fewest numbers of calyces in the US with up to 30% being mono-caliceal. Furthermore, US calyces are drained by a single midline infundibulum in 92% of the cases. In contrast, no fused single caliceal infundibulum was observed in the MS. Fused infundibula were only reported in 18% in the LS. The same findings were noted by Sampaio and Aragão who reported 98% and 42% single midline drainage of the superior and inferior pole respectively[18]. When approaching the pyelocaliceal system urologists should be aware of the differences in polar region drainage as multiple smaller infundibula would make it more difficult to remove renal stones.

The use of and need for minimally invasive endourologic procedures like PCNL and flexible ureterorenoscopy (fURS) is growing. Instruments require increasingly more flexibility, smaller size and better handling of the instruments by the surgeon. Interventional radiologists need to access the optimal calyx for later renal stone surgery. Urologist needs to be informed of the 3D anatomy of the individual pyelocaliceal system in order to optimally navigate into the different calyces. In contrast to previous research, which was intensively focused on the anatomy of the lower pole and its prognostic values, we described the entire pyelocaliceal system. We provide a simple way of thinking and handling. One should be aware of the number of the calices, their locations and their orientation.

In our study however, a mean lower segment IL of 16.0 ± 6.0 mm was reported which has a favourable outcome on the stone free rate after both URS and ESWL[9,13]. Furthermore, we reported a mean IW of the lower segment of 4.9±2.2 mm, which has a positive effect on the stone clearance after ESWL[13]. Unfavourable outcomes, including a long mean IL of 30.6 ± 7.9 mm and a narrow mean IW of 3.7 ± 1.9 mm in the upper and mid segment respectively, were also measured. Evidence in literature on the impact of the upper and mid segment renal anatomy on the success rate of endourologic interventions, however, is lacking.

PCNL/URS devices and procedures

Technical advances of endourological equipment over the years including improved deflection mechanism, superior (digital) imaging and miniaturisation of the device led to an increased use of both URS and PCNL[2]. Moreover, the new generation ureterorenoscopes show an increased success rate compared to their predecessors[19]. When PCNL is concerned, technical evolutions have led to success rates that vary from 72% to 98%[6]. The anatomical architecture affects the results of the endourological procedure and hence needs to be clear preoperatively. Our results support the opinion that preplanning of URS and PCNL in order to decide for the puncture trajectory of PCNL and the route of (the difficult) URS is mandatory.

URS, despite the described technical evolution over the past years, also has its limitations. A long IL and an acute infundibulopelvic angle (<30°) of the lower pole decrease the success rate[7,14]. Jessen et al. reported a mean IL of the lower pole in the not stone free group of 28.3 mm which was significantly larger than the mean of the stone free group

(22.5 mm) [14]. Dorsal or ventral orientation of calyces, particularly in the LS makes it difficult to reach stones, also when using the newest generations of the flexible URS. This should be taken into account when studying the images of CTU.

Although less studied, the IL and IW seem not to negatively affect the success rate of PCNL. Only a large (>20.5 cm2) pelvis surface diminishes the success rate due to large area that may facilitate the escape of the stone to a not reachable place in the kidney[6].

Securing a proper percutaneous access of the pyelocaliceal system is the most crucial step in PCNL. Incidence of access related complications have been reported between 3% and 18% and include injury to adjacent organs, renal haemorrhage, failed access and pneumothorax[20]. A proper preoperative analysis of imaging of the pyelocaliceal system is therefore mandatory. We perform PCNL in a hybrid operating theatre to be able to access accurately. The target calyx for percutaneous puncture depends on the accessibility of a calyx, which is influenced by its orientation. Defining the orientation of each calyx has been found difficult by investigators and clinicians in 2D images. However, with the use of CTU volume rendering technique, the calyx orientation becomes more reliable[21]. We have chosen to define the orientation of each calyx as clock hours, which are clear and easily reproducible parameters.

Literature suggests that a posterior calyx should be punctured since it has a low potential for bleeding complications[21]. A solely posterior orientation was rare in our study, it was most frequently found in the upper segment of the kidney. Besides a posterior orientation we also preferred a more lateral orientation since these calyces are easily accessible. Puncturing a medial orientated calyx in the upper pole is associated with significant risk of causing injury to the posterior segmental artery[21]. Care should be taken when the US is planned to puncture during the PCNL. We found a predominantly mediolateral orientation of the upper pole with almost 20% of the calyces medially orientated. These findings correlate with Miller et al. who found that the primary plane of the upper pole in 95% of the kidneys was mediolateral orientated[16].

Limitations of our study

This study was limited to the CTU volume renderings of 50 kidneys. Although we have been consistent in our measurement technique, one may debate about the tail ends of each measurement. Repeating the measurements by a second individual researcher minimized intra-observer variability.

We preferred to describe the orientation of the calyces according to a clock, since this is an easily reproducible method. The infundibulopelvic angle, a common measurement used in previous studies was avoided as there was a great intra-observer variation due to curved shape of the renal pelvis and the calyces.

CONCLUSION

This study comprehensively describes the anatomic properties of the pyelocaliceal system. It emphasises the accessibility for percutaneous puncture of the MS and LS calyces. Care should be taken when US calyces are planned to be punctured for PCNL, since some are medially and thus not accessible oriented. Also, the narrowest infundibula were reported in the MS, which could make it less accessible for URS. For URS, dorsoventral orientation of some calyces makes access difficult. Preoperative imaging using CTU and knowledge of the individual anatomy is important when optimizing outcome of URS and PCNL.

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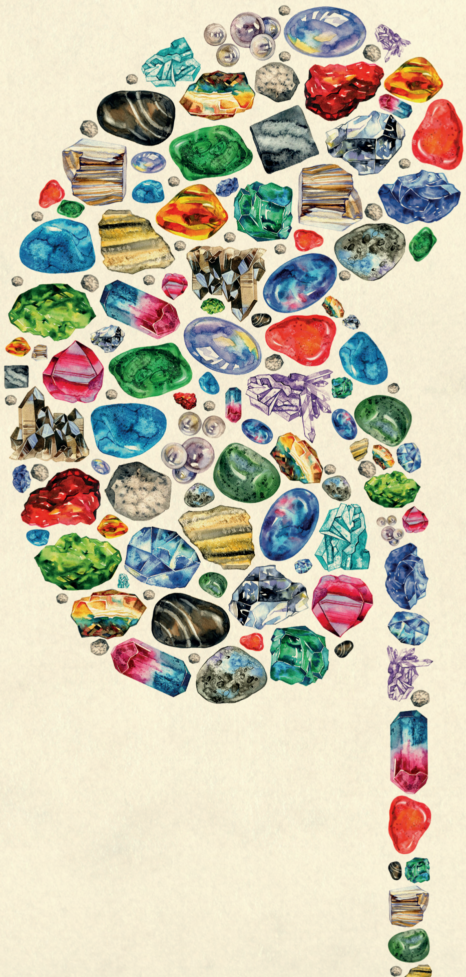

The influence of pelvicalyceal system anatomy on minimally invasive treatments of patients with renal calculi

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ABSTRACT

Introduction & objectives:

Nephrolithiasis has a multifactorial etiology, wherein, besides metabolic factors, the anatomy of the pelvicalyceal system might play a role. Using 3D-reconstructions of CT-urography (CTU), we studied the morphometric properties of pelvicalyceal anatomy affecting kidney stone formation and compared those with existing literature on their effect on minimally invasive treatment techniques for renal calculi.

Methods

CTU's were made between 01-01-2017 and 30-09-2018. Patients were chronologically included in two groups: a nephrolithiasis group when ≥1 calculus was present on the CTU and a control group of patients with both the absence of calculi on the CTU and no medical history of urolithiasis. Patients with a medical history of diseases leading to higher risks on urolithiasis were excluded. In the nephrolithiasis group affected kidneys were measured. In the control group left and right kidneys were alternately measured.

Results

Twenty kidneys were measured in both groups. Mean calyceopelvic tract width was significantly larger in the lower segments of affected kidneys (3.9 vs 2.7 mm). No significant differences between the groups were found in number of calyces, infundibular length, infundibular width, calyceopelvic angle, upper-lower angle and diameters of the pelvis. Transversal calyceal orientation in hours was significantly smaller in the upper and lower segments of the nephrolithiasis group (7.69 vs 8.52 and 8.08 vs. 9.09 hrs.), corresponding with more dorsally located calyces in stone forming kidneys.

Conclusion

Pelvicalyceal anatomy differs between stone forming and non-stone forming kidneys. Understanding the pelvicalyceal system and etiology of stone formation can improve development of endourological techniques.

INTRODUCTION

Urolithiasis is a common disease in countries with a high standard of life, with a prevalence in Dutch general population of 5.5%. [1] The formation of renal stones has a multifactorial pathogenesis, wherein not only environmental, metabolic and dietary factors but also anatomical properties of the kidney play an important role. [2-5] Besides gross anatomical abnormalities, e.g. horseshoe kidneys, smaller-scale morphometric properties of the pelvicalyceal system are postulated to play a role in the pathogenesis of nephrolithiasis. [6,7] Understanding these properties may influence improvement of minimally invasive surgical techniques for renal stones.

Starting in the early nineties, pelvicalyceal anatomy in correlation with urolithiasis has been described frequently. [8] Measurements on the lower pole renal infundibulum were used as primary outcome in many previous studies. Most of these studies have been performed using two-dimensional (2D) intravenous urography's (IVU), with the aim to investigate the influence of pelvicalyceal anatomy on success and complication rates of nephrolithiasis treatments. [9] In contrast to the 2D IVU's, modern radiological techniques enable measurements in three-dimensional (3D) planes. When compared to traditional methods, 3D-visualisation techniques are more effective in improving understanding of anatomy. [10] Furthermore, performing measurements on 3D computed tomography urography-images (CTU) could lead to higher accuracy of those measurements when compared to IVU's. [11] Additionally, the possibility of using transversal images has led to the development of new measurement techniques, that could not be performed on anteroposterior IVU's. [12]

As before mentioned, the most frequent reason to study renal anatomy is because the outcome of an endourological treatment is influenced by the morphometric properties of the pelvicalyceal system. [13,14] With improvement of technology in endourology such as digital flexible ureterorenoscopes (fURS) and percutaneous nephrolithotomy (PCNL), success-rates of stone treatment have increased and operating time has decreased. [15,16] Still, a limitation of the current generation of flexible ureteroscopes is their disability to reach difficult places due to the anatomy of the kidney such as (the anterior/dorsal calyx of) the lower pole, as a result of the relatively limited bending mechanism of the fURS. If certain morphometric properties of the pelvicalyceal system would both amplify kidney stone formation and impede intrarenal treatment success, a difficulty for the endourologist is imposed.

In our recent manuscript, we reported a technique to quantitively describe the pelvicalyceal anatomy. [12] Now, we question which morphometric properties of pelvicalyceal anatomy lead to a higher risk of kidney stone formation. Moreover, we studied if those correspond with the morphometric properties described in literature as making areas of the kidney harder to reach in intrarenal surgery. In this manuscript, we compare pelvicalyceal anatomy between stone-forming and non-stone-forming kidneys. Using multiplanar reconstruction of CT urography, we performed a broad span of measurements on upper, interpolar and lower segments of 20 stone forming and control kidneys.

METHODS

A list of all CTU made in Haga Teaching Hospital between 01-01-2017 and 31-09-2018 was obtained from the radiology department. Patients were divided in two groups: a nephrolithiasis and a control group. In both groups only adult patients (age ≥18 years) were included. For inclusion in the nephrolithiasis group, at least one nonobstructive calculus ≥3 mm had to be present in the ureter or pelvicalyceal system on the CTU. Calculi causing hydronephrosis were not included. A CTU without nephrolithiasis was only assigned to the control group when the patient did not have urolithiasis in his previous medical history. Indication for CTU was either hematuria or suspicion of urolithiasis. Measurements were performed on one kidney per patient. For the nephrolithiasis group, only the affected kidney was used. For the control group left and right kidneys were alternately used. Exclusion criteria were evident urological pathology on the CTU (including hydronephrosis and congenital malformations) and previous surgery of the urogenital tract. Furthermore, patients with a medical history of diseases associated with an enlarged risk of nephrolithiasis as described in the latest EAU-guideline were excluded, including patients with metabolic disorders causing stone formation. [17] The radiology reports and patient records were checked for eligibility for inclusion in the nephrolithiasis or control group.

Patient data such as age, length, weight, body mass index (BMI) and medical history were obtained from patients' electronical medical record. 3D-reconstructions of late phase scans of CTU (+10 minutes) were used for all measurements, made by the multiplanar reconstruction and maximum intensity projection functions of Phillips Intellispace Clinical Applications 8.2©.

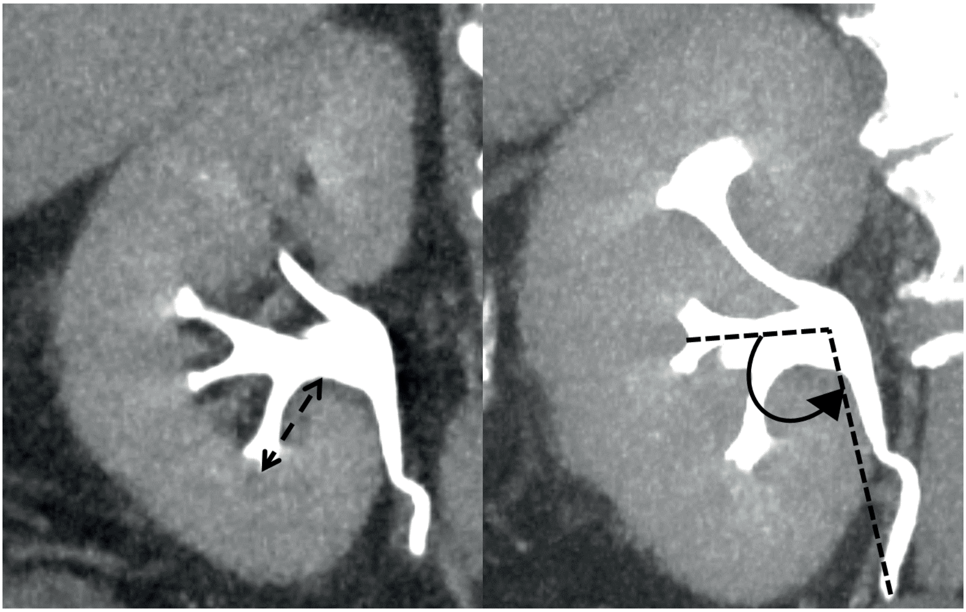
Based on the configuration of the pelvicalyceal system the kidneys were split into upper, interpolar and lower segments. The number of calyces was counted per segment. For the nephrolithiasis group locations and largest diameter of calculi ≥3 mm was noted. For each calyx infundibular length (IL), calyceopelvic angle (CPA), infundibular width

(IW), calyceopelvic tract width (CPTW) and transversal calyceal orientation (TCO) were measured. IL was measured as a straight line between the infundibulopelvic junction and the most distal point of the corresponding calyx. CPA was measured as the inner angle of the intersection of the ureteropelvic axis and calyceal axes. Ureteropelvic axis links the center of the ureter at the level of the lower pole to the center of the pelvis. IW was measured as the smallest point on the infundibular axis. CPTW was measured as the smallest point of the tract from each calyx to the pelvis. Measurements of IW and IL were performed as described by Elbahnasy. CPA and CPTW were derived from IW and infundibulopelvic angle (IPA) as described by Elbahnasy[9]. TCO was measured based on a clock system, as described in our recent publication[12]. Renal hilum was positioned on three o'clock. Measurements were performed clockwise for right and counterclockwise for left kidneys. Consequently, nine, twelve and six o'clock positions represented lateral, anterior and posterior positions, respectively. See figure 1 for additional illustrations. Furthermore, craniocaudal, mediolateral and anteroposterior diameters of the renal pelvis were measured. Upper lower calyceal angle (ULA) was measured as the angle between the axes of the two upper and lower calyces.

Data was analyzed with SPSS 25.00 (IBM corp., 2017). Numerical data was, if normally distributed, noted as mean (standard deviation) and analyzed using independent samples t-tests. IL, CPA, IW, CPTW and TCO were analyzed separately for upper, interpolar and lower segments. Linear mixed models were used to analyze these repeated measurements. Chi-square tests were used to analyze categorical data. P-values < 0.05 were considered statistically significant.

A. IL as measured for a lower pole calyx.

B. CPA as measured for an interpolar calyx.



C. IW and CPTW (marked with arrow) as measured for an interpolar calyx.

D. TCO measured using the clock system.

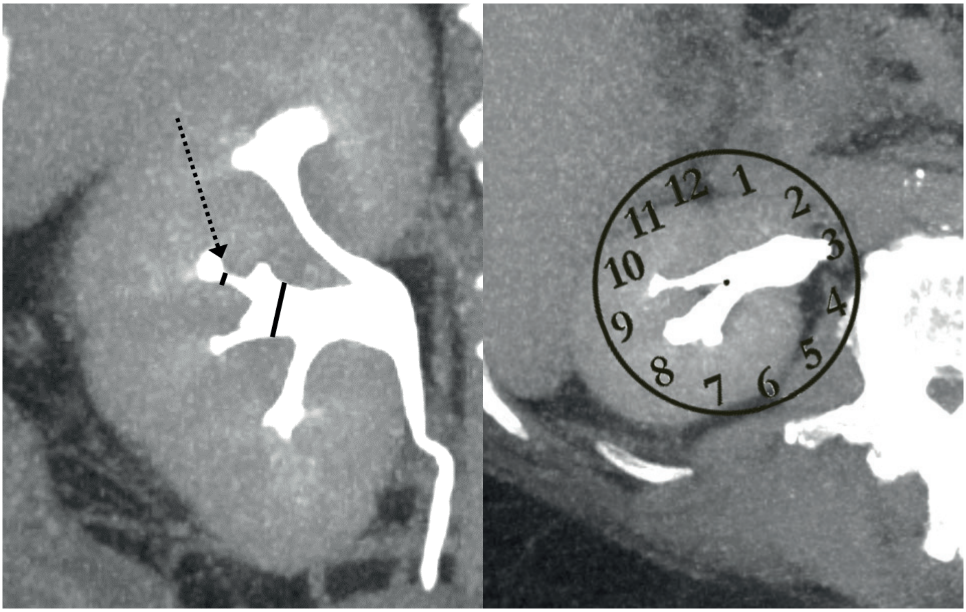


FIGURE 1. Illustration of the measurements on pelvicalyceal anatomy. Panel A shows IL as measured for a lower pole calyx, panel B shows CPA as measured for an interpolar calyx, panel C shows IW and CPTW (marked with arrow) as measured for an interpolar calyx and panel D shows TCO as measured using the clock system.

RESULTS

A total of 350 patients were checked for eligibility for inclusion. A total of 188 (53.7%) patients were excluded, based on the radiology report (n = 138, 73.4%), medical history (n = 37, 19.7%) and inappropriate quality of the imaging (n= 13, 6.9%). Of the remaining 162 patients eligible for inclusion, twenty were eligible for the nephrolithiasis and 142 for the control group. Chronologically, based on date of the CTU, twenty patients were included in both groups, starting with the first eligible CTU made in 2017. Table 1 illustrates the characteristics of the nephrolithiasis and the control group.

TABLE 1. Patient characteristics per group. Data is described as number (%) or mean (standard deviation).

	Nephrolithiasis group	Control group	
	N = 20	N = 20	p-value
Gender (male)	15 (75.0%)	12 (60.0%)	0.311*
Measured kidney side (left)	12 (60.0%)	10 (50.0%)	0.525*
Age (years)	58.1 (14.9)	64.9 (15.0)	0.158†
Length (m)	1.75 (0.06)	1.71 (0.12)	0.329†
BMI (kg/m^2)	26.6 (5.1)	27.7 (5.6)	0.593†

*Data was analyzed with: * Pearson chi-square test and † independent t-test.*

Average age of the patients was 58.1 and 64.9 years for the nephrolithiasis and control group respectively. In the nephrolithiasis group 75.0% (n = 15) of patients was male and in the control group 60.0% (n = 12). Average length and BMI did not differ significantly between both groups. Left kidneys were measured in 12 patients (60.0%) of the nephrolithiasis group and in 10 patients (50.0%) of the control group. For the nephrolithiasis group most of the calculi were

located within the kidney (n = 16, 80.0%), of which three (15.0%), six (30.0%) and seven (35.0%) were in the upper, interpolar and lower segment respectively. Remaining patients had a calculus located in the ureter (n = 2, 10.0%) or pelvis (n = 2, 10.0%). All patients in the nephrolithiasis group had one calculus ≥ 3 mm (n = 20, 100%). Median diameter of calculi was 5.2 mm (3.0-13.2). Table 2 shows the outcomes of morphometric measurements for both groups.

TABLE 2. Measurements of pelvicalyceal anatomy compared between both groups.

	Nephrolithiasis group	Control group	p-value
Total kidney calyces (n)	9.0 (5 - 15)	7.5 (5 - 20)	0.277*
Upper segment calyces (n)	3.0 (1 - 8)	3.0 (1 - 7)	0.968*
Interpolar segment calyces (n)	3.0 (1 - 5)	2.5 (0 - 6)	0.678*
Lower segment calyces (n)	3.0 (2 - 4)	3.0 (1 - 7)	0.398*
Upper segment IL (mm)	27.1 (7.8)	29.3 (10.1)	0.478†
Interpolar segment IL (mm)	19.3 (6.7)	17.8 (7.6)	0.361†
Lower segment IL (mm)	25.1 (6.7)	25.2 (7.5)	0.838†
Upper segment IW (mm)	4.1 (1.9)	3.8 (1.9)	0.390†
Interpolar segment IW (mm)	3.0 (1.8)	2.3 (1.6)	0.236†
Lower segment IW (mm)	5.5 (1.8)	4.4 (2.3)	0.105†
Upper segment CPTW (mm)	3.4 (1.5)	2.8 (1.7)	0.182†
Interpolar segment CPTW (mm)	2.5 (1.5)	2.3 (1.6)	0.768†
Lower segment CPTW (mm)	3.9 (1.8)	2.7 (1.7)	0.039†
Upper segment CPA (°)	115.7 (34.1)	116.3 (35.4)	0.888†
Interpolar segment CPA (°)	115.4 (26.1)	114.1 (28.9)	0.710†
Lower segment CPA (°)	70.8 (37.5)	73.3 (41.1)	0.092†
Upper segment TCO (hrs)	7.69 (2.24)	8.52 (2.07)	0.045†
Interpolar segment TCO (hrs)	9.25 (1.25)	9.42 (2.30)	0.657†
Lower segment TCO (hrs)	8.08 (2.44)	9.09 (1.65)	0.030†
ULA (°)	191.0 (57.1)	201.7 (58.5)	0.562†
CC diameter pelvis (mm)	16.9 (6.6)	13.5 (3.9)	0.052†
ML diameter pelvis (mm)	19.8 (4.7)	18.1 (5.0)	0.271†
AP diameter pelvis (mm)	9.8 (3.6)	8.3 (3.1)	0.166†

*Number of calyces (total kidney and per segment) is described as median (range), the other outcomes are described as mean (standard deviation). Data was analyzed with: * Mann-Whitney U test and † mixed linear models.*
IL = infundibular length, IW = infundibular width, CPTW = calyceopelvic tract width, CPA = calyceopelvic angle, TCO = transversal calyceal orientation, ULA = upper-lower calyceal angle, CC = craniocaudal, ML = mediolateral, AP = anteroposterior

Median numbers of calyces did not significantly differ between the nephrolithiasis group and the control group (7.5 vs 9.0 calyces, p=0.28). In addition, when the total of calyces was split per segment, no significant differences were found.

