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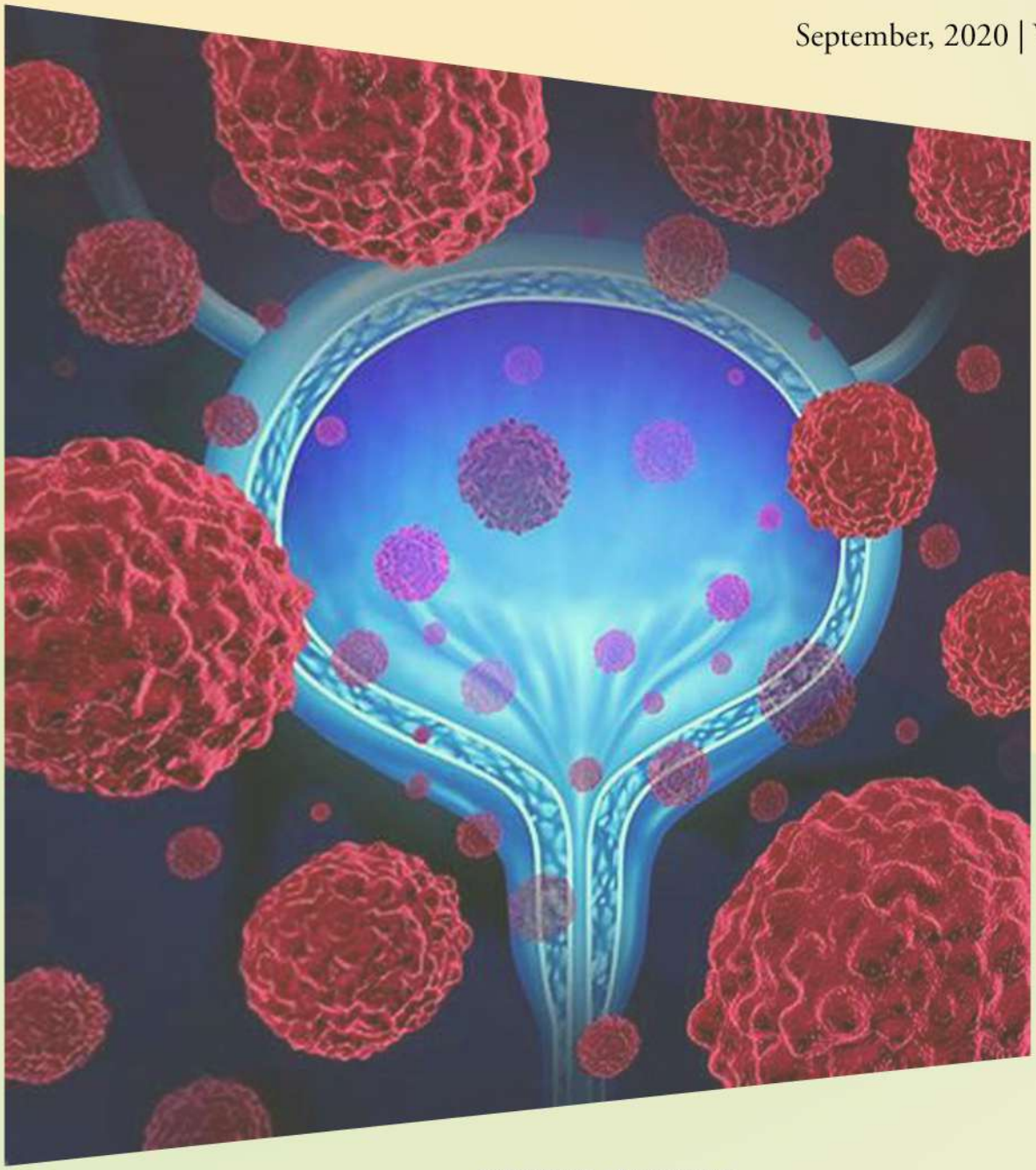

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Original Research

Evaluation of Upright Magnetic Resonance Imaging in Female Genuine Stress Urinary Incontinence before and after Monarc^R Bladder Neck Suspension: A Prospective Cohort Study

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ABSTRACT

Aim
Current methods used to assess patient suitability for bladder neck suspension prior to surgery are limited due to their inability to examine patients in physiologic positions. The purpose of this study was to examine the usefulness of upright magnetic resonance imaging (MRI) in the evaluation of patients with genuine stress urinary incontinence (GSUI) prior to undergoing Monarc^R bladder neck suspension.

Materials and Methods
Twenty-seven female patients with known GSUI were selected to participate in the study. Each patient was asked to complete an incontinence symptom score and then have 300 ml of sterile water instilled into their bladder. While standing in an upright MRI scanner a T2-weighted image at 0.6 tesla was then obtained while at rest and then undergoing standardized Valsalva maneuver. Special attention was then given to the downward movement of the H-line against the M-line. Measurements were taken to determine excursion of the H-line against the M-line. The procedure was then repeated for each patient three-months after surgery. The change in H-line excursion following surgery was compared to the change in symptom score using Spearman's rank correlation test.

Results
A positive correlation was found between the pre- and post-operative improvements in international consultation on incontinence questionnaire female lower urinary tract symptoms modules (ICIQ-FLUTS) and the post-operative reduction of excursion of the pelvic floor. These correlations were found to be statistically significant (p<0.001) using Spearman's rank correlation test.

Conclusion
A greater degree of pelvic floor prolapse visible on magnetic resonance imaging (MRI) with a standardized Valsalva maneuver prior to Monarc^R bladder neck suspension surgery predicts for better patient symptom score outcomes as determined by ICIQ-FLUTS.

Keywords
Magnetic resonance imaging (MRI); Bladder neck suspension; Stress urinary incontinence.

INTRODUCTION

Genuine stress urinary incontinence (GSUI) is a common bothersome medical condition affecting primarily parous older women. It is estimated that more than thirty million women suffer from the condition in North America alone[1] and about 25% of women are expected to suffer from symptomatic GSUI at some

point in their lifetime.[2]

Obesity, multiparity, chronic obstructive pulmonary disease and previous hysterectomy are all independent risk factors for the disease.[3] GSUI is debilitating when patients are compelled to limit their fluid intake or to limit their physical activity in order to control symptoms of the disease.[4]

The underlying pathophysiology of GSUI is generally considered to be due to laxity of the pelvic floor muscles resulting from labor and delivery.[5,6] As a result of this relaxation the bladder outlet continence mechanism does not function properly, and urine leakage can occur during episodes of increased abdominal pressure. The precise etiology and pathophysiology of the disease is still unclear and GSUI can also occur in nuliparous women.[7]

Weight loss,[8] risk factor management and physiotherapy[9] are all helpful in controlling the symptoms of GSUI. Symptomatic patients who do not improve with non-surgical management usually proceed to a minimally invasive surgical procedure involving placement of a polymer micromesh "tape" implant.

The tension free vaginal tape (TVT) procedure was first introduced in 2001 by Dr. C Falconer[10] and it has revolutionized the surgical treatment of GSUI with an overall satisfaction rate of over 90%.[11] A trans-obterator tape procedure for GSUI was first proposed by Delorme in 2001 and has gained in popularity as it is less invasive than the original TVT.[12] The Monarc^{R}-TOT procedure is a variation of tape suspension inspired by Delorme. TVT (and its variants) is not always successful however, and the reason(s) for failure are not always known.[13]

The normal physiology of the female pelvic floor has proved uniquely difficult to study.[14] Beginning in the 1960's multichannel urodynamics has been used to characterize pressure changes between the bladder and the urethra. Over the years ambulatory urodynamics was developed as an investigative tool to control for postural changes in incontinent subjects.[15] The more recent addition of video-urodynamics and dynamic magnetic resonance imaging (MRI) has further improved our understanding of female pelvic floor function.[16] However, a complete picture of normal pelvic floor function continues to elude us.