In all three segments, no significant difference in IL was found between both groups. IW was larger in the nephrolithiasis group in all three segments, but did not differ significantly from the control group. CPTW was larger in the nephrolithiasis group in all three segments as well, with a significantly larger mean lower segment CPTW in the nephrolithiasis group (3.9 vs 2.7 mm, p = 0.039). Mean CPA was bigger in the upper and interpolar segments compared to the lower segment, but no significant differences between the groups were found.

Mean TCO in hours was smaller in the nephrolithiasis group in all three segments, compared to the control group. Upper segment TCO (7.69 vs 8.52 hrs.) and lower segment TCO (8.08 vs 9.09 hrs.) were significantly smaller in the nephrolithiasis group (p = 0.045 and p = 0.030). This corresponds to significantly more dorsally located calyces in the nephrolithiasis group, compared to relatively more laterally located calyces in the control group.

Diameters of the pelvis did not significantly differ between both groups, with mean craniocaudal diameters of 19.8 and 13.5mm (p = 0.052), mean mediolateral diameters of 19.8 and 18.1 mm (p = 0.27) and mean anteroposterior diameters of 9.8 and 8.3 mm (p = 0.17) for the nephrolithiasis and control group respectively. Mean ULA was 191.0 degrees for the nephrolithiasis group and did not differ significantly from the control group (201.7 degrees, p=0.562).

DISCUSSION

Although metabolic factors have proven to play an important role in the etiology of urolithiasis, current knowledge on this subject is inconclusive to explain the complete process of kidney stone formation. In this manuscript, our main goal is to investigate the role of pelvicalyceal anatomy in the formation of renal calculi by performing morphometric measurements on both stone forming and control kidneys using 3D reconstructions of CTU. We found significantly more dorsally located calyces in both upper and lower segments and a significantly wider CPTW in lower segments of stone forming kidneys.

We postulate that if a role of pelvicalyceal anatomy in stone formation was to be found, the complete tract from calyx, where the renal papillae empty their urine, to pelvis had to be investigated. Common opinion is that stone formation initiates within the renal papillae, either by stone formation on Randall's plaques, plugging of Bellini's ducts or by free solution stone formation. [18] Starting in the calyx, the urinary flow-pattern might be influenced by the width and length of the tract and the sharpness of the corners in this tract. As this tract is different for each calyx, we decided, enabled by modern imaging and software techniques, to individualize measurements for each calyx. In addition to IW, we measured CPTW as the narrowest point from calyx to pelvis and, in contrast to most previous studies, we measured CPA instead of IPA. The CPA was derived from IPA as described by Elbahnasy; the individualized calyceal axis is used instead of the infundibular axis, while the same ureteropelvic axis is used. [9]

Few studies have been published with focus on the correlation between pelvicalyceal anatomy and the etiology of stone formation. Kupeli et al. performed measurements of pelvicalyceal anatomy in all three segments of lower pole stone bearing kidneys and contralateral kidneys, using 2D IVU's. Their main findings were a smaller interpolar IPA, larger upper IL and larger upper and lower IW. [7] Thus, even though calculi were only present in lower poles of kidneys, they found significant differences in the upper and interpolar segments, leading to the conclusion that stone formation does not depend solely on the lower pole pelvicalyceal anatomy. Stones can migrate over time and this could be a possible explanation for Kupeli's finding of significant differences in upper and interpolar segment anatomy: some of the lower pole calculi included by Kupeli might have originated from upper or interpolar segments and migrated to the lower segment. We likewise found a significant correlation between kidney stone formation and both upper and lower segment anatomy.

We found a trend of larger IW's and CPTW's in the nephrolithiasis group, with significantly larger CPTW in lower segments of stone forming kidneys. Likewise, both Kupeli and Gökalp et al. found significant larger IW in the stone forming kidneys. [7,6] Gökalp et al. measured lower pole pelvicalyceal anatomy on IVU and compared 119 kidneys with a unilateral single lower pole calculus with 80 kidneys from 40 random control patients. Gökalp found a significantly larger lower infundibulum diameter (corresponding with IW) and longer inferior calyceal length in stone forming kidneys. They measured inferior calyceal length from the most distal point of a calyx to the medial side of the pelvis opposing the infundibulum. Consequently, a larger pelvis would as well lead to a larger inferior calyceal length. We individually measured IL and the mediolateral diameter of the pelvis and found no significant correlation with stone formation.

Similar to our study, Balawender et al. used CTU for performing measurements on lower pole pelvicalyceal anatomy. They compared lower pole anatomy of 75 kidneys with a single lower pole calculus with the contralateral kidney. Of all measured outcomes, Balawender found only a significantly smaller IPA as described by Sampaio in the stone-bearing kidneys. We compared CPA instead of IPA and found no difference between the groups.

A possible explanation of our finding of more dorsally located calyces in stone forming kidneys could be an increased stasis of urine in those calyces, due to gravitational effects during sleeping in a supine position. As measurements on the pelvicalyceal anatomy in the transversal plane have only become possible after the development of the multiplanar CT's, very limited number of comparable studies have been performed with measurements on the transversal plane as outcomes. Sanal et al. compared transversal rotation of stone-forming and contralateral kidneys by measuring the angles between the renal pelvic line and median sagittal line of the vertebrae on unenhanced CT-scans. They found that stone forming kidneys have a more anteriorly faced pelvis. [19] Our results show that the average calyx is located nearly opposite to the renal hilum. Thus, a more anteriorly faced renal hilum corresponds with more dorsally located calyces in stone forming kidneys, making their finding complementary to ours.

Furthermore, a meta-analysis on the role of pyelocaliceal anatomy in the outcomes of retrograde intrarenal surgery was recently published by Karim et al. Their meta-analysis showed no significant differences in IPA, IL and IW between kidneys with successful and unsuccessful procedures. [20] Although we did find a trend of larger IW and significantly larger lower CPTW in stone forming kidneys, ureterorenoscopic treatment success is not influenced by it. All studies reviewed in Karim's manuscript performed measurements on 2D IVU's or retrograde pyelography. Consequently, no measurements in the transversal plane were performed in those studies. In retrograde intrarenal surgery, the pelvicalyceal system is entered at the ureteropelvic junction at the renal hilum. Calyces located straight opposite to the hilum, corresponding with a TCO at 9 o'clock, require minimal turning of the scope for accessing the calyx, though flexing of the scope is frequently necessary because of the IPA. We found that in stone forming kidneys the mean upper and lower calyx was orientated further away from the 9 o'clock point. Thus, these calyces require a sharper turn that has to be made for accessing the calyx. One could imagine that an increased sharpness of the turn would influence the difficulty of accessing areas of the pelvicalyceal system, thereby impeding treatment success rates, though no studies have objectively investigated this. Furthermore, calyces with both a dorsomedial orientation and a small IPA would require sharp turning as well as extensive flexing of the ureterorenoscopes. In the future, a ureterorenoscope with the ability to flex in two planes could prove to be a better solution for such calyces and might improve treatments success rates. Further research using individualized measurements on the stone bearing calyx, including measurements on the transversal plane, is advised to improve prediction of success rates of intra renal surgery.

One of the limitations of this study is that control kidneys came from different patients than the stone forming kidneys. Even though we found no significant differences between both groups in age, length, BMI and side of kidney measured, differences in metabolic states between both groups could be present. Moreover, morphometric properties of the pelvicalyceal system were measured at one point in time. These static measurements do not take possible dynamics of pelvicalyceal system anatomy into account. Furthermore, as only part of the included patients had calculi located in calyces and migration between calyces could have occurred, no conclusions could be drawn for individual calyces and no correlation between calculus location and pelvicalyceal anatomy was studied. Finally, we performed a retrospective study on a limited number of kidneys. Prospective research on a larger number of kidneys could further improve accuracy of results.

CONCLUSION

Pelvicalyceal anatomy differs when comparing stone forming kidneys with a non-stone forming control group. While we did find significant differences in anatomy in more than just the lower segment, none of our outcomes showed significant correlations in all of the three segments. These differences could have implications in minimally invasive treatment of renal calculi. Understanding the pelvicalyceal system and etiology of stone formation can improve development of endourological treatment techniques.

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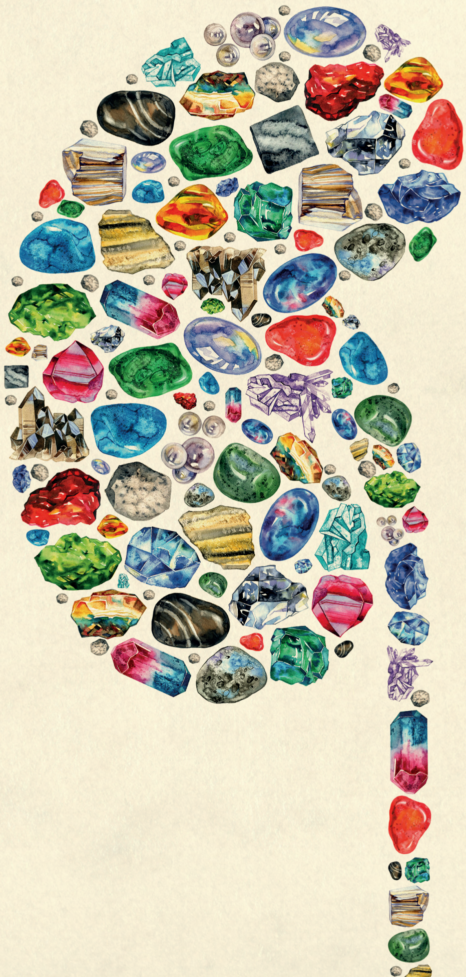
Part 2

Treatments evaluated

3



URS and PCNL: A quality control study

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ABSTRACT

Background

The use of minimally invasive surgery is increasing. Evaluating the quality of care brings new insights in the optimization of operating techniques.

Methods

We included all procedures performed in two hospitals during 2010 and 2011. A total of 264 patients were included in the ureterorenoscopy (URS) group and 77 patients in the percutaneous nephrolitholapaxy (PCNL) group. Data were gathered by retrospectively reviewing medical records.

Results

Mean stone diameter in the URS group was 9 mm. Patients suffered from a single stone in 79% of the cases. Calculi in the distal ureter, defined as the part of the ureter below the lower border of the sacroiliac joint, were most likely to be removed. A stone-free status was reached in 69% of the cases using URS. Mean stone diameter in the PCNL group was 23 mm. PCNL was successful in 70% of the cases in Haga Hospital versus 53% in Medisch Centrum Haaglanden. Incidence of complications was comparable between the hospitals ($p = 0.5$). Outcome and quality of both PCNL and URS was not influenced by sex, age or body mass index.

Conclusion

The clinical results were comparable with results in the literature. Further improvement can be made by optimization of technical aspects and centralization of treatment by urologists experienced in minimally invasive techniques.

INTRODUCTION

Incidence of stone formation in the urinary tract is increasing. It forms a major global medical problem in different healthcare systems [1]. Urolithiasis may cause severe pain, damage of renal function or even life-threatening septicemia. Extracorporeal shock wave lithotripsy (ESWL), ureterorenoscopy (URS) and percutaneous nephrolitholapaxy (PCNL) are the main treatment modalities for patients suffering from urolithiasis. Minimally invasive therapy for stones in the urinary tract has expanded over the last years, due to better imaging and technical modalities. In clinical practice, semi-rigid or flexible URS is usually applied for stones in the urinary tract when ESWL fails or is contraindicated. Semi-rigid URS is mainly used for distal ureteral stones. Flexible URS is preserved for the more proximal ureteral stones and renal calculi or migrated ureteral stones during semi-rigid procedure. PCNL is the treatment of choice for larger renal calculi [2, 3].

The outcome of these procedures varies in the literature, partially depending on the definition of stone-free status, which differs between publications. Social awareness, governmental authorities, insurance companies and patient organizations increasingly demand objective quality-controlled data in different fields of medicine, including care in urolithiasis [4]. Due to these requirements, medical specialists are increasingly starting to work in subspecialties. An effort is made to provide state of the art care by centralization and concentration of particular medical conditions. The treatment of calculi is one of these subspecialties in urology.

The goal of this study was to provide a clear view of the quality, obtained by URS and PCNL, in 2 hospitals in a major city in the Netherlands. We compared our results with the literature in order to detect possible points of improvement. We discussed technological aspects that could improve the quality and safety of these procedures.

MATERIAL AND METHODS

The URS and PCNL procedures, performed in Haga Teaching Hospital (Haga) and Medisch Centrum Haaglanden (MCH) during 2010 and 2011 were included in this study. A total of 264 patients were included in the URS database. Of this group, 196 patients were treated in Haga and 68 in MCH. PCNL was performed in 77 patients during the study period, of which 47 were operated in Haga and 30 in MCH. A database was created in Windows Office Excel 2010 with variables of quality. Patient data were gathered by retrospective viewing of the medical records. The software of IBM SPSS Statistics 20.0 was used to perform statistical analyses. These analyses were individually done for each hospital and were also combined. All outcomes were compared with the literature.

Pearson's chi-squared test was used to assess categorical variables. When analyzing smaller amounts of patients, Fisher's exact test was used. The Mann-Whitney U test was used to compare non-normal distributed variables between 2 groups. Univariate and multivariate logistic regression analysis was performed to show associations between independent categorical variables. When continuous variables were compared with more than 2 groups, the ANOVA test was used with a Bonferroni correction for multiple testing. A P-value of $p < 0.05$ was assumed to be statistically significant. The local ethical committee was informed.

RESULTS

URS

The average age of the 264 patients (male = 179, female = 85) included in the URS group was 55 ± 16 years. Their average body mass index (BMI) was 27 ± 4.7 kg/m2. Most patients (79%) suffered from only a single stone. The mean stone diameter (measured by kidney, ureter and bladder) was approximately 9 mm (8.9 ± 4.2 mm). Indication for semi-rigid or flexible URS was based on EAU guidelines. A safety wire was introduced in all semi-rigid procedures. An access sheet was used for introduction of the flexible ureteroscope. A Holmium laser was applied for defragmentation in the majority of cases. Small fragments were removed using a grasper. Patients were not pre-interventionally stented. The procedure was successful in 69% of all patients, as intra-operatively estimated by the surgeon. Stones in the distal ureter were most likely to be removed. In Haga a flexible URS for ureteral calculi was significantly more often used (39%) than in MCH (6%, $p < 0.01$). Mean operating time (55 minutes) was significantly longer in Haga, than it was in MCH (35 minutes, $p < 0.01$) (table 1).

Complications were more likely to occur when the number of stones to be removed was more than 1 ($p = 0.04$). The number of stones varied between 1 and 3, but in 1 case, 4 stones were treated. The number of complications were comparable between the hospitals ($p = 0.5$). The type of complication and its grade, using the Clavien grading system, varied. For example, abrasions or perforation of the ureter/renal pelvis occurred more often in MCH, whereas in Haga more postoperative infections were observed (table 2).

TABLE 1. URS type, operating time, stone removal and postoperative complaints

	MCH (n=68)	Haga (n=196)	Total (n=264)
URS type			
Semirigid	87% (59)	52% (102)	61% (161)
Flexible	6% (4)	39% (76)	31% (80)
Both	7% (5)	9% (18)	8% (23)
Mean operating time (range)	35 (7-123)	55 (11-152)	50 (7-152)
Stones removed			
yes	63% (43)	71% (138)	69% (181)
no	34% (23)	19% (38)	23% (61)
yes, but residual fragments	3% (2)	10% (20)	8% (22)
Free of complaints*			
yes	62% (42)	72% (141)	69% (183)
no	38% (26)	25% (49)	28,5% (75)
missing	0% (0)	3% (6)	2,5% (6)

**at follow up 4 weeks post-operative, no relapse in 1 year*

TABLE 2. URS complications

	MCH (n=68)	Haga (n=196)	Total (n=264)
Complication			
yes	28% (19)	22% (46)	23% (65)
no	72% (49)	76% (146)	75% (195)
missing		2% (4)	2% (4)
Clavien grade			
0	72% (49)	76% (146)	75% (195)
1	19% (13)	7% (14)	10% (27)
2	6% (4)	13% (25)	11% (29)
3a	-	0,5% (1)	0,5% (1)
3b	3% (2)	3% (5)	3% (7)
4	-	-	-
5		0,5% (1)	0,5% (1)

The mean hospitalization time for URS was 3 days. Additional treatment of residual fragments or newly formed calculi was considered to be needed in about 1 of every 3 patients during follow-up. In most cases ESWL or URS was used for retreatment. Stone free status after retreatment has not been evaluated. Sex, age and BMI did not have any influence on quality and outcome of URS.

PCNL

The mean age was 54 ± 15.4 years in the PCNL group. The proportion of male and female patients was 46 and 31 respectively. The average BMI was 27 ± 4.8 kg/m2. The average stone diameter was 23 ± 16.3 mm. Stones were located in the renal pelvis and its different calyces. The pyelocaliceal system was accessed by a thin needle, using ultrasound and X-ray control. A guide wire was introduced and preceded into the ureter. After this step, the tract was dilated using a balloon dilator. A 30F Amplatz sheath was subsequently placed in situ, through which the scope was inserted. The procedure was significantly more successful in reaching a stone-free status in Haga (70%) compared to MCH (53%) (p = 0.02). Operating time was longer when the stone diameter was larger than 20 mm (p = 0.03) (table 3).

TABLE 3. PCNL stones removed, postoperative complaints and operating time

	MCH (n=30)	Haga (n=47)	Total (n=77)
Stones removed			
yes	53% (16)	70% (33)	64% (49)
no	27% (8)	4 % (2)	13% (10)
yes, but residual fragments	20% (6)	26% (12)	23% (18)
Free of complaints			
yes	73% (22)	67% (31)	70% (53)
No	27% (8)	33% (15)	30% (23)
Mean operating time (range)	83 (34-143)	77 (31-173)	79 (31-173)

Again, there was a difference in type of complication and its Clavien grading (table 4) between the hospitals. Postoperative bleeding occurred in MCH in 10% of patients versus in 2% in Haga. Blood transfusions were more often necessary in MCH (table 4), but this was not significant. Unlike MCH, Haga preferred to use a nephrostomy tube postoperatively in most cases. The hospitalization time was longer in Haga (5 days), compared to MCH (4 days, p = 0.28). Sex, age and BMI did not have any influence on quality and outcome of PCNL.

TABLE 4. PCNL complications

	MCH (n=30)	Haga (n=47)	Total (n=77)
Complications (n)	30% (9)	33% (15)	32% (24)
Clavien grade			
1	3% (1)	13% (6)	9% (7)
2	17% (5)	9% (4)	12% (9)
3a	7% (2)	-	3% (2)
3b	3% (1)	11% (5)	8% (6)
4	-	-	-
5	-	-	-
Transfusion received (n)	13%(4)	4%(2)	8%(6)
Type of complication			
Fever / infection	10,0% (3)	9% (4)	9% (7)
Postoperative bleeding	10% (3)	2% (1)	5% (4)
Parenchymal laceration	-	13% (6)	8% (6)
Readmittance because of pain	3,3% (1)	2% (1)	3% (2)
Hydronephrosis	3,3% (1)	-	1% (1)
Parenchymal laceration + infection	-	2% (1)	1% (1)
Parenchymal laceration + hydronephrosis	3,3% (1)	-	1% (1)
Re-intervention < 4 weken	-	5% (2)	3% (2)

3

DISCUSSION

Average URS operating time in both clinics was comparable to the mean value reported in the literature (18– 93 minutes) [5, 6]. Flexible URS, in contrast to semi-rigid, was more often performed in Haga. This fact, as well as the larger number of residents performing surgery in this hospital, may be a cause of a longer operating time in Haga [6].

Complication rates of URS were largely the same in both hospitals. Minor lesions of the ureter or renal pelvis were most frequent, with percentages in the literature ranging from 0 to 15.4% [7]. In Haga minor lesions of the urinary tract occurred in 2% and in MCH in 16% of the patients. The more frequent use of semi-rigid URS in MCH may cause this higher percentage. However, the literature does not support this conclusion.

For PCNL there was an important difference between MCH and Haga. Access to the pyelocaliceal system and the stone site in MCH was established in the operating theatre, using ultrasound for guidance during puncture. In Haga this procedure was pre-planned, based on CT reconstruction images and access was preoperatively established under ultrasound and fluoroscopy. In MCH, a stone-free status, based on abdominal X-ray (kidney, ureter and bladder) was achieved in 53% of the cases and in 70% of the cases in Haga. Preoperative stone load per patient appeared to be similar in both hospitals. Successful PCNL is reported in the literature as ranging from 74 to 92% [8]. The definition of clinically insignificant residual fragments and stone-free status is often reported differently in publications and may cause confusion in the interpretation of these results [9, 10]. Average hospital stay in both hospitals was comparable with the literature [11].