Contributing to the difficulty in female pelvic floor assessment is the problem of testing patients in the upright position.[17] In addition, trans-urethral pressure probes can interfere with bladder functioning during testing by stimulating the rather sensitive surfaces within the urethra and within the bladder itself. The result of this iatrogenic stimulation can lead unwelcome artifact on urodynamics testing.[18]

The gradual advancement of MRI technology has led to the development of upright (open positional) imaging systems.[19] The newer upright MRI systems were first introduced in 2008 and allow for the MRI assessment of anatomical changes related to position and weight bearing. Upright MRI is currently most used to evaluate vertebral changes created by stress loading.

This prospective cohort study is the first to use upright MRI in the investigation of GSUI in women.

Aim

To gather anatomical data of the female pelvic floor using an upright MRI scanner in women who are known to have type 2 GSUI before and then after Monarc^{R} Trans-obterator tape (American Medical Systems, Minnetonka, MN, USA) suspension. Concurrent collection of psychometrically valid symptom scores will allow for direct comparison of symptom changes to the anatomical changes noted on upright MRI.

MATERIALS AND METHODS

Thirty otherwise healthy multiparous female Monarc^{R} TOT candidates with proven GSUI were recruited from participating surgeons to take part in the study. Subjects were excluded from the study if they had any element of an overactive, uninhibited, or small capacity (<200 ml) bladder. Any history of endometriosis or ongoing pelvic pain led to exclusion from the study as did any pre-operative evidence of microhematuria or leukocyturia. A history of urinary tract infection within three-months of recruitment also led to exclusion from the study. These criteria were established during the process of recruitment by the participating surgeons.

Prospective trial protocol approval was obtained from the Western Institutional Review Board (IRB) (WIRB study # 1134614, protocol # 20121442) prior to, and at regular periods during, the course of the 22-month trial in accordance with the revised Declaration of Helsinki of 1989.

Each participant in the study had a history of GSUI type 2 with a diagnosis considered "very likely" after history and physical examination by a participating urologist or gynecologist. Each patient then completed an initial 12 question 48-point international consultation on incontinence questionnaire female lower urinary tract symptoms modules (ICIQ-FLUTS) questionnaire[20] (ICIQ group, Bristol Urological Institute, Southmead Hospital, Bristol, UK). A comprehensive informed consent was then obtained from each subject. After completing the symptom score and consent form each patient was then asked to void completely. After each patient had emptied their bladder completely, a sterile #14 French catheter was inserted in their urethra and 300 ml of sterile water was instilled into their bladder and left to dwell. Any residual urine was removed from the patients bladder at the time the catheter was inserted.

After standardizing for bladder volume of 300 ml each participant was transferred to a nearby Fonar^{R} (Fonar Corporation, Melville, NY, USA) 0.6 T-upright MRI machine. Once inside the MRI suite each subject underwent a pelvic MRI scanning series while standing at rest. A second series of pelvic MRI images was then obtained as each subject was asked to perform a standardized Valsalva's maneuver. In order to standardize the Valsalva[21] maneuver a Laborie (Laborie International, Mississauga, Ontario, Canada) Peritron^{R} digital pressure gauge was used. Each subject was asked to blow into a custom made 3 m tube producing an abdominal

pressure of 53 mmHg. The Peritron[R] device was adjusted to deliver auditory and visual feedback to each research subject so that appropriate standardized pressure could be maintained for the eight seconds that were necessary to obtain an adequate image. During this process, each subject was monitored by the principal investigator in the study to ensure compliance. Finally, each subject was asked to void completely and subsequently an abdominal MRI series was obtained while each subject was supine.

After the MRI data was acquired it was saved to a secure database (McKesson, one post street, San Francisco California, USA) and each patient then went on to have a Monarc[R]-TOT type bladder neck suspension. Each Monarc[R]-TOT suspension was carried out in a standardized manner by one of five separate participating surgeons. After the surgery, each subject waited a minimum of three months before returning to the MRI suite for a follow-up MRI study series. Each follow-up study was performed using the same protocol as the preliminary study, but an abdominal series was not collected on the second study.