Our results support the evidence that both PCNL and URS are treatment options of choice, for aged and/or overweight patients, male or female. Outcome is not influenced by any of these characteristics [12, 13]. Endurance of quality and further improvement of URS and PCNL is demanded by both care providers (government, doctors and social authorities) and consumers (patients). We investigated the quality of stone care in 2 hospitals. Our results support that URS, as a treatment for smaller calculi in the urinary tract, can be safely used in both hospitals. It is clear that a single simple stone in the distal ureter can be treated by all urologists practicing endourology. However, flexible URS and PCNL are also used as a treatment modality for larger and more complex stones in the upper urinary tract. These more complex treatments need a precautionary plan. Knowledge of renal anatomy is of utmost importance in order to find and eliminate calculi. When preplanning URS or PCNL, these anatomical data need to be applied and personalized for the renal anatomy of individual patients in order to provide optimal surgical information for the urologist. In our PCNL group, 90% were evaluated using CT abdomen in order to establish optimal anatomical data pre-operatively.

Rigid PCNL is limited in its maneuvers in the curved pyelocaliceal system and a flexible URS is often unstable in the ureter. Optimization of technical aspects and instruments can provide better outcome of minimally invasive procedures. For example, a (short) flexible renoscope can be used for PCNL to facilitate sight and operative maneuvers in order to work around narrower angles.

Another example is a thinner flexible URS, is able to pass any narrow points in the ureter.

When it comes to large, hard stones or those situated in an unattainable position, we believe that centralization and sub-specialization will improve quality of minimally invasive procedures. The two hospitals discussed in our quality analysis have decided to refer and to treat more difficult cases in Haga.

CONCLUSION

The success rate of URS in both clinics and PCNL in Haga concur with those reported in the literature. Complication rates, operating and hospitalization time correspond with the literature for both procedures and clinics. Outcome and quality of PCNL and URS is not influenced by sex, age or BMI. Further improvement in minimally invasive surgery for renal and ureteric calculi is feasible and can be made by optimization of technical aspects and knowledge of renal anatomy. Also, sub-specialization and centralization in the treatment and care of urolithiasis is mandatory. A study group has been initiated with a main focus on stone pathology, technical aspects of minimally invasive surgery, and improvement of care in urolithiasis.

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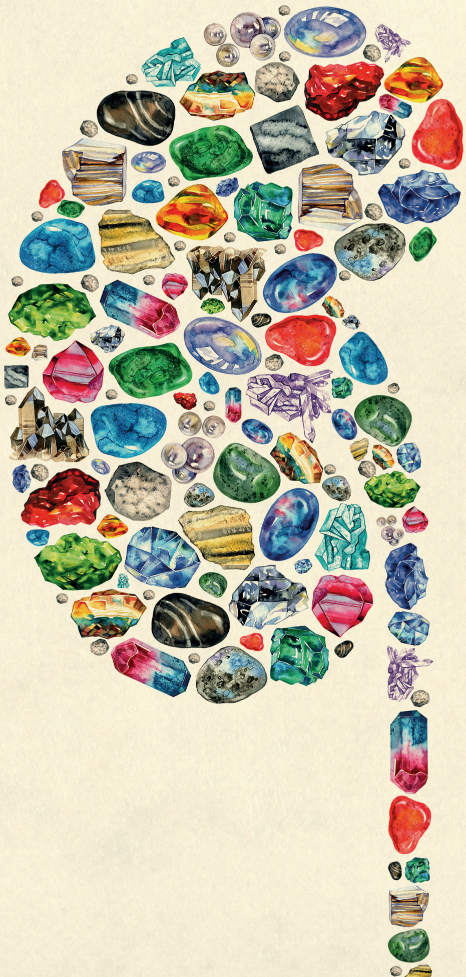

PCN versus JJ – A systematic review

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ABSTRACT

Purpose

To review the literature on optimal methods of drainage for obstructive urolithiasis in adult patients, comparing percutaneous nephrostomy (PCN) to retrograde ureteral catheterization (JJ) regarding success of procedure, efficacy, complications, quality of life (QOL) and costs.

Methods

Web of Science and the Medline, Embase, Emcare and Cochrane controlled trial databases were searched for all relevant publications until November 2018. A review protocol was created, using the PRISMA-statement. Two reviewers independently screened the titles and abstracts in Endnote X8, using criteria as stated in the research protocol. A total of 1108 abstracts were screened of which nine were included in the qualitative synthesis. Level of evidence of the studied articles varies between 1b and 2c.

Results

Both JJ and PCN have high success rates (80-100% and 99-100% respectively). No major complications were reported in both groups. Procedural and fluoroscopy times are significantly shorter for JJ compared with PCN (31-33 minutes vs 35-49 minutes and 5 minutes vs 7 minutes respectively). Time to clinical improvement did not differ. In the JJ group analgesics were used more frequently than in the PCN group. Data regarding procedural costs were contradictory, but overall the PCN group was associated with higher costs. In pregnant women, PCN placement appears to be significantly more successful than placement of JJ. A significant decrease between pre- and post-intervention quality of life was found with patients receiving a JJ. Back pain was reported more frequently in the PCN group; urinary symptoms were more common in the patients with a JJ.

Conclusions

Both PCN and JJ have comparable success rates for patients with obstructive urolithiasis and procedure related complications are rare. Overall, higher rates of sepsis, longer hospital stay and higher costs were found in the PCN group, but that could be explained by patient selection. Patients with JJ experienced a lower quality of life and experience more lower urinary tract symptoms (LUTS).

INTRODUCTION

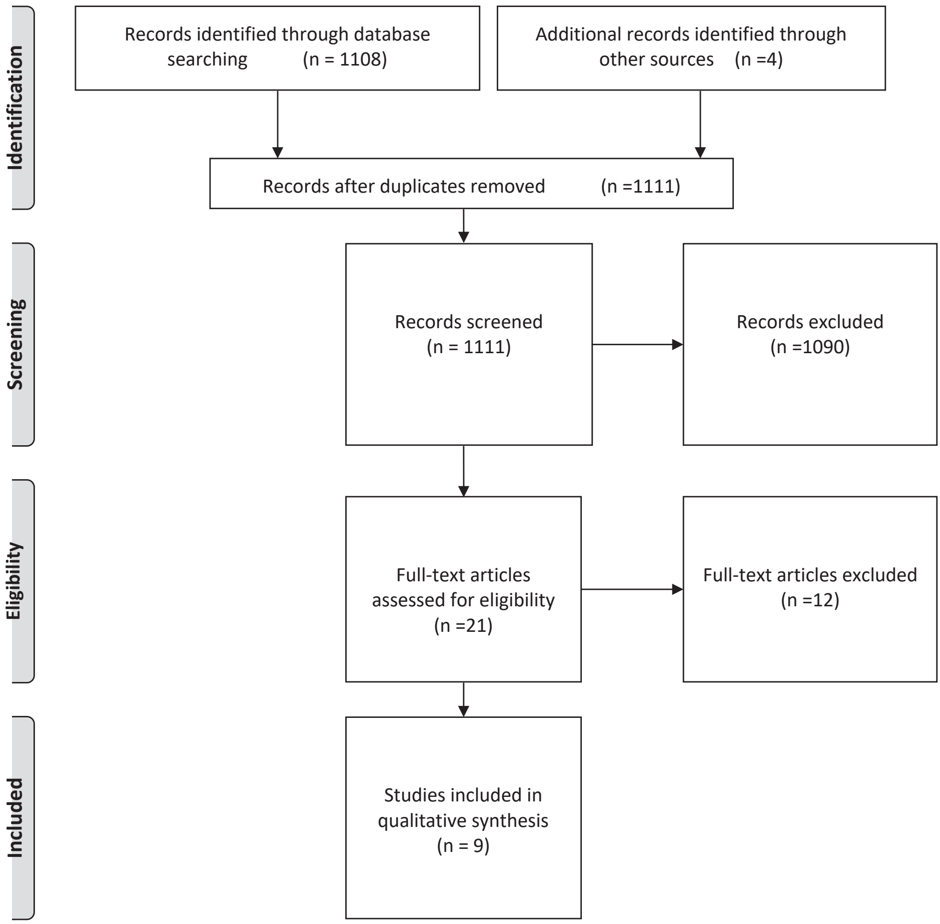
Drainage of the urinary tract is necessary when obstruction of the upper urinary tract causes infection, loss of renal function or uncontrollable pain. Untreated obstruction in patients with infection may induce significant morbidity such as sepsis, pyonephrosis and death [1]. Decompression of the urinary tract can be realized by retrograde or antegrade route. Most methods used are either percutaneous nephrostomy (PCN) or ureteral catheterization or stenting (JJ) [2].

Both procedures have pros and cons concerning complications, costs, quality of life and further treatment. However, for some patients timing is essential and may influence the choice of treatment[3]. EAU guidelines recommend PCN as well as retrograde JJ insertion for adequate decompression[4]. It is recommended that local expertise and resources should guide this choice.

The recommendation in the EAU guideline of 2018 is based on a review of data up till 2010. More than eight years later, the optimal method of decompressing the upper urinary tract is still a topic of discussion. High quality data on this subject are rare. In this review we aim to give a complete overview of available data on both drainage methods concerning success, efficacy, complications, costs and quality of life.

METHODS

A review protocol was created, using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)-statement. A search was performed in November 2018, using PubMed, Embase, Web of Science, Wiley/Cochrane Library and Emcare. Search terms: urolithiasis, nephrolithiasis, calculi, stones, drainage, nephrostomy, JJ, stent, decompression, obstruction, ureteral, hydronephrosis, dilatation, acute and costs were used and filters [human] and [English] were applied. No date restrictions were applied. Two reviewers (S.W. and B.S.) independently screened the titles and abstracts in Endnote (EndNote X8; Thomson Reuters, Philadelphia, PA, USA), using the criteria as stated in the protocol on PROSPERO. The full text of all potentially eligible publications was independently screened using a standardized screening form. Reasons to exclude articles were: inclusions of patients with malignancy as a cause for obstruction, no comparison between PCN versus JJ or describing only technical aspects and no outcomes. A third reviewer (R.P.) resolved any disagreements between the two reviewers.



A. PRISMA flow chart of inclusion

The different types of interventions were insertion of PCN or that of a JJ. This review addresses drainage of obstruction by stones in the kidney or ureter. Excluded were children and patients with renal transplantation. Also, case series including less than 10 patients, case reports and meeting abstracts were excluded. No date restrictions were applied. Duplicates were removed. Relevant reviews were screened for additional articles to be included. The Cochrane Risk of bias Assessment Tool was used to perform a risk of bias analysis for included nonrandomized comparative studies. Studies were assessed according to risk of selection, performance, detection, attrition and reporting bias, and were graded as low, high or unclear. A PRISMA flow chart of our search is included (A).

A total of nine articles were included in the final review. Level of evidence of the used articles varies between 1b and 2c. The data table is included (B). The complete search string is shown at the end of the article (C).

RESULTS

Of all included articles, most patients experienced infection as the main cause for decompression of the urinary tract. An overview is given in the data table (B).

The need for drainage and choice of procedure

Since patients in only three out of the nine articles included were randomized, a choice for either JJ or PCN was made in the other six studies. When time from randomization to drainage procedure was reported, no significant difference was found between the PCN and JJ group [5].

Overall, patients in the PCN group had larger stones compared to the JJ group; in the study of Goldsmith(7) stones had a median size of ten mm in PCN versus seven mm in the JJ group (p=0.031); in the study of Yoshimura(8) a mean stone size of 9.7 mm in the PCN versus 2.6 mm in the JJ group (p=0.006). Also stone burden was significantly higher in the study of de Sousa[6] in the PCN (median 92 mm^2) compared to the JJ group (median 47 mm^2, p = 0.012). Stone location did not differ[7, 8].

Compared to patients receiving JJ, patients in the PCN group appeared to be more severely ill with higher APACHE scores[7]. A large retrospective data analysis from the USA amongst 396.385 patients with urolithiasis and associated infection showed that with emergency decompression most of the time JJ was chosen (87.7%). A PCN was more likely to be placed at large urban teaching centres and males were significantly more often treated with PCN compared to females [9]. When requiring emergency drainage, more additional interventions and a longer hospital stay was necessary compared to patients with urolithiasis without need for emergency drainage[8].

Technical aspects; success and complications

Five studies described the type of anaesthesia used when intervention took place. In 4 out of these, placement of both PCN and JJ were performed under local anaesthesia. During procedures, analgesics were used more frequently in the JJ group compared to PCN (p=0.061) [10]. Fluoroscopic guidance was used in most procedures. Most commonly 8-14 French nephrostomy tubes and 4.5-7 French JJ were used. Location to perform the procedures varied from operating theatre (most frequent) to angiography suite or the urology outpatient department. Concerning procedural and fluoroscopy times, two randomized studies showed significantly shorter times for JJ compared to PCN insertion ($P<0,05$)[5, 11]. PCN insertion was successful in 95-100% and introduction of JJ in 80-100% of the procedures. JJ failure occurred more frequently in patients with high ureteral stones and age above 60 years [10]. When either procedure failed, the other procedure was performed in a second attempt [5, 7, 10, 12, 13].

Besides failing procedure, complications were rare. Dislocation of nephrostomy occurred in one patient in the nephrostomy group [11]. One study reported that antibiotics were administered for more than five days in 64% of patients in the JJ versus 0% in the PCN group[10]. However, a large epidemiological study reported in matched analysis the rates of sepsis and morbidity were significantly higher in the PCN group compared to JJ placement [9]. In the recent study of de Sousa no significant difference for need of antibiotics and urinary infections was found[6].

Efficacy, length of stay and costs

Two of the randomized studies showed that clinical improvement and normalization of index parameters such as white blood count and body temperature were not different between groups[5, 11]. One other study stated that patients in the JJ group had more rapid progression of inflammation and more severe thrombocytopenia. Peak CRP and WBC however did not differ between groups[8].

Difference in length of hospital stay was not different in one of the randomized studies (4.5 days in PCN vs. 3.2 days in JJ group) [5]. But two other studies reported significant longer hospital stay ($p=0.001$) and higher rates of Intensive Care Unit (ICU) admission ($p=0.016$) for the PCN group[7]. When matched analysis was performed in a large demographic study from the USA, higher rates of sepsis, severe sepsis, prolonged length of hospital stay, elevated hospital charges and mortality for patients in the PCN group were found. When comparing JJ and PCN within subsets (pyelonephritis versus cystitis, elective versus urgent) these differences were also found[9]. Yoshimura showed that hospital stay was ten days longer in patients undergoing immediate drainage compared to other urolithiasis patients[8].

In one of the randomized studies costs of JJ insertion was twice as high ($2401) as PCN ($1137)[5]. Large demographic data analysis for elevated hospital charges (beyond the 75^{th} percentile of $28 245) showed significant differences between groups, favouring the JJ group for lowest costs (26.5% versus 46.3%, $p<0.001$).

Drainage during pregnancy

Two retrospective studies described the treatment of obstruction due to urolithiasis during pregnancy. The indication for intervention varied from loss of renal function, infection and pain to positive urine culture. PCN and JJ but also ureterorenoscopy (URS) were chosen as first treatment option. Both PCN placement and JJ insertion were carried out under local anaesthesia. PCN was successful in 100% and complications were reported in 31.2%. Besides skin infection also pain was accounted for as a complication. JJ placement was successful in 71%-89%. Failure of JJ placement occurred more frequently in patients with stones larger than 2 cm. Complications were reported more frequently in the JJ group (52.9%), comprising pain, bladder irritation, but also an encrusted JJ and preterm labour. JJ replacement was needed twice for uncontrollable infection and stent migration. Procedural time, costs and length of hospital stay were significantly different, favouring the JJ group ($p<0.001$). Both PCN and JJ were reported to be uncomfortable. All patients underwent successful delivery[12] [13].

Quality of life

Of our nine selected articles, five described QoL as study outcome. Anaesthesia and analgesics did not only influence success of a procedure, but also patients' quality of life [14, 15].

Back pain was frequently reported and was more present in the PCN compared to the JJ group ($P<0.05$)[5, 11]. A difference in the use of analgesics was not reported and duration of pain was comparable. Another randomized study did report more frequent use of analgesics in the JJ group compared to the patients in the PCN group[10]. Urinary symptoms such as haematuria were more common in patients with a JJ (68.7%) compared to PCN (16.7%, $p< 0.001$). Also, dysuria was reported significant more frequently in the JJ vs the PCN group (78.3% vs 16.7%, $p < 0.001$).

A significant decrease was found between pre- and post-intervention quality of life (QoL) in patients receiving JJ ($p < 0.001$), but not in the PCN group ($P=0.206$) [6]. Quality of life reduction was also found to be more prominent in the JJ group of a randomized study, especially in males and patients <40 years of age. However, these results were not significant[10].

Spontaneous stone passage and stone management

Spontaneous stone passage was described in 2 studies and both presented no significant difference between the groups. One showed similar rates of passage between JJ and PCN group (12-14%, $p=0.786$). The most recent article with spontaneous stone passage

TABLE B. Included studies in order of clinical relevance and then year of publication. An overview of study patients and methods

Study	Study design (level of evidence)	Gender distribution (M:F)	Mean age in years (range or SD)	N total (PCN/JJ)	Reason for drainage	Inclusion criteria	Primary outcome
Pearle et al 1998	Randomized controlled trial (1b) 1995-1997	PCN group: (8:13) JJ group: (10:11) P value not significant	PCN group: 41.3 (+/- 13) JJ group: 41.3 (+/- 14.5)	42 (21/21)	- infection	Obstructing ureteral calculi + clinical signs of infection * *T>38C and/or white blood count (WBC) > 17,000/mm	Time to normalization of WBC or temperature
Mokhmalji et al 2001	Randomized prospective study (1b) 1996-1998	PCN group: (12:8) JJ group: (9:11) Comparable groups	PCN group: 55 (24-78) JJ group: 49 (24 - 76) Comparable groups	40 (20/20)	- infection - pain - loss of renal function	Hydronephrosis caused by urolithiasis and: Renal colic or T>38 or stone >15 mm or urosepsis or creatinin increase or _ UTI and incipient sepsis in blood count	Course of procedure, subsequent progress and quality of life (QoL)
Rammohan et al 2015	Randomized prospective study (1b) 2012-2014	PCN group: (8:12) JJ group: (9:11) P value not significant	Overall 46.47 (+/- 9.36)	40 (20/20)	- infection	Obstructing ureteral or renal pelvic stones with clinical signs of infection* *fever, WBC elevated	Time to normalization WBC, normalization of temperature, resolution of pyuria if seen
Sammon et al 2013	Observational cohort (2b) 1999-2009	PCN group: (35:65) JJ group: (28:72) P< 0.001	PCN group: 53 (40-68) JJ group: 51 (37 - 65) P< 0.001	396.385 (13.967 / 99.492)	- infection	Adult patients hospitalized with infected urolithiasis	Sepsis, organ failure, mortality length of hospital stay, cost
De Sousa Morais et al 2018	Prospective cohort (2b) 2017	PCN group: (6:12) JJ group: (19:13) P=0.077	PCN group: 63.1 (+/- 12.5) JJ group: 54.5 (+/- 15.5) P=0.048	50 (18/32) = 36% vs 64%	- infection - pain - loss of renal function	Adult patients with urinary tract obstruction due to kidney stones, confirmed on non-contrast enhanced computed tomography (NCCT)	Spontaneous stone passage (SSP) and quality of life (QoL

TABLE B. Continued

Study	Study design (level of evidence)	Gender distribution (M:F)	Mean age in years (range or SD)	N total (PCN/JJ)	Reason for drainage	Inclusion criteria	Primary outcome
Yoshimura et al 2005	Retrospective case study (2c) 1994-2003	PCN group: (12:12) JJ group: (12:23) P=0.034	PCN group: 67.3 (+/- 15.7) JJ group: 59.5 (+/- 17.4) P=0.042	59 (24/35) = 41% vs 59%	- infection	Patients with urosepsis associated with upper urinary tract and requiring emergency drainage	Course of procedure and subsequent progress
Song Yan et al 2012	Retrospective comparative study (2c) 2001-2012	all pregnant women	PCN group: 26.9 JJ group: 27.2 P=0.973	54 (16/17)	- infection - loss of renal function - pain	Pregnant women who required medical intervention for urolithiasis, diagnosed by creatinine levels/ urine analysis / ultrasound or MRI	Efficacy; = success of procedure
Goldsmith et al 2013	Retrospective case study (2c) 1995-2011	NR	56 (19–88)	130 (59/71) = 45% vs 55%	- infection	CT diagnosis of obstructive urolithiasis and 2/4 SIRS criteria (T / HR / RR / WBC)	Stone related and clinical variables which predicted use of each treatment method APACHE/ BMI / CCI / age etc)
Wang et al 2014	Retrospective comparative study (2c) 2006 - 2012	pregnant women	26 (17-39)	87 (4 / 19) Ureterolithotripsy (n=64)	- infection - loss of renal function - pain	Pregnant women who were treated with invasive procedures for proximal symptomatic ureteral stones between 2006-2012	Success

NR = not reported

SIRS = Systemic inflammatory response syndrome

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as a primary outcome reported spontaneous passage in 25% of JJ patients compared to 38.9% in the PCN group (p= 0.304)[6]. Evidence of impact of the type of intervention on stone passage was not found on univariate analysis in this last study, but after adjusting for predictors in multivariate analysis (stone size, previous surgery, medical expulsive therapy and stone site), PCN was associated with significant increase of spontaneous passage (OR 6.667, 95% CI 1.1034-42.970)) [6]. In 30.2% of patients (n = 13) in the JJ group, stones were displaced upwards with retrograde endoscopy[6].

Time to definitive treatment differed between studies and where one of the randomized studies reported a significantly shorter indwelling time of PCN compared to JJs. Another study reported an equal time to treatment of median 30-31 days[7, 10]. Method of drainage correlated with the later treatment method in this last study. Patients receiving PCN were significantly more likely to be treated with a percutaneous approach and patients receiving JJ were significantly more often treated ureteroscopically[7].

DISCUSSION

With this systematic review we aimed to identify the optimal drainage method in patients with obstructive urolithiasis considering the technical aspects of the procedure, efficacy, complications, costs, patient comfort and quality of life.

There are few randomized studies on this subject limited by low inclusion rates. Most studies included focus on infection as the main cause for decompression and do not perform a sub analysis of the groups on indications for drainage: pain, loss of renal function and infection. We aimed to give an overview of the present literature. Since the last review of Ramsey in 2010 six studies were published comparing JJ and PCN for drainage in obstructive urolithiasis[16]. Evaluation of quality of life and the use of patient reported outcome measurements (PROMS) are introduced nowadays in order to assess outcome of procedures from a patient centred view, ashift from a treatment centred view. This is clearly visible in outcome parameters of the more recent studies.

Clinical practice

Preferences for JJ or PCN varied between specialties. A survey amongst radiologists and urologists in 2006 in the UK (response rate of 19.3%) showed that urologists significantly preferred PCN more often than JJ. Only in patients with uncomplicated benign disease and with coagulopathy JJ was the first choice of urologists[3]. Distinction in urgency also appeared to be an important factor in clinical decision-making. In contrast to infection, drainage for pain or loss of renal function may usually be safely delayed for a limited period of time and logistics can be taken into account. Availability, logistics and experience with PCN or JJ techniques vary during office hours versus on call period, and result in local, regional, national and international differences.

Symptoms and patient selection

Arguments for choosing PCN over JJ were monitoring of diuresis, less manipulation of the urinary tract and the variety of tube sizes for irrigation in a patient with urosepsis. Urinary symptoms such as haematuria and dysuria are reported less frequently in patients with a nephrostomy tube.

Reasons to choose JJ over PCN was the belief of lower rate of complications and no use of external tubes or collecting bags[11]. An external tube and collecting bag are known to give back pain, and is reported more frequently in the nephrostomy group. Also, the risk for congestion and luxation is higher when a nephrostomy tube is present compared to an internal stent.

Patient-specific factors such as anatomic difficulties (BPH / altered lower tract anatomy) and expected definitive treatment may also play an important role in the individual decision-making process, which makes this process difficult to standardize.

A higher risk of bacteraemia during retrograde manipulation was stated previously, but is doubted because of insufficient evidence. Demographic data, using the Nationwide Inpatient Sample of the United States between 1999 and 2009 even supports the opposite[9]. One of our included randomized studies reported this as a secondary outcome and stated there was no significant difference in length of stay or normalizations of infectious parameters[5, 16].

Success and complications

Success of procedure was reached in almost all patients in the JJ and PCN group as well. Since most studies were non-randomized, there has probably been patient selection for choosing either procedure, influencing outcome. In the few cases of either unsuccessful JJ placement or introduction of a nephrostomy, a second attempt crossover to the other procedure was sufficient. Sufficient use of analgesics or anaesthesia could result in better procedural outcome. Most patients in the three randomized studies were treated under local anaesthesia; only Pearle reported JJ placement under general anaesthesia in some cases. Overall success rates in literature for PCN and JJ in patients with obstructive urolithiasis ranged from 98%-100% and 96-100%, respectively[17-19] and are comparable to our review when compensating for low numbers.

Complications in our data were low compared to procedure specific complications reported in literature. Major complication rates for nephrostomy tube placement in urolithiasis patients reached up to 3 to 5% in literature (colon puncture, sepsis, pneumothorax, macroscopic haematuria requiring transfusion) and minor complications were reported up to 4 or 5% (urine extravasation, haematuria and clot retention)[20-23]. In the randomized data included in this review, dislodgement of a nephrostomy tube occurred in one case, but no other complications were seen. Data on retrograde JJ placement in urolithiasis patients showed similar complication rates. The main difference is that these were mostly minor complications. Major haemorrhagic problems or death were not reported for patients receiving JJ[17, 24].

Costs and length of hospital stay

A large variety in outcome was found when evaluating costs. Differences between financial systems of countries and other factors such as materials used, type of anaesthesia, success rates and outpatient versus inpatient procedure make comparison of costs difficult. Length of hospital stay and location of procedure (operating theatre or outpatient department) or use of anaesthesia, are strong influencers of costs. As seen in the article of Pearle, general anaesthesia was used often for JJ placement. Costs were twice as high compared to PCN procedures under local anaesthesia, mainly due to additional costs for using the operating room, extra staff, anaesthesia and supplies. If a hospital provides possibilities for JJ insertion under local anaesthetic in the outpatient department, the comparison would completely be different.

Length of hospital stay can be influenced by a selection bias introduced by the choice of PCN versus JJ. Sammon reported in his retrospective data analysis that patients in the JJ group significantly differed from the PCN group, both patient and hospital characteristics. Patients undergoing PCN experienced significantly higher rates of (severe) sepsis and in-hospital mortality. Also, home healthcare after hospital discharge can take a longer time if PCN was performed and influences total length of stay.

A shorter time to definitive drainage could result in lower costs. A multi-centre analysis in Romania amongst patients with hydronephrosis and infection showed that increased costs of hospital stay were in retrospect significantly related to a longer time to definitive drainage. The group that received drainage within 9 hours of first presentation was associated with the lowest costs and drainage after 15 hours was associated with longer hospital stay and a significant increase in costs [25].

Pregnancy

For pregnant women, two studies were found and concluded that PCN seemed more successful than JJ insertion. Both JJ induced bladder irritation and PCN carrying an external tube or collecting bag were described as uncomfortable. When choosing JJ placement in this group of patients, rapid encrustation needs to be taken into account. During pregnancy, hyperuricosuria, high calcium diet, hypercalciuria and asymptomatic bacteriuria is common, enlarging the chance of complications[26, 27]. With a higher chance of stent replacement, a JJ could be placed in the third trimester of pregnancy[28]. However, in the first and second trimester, a PCN is preferred over a JJ.

Patient reported outcome measurements (PROMS) in urolithiasis

Conclusions on pain and quality of life are contradictory. Back pain was significantly reported more in PCN compared to JJ. Where some opinions opt for a JJ as having greater patient comfort, this burden was considerable. Having a JJ may result in urinary tract symptoms such as dysuria, frequency and haematuria and influence quality of life [6, 10, 29]. Haematuria in literature ranged from 2-21% for patients with JJ and additional analgesia was required in up to 70% of patients in the first week after JJ placement[30, 31]. A solution for this problem could be placement of an antireflux stent, which has proven to reach a higher acceptance rate with significantly less flank pain or pain in the bladder. However costs of these type of stents are higher, which should be taken into account[32].

Age seems to influence quality of life. One of our studies found that patients under 40 years of age appeared to experience more complaints with a JJ than patients above 40 years of age[10]. Also Borofsky reported in his PROMS study that patients <30 years and also between 30 and 65 years of age experienced more stent related side effects compared to patients older than 65[33]. Thus burden of JJ may be greater for younger patients than older patients.

In 2001 Joshi analysed a group of 34 patients in a prospective study comparing PCN with JJ using the EuroQol EQ-5D. Patients in the JJ group had significantly more LUTS compared to the PCN group, but overall analysis showed no significant difference in impact on quality of life[34]. However, intervention specific PROMS regarding decompressing treatments comparing patients with indwelling JJ or nephrostomies have not been developed yet.

CONCLUSION

Both PCN and JJ have comparable success rates for patients with obstructive urolithiasis and procedure related complications are rare. Overall, higher rates of sepsis, longer hospital stay and higher costs were found in the PCN group, but that could be explained by patient selection. Patients with JJ experienced a lower quality of life and experience more LUTS. Selection to date is made by local practice, patient characteristics and expertise as well as facilities. Also, reimbursement may influence preferences. Evaluations of quality of life and PROMS in urolithiasis are gaining ground, but intervention specific PROMS still have to be developed.

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C. OVERVIEW OF THE SEARCH STRATEGY

Search

Reguliere referenties: totaal d.d. 18-6-2018: 997 referenties, afkomstig uit:
PubMed: 675, waarvan 109 nieuw&uniek [RefID/Label 840-948]
Embase: 417, waarvan 9 nieuw&uniek [RefID/Label 949-965]
Web of Science: 463,waarvan 28 nieuw&uniek [RefID/Label 966-997]
COCHRANE Library: 73,waarvan 11 nieuw&uniek [RefID/Label 998-1010]
Emcare: 139,waarvan 11 nieuw&uniek [RefID/Label 1011-1021]
*ontbrekende RefID/Labels betreffen met de hand verwijderde dubbele referenties

Meeting abstract referenties: totaal d.d. 18-6-2018: 401 referenties, afkomstig uit:
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COCHRANE Library: 19,waarvan 0 uniek

Search terms:

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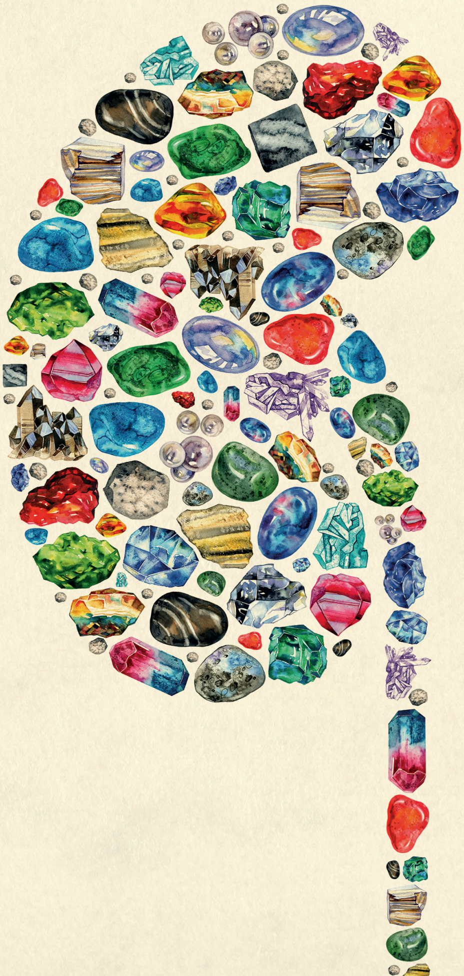
Part 3

New insights

5



The BUSCOPAN study

The content of this chapter has been published as; The BUSCOPAN study; a randomized controlled non-inferiority trial of a continuous butylscopolamine infusion versus placebo in patients with a renal colic not responding to oral non-steroidal anti-inflammatory drugs. World Journal of Urology 2020

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ABSTRACT

Purpose

To investigate whether placebo is non-inferior to continuous infusion of butylscopolamine in patients with renal colic.

Methods

We conducted a placebo-controlled, multicenter, double-blind randomized clinical trial (RCT) including 128 patients with renal colic (confirmed by ultrasound or CT-scan). Patients were randomized to receive either continuous intravenous (IV) butylscopolamine 100mg/24 hours or placebo (saline).

Primary outcome is the amount of opioid escape medication used, measured in doses administered. Secondary outcomes are pain measured on a Numeric Rating Scale (NRS), side effects and time of drug administration. Non-inferiority was assessed using linear regression with robust standard errors, with non-inferiority limit set at 0.5 units of escape medication.

Results

Median number of doses of escape medication was one in both groups. Number of extra doses in the placebo group compared with the butylscopolamine group was 0.05, with a 95% robust confidence interval (CI) of –0.38 – 0.47. Upper limit of the CI remained below the non-inferiority limit of 0.5 (p=0.04) No differences in secondary endpoints were seen between the groups.

Conclusion

Placebo is non-inferior to continuous IV butylscopolamine for pain relief in patients with renal colic. Based on this study and previous evidence, there is no role for continuous butylscopolamine IV in the treatment of renal colic.

Trial NL7819

INTRODUCTION

A renal colic, mostly produced by a calculus in the upper urinary tract, is one of the most severe forms of pain known. Non-steroidal anti-inflammatory drugs (NSAIDs) are the agents of first choice to control the pain in these patients. If NSAIDs are insufficient or contra-indicated, titrated intravenous (IV) or intramuscular opioids are generally recommended as a second step [1.2]. Additionally, anticholinergic spasmolytic drugs have been prescribed to patients with renal colic since the 19th century [3]. The rationale is that such drugs may induce smooth-muscle relaxation by inhibition of the action of acetylcholine on the muscarinic receptors in the wall of the ureter. One type of antimuscarinic that received interest over the past decades is butylscopolamine.

In the Netherlands, continuous IV infusion of butylscopolamine has long been used for pain control in patients hospitalized for renal colic. It is advised by the Dutch national guideline on kidney stones to consider as a second step after administering NSAIDs, and before opioids [4]. IV butylscopolamine is an integral part of renal colic management in the Netherlands, and we estimate that it is administered to several thousands of patients per year. Its use in other countries varies between institutions; there is no data on how widespread this practice is.

The use of butylscopolamine stems from tradition, not based on scientific evidence[3]. Previous studies dismissing buscopan as ineffective have noteworthy flaws. A handful of studies failed to prove effect of *oral* butylscopolamine on pain in renal colic [3,5-8]. A few trials assessed efficacy of IV butylscopolamine with a single dose of 20 mg [9]. No benefit of butylscopolamine in reducing opioid or metamizole need in renal colic was seen. Because of the rapidly declining plasma concentration of butylscopolamine, a single dose might not suffice for a therapeutic effect [9]. One recent RCT studied the effect of 80 mg IV butylscopolamine compared to placebo on renal colic and concluded there was no statistical difference between the placebo and butylscopolamine group [10]. However, this study was poorly suited to detect a beneficial effect of butylscopolamine, because patients in both groups received an initial dose of butylscopolamine.

In 2016 the uncertain benefit of a continuous butylscopolamine infusion was identified as an important clinical knowledge gap by the Dutch Association of Urology, supported by the Netherlands Patients Federation [4,11].

We conducted a multicenter double blind randomized controlled trial (RCT). The primary objective was to assess whether placebo is non-inferior to continuous intravenous infusion with butylscopolamine in patients admitted for pain due to renal colic with regards to amount of opioid escape medication needed.

MATERIAL AND METHODS

This randomized controlled clinical trial recruited patients in two general hospitals in the Netherlands between January 2018 and November 2019. The trial was registered in the Netherlands Trial Registry (Trial NL7819). The protocol was approved by the independent ethics committee (IEC, approval number 17-081) and participants gave written informed consent prior to inclusion. The study has been conducted following the Guideline for Good Clinical Practice.

Patients

Eligible patients were adults presenting with a renal colic, when pain was not under control with oral NSAIDs, they were admitted to the urological ward for analgesics. Confirmation of a renal calculus by ultrasound or CT-scan was required for inclusion. Exclusion criteria were pregnancy or lactation, contra-indication or known allergy to any of the drugs used (NSAIDs, morphine, paracetamol), temperature > 38.5°C in the 24 hours before inclusion or receiving antibiotics for urinary tract infection, or indication for immediate drainage of the upper urinary tract.

The primary outcome in this study was the amount of escape medication used during the 24-hour period of observation, measured in doses administered. Secondary endpoints were reduction in pain, measured using Numeric Rating Scale (NRS), time until last need for a dose of escape medication, side effects, use of anti-emetics and surgical interventions necessary for ongoing pain.

Randomization and blinding

Patients were randomized in a 1:1 ratio to one of two study-arms using sequentially numbered opaque sealed envelopes. No stratification was done. Randomization of treatment was determined in advance using a random numbers table. Patients, clinical staff and investigators were blinded to the allocation. Study allocation remained blinded until completion of the entire study.

Study procedures

All patients were given 1000mg oral paracetamol four times daily and 50mg oral diclofenac three times daily. They also received oral tamsulosin 0.4mg once daily. Escape analgesics consisted of piritramide 15mg subcutaneously as needed up to a maximum of five times. Furthermore, an IV anti-emetic was prescribed as needed. In one arm, patients received butylscopolamine (Buscopan®, Sanofi SA) 100 mg/24 hours via an intravenous continuous infusion, and in the control arm saline was given as a placebo.

Patients were asked to rate their level of pain using NRS at the start of the study period and subsequently at one hour, four hours, eight hours and 24 hours. Also, experience of side effects was asked. Escape medication was used to maintain adequate pain relief, a pain score below 4 was accepted as adequate pain management. After 24 hours, the study period ended and patients received standard care from there onwards.

Sample size and statistical analysis

The sample size was calculated using a one-sided, two-sample t-test (PASS version 08.0.16 (Hintze J, 2008); NCSS, LLC, Kaysville, Utah, USA).

The null hypothesis assumed that placebo is not inferior to treatment with butylscopolamine on the effect of using extra analgesics. We deemed a non-inferiority margin of 0.5 as clinically relevant. With the power fixed to 80% and a one-sided significance of α=5%, the required sample size to detect non-inferiority was calculated to be 51 patients in each arm. The data are drawn from populations with standard deviations of 1.0 and 1.0. Allowing for 20% dropout, inclusion of 128 patients was planned.

All statistical analyses were performed using SPSS statistics, version 26.0 (IBM, Armonk, NY, USA). After exclusion of patients that did not meet inclusion criteria, all analyses were performed on an intention-to-treat basis. Normality of data was analyzed using the Shapiro–Wilk test. Data with skewed distribution were analyzed using non-parametric tests, with exception of the primary endpoint. Since the primary endpoint is analyzed in the context of a noninferiority study, analysis of the primary endpoint was performed using linear regression with robust standard errors, to protect against non-normality of the outcome. The 95% confidence interval (CI) of the difference between the randomized treatment groups is based on these robust standard errors. For the other endpoints, numerical continuous data was analyzed using the independent t-test (and the Mann–Whitney U test for data showing skewed distribution). A p-value <0.05 was considered statistically significant.

RESULTS

During the study period a total of 290 patients were admitted for renal colic in the two participating centers. After assessing for eligibility and exclusion criteria, 128 were randomized and data of 124 patients was available for analysis. Three of the four patients that were excluded after randomization developed fever soon after admission and required urgent upper tract drainage. The fourth patient withdrew for personal reasons. There were a few minor protocol violations: administration of morphine instead of piritramide in two cases and refusal of diclofenac in eight cases, these were evenly spread among the two arms.

Sixty-two patients remained in each arm. Groups were not different when comparing for baseline characteristics, stone location or stone size, as shown in table 1.

TABLE 1: baseline characteristics

	Buscopan (n=62)	**Placebo (n=62)**
Gender, n (%)	44 (71%)	41 (66%)
Male	18 (29%)	21 (34%)
Female		
Age, mean ± SD	49 ±14	45 ±15
BMI, median (range)	28.2 (18.8-42.5)	26.6 (20.0-47.0)
Creatinin at admission in mmol/L, median (range)	91 (49-180)	90 (53-169)
Stone side, n (%)	34 (55%)	38 (61%)
Left	28 (45%)	24 (39%)
Right		
Stone size in mm, median (range)	5 (2-20)	5 (2-18)
Stone location* n (%)		
Proximal	24 (39%)	22 (37%)
Distal	38 (61%)	39 (63%)
Hydronephrosis, n (%)	8 (13%)	9 (15%)
None	47 (76%)	44 (72%)
Mild (grade 1-2)	7 (11%)	8 (13%)
Severe (grade 3-4)		
Primary diagnostics, n (%)	42 (68%)	37 (60%)
Ultrasound	53 (86%)	55 (89%)
CT		
NRS score, mean ± SD		
At start of study	4.7 ±2.7	4.7 ±2.8

**Proximal; cranial of crossing ureter and iliac vessels. Distal; caudal of crossing ureter and iliac vessels.*

Primary outcome

A total of 68 patients (55%) required opioid escape medication. The number of doses of escape medication required was 1.0 (95% CI 0.7 – 1.4) in the placebo group and 1.0 (95% CI 0.7 – 1.3) in the buscopan group. The number of extra doses of escape medication needed in the placebo group compared to the buscopan group was 0.05 (95% robust CI –0.38 - 0.47). The upper limit of the confidence interval remained below the non-inferiority margin of 0.5 (p=0.04). This indicates that placebo is non-inferior to butylscopolamine.

Secondary outcomes

Both groups showed a similar decrease in pain measured by NRS over time (figure 1). There was no statistical difference in time until last escape medication: a median of 7.0 hours in the butylscopolamine arm and 9.3 hours in the placebo arm. Side effects were reported by twenty-four patients with no statistical differences between the groups. There was no difference in amount of anti-emetics used and there were no surgical interventions for ongoing pain during the study period. Seventy-two patients left the hospital after the study period of 24 hours to be further monitored in the outpatient department. The other fifty-six patients were given either standard care with analgesics or intervention e.g. JJ catheter, nephrostomy or ureteroscopy.

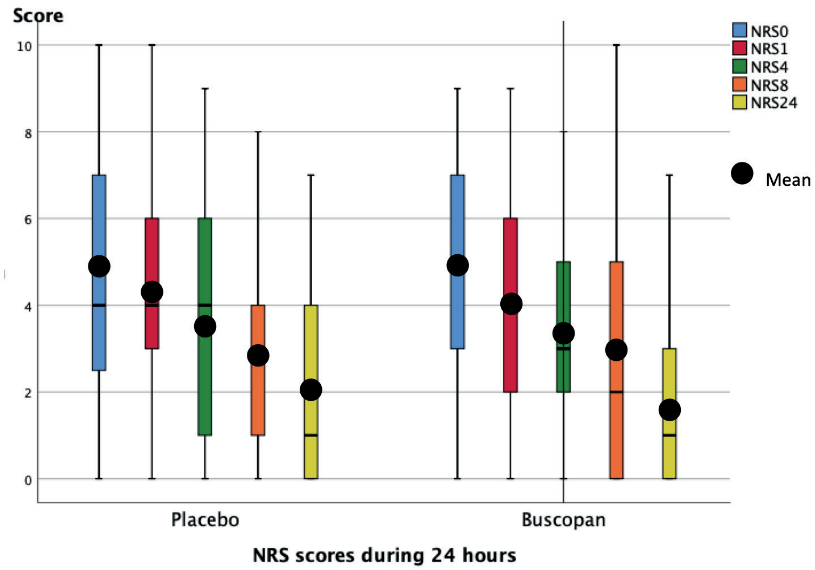

FIGURE 1: NRS scores during study period

Follow up

The mean follow-up was 68 days in the butylscopolamine group and 60 days in the placebo group. More than 90% of the patients were stone free at approximately 2 months follow up, of whom just under half had had a surgical intervention or ESWL in the meanwhile.

DISCUSSION

Placebo was demonstrated in our study to be non-inferior to continuous intravenous butylscopolamine in terms of need for opioid escape medication. Furthermore, no difference was seen in the pain scores during the course of 24 hours. These results warrant a re-evaluation of the recommendation for butylscopolamine by the Dutch Association of Urology, and by any institution currently administering this drug.

Pain caused by ureteral obstruction is related to increased tension in the walls of the renal pelvis on release of prostaglandins. Symptoms can be worsened by edema or inflammation in the ureter [3]. NSAIDs inhibit prostaglandin synthetase, which results in suppression of pain sensation and inflammation [7]. NSAIDs have already shown to be superior to opioids and paracetamol for the relief of pain in patients with a renal colic, resulting in less vomiting and less need for rescue analgesia[12]. Hyperperistalsis of the ureter, modulated by alpha- and beta-adrenergic receptors, play a part in this physiologic process as well. Alpha adrenergic receptor antagonists provide smooth muscle relaxation of the urinary tract, facilitating stone passage, but an analgesic effect has not been proven[13]. Antimuscarinic agents such as butylscopolamine can induce smooth muscle relaxation and decrease of ureteral spasm as well[14]. Their effect on the gastrointestinal and biliary tract has been widely studied and accepted, but an analgesic effect in renal colic has neither been proven [15,16].

A fair number of previous studies have been performed using different administrations of butylscopolamine; e.g. oral, intramuscular or, in few cases, intravenously [3,10]. Mostly single dose was used in these trials and mainly butylscopolamine was used as an additive in comparing different types of analgesics in patients with colic pain such as NSAIDs or opioids. A recent Cochrane analysis showed that addition of antimuscarinics to NSAIDs is not superior than NSAID monotherapy regarding pain reduction and use of escape medication [17,18].

All previous studies with *oral* butylscopolamine showed no benefit of this drug on renal colic [5]. This is hardly surprising since oral administration results in a poor resorption of butylscopolamine of approximately 8% [16,19]. Any significant effect of butylscopolamine is therefore only to be expected after parenteral administration. After intravenous administration, plasma concentration of butylscopolamine declines rapidly and the elimination half-life ranges between 1 and 5 hours. The total clearance is 1.2 L/min, of which 50% is excreted as unchanged drug through the kidneys [9]. The pharmacological effect of a single dose completely wears off after 30-40 minutes [9]. A continuous intravenous drip instead of a bolus may therefore be given to maintain a pharmacotherapeutic effect.

Three studies were performed with a single dose of intravenous butylscopolamine. One RCT of Holdgate concluded that there is no support for the addition of butylscopolamine IV to reduce the need for opioids. However, this research studied the effect of a single dose of 20mg butylscopolamine IV in patients suspected of renal colic, not confirmed in 40 cases [5]. One single blind study of Stankov et al in 1994 showed a pain intensity reduction at 30 and 50 min after a 20mg bolus of butylscopolamine similar to tramadol (100mg IV), but significantly lower than values reached with metamizole (2.5g IV) [6]. A third study compared a single dose of butylscopolamine (20mg IV) with papaverine (60mg IV) and pethidine (50mg IV) and concluded VAS scores were significantly higher in the butylscopolamine group [20].

Only one group studied the effect of continuous infusion of butylscopolamine (80mg IV) on renal colic, comparing it with a placebo and a tramadol arm. They concluded a tramadol drip alone is a safe alternative for infusion with antispasmodic drugs. This study however had limited power to detect a benefit of butylscopolamine because patients in both groups received an initial single dose of butylscopolamine [10]. Furthermore, the medical staff was not blinded to the study medication.

Our study was adequately powered and double blinded. All patients had confirmed renal stones on CT-scan (88%) or ultrasound. The study recruited a remarkably high proportion of all eligible patients and accrual was completed well within the planned time-frame of 24 months. The drop-out rate was low at 3%. It is therefore reasonable to assume that the study population accurately reflects the entire population of patients with renal colic and the findings may be extrapolated as such.

The study has a few potential limitations. In some hospitals 120mg of butylscopolamine per 24 hours is used, rather than the 100mg in this study. It is unlikely, but cannot be completely excluded, that the additional 20mg would have changed the outcome of this study. A further limitation are the few minor protocol violations as described in the results section. Eight patients refused diclofenac but did receive piritramide when a renal colic arose.

On first thought, one might not expect a great impact of no longer administering continuous butylscopolamine for renal colic, considering that the drug is very cheap and has a favorable side effect profile. However, the preparation and monitoring of a continuous infusion does form a burden on the nursing staff. The patient is far more mobile without a continuous drug pump. Although butylscopolamine is generally safe, a recent update in the United Kingdom emphasizes potential dangers of this drug in patients with underlying cardiac disease [21] . Finally, it is common practice to advise the patient to stay hospitalized for several hours after stopping the infusion to evaluate if he or she remains pain free without butylscopolamine. Eliminating butylscopolamine from the treatment of renal colic could therefore shorten admission times and relieve pressure on emergency care beds.

CONCLUSION

Placebo is non-inferior to intravenous butylscopolamine for pain relief in patients with renal colic. This adequately powered and double blinded trial confirms what previous limited studies already suggested: there is no benefit of intravenous butylscopolamine for renal colic. In our opinion no additional studies are necessary for application of butylscopolamine for this indication. Patients experiencing renal colic should be treated with adequate analgesics (paracetamol, NSAIDs and opioids if necessary) and there is no role for a continuous administration of IV butylscopolamine.

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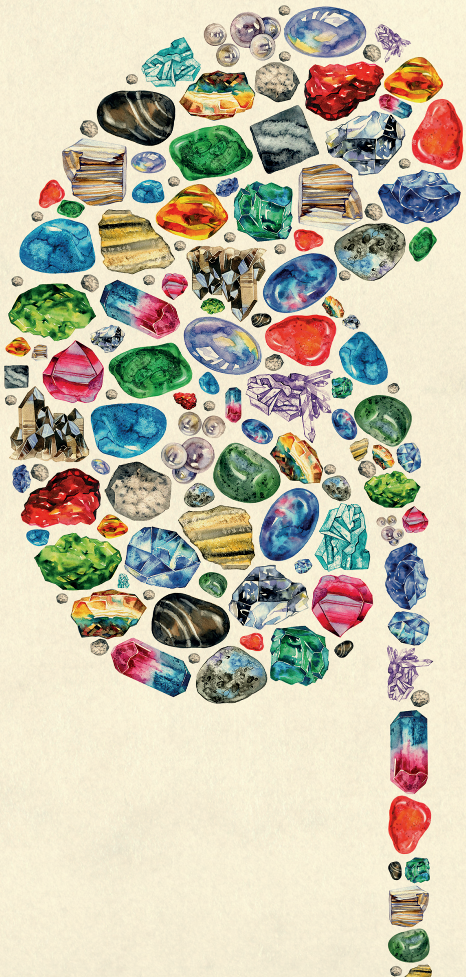

The influence of pain on the outcome of Extracorporeal Shockwave Lithotripsy (ESWL)

The content of this chapter has been published as: The influence of pain on the outcome of Extracorporeal Shockwave Lithotripsy, Current Urology, 2018. European Urology Supplements, 2017

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ABSTRACT

Introduction

The aim of this study was to determine the predictive value of pain scores on the efficacy of extracorporeal shockwave lithotripsy (ESWL) and to identify other predictive risk factors for treatment success.

Materials and methods

A total of 476 patients who underwent ESWL (piezoelectric lithotripsy) for urolithiasis between September 2011 and December 2015 were identified. The primary endpoint of this study was success rate, which was evaluated four months after ESWL. The secondary outcome was the occurrence of complications as a result of ESWL.

Results

The average pain perception was reported at 5 on a scale from 0 to 10. The overall success rate of ESWL was found to be 43.9% and the success rate after the first ESWL was 35.1%. Univariate analysis showed no significant correlation between pain score and success of ESWL ($p=0.135$). The level of intensity was correlated with pain scores (Pearson correlation -0.423, $p<0.001$). Univariate analysis identified five predictive factors: sex, stone location, stone size, hydronephrosis and the use of tamsulosin. Multivariate logistic regression analysis showed that sex, stone location and size independently influenced the success of ESWL ($p=0.045$, $p=0.001$ and $p<0.001$).

Conclusions

No correlation was found between the pain scores and efficacy of ESWL. Despite this absence, pain scores during ESWL sessions remain high and additional analgesia would improve patient satisfaction.

INTRODUCTION

Since the introduction of extracorporeal shockwave lithotripsy (ESWL) in the early 1980s, it has been recommended as a first-line treatment for renal and ureteral calculi less than 20 mm in diameter. Contrary to percutaneous nephrolithotomy (PCNL) and ureteroscopy, the procedure can be performed without the use of general anesthesia and in an outpatient setting. Success rates of ESWL range from 33 to 91%, depending on the efficacy of the lithotriptor, stone factors, patient habitus and the competence of the operator [1]. Predicting the efficacy of ESWL is key in reducing repetitive treatment, hospital costs and patient burden [2].

After the introduction of ESWL, the procedure was performed under general anesthesia. Technical improvement of lithotripters has enabled the treatment to be performed without the use of general anesthesia, although a lower level of intensity was generally being used. However, ESWL is still generally considered to be a painful procedure. This could be caused by shockwaves reaching superficial (skin and muscle) and deeper structures (ribs, nerves and the kidney capsule) [3,4].

It has commonly been assumed that pain effects the outcome of ESWL due to involuntary pain-induced movements and excessive respiratory excursions during the procedure, which impedes the operator's efforts to maintain focus on the stone. High pain perception might also limit opportunities to apply an adequate dose of energy [5]. However, little evidence is available to confirm the direct effect of pain on success rates of ESWL [4,5,6].

The aim of this study is to evaluate the correlation between pain perception during treatment as well as other potential predictive risk factors and the stone-free rate (i.e. rate of success) after ESWL.

MATERIALS AND METHODS

Cohort selection criteria

We included patients diagnosed with urolithiasis who were referred to a urology outpatients' clinic for ESWL between September 2011 and December 2015. They were identified from a prospectively collected database. These patients were adults (> 18 years) receiving their first ESWL for a solitary stone located in the kidney or the ureter or those who had not received an ESWL within the previous 2 years. We excluded patients whose essential variable "pain-score" was missing (n = 19), those whose diagnosis was uncertain (n = 16), along with those who had been lost to follow-up (n = 46) (Figure 1). This study was approved by the local institutional review board (METC Zuidwest Holland) and is in compliance with the Helsinki Declaration.

FIGURE 1. Flow diagram of our cohort selection

Review of patient data

Patient characteristics (age and sex), urologic presentation (previous ESWL, antibiotics, hydronephrosis, double-J catheter, nephrostomy catheter, use of tamsulosin, use of butylscopolamine and number of reinterventions), stone characteristics (side, size and location) and treatment parameters (level of intensity, applied amount of shocks, operator and fluoroscopy time) were obtained from the database. Use of tamsulosin was defined as use of 0.4 mg once daily at the moment of ESWL or for several days prior to the first follow-up. Stone size was measured using the largest measured diameter.

The primary endpoint of this study was the success rate defined as completely stone-free or with fragments smaller than 4 mm. Since all patients received an appointment at 3 weeks after treatment and if necessary followed by another appointment at 3 months, success rate was evaluated within 4 months of follow-up.

The need for additional treatment or reintervention (ESWL, ureteroscopy or PCNL) within 6 months was evaluated by urologist, in case of persisting stone or patients with recurrent urolithiasis. The secondary outcome was the complication rate due to ESWL, measured using the Clavien-Dindo classification [7].

Extracorporeal Shockwave Lithotripsy

Shockwave lithotripsy was performed using the PiezoLith 3000 (Wolf®), a third-generation piezoelectric shockwave lithotriptor. All patients received 1,000 mg oral paracetamol and 100 mg diclofenac per rectum half an hour prior to their procedure. Anticoagulants were stopped 1 week before treatment. Fluoroscopy or ultrasound was used to locate the stone. The target was to deliver 3,000 shocks for renal stones and 4,000 shocks for ureteral stones with a frequency of 2 Hz. Depending on the patients' pain tolerance, the intensity level was gradually increased to a maximum of 17 for renal stones and 20 for ureteral stones (Supplementary table; metric scale of power as indicated by Wolf). No ramping was performed. Patients were asked to indicate their degree of pain on a scale from 0 to 10 (0, describing “no pain” and 10, describing “maximal possible pain”) multiple times during ESWL.

The highest pain score was reported. A pain score less than 4 was considered as acceptable. Three weeks after treatment, their stone status was evaluated by kidney-ureter-bladder radiography and, in case of radiolucent stones, ultrasonography or an abdominal computerized tomography (CT) scan. The procedure was carried out by urologists or specially trained nurses.

Statistical analysis

SPSS-version 23.0 was used to perform statistical analyses. The Pearson correlation coefficient was used to evaluate the correlation between intensity levels and pain scores. Univariate and multivariate logistic regression analyses (stepwise backward method) were used to determine the predictive value of pain and other variables for the efficacy of ESWL. The Hosmer-Lemeshow test was used to evaluate the quality of the prediction model. A p-value < 0.05 was considered statistically significant.

RESULTS

Patient, stone and procedure characteristics

The patient and demographic characteristics are summarized in table 1. A total number of 476 patients with urolithiasis is analyzed in this study. The median age is 52 years and sex ratio (M/F) is 3:1. A double-J catheter was in situ in 11 patients (2.3%)

and a nephrostomy catheter in 21 patients (4.4%). For renal stones, a median of 3,000 shockwaves was applied with a median intensity level of 12.9, while ureteral stones were treated on with 3,500 shockwaves and an intensity level of 13.9. The level of intensity was correlated with the pain scores (Pearson correlation –0.423, $p < 0.001$). The higher the pain scores, the lower the level of intensity.

TABLE 1. Baseline patient and stone characteristics by pain score.

Baseline characteristics	N of patients (%)	
Age (yr)	51.36 ± 15.17	(range 18 – 87)
Sex, n (%)		
Male	347 (72.9)	
Female	129 (27.1)	
Pain score (0-10)	5.18 ± 2.0	(range 0 – 9)
Laterality		
Right	209 (43.9)	
Left	267 (56.1)	
Stone location		
Renal	179 (37.6)	
Upper pole	50 (10.5)	
Lower pole	129 (27.1)	
Ureter	297 (62.4)	
Upper	191 (40.1)	
Lower	106 (22.3)	
Stone size (mm)	8.46 ± 4.09	(range 2.5 – 28)
Persistent stone, n (%)		
Yes	25 (5.3)	
No	451 (94.7)	
Hydronephrosis, n (%)		
Yes	205 (43.1)	
No	271 (56.9)	
Opiates, n (%)		
Yes	46 (9.7)	
No	430 (90.3)	
Mean applied energy level (0-20)	13.50 ± 2.67	(range 3.7 – 19.9)
Tamsulosin, n (%)		
Yes	152 (31.9)	
No	324 (68.1)	

Primary outcome

The median pain score is reported as 5. Two patients (0.4%) experienced no pain (pain score 0), 104 patients (21.8%) mild pain (pain score 1-3), 224 patients (47.1%) moderate pain (pain score 4-6) and 146 patients (30.7%) severe pain (pain score 7-10). The pain score was significantly higher among patients younger than 60 years old (5.4 vs. 4.7, p = 0.001). A total of 46 patients (9.7%) required extra use of opiates (oxycodone, tramadol, piritramide or morphine), resulting in a mean pain score of 4.96. There was no significant difference in pain score between the group with and without use of extra opiates (4.96 vs. 5.20, p = 0.432). The use of butylscopolamine as analgesic was reported in 30 patients (6.3%). There was no significant difference between pain scores for renal and ureteral stones (5.4 vs. 5.1, p = 0.113).

The success rate of the first ESWL in our department was recorded as 35.1%. One hundred thirty-seven patients received a second or third ESWL session, resulting in an overall success rate of 43.9% with a mean of 1.37 sessions. Most of those patients (93.4%) received re-ESWL within 6 months. Univariate analysis showed no significant correlation between the pain score and the success of ESWL (p = 0.135). Univariate analysis identified sex, stone location, stone size, hydronephrosis and the use of tamsulosin as potentially predictive factors (Table 2). Multivariate logistic regression analysis showed that sex, stone location and size independently influenced the success of ESWL (Table 3). The Hosmer-Lemeshow test indicates a good quality of the prediction model (p = 0.177). An additional operation after ESWL was required to 115 patients (24.2%) who were not stone-free after ESWL. Ureteroscopy was performed in 106 patients (22.3%) and PCNL in 9 patients (1.9%).

Secondary outcome

Complications were reported in 12.4% of patients (Table 4). The majority of complications reported during the study period were minor and without the need for an intervention, such as hematuria and pain. In 1 case, a transient ischemic attack occurred due to a temporary stop of anticoagulants. One patient developed an acute renal insufficiency, but spontaneously recovered after several days.

TABLE 2. Univariate analysis of factors influencing the effectivity of ESWL.

Variables	Odds ratio	95% confidence intervals	p-value
Age (yr)	0.990	0.978-1.003	0.133
Sex (male)	1.910	1.213-3.010	0.005
Stone location[a]			<0.001
Renal lower pole	0.486	0.231-1.019	0.056
Proximal ureter	1.499	0.774-2.901	0.230
Distal ureter	1.789	0.882-3.631	0.107
Stone size	0.806	0.752-0.865	<0.001
Persisting stone	0.567	0.222-1.448	0.236
Hydronephrosis	2.066	1.409-3.030	<0.001
Opiates	0.789	0.409-1.524	0.481
Energy ESWL (0-20)	1.024	0.954-1.099	0.514
Tamsulosin	2.290	1.536-3.414	<0.001
Pain score	0.930	0.847-1.023	0.135

[a]*Renal upper pole as reference*

TABLE 3. Multivariate analysis of factors influencing the effectivity of ESWL.

Variables	Adjusted odds ratio	95% confidence intervals	p-value
Sex (male)	1.648	1.011 – 2.686	0.045
Stone location			<0.001
Renal lower pole	0.450	0.203 – 0.999	0.050
Renal pelvis/proximal ureter	1.481	0.718 – 3.056	0.288
Distal ureter	1.197	0.557 – 2.572	0.645
Stone size	0.802	0.744 – 0.864	<0.001

[a]*Renal upper pole as reference*

TABLE 4. Complication rates of ESWL

Grade	Complication	Number of patients	Percentage
I	Hematuria (n=19), pain (n=27), acute renal failure (n=1)	47	9.9
II	TIA, fever eci, urosepsis	3	0.6
IIIa	Stone street treated with ESWL, urosepsis and pyelonephritis treated with nephrostomy (n=2)	3	0.0
IIIb	Stone street treated with URS	6	1.3
Total		59	12.4

DISCUSSION

The introduction of ESWL has been revolutionary for the treatment of urolithiasis. However, ESWL causes shockwave-induced pain during the treatment. The correct dosage of analgesics is mandatory to maintain patient comfort and may improve treatment outcomes [8]. The hypothesis is that adequate treatment of pain during ESWL would result in higher success rates due to less involuntary movements and better stone focus. We designed this study in order to evaluate this assumption.

Parameters for stone fragmentation and clearance

Stone fragmentation and clearance are multifactorial events. The success of ESWL depends on many factors, including stone factors, patient habitus, competence of the operator, and the efficacy of the lithotriptor. The size of stone is inversely correlated with higher success rates. High-density stones and lower pole renal stones are associated with worse results [1]. The use of alpha-blockers to improve elimination rates by relaxing smooth muscle cells in the urinary tract, remains controversial [9]. Electrohydraulic, electromagnetic, and piezoelectric are three different types of shockwave generators which are being used in practice [10]. These generators seem to produce different rates of success and complications [3,10].

Our data and the literature

The wide variation in success rates in the current literature might be due to differing definitions of success and stone-free status [1]. Success is determined after one or multiple sessions and after several weeks or months. It is defined as completely stone-free or as the fragmentation of stones into smaller concrements using different types of imaging.

A few studies have been published concerning our study hypothesis. Cleveland et al. [11] observed that movement of calculi in vitro during ESWL caused a significant reduction in fragmentation rates due to the stone being out of focus. Furthermore, a prospective study of 222 patients from Vergnolles et al. [5] describes a significantly higher fragmentation rate in patients with a visual analog scale of lower than 3, compared to patients needing additional analgesia. However, this correlation could be due to the fact that the session was interrupted in 16.9% of treatments, when visual analog scale remained at 3 or higher, despite the use of additional analgesia. In addition, Sorensen et al. [12] reported a significantly higher stone-free rate in patients treated with general anesthesia, compared to patients receiving intravenous sedation using a second-generation lithotripter.

Our study reveals that the outcome of ESWL is not affected by pain during the treatment, according to the numeric pain scale. The level of intensity correlates with pain scores (Pearson correlation –0.423, $p < 0.001$), but does not seem to influence the success of ESWL (t-test, $p = 0.88$). The negative results of our study concerning the correlation between pain perception and success rates contradict the aforementioned literature. In contrast to our study, Vergnolles et al. [5] and Sorensen et al. [12] compared success rates in groups, with or without additional analgesia, or compared different forms of anesthesia instead of using pain scores. In addition, other types of shockwave generators were used. These factors make it difficult to compare the results of these studies with our own results. In general, pain scores are widely used due to their simplicity and adaptability to a broad range of populations and settings. However, using a pain score is very subjective when evaluating pain perception. Pain itself is multifactorial and affected by many factors such as age, gender, ethnicity, social status, education, personality and degree of understanding about the intervention. Individual variation is difficult to establish.

In our cohort, the success rate was 35.1% after the first treatment and 43.9% after subsequent ESWL sessions. No additional intervention was needed in 62.6% of treated patients within 6 months after ESWL, since complaints and hydronephrosis were absent while some small residual fragments persisted. An additional operation (ureteroscopy or PCNL) was required in only 24.2% of cases, which would suggest that ESWL is a viable option to prevent operative procedures.

Multivariate logistic regression analysis revealed male gender, stone size and location as predictive factors for success. Stone size was inversely associated with the success of the treatment. In our study, the success rate for renal lower pole stones was found to be 18.6%. ESWL on stones located in the lower renal pole is less likely to be successful compared with the treatment on stones in the renal upper pole (OR 0.450, $p = 0.05$). Our findings on the predictive value of stone size and its location are supported by various studies. The predictive value of male gender is not found in other studies and might be an incidental finding [2,3,13].

Study limitations

A potential limitation of our study is the lack of use of non-contrast spiral CT-scan as assessment prior to treatment, since that is the investigation of choice for urolithiasis. Contrary to X-ray, Hounsfield unit, stone volume, inflammation of ureter, and skin-to-stone distance could be easily assessed [1]. In our department it is not used as first choice due to its potentially higher dose of radiation and associated costs.

Recommendations

The median pain score in our study was described as "5", which is a relatively high level of pain sensation, considering that analgesics are given. In addition, one third of the patients experienced severe pain (pain score 7-10) and our data show that high pain scores are correlated with a lower level of intensity during ESWL. This suggests that our current pain prevention protocol is not sufficient and should be revised. Additional analgesia (a combination of paracetamol, NSAID and opioid) might lower the mean pain score and improve patient comfort. In our study no significant difference in pain score could be found between the patients who did (n = 46) and did not (n = 430) receive extra opiates. This is probably due to the small group of patients who received opiates. A study of Tokgöz et al. [3] analyzing pain perception during ESWL, supports our findings by describing a mean pain score for a first ESWL session as being 4.67. Since anxiety could also be an influencing factor on pain perception, patient education regarding the procedure and potentially a low dose of sedation might also help in lowering the pain score [4,5,6]. More random controlled trials are required to determine the best possible management of pain medication during ESWL.

CONCLUSION

Contrary to the general view that pain influences the treatment outcomes of ESWL, our results suggest that high pain perception does not correlate with the effect of ESWL. Despite the absence of a correlation with the outcome, pain scores during ESWL sessions remain high. Therefore, additional analgesia is recommended to improve patient comfort. Finally, our results support previous studies where stone size and stone location are predictive factors on the outcome of ESWL.

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SUPPLEMENTARY TABLE. Performance parameters

Intensity stage	Charge voltage (kV)	Pressure range (MPa)	Energy flow density (mJ/mm^2)
1	2.4	20	0.12
2	2.5	21	0.13
3	2.6	23	0.14
4	2.8	26	0.17
5	3.0	30	0.21
6	3.2	34	0.24
7	3.4	38	0.27
8	3.7	49	0.35
9	4.0	66	0.44
10	4.3	76	0.48
11	4.6	87	0.62
12	5.0	95	0.70
13	5.4	102	0.86
14	5.8	103	0.94
15	6.3	107	1.12
16	6.8	110	1.24
17	7.3	111	1.32
18	7.8	112	1.44
19	8.3	116	1.54
20	8.9	120	1.57

The tolerance of all values listed in the table is ± 10%.

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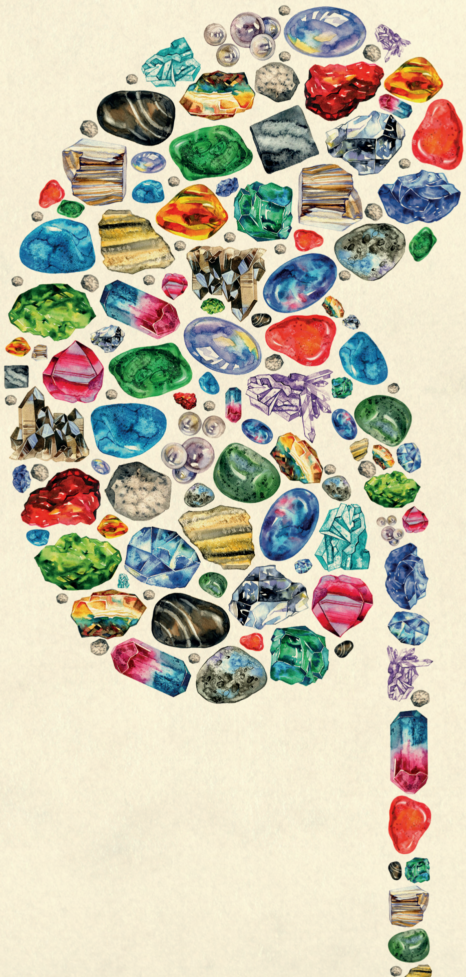

Ureteral stenting; Antegrade versus retrograde

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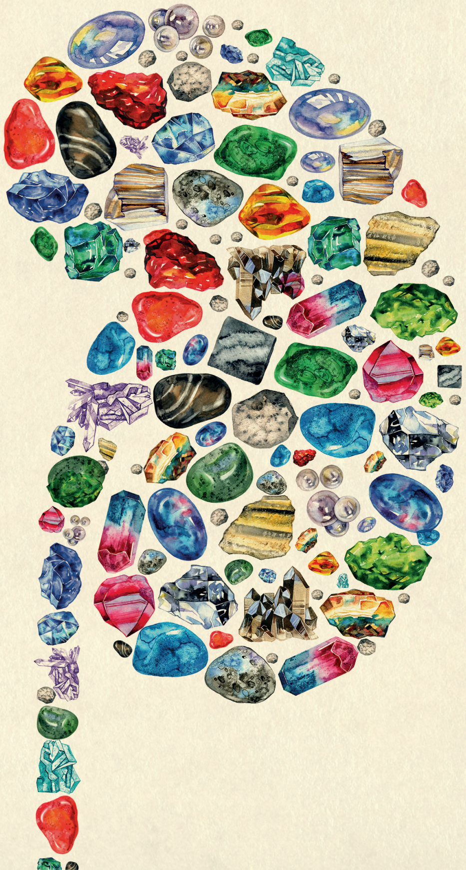

ABSTRACT

Background/Aims

Double J (JJ) stents for treating obstructive ureteral pathology are generally inserted through a retrograde route with cystoscopic guidance. Antegrade percutaneous insertion using fluoroscopy can be performed alternatively but is less known. Indications, success rate and complications of antegrade ureteral stenting were evaluated.

Methods

Data of consecutive patients in which antegrade ureteral stenting was performed were retrospectively analysed using the radiology information system and patient records. Patient characteristics, details of the antegrade JJ stent insertion procedure and registered complications were collected. Furthermore, it was investigated if prior to the antegrade procedure a retrograde attempt for JJ stent insertion was performed.

Results

Total 130 attempts for antegrade JJ stent insertion were performed in 100 patients. A percutaneous nephrostomy catheter had already been placed in the majority of kidneys (n = 109) for initial treatment of hydronephrosis. Most prevalent indication for a JJ stent was obstructive ureteral pathology due to malignancy (n = 63). A JJ stent was successfully inserted in 125 of 130 procedures. In 21 cases, previous retrograde ureteral stenting had failed but, subsequent antegrade ureteral stenting was successful. There were 8 procedure related complications; 6 infections, 1 false tract and 1 malposition.

Conclusion

Antegrade percutaneous insertion of a JJ stent is a good alternative for retrograde insertion.

INTRODUCTION

Percutaneous nephrostomy is commonly used as treatment for acute hydronephrosis aiming at preservation of kidney function and evacuation of infected material. Drawbacks of externally draining nephrostomy catheters are the risk of infection [1] and drain dislocation [2]. In addition, patients can experience severe discomfort from a percutaneous nephrostomy catheter.

JJ stents can be used alternatively, especially for long-term treatment of ureteral obstruction. JJ stents are mostly inserted through a retrograde route with cystoscopic guidance. Retrograde placement however can be difficult or even impossible, especially in patients with obstructive malignancies [3, 4]. In patients with an ileal conduit urinary diversion or a transplant kidney, a retrograde insertion of a JJ stent can be difficult because of the altered anatomy. Finally, especially in men retrograde insertion of JJ stents is mostly performed using spinal or even general anesthesia. Especially general anesthesia can have serious complications and may be contra-indicated in critically ill patients. In these situations, antegrade percutaneous insertion of a JJ stent through the kidney using fluoroscopic guidance and local anesthesia can be used as an alternative technique.

The purpose of the present study was to evaluate the indications, success rate and complications of antegrade ureteral stenting in our institutions.

METHODS

Data of consecutive patients in whom antegrade ureteral stenting was performed were retrospectively analyzed using patient records and radiology reports. Patients were treated in the Haga hospital, the Hague, the Netherlands, a large teaching hospital, between May 2005 and December 2012 or in Leiden University Medical Center, Leiden, the Netherlands, between April 2008 and February 2013. All procedures were performed by an interventional radiologist using ultrasound and fluoroscopy guidance. Preferentially, local analgesia with or without conscious sedation was used. General anesthesia was only used exceptionally on demand of the patient. Patients received prophylactic antibiotics preceding the procedure.

Non-heparin coated JJ stents were used (mainly Bard Urosoft®, 7 French; Bard Inlay Optima®, 7 French or Boston Flexima®, 8 French).

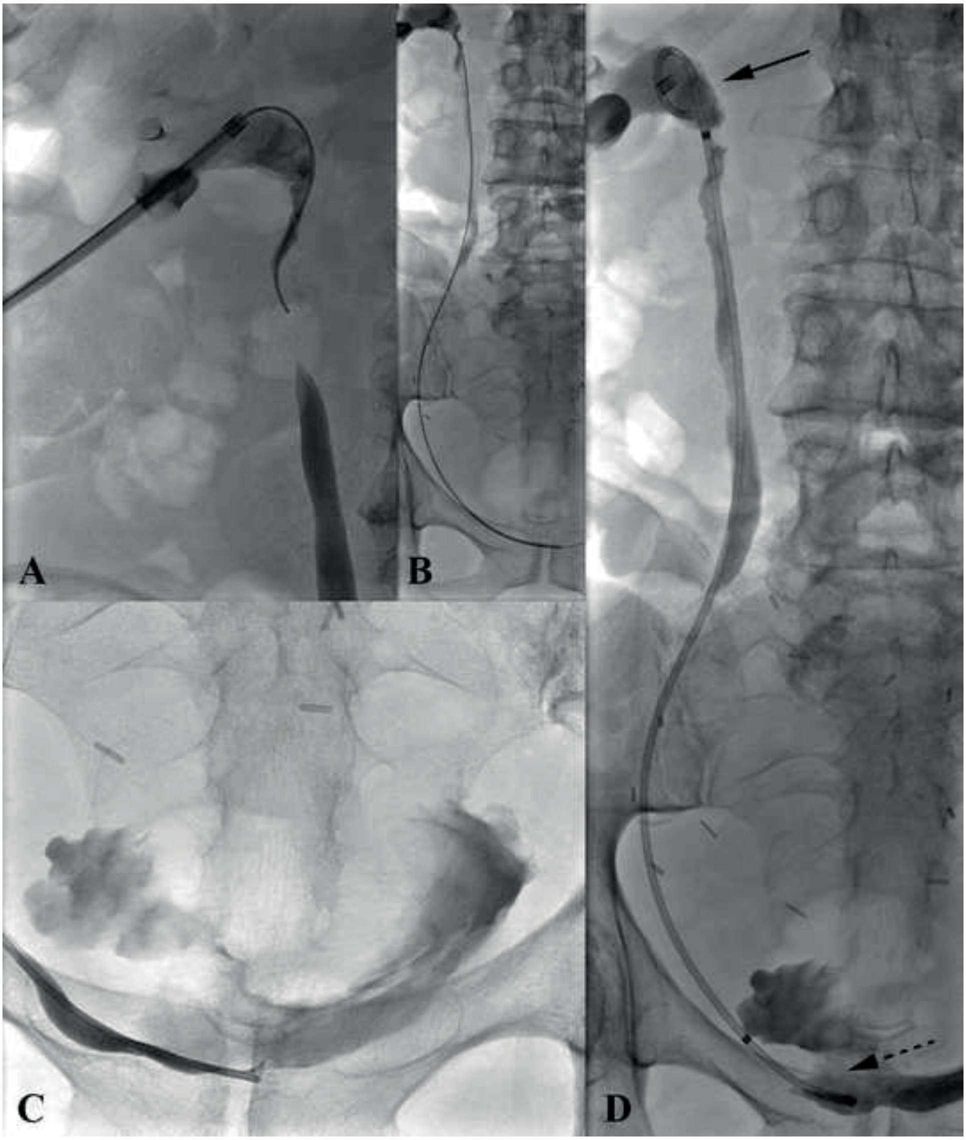

FIGURE 1. Antegrade insertion of a JJ ureteral stent. A: A 9 French sheath is inserted into the renal pelvis. B: Catheterization of the ureter into the urinary bladder with a hydrophilic guidewire and a 4 or 5 French catheter. C: Confirmation of catheter position in the urinary bladder using radiopaque contrast material. D: Final position of the JJ stent after positioning of the JJ stent using a stiff guide wire. Arrow points at the proximal J within the pelvis of the kidney, the dotted arrow points at the distal J in the urinary bladder.

In patients without a previously inserted percutaneous nephrostomy catheter, a "Neff percutaneous access set" (Cook Medical) was used to gain access to a renal calyx with the patient preferably positioned in the prone position. Access was preferentially obtained through an interpolar (mid kidney) calyx which offers easiest access to the ureteropelvic junction, or through a posterolateral oriented lower pole calyx which provides a safe, relatively avascular and easy puncture route [5]. After fluoroscopic confirmation of correct position of the Neff catheter, a stiff guide wire was used to change the Neff catheter for an 8 or 9 French introducer sheath (fig. 1).

If a percutaneous nephrostomy catheter had already been placed in an earlier stage, this catheter was changed using a stiff guide wire for an 8 or 9 French introducer sheath.

Thereafter, a hydrophilic 0.035 inch guide wire (Terumo glidewire®) and a steerable angiography catheter were used to catheterize the ureter all the way to the urinary bladder (figure 1). The hydrophilic guide wire was then changed for a stiff guide wire, and the JJ stent was advanced until a correct position was reached (figure 1). When the angiographic catheter or the JJ stent could not pass the obstruction, an attempt was made to advance a 4–5 mm dilatation balloon across the obstruction which could be inflated to dilate the ureter. Correct placement and patency of the JJ stent was checked by insertion of a small amount of contrast material through the sheath and if necessary, the position of the JJ stent was adjusted. Finally, the sheath was removed. Occasionally, when the procedure was troublesome or the aspirated urine was bloody, a closed percutaneous nephrostomy catheter was left in place for a day to secure access to the renal pelvis. In those cases, a check antegrade pyelogram was performed a day later. The nephrostomy catheter was removed when patency of the JJ stent was confirmed.

The radiology information system and patient records were used to collect patient characteristics, details of the antegrade JJ stent insertion procedure and registered complications. Furthermore, it was investigated if prior to the antegrade procedure a retrograde attempt to insert the JJ stent was performed.

Statistical analysis (*X*2 testing) was performed using SPSS, version 20 (SPSS, Chicago, Ill). A p value < 0.05 was considered statistically significant.

RESULTS

Totally 130 attempts for JJ stent placement were performed. Because some patients needed a JJ stent bilaterally (n = 16) and some patients needed a JJ stent more than once in the period studied, our procedures were divided over 100 patients (56 men and 44 women aged 18–92 years). A percutaneous nephrostomy catheter was already present in 109 renal units before JJ stent placement for initial treatment of hydronephrosis. Most prevalent indication for a JJ stent was obstructive ureteral pathology due to malignancy (n = 63), stricture (n = 30), or stones (n = 12) (table 1).

A JJ stent was successfully inserted in 125 of 130 procedures (96%). In 2 patients it was impossible to cross the obstruction. In one patient the ureter could not be catheterized due to gross hydronephrosis. In the fourth patient two separately scheduled attempts were performed. However, in both procedures it was impossible to pass an iatrogenic defect in the ureter that was a complication of a prior surgical procedure.

TABLE 1. Indications for JJ placement

Indicatie JJ	Aantal
Tumorobstructie	63
Litteken	30
Concrementen	12
Obstructie / lekkage na OK	10
Retroperitoneale fibrose	8
Obstructie eci	3
Infectie	2
Endometriose	2

In 13 procedures it was necessary to dilate the ureteral obstruction with a balloon before the JJ stent could pass. Obstructions that needed to be dilated were usually caused by a stricture.

In 19 patients with an ileal conduit urinary conversion and in 12 patients with a kidney transplant, the antegrade approach was the initial approach for JJ stent placement. In these patients with previous ureter reimplantation, scarring of the ureter was the most prevalent indication (n = 20). Other indications were obstruction caused by a malignancy or ureteral damage after surgery (both n = 4), and in the remaining 3 patients the mechanism of obstruction is not known.

In patients without a previous ureteral reinsertion, a retrograde attempt had failed in 18 patients (21 attempts). Twelve of these patients suffered from ureteral obstruction due to malignancy, 3 from a ureteral stricture, 2 from ureteral stones and 1 from retroperitoneal fibrosis. In all these patients antegrade ureteral stenting was subsequently performed successfully.

After 14 JJ stent insertions (11%), complications occurred within 30 days. One of the complications, a urosepsis, occurred in a patient with an extensive oncologic history and end-stage disease who was already on a palliative regimen. Because of the underlying oncologic disease, it was decided not to treat the infection and this patient died consequently.

Eight of the complications (6%) could be directly related to the antegrade procedure. During these procedures, a JJ stent was inserted unilaterally. Six patients developed urinary tract infection (UTI) (as confirmed by urine sediment analysis or a urine culture) within 30 days after antegrade JJ stent insertion. In 1 patient a false tract was created and in one patient the JJ stent was positioned incorrectly.

The remaining 6 complications within 30 days were related to the JJ stent itself: 5 times the JJ stent dislodged and once the JJ stent became obstructed.

One of the patients who developed a UTI received a percutaneous nephrostomy catheter for the treatment of a pyelonephritis 5 days prior to the JJ stent insertion. None of the other patients with a UTI after JJ stent insertion where diagnosed with an infection prior to the procedure. UTIs were treated with antibiotics; however, in one patient it was also necessary to remove the JJ stent in order to treat the infection effectively.

In 10 cases, complications occurred more than 30 days after antegrade JJ stent insertion. None of these complications seemed directly related to the procedure: The JJ stent became dislodged twice. In 4 patients the JJ stent became obstructed, and 1 patient developed several UTI. In 3 patients it was not possible to remove the JJ stent at the outpatient clinic as usual. Therefore 2 times general anesthesia was necessary to remove these JJ stents. And in one case the JJ stent was left in situ in a patient with a short life expectancy. Most of the patients with dislodged JJ stents at short- or long-term follow-up had a history of an ileal conduit urinary deviation (n = 6).

Fifteen patients complained of mild pain or "lower urinary tract symptoms" shortly after JJ stent insertion. These symptoms were mostly self-limiting. Mild hematuria was reported in 6 patients. None of these patients needed blood transfusion.

DISCUSSION

This retrospective study shows that antegrade, percutaneous insertion of a JJ stent is possible with a high technical success rate (96%) and a low risk of complications. Therefore, antegrade, percutaneous insertion of a JJ stent seems to be a good alternative when retrograde insertion fails.

Retrograde stenting has several advantages over the antegrade approach. Using the retrograde route, it is for example possible to manage obstructive stones, to take a biopsy of intra-ureteral malignancy or to incise strictures. It is known however that retrograde insertion of a JJ stent may be unsuccessful in up to 50% in patients with distal and extra-ureteral obstruction caused by malignancies [4, 6, 7]. In our series of 130 antegrade JJ stent insertions, retrograde placement of a JJ stent had not been successful in 18 patients. In these patients it had usually not been possible to pass the ureteral obstruction with a JJ stent retrogradely. One of the advantages of the antegrade route is the possibility to predilate the ureter with a dilatation balloon which facilitates passage of the JJ stent through the obstruction. Furthermore, retrograde insertion of a JJ stent is often performed using spinal or general anesthesia whereas antegrade ureteral stenting is performed using mainly local anesthesia.

Antegrade insertion of a JJ stent should not only be considered when retrograde insertion fails but also when a patient is already having a percutaneous nephrostomy catheter. In those cases, access to the renal pelvis has already been secured which simplifies the antegrade procedure and lowers the complication rate [8–10].

Several complications of antegrade JJ stent placement have been described [11]. Six percent of our JJ stent insertions were followed by a complication within 30 days that could be directly related to the procedure. UTI was the most commonly registered complication even though antibiotic prophylaxis has been administered prior to the procedure. Absolute numbers of infection after antegrade JJ stent insertion cannot be found in the literature. Usually, UTIs can be treated well with antibiotics. However, it might be necessary to remove the JJ stent catheter when the infection does not respond to medical treatment.

Mild hematuria is a common finding shortly after JJ stent insertion that might be caused by damaged urothelium and is mostly self-limiting. Mild hematuria was reported in only 6 cases in our patient group which may be due to underreporting. Another, rarely reported cause of hematuria which is irrespective of antegrade or retrograde insertion is a fistula between the ureter and an artery which were not encountered in our series. In the literature authors report that JJ stent catheters can be predisposing factors [12]. The risk of hematuria caused by a bleeding originating from the kidney is reported to be higher when no percutaneous nephrostomy catheter is placed several days prior to the JJ stent insertion. The risk of a kidney bleeding is most prevalent when the kidney parenchyma is punctured and has been reported to occur in about 3% of cases after percutaneous nephrostomy catheter placement [13].

JJ stent catheters can be positioned incorrectly. Mostly this will be noticed during the procedure and therefore direct action can be taken to reposition the catheter. However when the catheter is positioned too proximal and the delivery device has already been detached from the catheter, antegrade correction cannot be performed. Using cystoscopy, the catheter can be pulled back into the correct position. When a catheter is placed too distally, the JJ stent can be repositioned antegrade using a snare if the introducer sheath is still left in place. Alternatively, a wait and see policy can be executed as long as the proximal holes in de catheter are cranial to the obstruction.

Creation of false tracts is rarely reported. However, the possibility of a false tract should be kept in mind with a malfunctioning catheter [14]. When a perforation of the ureter occurs, placement of a percutaneous nephrostomy catheter will relieve the pressure of the perforated ureter, usually allowing the ureter to heal.

The present study is limited by its retrospective nature. Therefore, the interventional procedure was not standardized and indications for stenting were heterogeneous. Furthermore, it was not always clear why in some cases retrograde attempts were performed or why a decision was made for primary insertion of a nephrostomy or for primary ureteral stenting using a JJ stent.

To our knowledge randomized controlled clinical trials comparing antegrade and retrograde ureteral stenting have not been performed. A trial in patients with extrinsic ureteral obstruction caused by malignancy is now conducted by the authors to get more insight in the best approach for ureteral stenting.

CONCLUSION

Studies randomizing between antegrade and retrograde JJ stent insertion are not known to the authors but this retrospective study shows that antegrade percutaneous insertion of a JJ stent has a high success rate and a low risk of complications. It seems to be a good alternative for retrograde insertion, especially when a percutaneous nephrostomy catheter has already been placed or when the retrograde approach has failed.

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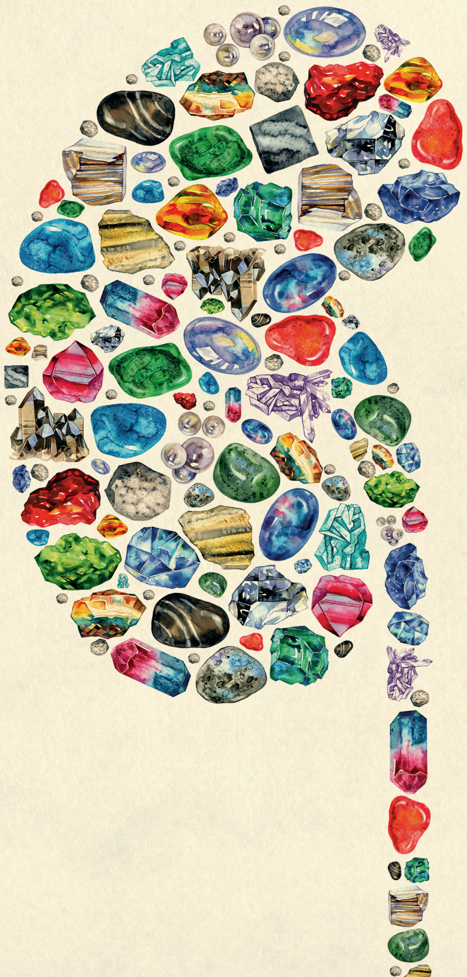
Part 4

Conclusion

8



Discussion and future perspectives

Knowledge gaps

The incidence of urolithiasis continues to increase. This increase can be primarily explained by diet and welfare. Improved radiodiagnostics and treatment options also result in more renal stones being diagnosed. Our focus should be on which stones need to be treated and even more on prevention. Expanding our knowledge of urolithiasis helps us to maintain this focus.

There are gaps in our knowledge. Many of our decisions and standards in daily practice are still based on experience and physiological principles. For example, we still do not completely understand why some patients with stones of two mm in size may be extremely painful and others with larger ureteral fragments pass their stone without being aware. Some patients suffer from a renal colic when stones on an abdominal CT scan do not show any signs of obstruction while others with hydronephrosis are painless.

We need to understand pathophysiology to decide which patients need surgery and which patients need to be treated with analgesics and support. Better decision making will help us to meet outcome expectations.

In this thesis we investigated the main research question; how can we improve our knowledge, our practice and our standards when treating urolithiasis? The previous chapters consist of different types of research to expand knowledge and improve care in urolithiasis.

Renal anatomy

A very important consideration in selection of endourological treatment is the anatomy of the pyelocaliceal system. A horseshoe kidney or a duplicated ureter needs to be identified to prepare for surgery. But even without anatomical abnormalities, accessing a renal stone can be difficult. A stone in a lower pole calyx is sometimes impossible to reach via the retrograde route due to sharp angles and limited bending of the tip of the scope. Studying anatomy of the pyelocaliceal system before choosing one approach over the other improves the chance of a successful procedure.

Chances of stone discharge from a lower pole are influenced by calyceal tract diameter (worse when a tract is less than 4mm in diameter) or by an acute infundibulopelvic angle and complex caliceal patterns[1]. These clinical features help determine the choice for URS with stone extraction over ESWL with stone fragmentation[2].

Our study on pyelocaliceal anatomy, using 3D contrast enhanced CT shows the medial orientation of some upper pole calices and a narrow aspect of middle pole infundibula. Awareness of anatomical differences when creating an access for PCNL or performing ureterorenoscopy increases the probability for a successful procedure. Innovation in radiodiagnostics such as 3D reconstruction, help the endourologist with preparation and treatment selection due to better orientation[3].

Retrospective research and transparency

In the second part of this thesis, treatments were evaluated. The last few years, healthcare has changed towards a patient centered view. Patients have the possibility to choose a healthcare provider and want to know where they should go for their treatment. With this change database registry and transparency in results has become more important.

Our retrospective quality analysis in URS and PCNL, described in chapter 3, showed that comparing outcomes with literature provides insight in aspects that need extra focus. The number of patients in the analysis was small, but different strategies in indication, treatment and follow up were recognized and improved our understanding.

The evaluation of pain during ESWL in chapter 6 provides information to reject the adopted hypothesis that pain influences outcome. Although the study was also performed with a small number of patients, practical studies like these provide new insights to improve daily practice. The pain levels presented in this study show that our assumptions sometimes underestimated and sometimes overestimated actual experiences.

Database registry for outcome parameters, has already become mandatory in a number of oncological treatments. Publication of quality statistics however, could create both advantages and disadvantages. When below average performances become visible, it can be a motivation to improve the quality of care and health outcomes. Registration of achieved results supports awareness and a critical view of performance.

There are also many negative aspects of this transparency. Data collection may feel compulsory, bring an enormous extra work load and distract attention from more important work during daily practice. The publication of data creates vulnerability and might lead to undermine trust. The wrong conclusion can be reached if data without context or with bias is analyzed.

Our results in chapter 3 analyzed retrospective data gathered in 2 hospitals. Larger volume of PCNL in one hospital appeared to result in better outcome parameters.

One example was a shorter operating time in this hospital. Further analysis however showed two very different approaches in performing PCNL explaining for a difference in operating time. In the hospital with longer operating time, the access to the kidney was obtained in the operating room in the same procedure. In the other hospital, the nephrostomy was placed a day before, resulting in shorter operating time for PCNL the next day. Interpretation of data always needs to be taken with care.

Optimizing clinical care

Recent research in epidemiology has confirmed what we already know; increasing risk for urolithiasis, prevalence across the globe and a growing rate of incidence[4]. To improve daily practice, new insights are needed. Part three of this thesis discusses what we have learned.

Evidence based medicine is the basis of gaining new knowledge in practicing medicine. However, there is a lack of empirical evidence needed to provide optimal medical care. Efficacy for example has not been evaluated in approximately half of our treatments. An efficacy unequivocally proven, is only reached in about 13% of our interventions[4].

The systematic review in chapter 4, comparing PCN and JJ placement, served as a basis for a new RCT which has started in 2020. This project named the STONE study, will compare both procedures prospectively, to evaluate efficacy and superiority of either treatment.

The buscopan study in chapter 5 showed diversity of clinical opinion and standards in medical treatment in different countries in Europe and across the globe. A treatment that has been in use in the Netherlands for many years is not used at all in most other countries. When asking the Dutch urologist why buscopan is still in use, the response will be that a gut feeling says it is effective. The origin for the use of buscopan is not completely clear, but logically the antispasmodic drug was deployed for its spasmolytic effect on the smooth musculature of the urinary tract. Previous research did not show a benefit of administration of buscopan in its oral form or when a single dose is being used. Also, addition of the drug to NSAID's or opioids has not shown benefit in the past. As a result of this new double blind and randomized clinical trial, the expectation is that the use of buscopan for treating renal colic will be discontinued in the Netherlands and Belgium. We suggest that European guidelines should be followed when analgesics need to be administered.

These clinical studies narrow the gap between clinical and empirical knowledge. More study will help evaluate other treatments with doubtful that continue in daily practice.

Use of established techniques

This thesis provides new information on surgical procedures and therapeutic regimens that are already widely accepted. Diagnostic modalities, surgical instruments and treatment standards have significantly changed over the last few years. Lumbotomies for kidney stone removal have become rare in first world countries and laparoscopic procedures for urolithiasis are used only in complex cases. Minimally invasive surgery is the new standard and technical aspects are evolving rapidly[5].

Rapid advances in surgical techniques and armamentarium have an enormous influence on procedures and daily practice. Ureteroscopes and nephroscopes have smaller fiberoptics, new energy sources, wider ranges of movement and stronger accessories[8]. According to the EAU guideline of 2019, PCNL is the first choice for treatment of kidney stones over 20 mm. However, with the introduction of mini, micro and super mini PCNL, these boundaries fade and PCNL is used more often for smaller stone sizes of 10-20 mm. On the other hand, stones in the lower pole that were previously inaccessible using the retrograde route, are now more easily reached with the introduction of new ureterorenoscopes with secondary deflection, wider ranges of movement and smaller laser fibers of 200 microns.

Since we're using smaller instruments than a few years ago, we could be more flexible when choosing a surgical approach. Guidelines help us to optimize patient care with recommended strategies. However, a standard patient does not exist. Many treatments and approaches have become "in use" with larger instruments causing more bleeding and with less technical possibilities. With less manipulation, an antegrade route to reach the renal pelvis or ureter could become more attractive in the future. As shown in chapter 7, antegrade stenting is a good alternative for retrograde stent placement. We have to stay aware of our possibilities and think out of the box when performing endourology.

Future research

Expanding knowledge on pathophysiology of renal colic could help development of new analgesic therapies. Different thoughts on the mechanism of renal colic exist and identifying non-efficacious therapy such as buscopan is only a small part of resolving the puzzle.

Optimizing prevention strategies is expected to be a main research focus in the future with a higher incidence of urolithiasis. Scientific projects on cell biology that have not been performed in this thesis, are expected to be of utmost importance in the upcoming years. Examining the steps in stone formation and research on modulators of urinary saturation, crystal aggregation and crystal-cell adhesion provide a key to stone prevention[9].

Not too long ago decreasing calcium intake was a common advice to prevent intestinal absorptive hypercalciuria in urolithiasis patients[10]. A few years later we learned that calcium restriction increases bone demineralization and increases the risk for stone formation[11]. Improving dietary recommendations or developing pharmaceutical regimens may help in lowering the recurrence rate in kidney stone patients by 50% and therefore decrease disease burden and health care costs.

New technological trends

There are constant innovations in instruments and techniques. In 2017, a new pulse modulation technique named the Moses effect was introduced which brings longer or variable pulse widths when using Holmium-Yttrium-Aluminium-Garnet (Ho:YAG) laser[12]. In 2020, the Thulium laser fiber is gaining interest for the treatment of urolithiasis, with promising features such as smaller laser fibers, lower pulse energy and a very high frequency[13].

In addition to improvements in the technical aspects and miniaturization of instruments, there is more study of ergonomics. Robotic ureteroscopy is a recent trend that has not reached public interest worldwide. In 2013 a robot (the Avicenna Roboflex) was developed for flexible ureterorenoscopy. First results are promising. A study of 395 patients treated for urolithiasis with this robot showed low complication rates and a comparable operating time with the standard flexible URS. Use of the robotic system has a short learning curve of only 5 patients. The definitive role for robotics in endourology still has to be evaluated since costs of the robotic system and instruments are high[14].

There are several future possibilities for new techniques to improve efficiency and success rates in endourology. Computer assisted navigation systems to access the preferred calyx for access in PCNL are being tested. These systems fuse ultrasound and fluoroscopy images to help planning the puncture trajectory and automate needle positioning[9]. Also augmented reality, 3D printing and wider implementation of e health is not too far away. New techniques are expensive. Cost efficiency needs to be taken into account in all of these new strategies.

Developments in endourology for treatment of urolithiasis are in full swing and will continue to progress rapidly in the future.

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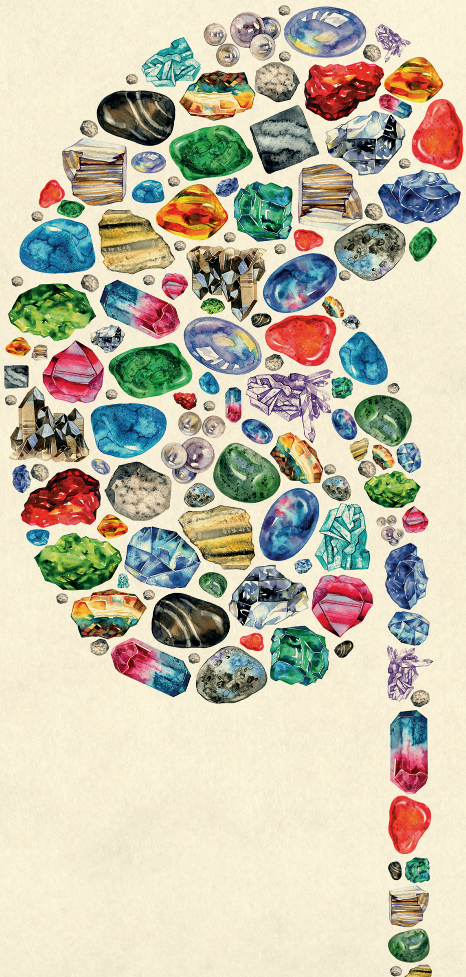

Summary

The main focus of this thesis is on pain management and treatments of urolithiasis. Urolithiasis causes a high burden for the health care economy due to the cost of hospitalization, treatments and its high risk of recurrence. The aim of this thesis is to contribute to improvement of our knowledge, our practice and our standards when treating urolithiasis.

Part 1: Anatomy and diagnostics

A good orientation in the pyelocaliceal system can help insure a successful endourological procedure. Studies of the renal anatomy in **chapter 2A** illustrate that puncturing upper pole calyces should be performed with extra care because they are more frequently medially oriented. The middle segment of the kidney has the narrowest infundibula, the funnel shaped parts between the renal pelvis and calyx. This could make the calyces located in this segment less accessible for a retrograde approach with the ureterorenoscope. Preoperative imaging using urography CT is recommended when preparing for surgery and to make necessary adjustments to the treatment plan.

There are differences in structure when you compare the anatomy of kidneys which have formed stones and kidneys that do not form stones. In **chapter 2B**, measurements are described, compared and analyzed. A larger width of the calyceopelvic tract in the lower segment was found in patients with stone forming kidneys. This finding was confirmed by results of other published anatomy studies as referred to in chapter 2. However, dynamics have not been taken into account, since our measurements were static. It does not imply that these segments in the kidney are more or less likely to form stones. Small fragments can migrate after having originated in a different part of the pyelocaliceal system.

These two studies aim to increase understanding of the pyelocaliceal system. This knowledge can help in creating a preoperative plan, to improve surgical outcome and to find new paths for prevention.

Part 2: Treatments evaluated

The quality of care of URS and PCNL at two hospitals in the Hague was studied in **chapter 3**. Important parameters, such as outcome, operating time, hospitalization days and complications were evaluated. Outcomes of both hospitals concur with data as reported in literature. Other parameters including of gender, age and BMI were analyzed. They did not influence the outcome of the procedure. This retrospective study provides insight in the outcomes of two hospitals in the Hague for a critical view on performance.

In **chapter 4**, the two most frequently used treatment options for obstruction of the pyelocaliceal system due to urolithiasis were systematically reviewed. Placement of nephrostomy or JJ have comparable success rates when comparing the procedures. An advice on when to use either technique cannot be given. Side effects were different; a JJ stent increases LUTS and a nephrostomy tube is uncomfortable due to an external drain and urine bag. The ideal choice for one over the other depends on factors such as stone location, stone size, patient preference and treatment plan. However, in an acute setting factors such as patient anatomy, clinical health, hospital logistics and opinion of the clinician are mostly decisive.

Part 3: New insights

An important clinical knowledge gap was assigned by the Dutch association of urologists, to find evidence for the use of butylscopolamine (Buscopan) in patients with renal colic that are not adequately responding to NSAIDs. To evluate the nationally accepted use of buscopan, we compared buscopan with placebo in a double blind, randomized trial, reported in **chapter 5**. Results showed that placebo was non-inferior to buscopan in patients with renal colic. Pain scores decreased gradually and were comparable during hospitalization. Secondary parameters such as time until last escape medication used and side effects were not significantly different. There is no role for buscopan in the treatment of pain for patients with renal colic.

In **chapter 6** the influence of pain on the outcome of ESWL was studied. The general assumption is that more pain during the procedure will negatively affect the outcome of the therapy. In our study no correlations between level of pain and efficacy of ESWL were found. A relatively high level of pain sensation was discovered. The average pain perception during the procedure was 5 on a scale of 10. Additional use of analgesics could improve patient comfort during treatment with ESWL.

Antegrade ureteral stent placement is performed less frequently when compared with retrograde placement and is evaluated in **chapter 7**. Frequently retrograde JJ insertion is the first step performed by the urologist in relieving ureteral obstruction. Antegrade placement of a JJ has a high success rate of 96% with a low risk for complications. The antegrade approach can be considered when a patient is receiving a nephrostomy tube or when retrograde placement has failed.

Part 4: Conclusion

Chapter 8 is a general discussion on the subjects of this thesis. The chapter starts with the role of anatomy in research and daily practice. The role of retrospective research and considerations regarding transparency of data are presented in the second part, followed by new insights of prospective studies. Finally, future perspectives and suggestions for further research are presented.

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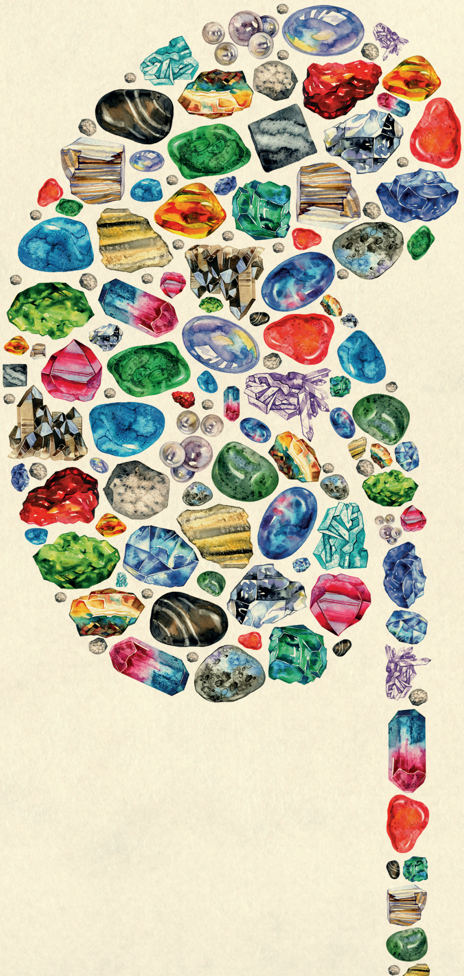

Supplements

Nederlandse samenvatting

Appendix metafylaxe

List of abbreviations

List of publications

Curriculum vitae

Dankwoord

NEDERLANDSE SAMENVATTING

Dit proefschrift gaat over diverse behandelingen van urolithiasis, ook wel niersteenlijden. Het behandelen van pijnklachten en de behandeling van steen staat hierbij centraal. Urolithiasis veroorzaakt hoge lasten voor de gezondheidseconomie vanwege de kosten van ziekenhuisopnames, interventies en een hoge recidiefkans. Het doel van dit proefschrift is een bijdrage leveren aan de verbetering van onze kennis, ons handelen en onze standaarden bij de behandeling van nierstenen.

Deel 1: Anatomie en diagnostiek

Een goede oriëntatie in het verzamelsysteem van de nier kan bijdragen aan een voorspoedige endourologische ingreep. Het bestuderen van de anatomie van de nier in **hoofdstuk 2A** laat zien dat het aanprikken van de kelken in de bovenpool met extra voorzorg uitgevoerd dient te worden, gezien deze kelken vaker richting mediaal liggen. Het middelste deel van de nier heeft de meest nauwe infundibula, ofwel de tunnelachtige weg van verzamelsysteem naar de kelk, waardoor de kelken in dit segment minder bereikbaar zijn voor retrograde benadering met de ureterorenoscoop.

Preoperatieve beeldvorming met CT-urografie is aanbevolen voor de chirurgische voorbereiding en om het behandelplan zo nodig aan te kunnen passen.

Bij het nauwkeuriger bekijken van de anatomie en wanneer een nier die stenen heeft gevormd met een nier zonder steenvorming in het verleden wordt vergeleken, zijn er verschillen in de opbouw. In **hoofdstuk 2B** worden metingen beschreven, vergeleken en geanalyseerd. Bij patiënten met een verleden van urolithiasis, werd in de onderpool van de nier een bredere weg van het pyelum naar de kelk gevonden. Dit gegeven werd bevestigd door de bevindingen van andere gepubliceerde anatomische onderzoeken waar naar verwezen wordt in hoofdstuk 2. In onze resultaten werd echter de dynamiek van de nier niet meegenomen, gezien statische metingen zijn verricht. Het betekent niet direct dat deze delen van de nier dus meer of minder stenen zullen vormen. Kleine fragmenten kunnen namelijk verplaatsen nadat ze in een ander deel van het nierbekkensysteem zijn ontstaan.

Beide studies beogen de kennis van het pyelocalicieel systeem te vergroten, aangezien deze kennis kan bijdragen aan de vorming van een preoperatief plan en aan het verbeteren van de uitkomst van de behandeling. Ook zouden nieuwe mogelijkheden voor preventie gevonden kunnen worden.

Deel 2: Evaluatie van behandelingen

De kwaliteit van de behandelingen door middel van URS en PCNL in twee perifere ziekenhuizen in Den Haag werd bestudeerd in **hoofdstuk 3**. Belangrijke parameters, zoals resultaat, operatieduur, opnameduur en complicaties werden geëvalueerd. Uitkomsten van beide ziekenhuizen voldeden aan data zoals in de literatuur beschreven. Andere parameters zoals geslacht, leeftijd en BMI werden geanalyseerd, maar waren niet van invloed op de procedure. Dit retrospectieve onderzoek geeft een transparante blik op de resultaten van twee grote ziekenhuizen in Nederland.

In **hoofdstuk 4** worden de twee meest gebruikte behandelopties voor obstructie van het pyelocalicieel systeem door urolithiasis systematisch beoordeeld. Het plaatsen van een nefrostomie katheter of dubbel J heeft een vergelijkbaar succespercentage wanneer de procedures worden vergeleken. Er is dan ook geen advies wanneer de ene of de andere techniek ingezet moet worden. De neveneffecten waren echter verschillend; een dubbel J kan blaas- en plasklachten doen toenemen en een nefrostomiekatheter is oncomfortabel door een externe slang en urineopvangzak. De ideale keuze voor de ene of de andere behandeling hangt af van factoren als steenlocatie, steengrootte, keuze van de patiënt en het toekomstige behandelplan. Echter in het acute moment zijn factoren als conditie en anatomie van de patiënt, ziekenhuislogistiek en keuze van de arts vaak doorslaggevend.

Deel 3: Nieuwe inzichten

Een belangrijk kennishiaat is kenbaar gemaakt door de Nederlandse Vereniging voor Urologie, namelijk het bewijs voor de effectiviteit van butylscopolamine (Buscopan) bij patiënten met niersteenkolieken welke niet voldoende reageren op NSAID's.

Om de juistheid van het nationaal geaccepteerde gebruik van Buscopan te onderzoeken, vergeleken wij buscopan met placebo in een dubbelblind gerandomiseerde studie, welke beschreven staat in **hoofdstuk 5**.

Resultaten lieten zien dat placebo niet inferieur was aan buscopan bij patiënten met een niersteenkoliek. Pijnscores in beide groepen daalden geleidelijk en vergelijkbaar gedurende de ziekenhuisopname. Secundaire parameters zoals tijd tot het gebruik van de laatste gift morfine als pijnstilling en de bijwerkingen van de medicatie waren ook niet significant verschillend. Er is geen rol voor buscopan in de behandeling van patiënten met een niersteenkoliek.

In **hoofdstuk 6** werd de invloed van pijn op de uitkomst van ESWL onderzocht. Algemene aanname is dat meer pijn tijdens de procedure, het resultaat van de behandeling negatief kan beïnvloeden. In onze studie werd geen correlatie tussen de mate van pijn en de effectiviteit van ESWL gevonden. Met een gemiddelde pijnscore van 5 op een schaal van 10 tijdens de behandeling, werd een relatief hoge mate van pijnklachten ontdekt. Aanvullend gebruik van pijnstilling zou op zijn minst het comfort van de patiënt kunnen verbeteren tijdens een behandeling met ESWL.

Antegrade stentplaatsing wordt minder vaak uitgevoerd vergeleken met retrograde stentplaatsing en is onderzocht in **hoofdstuk 7**. Het retrograad inbrengen van een JJ, uitgevoerd door de uroloog, is vaak een eerste stap in het opheffen van ureterale obstructie. Antegrade plaatsing van een JJ heeft een succes ratio van 96% en een laag risico op complicaties. De antegrade benadering kan worden overwogen wanneer een patiënt een nefrodrain krijgt of wanneer de retrograde benadering niet succesvol was.

Deel 4: Conclusie

In **hoofdstuk 8** wordt een algemene discussie van de onderwerpen van dit proefschrift beschreven. Het hoofdstuk begint met de rol van anatomie in onderzoek en in de dagelijkse praktijk. De rol van retrospectieve analyses en overwegingen ten aanzien van transparantie van data worden in het tweede deel gepresenteerd, gevolgd door nieuwe inzichten van prospectieve onderzoeken. Als laatste wordt een toekomstperspectief en suggesties voor verder onderzoek gepresenteerd.

APPENDIX METAFYLAXE

Introductie

De prevalentie van urolithiasis is gedurende de 20e eeuw gestegen. In de VS is het risico op ontwikkelen van urolithiasis voor mannen al 12% en voor vrouwen 6%. Een belangrijke reden voor de stijging is het dieet en leefpatroon. Hierdoor wordt ook het verschil in incidentie tussen mannen en vrouwen kleiner. Toename van de incidentie, de hoge recidiefkans van > 50% in 10 jaar tijd en een eventuele chirurgische behandeling, zorgen voor hogere zorgkosten.

De diagnostiek van urolithiasis is gericht op detectie van de steen met behulp van urineonderzoek, bloedonderzoek en beeldvorming. Wanneer tot steensanering wordt overgegaan, zijn er diverse behandelmethoden, zoals ESWL, URS en PCNL.

Dit artikel is gericht op metafylaxe, ofwel het voorkomen van steenvorming, bij volwassenen. Door middel van steenanalyse, (24 uurs) urineanalyse kunnen gerichtere preventieve adviezen worden gegeven. Deze appendix bevat de volgende punten;

- Analyse
- Laag risico versus hoog risico patiënt
- Essentiële anamnese
- Algemene metafylaxe adviezen
- Aanvullende adviezen / medicamenteus beleid per steensoort
- Aanvullende adviezen / medicamenteus beleid per metabool doel

Analyse

1. Anamnese en lichamelijk onderzoek
2. Serum analyse
   - kreatinine, calcium, fosfaat, urinezuur (PTH indien hoog calcium)
3. Urine analyse
   - pH, eiwit
     Indien afwijkend, advies een tweede urine analyse te verrichten
4. Steenanalyse
   - Dient bij iedere episode van urolithiasis opnieuw plaats te vinden.
     Doel: oorzaak van het steenvormen achterhalen en eventuele metafylaxe inzetten.
     Veel stenen hebben een gemengde samenstelling

Laag risico patiënt: Geen aanvullende analyse

Hoog risico patiënt: Aanvullende analyse:

- Serum: natrium, kalium, chloor, magnesium en bicarbonaat
- 24-uurs urineonderzoek: volume, calcium, fosfaat, kreatinine, urinezuur, oxalaat, citraat, ureum, eiwit, natrium, kalium en magnesium.
  - Idealiter 1 maand na de steenlozing en bij hervatte, reguliere leefstijl

Laag risicopatiënt
een enkele episode van urolithiasis
unilateraal steenlijden
negatieve familieanamnese
weinig tot geen andere comorbiditeit

Hoog risicopatiënt	
Algemeen	Snel recidief niersteen (< 2 jaar) Bilateraal steenlijden of mononier Positieve familie anamnese Early onset / kinderen Risicofactoren zoals dieet, lage vochtintake Steentype: Brushiet, urinezuur of struviet
Anatomische afwijkingen	Medullaire sponsnier, UPJ stenose, calyxdivertikel, pyelumdivertikel, ureterocele, ureterstenose, hoefijzernier, vesicoureterale reflux
Comorbiditeit	hyperparathyreodie, nefrocalcinose, chronische darmziekten (M.Crohn), status na gastric bypass of malabsorptie, obesitas, hypertensie jicht, sarcoidose, nierinsufficientie, diabetes mellitus / metabool syndroom, polycysteuze nieren
Genetisch	Cystinurie, primaire hyperoxalurie, renale tubulaire acidose (RTA) type1, Lesch-Nyhan syndroom, cystic fibrosis, Xanthinurie, Adenine phosphoribosyltransferase (APRT)
Medicatie	Acetazolamide, furosemide, calcium, vit D

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Anamnese

Voorgeschiedenis en comorbiditeit

- Jicht
- Short-bowel syndrome
- Bariatrische chirurgie
- M. Crohn
- Sarcoidose
- Maligniteit/chemotherapie
- Urineweginfecties
- Obesitas
- DM2
- Hypertensie

Medicatie

- *pH* - acetazolamide (alkaliniseert)
- *Calcium* - antacida, vitamine D intoxicatie, glucocorticosteroiden, theophilline, lisdiuretica
- *Oxalaat* - piridoxylaat, vitamine C
- *Neerslag vorming* - triamtereen, sulfonamide, acyclovir, nitrofurantoïne, indinavir
- Diuretica gebruik

Familieanamnese

- Nierstenen
- Cystinurie
- Renale tubulaire acidose
- Toni Fanconi syndroom / Lesch-Nyhan syndroom
- primaire hyperoxalurie
- Cystic fibrosis
- APRT deficientie

Algemeen, leefstijl en dieet

- Diarree, braken, zweten
- Teveel aan dierlijk eiwit, zout, oxalaat of tekort aan vocht/ groenten.
- Vocht intake afhankelijk van activiteit / beroep
- Immobilisatie

Chronologie

- eerdere concrementen, duur van tussenperiode

Lichamelijk onderzoek: aandacht voor BMI / overgewicht, klinische conditie en anatomische afwijkingen

Algemene metafylaxe adviezen

Vocht;

- Ruime diurese (2.0-2.5 L/24h) door ruime vocht intake; (2.5-3.0 L/ 24h)
    - o Verlaagt supersaturatie. Verhoogt citraat excretie
  - Vochtintake gelijkmatig verdelen over 24 uur
  - Koolzuurhoudende dranken vermijden
  - Vruchtensap heeft een beschermend effect
    - o Verhoogt citraat
    - o Cave suiker; een exces verhoogt excretie urine calcium en oxalaat excretie

Dieet;

- Voldoende vezels
  - Veel fruit en groenten
    - o Heeft een alkaliniserend effect op de pH van urine
- Voedingsbestanddelen
  - Normale calcium inname (1-1,2g / dag) +/- 3 glazen melk, advies bij de maaltijd te nuttigen.
    Supplementen calcium hebben geen schermend effect
    - o Reabsorptie oxalaat (hyperoxalurie) voorkomen door beschikbaarheid van Ca om aan te binden
  - Natrium (beperken tot 4-5 gram per 24 uur)
    - o Exces verhoogt urine calcium excretie
  - Dierlijk eiwit (0,8-1g/kg/dag)
    - o Exces veroorzaakt lage urine pH, dit remt reabsorptie van calcium en bevordert steenvorming
    - o Ook hypocitraturie
  - Beperkte intake oxalaat
    *Vitamine C (> 4g/dag)
    - o Precursor van oxalaat

    *Chocolade, spinazie, soja, noten, rabarber, cacao, sla, thee, ijsthee, bieten, knolselderij
- Lifestyle
  - Voldoende lichaamsbeweging en stressreductie
  - Een adequate BMI tussen de 18 en 25 (beperk vet intake)

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Specifieke metafylaxe adviezen per steensoort

<u>Calciumoxalaat</u>

Meest voorkomende steensoort (80%)
Vaak lage urine pH
Radiopaak
Recidiefkans: 25-40% in 5 jaar, 50% in 10 jaar
Uitgebreide analyse bij hoog risicopatiënten inzetten

Calciumoxalaat monohydraat
= whewelliet $CaC_2O_4.H_20$
groeit langzaam, harde steen
vaak donker / zwart van kleur

Calciumoxalaat dihydraat
= weddeliet $CaC_2O_4.2H_20$
groeit snel, bros
vaak geel van kleur / zandroos

Bevinding	DD / mechanisme	Therapie	Medicatie	Dosering
pH constant > 5.8	RTA UWI	Gericht op type RTA Antibacterieel RTA en UWI uitgesloten: Urine aanzuren	L-Methionine	200-500mg 3dd
pH constant < 5.8	Kristallisatie urinezuur en calciumoxalaat	Alkaliniseren	Kaliumcitraat Natriumbicarbonaat	9-12g/dag 1.5 gram 3dd
Hypercalciurie mild >200-300mg/24 uur	Hyperparathyreoidie Sarcoidose	Ca verhogen	Tot 1000mg Evt calciumcitraat	dieet 200-400 mg/ dag
Hypercalciurie ernstig > 8 mmol/24 uur of >300mg/24 uur	Chronische acidemie	Ca inname beperken	Hydrochloorthiazide Indapamide	1d25mg of 1d50mg[1] 1d2.5 mg

Bevinding	DD / mechanisme	Therapie	Medicatie	Dosering
Hypocitraturie <1.7mmol/dag ♂ <1.9 mmol/dag ♀	Metabool (diarree, RTA) Hypokaliemie	Kaliumcitraat Eiwit inname beperken Vruchtensap	Kaliumcitraat	6-9 g/ dag
Hyperoxalurie enterisch >0,5 mmol/24uur of 100- 200mg/24uur	Intestinale hyperabsorptie Exces oxalaat	Oxalaat en vet inname beperken Vit C beperken < 1000mg/d pH verhogen	Calcium bij de maaltijd Magnesium Kaliumcitraat	>500mg/dag 200-400mg/dag 6-9 g/ dag
Hyperoxalurie primair (type1) >1 mmol/24uur of > 200mg/24uur	Genmutatie	Medicamenteus behandelen Hyperdiurese	Pyridoxine	5-20 mg/kg/d
Hyperuricosurie >4 mmol/24uur	Dieet, tumor lysis syndroom, enzymdefect, medicatie, jicht	Purines beperken	Kaliumcitraat Allopurinol	6-9 g/ dag 100 mg/dag*
+ hyperuricemie >380micro mol	Dieet, maligniteit, thiazide diuretica	Purines beperken	Kaliumcitraat Allopurinol Febuxostat	6-9 g/ dag 100-300 mg/dag* 80-120 mg/dag
Hypomagnesiurie <3 mmol/24 uur	Chronische diarree Te weinig intake	Suppletie	Magnesium	200-400mg/dag*
Idiopathisch	Hoog BMI / DM2			
Hypercalciemie >2.5 mmol/L	Hyperparathyreoidie Sarcoidose Exces vitamine D Maligniteit	Parathyreoidectomie		

[1] *Cave hypokaliemie, hierdoor ontstaat hypocitraturie*
[*] *Afhankelijk van de nierfunctie*

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Apatiet = Calciumfosfaat $Ca_{10}(PO_4)_6.(OH)_2$
Brosse steen
Vaak hoge urine pH
Middelmatig radiopaak
Geassocieerd met UWI

Bevinding	DD / mechanisme	Therapie	Medicatie	Dosering
pH > 5.8	RTA UWI	Gericht op type RTA Antibacterieel		
pH >6.8	Kristallisatie apatiet	RTA en UWI uitgesloten: Urine aanzuren	L-Methionine	200-500mg 3dd
Hypercalciurie mild >200-300mg/24 uur	Hyperparathyreoidie Sarcoidose Exces vitamine D	Ca verhogen	Tot 1000mg. Evt calciumcitraat	dieet 200-400 mg/d
Hypercalciurie ernstig > 8 mmol/24 uur of >300mg/24 uur	Chronische acidemie Maligniteit	Ca inname beperken	Hydrochloorthiazide	1d25mg of 1d50mg[1]
Hypocitraturie	Dieet	Eiwit inname beperken	< 80g/dag	
Hoog PTH	Hyperparathyreoidie	Parathyreoidectomie		

[1]*Cave hypokaliemie, hierdoor ontstaat hypocitraturie*

Erfelijk	Verworven
Genmutatie	Autoimmuun ziekte (Sjogren, sarcoidose)
Carbonic anhydrase 2 deficientie	Acetazolamide gebruik
	Niertransplantatie
	Recidiverend pyelonefritis
	Hypercalciurie

***RTA** (bekende oorzaak van calciumfosfaat stenen)
Diagnose door middel van ammoniumchloride test volgens Sommerkamp:
Induceren van acidemie dmv toedienen van NH_4 Cl (0.1 g/kg) voor 3 dagen.
Urine < 5.4: RTA uitgesloten
Urine > 5.4: Bloedgas analyse doen

- Normaal bicarbonaat: incompleet RTA
- Laag bicarbonaat: compleet RTA

Behandeling: herstellen van pH en elektrolytenbalans dmv alkaliniseren

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Brushiet = Calciumwaterstof fosfaat $PO_4.2H_20$
Snel groeiende steen
Zeer hard, hoge recidiefkans
Radiopaak
Meestal niet geassocieerd met UWI
Hoog risicopatiënten

Bevinding	DD / mechanisme	Therapie	Medicatie	Dosering
pH > 5.8	RTA	Gericht op type RTA (alkaliniseren)		
pH 6.5-6.8	Kristallisatie brushiet	Geen RTA of UWI: urine aanzuren; doel pH 5.8-6.2.	L-Methionine	200-500mg 3dd
Hypercalciurie mild >200-300mg/24 uur	Hyperparathyreoidie Sarcoidose Exces vitamine D	Ca verhogen	Tot 1000mg. Evt calciumcitraat	dieet 200-400 mg/d
Hypercalciurie ernstig > 8 mmol/24 uur of >300mg/24 uur	Chronische acidemie Maligniteit Dieet rijk (Ca, eiwit, Na)	Ca inname beperken	Hydrochloorthiazide	1d25mg of 1d50mg1
Hypocitraturie	Dieet	Eiwit inname beperken	< 80g/dag	
Hoog PTH	Hyperparathyreoidie	Parathyreoidectomie		

[1]*Cave hypokaliemie, hierdoor ontstaat hypocitraturie*

Struviet = Magnesium ammonium fosfaat / infectiesteen $MgNH_4PO_4.6H_20$

Zachte steen, groeit snel	UWI beïnvloedt pH (hoger), vaak proteus mirabilis
Middelmatig radiopaak	Behandeling richten op steenvrij maken, antibiotisch uitbehandelen en de onderliggende oorzaak van de UWI aanpakken
2-15% van alle stenen	
Hoog risicopatiënten	NB Ook een kweek van de steen inzetten

Bevinding	DD / mechanisme	Therapie	Medicatie	Dosering
pH > 5.8	RTA UWI	Gericht op type RTA Antibacterieel		
pH steeds >6.2		Urine aanzuren; doel pH 5.8-6.2.	L-Methionine	200-500mg 3dd
Afgietselstenen / corpora aliena		Totale steenverwijdering + antibiotische behandeling		

Microorganismen struviet stenen
Urease producerend > 98 %
Proteus
Providencie rettgeri
Morganella morganii
Corynebacterium urealyticum
Ureaplasma urealyticum

Overige microorganismen
Enterobacter gergoviae
Klebsiella
Providencia stuartii
Serratia senescens
Staphylococcus

Minder vaak, maar niet uitgesloten
0-5% van de stamen van: E coli / enterococcus / pseudomonas

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Urinezuur** (C5H4N4O3) **en ammonium uraat

Radiolucent, harde steen
Hoog risicopatiënten

Urinezuur	5-10% van alle nierstenen
Ammoniumuraat	<1% van alle nierstenen

Chemolitholyse bij urinezuur steen mogelijk: streef naar pH 7.0-7.2 en hyperdiurese
Extra advies: Dieet met weinig purine, rijk aan kalium

Bevinding	DD / mechanisme	Therapie	Medicatie	Dosering
pH constant <6	Kristallisatie urinezuur Diarree/ thiazide diuretica / diabetes / hypoaldosteronisme	Alkaliniseren, doel pH 6.2-6.8 Chemolitholyse, doel pH 6.5-7.2	Kaliumcitraat Natriumbicarbonaat	9-12g/dag 1.5 gram 3dd
Hyperuricosurie >4mmol/24uur	Dieet (veel dierlijk eiwit/alcohol/cola/limonade), medicatie, jicht	Purines beperken Dieet optimaliseren	Allopurinol	100 mg/dag
+ hyperuricemie >380micro mol	Dieet, maligniteit, thiazide diuretica	Purines beperken	Kaliumcitraat Allopurinol Febuxostat	6-9 g/ dag 100-300 mg/dag* 80-120 mg/dag
Idiopathisch	Hoge BMI / DM2			

Cystine = $[SCH_2CH(NH_2)COOH]_2$
Harde steen, maar bros in alkalische urine
Middelmatig radiopaak
Genetisch transport defect voor dibasische aminozuren, verhoogde excretie cystine
Autosomaal recessief overervend (type A) en incompleet autosomaal recessief (type B)
Type B veroorzaakt cystinurie = hoog risicopatiënten

Bevinding	**DD / mechanisme**	**Therapie**	**Medicatie**	**Dosering**
pH < 6	Kristallisatie cystine			
Cystinurie mild < 3 mmol/24uur of <500mg/24uur		Hyperdiurese Alkaliniseren, pH doel 7.5-8.5	Kaliumcitraat	9-12g/dag
Cystinurie ernstig >3 mmol/24 uur of >500mg/24uur		Concentratie vrij cystine verlagen (dmv splitten van disulfide binding)	Ascorbinezuur Tiopronine Captopril	3-5g/dag 1-3dd 250mg 75-150mg

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Specifieke metafylaxe adviezen per therapeutisch doel

Doel	Middel	Dosering	Type steen
Alkaliniseren (streef pH 6.5-7.0)	Kaliumcitraat (Na-citraat) Natriumbicarbonaat	9-12 g/dag 3dd1,5g	Calciumoxalaat Urinezuur Cystine
Aanzuren	L-Methionine Ammoniumchloride	3dd200-500 mg	Infectiesteen Calciumfosfaat steen
Hypercalciurie	Hydrochloorthiazide	25mg of 50mg/dag +kaliumcitraat (cave hypokaliemie)	Calciumoxalaat Calciumfosfaat
Hypocitraturie	Natriumbicarbonaat	3dd1,5g	
Hyperuricosurie	Allopurinol	100-300mg/dag*	Calciumoxalaat Urinezuur
Hyperuricemie	Allopurinol	100-300mg/dag*	Calciumoxalaat Urinezuur
Hyperoxalurie enterisch	Calciumcitraat Magnesium	200-400mg/dag	Calciumoxalaat
Hyperoxalurie primair	Pyridoxine	5-20mg/kg/dag (+/- 300mg/dag)	Calciumoxalaat
Hypomagnesiemie	Magnesium	200-400mg/dag	Calciumoxalaat
Cystinurie	Tiopronine Ascorbinezuur Captopril Penicillamine	1-3dd 250 mg (max 2g/dag) 3-5g/dag 25mg/dag	Cystine

**afhankelijk van de nierfunctie*

Nota bene:

Medicamenteuze profylaxe wordt gereserveerd voor patiënten met hoge metabole activiteit en een groot recidief ratio. De therapietrouw is bij patiënten met lagere risicoprofielen zeer laag.

Deze appendix is tot stand gekomen met behulp van de volgende brondocumenten:

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LIST OF ABBREVIATIONS

BMI	Body Mass Index
CTU	Computed Tomography Intravenous Urography
EAU	European Association of Urology
ESWL	Shock Wave Lithotripsy
IVU	Intravenous urography
JJ	Double J ureteral stent
LUTS	Low urinary tract symptoms
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
PCN	Percutaneous nephrostomy
PCNL	Percutaneous nephrolitholapaxy
PROMS	Patient reported outcome measurements
QOL	Quality of life
RCT	Randomized controlled trial
URS	Ureterorenoscopy
UTI	Urinary tract infection
VAS	Visual Analog Scale

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- J.Verhoeven, **S.Weltings**, R. van Loenhout, J. van der Laan, H. Roshani. Ureteric metastasis of pancreatic carcinoma: a case report. SN comprehensive clinical medicine. Januari 2021

CURRICULUM VITAE

Saskia Weltings werd geboren op 8 november 1988 te Roosendaal als dochter van Hans en Erna Weltings. Zij groeide op in haar geboorteplaats, samen met haar broers Bart en Leon. Na het behalen van haar VWO diploma aan het Gertrudiscollege in 2006, begon zij met de studie geneeskunde aan de Universiteit Leiden.

Tijdens haar onderzoeksstage in het laatste jaar van de opleiding geneeskunde begon de wetenschappelijke samenwerking met dr. H Roshani en werd een eerste publicatie voltooid.

Na het behalen van het artsexamen in september 2012 werkte zij als arts-assistent urologie in het Westeinde ziekenhuis en in het Haga ziekenhuis. In 2015 startte de vooropleiding chirurgie in het Medisch Centrum Haaglanden. Het academische gedeelte van de opleiding volgde ze in het LUMC en de laatste twee jaar perifere urologie in het Haga ziekenhuis.

Tijdens het academische gedeelte van de opleiding tot uroloog in 2017 begon zij aan haar promotietraject, welke ze voltooide alvorens het afronden van de opleiding tot uroloog in 2021. Haar proefschrift staat in het teken van urolithiasis en de endourologische behandelopties. Het proefschrift werd samengesteld onder supervisie van prof. dr. R.C.M. Pelger en onder supervisie van dr. H. Roshani en dr. B.M.A Schout.

Saskia woont samen met Stijn Kouwenhoven, samen hebben zij 1 dochter; Ava (2020)

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