The second series of MRI images were again stored to a secure imaging database and symptom score results were stored to a secure Excel® database (Microsoft, 15010 Northeast 56th Street, Redmond, Washington, USA) which was operating on a PC compatible laptop computer.

The many MRI images that were collected were then evaluated by a qualified radiologist who classified and calibrated pelvic floor findings using the "Health Maintenance Organization (HMO)" grading system originally proposed by Drs. C. Comiter and S. Raz in 1999.[22] Pelvic floor excursion was carefully mapped out using the HMO system and an ordinal number approach was used to allow for direct statistical comparison(s) between the ICIQ-FLUTS results and the MRI results.[23]

The pre- and post-operative MRI results were then carefully compared and correlated to the pre- and post-operative ICIQ-FLUTS symptom score data using the statistical method of Spearman's rank correlation. The results of the analysis are presented below followed by a discussion of their significance.

RESULTS

Of the 30 patient subjects recruited into the study 27 completed the two-part MRI series and Monarc[R]-TOT surgery. Two subjects finished the first MRI series and the surgery but were then lost to follow-up. A third subject could not complete the first MRI series due to discomfort related to initial urethral catheterization.

The twenty-seven patients who completed the study had a median age of 51.5-years and an average age of 51.5-years. The observed population had an average weight of 75.5 Kg and the groups average body mass index (BMI) was 28.13. The youngest patient in the study was 35-years-old and the oldest was 82.

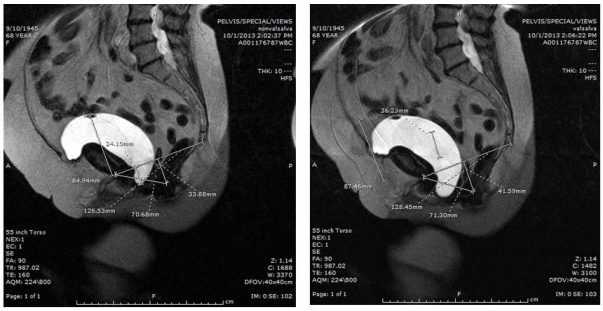
The average pre-operative ICIQ-FLUTS result was 19.96 (normal<5) improving to 11.15 post-operative. The average improvement in ICIQ-FLUTS was therefore 8.81 points (Figure 1).

Figure 1. *Box and Whisker Plot Showing the ICIQ-FLUTS Scores to Question 11.A) Pre- and Post-Monarc Suspension with Upper and Lower Quartiles (Blue). The ICIQ-FLUTS Scores and Quartiles for Question 11. B) Pre- and Post-Monarc are Shown in Green*

The above box and whisker chart illustrates the response by patients to Questions 11. A and 11. B before and then after Monarc[R] suspension. Question 11. A asks: "*Does urine leak when you are physically active, exert yourself, or sneeze?*" (score out of 5). Question 11. B asks: "*How much does this bother you?*" (score out of 10).

The MRI process, which included standardizing bladder volume and a standardized Valsalva's maneuver, was well tolerated by all patients. There were no patient dropouts during either MRI series, or all the image outcomes were of diagnostic quality (Figure 2).

Figure 2. *Sample of Two Pre-operative Images from One Patient (T2-weighted Image, Sagittal Section) in the First Upright MRI Series*

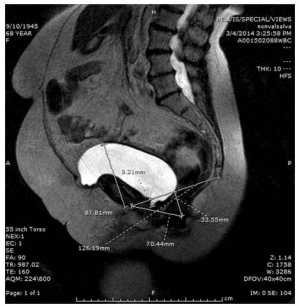


A sample of two pre-operative images from one patient (T2 weighted image, sagittal section) in the first upright MRI series. These two images show the measurements taken using the "HMO" system of S Raz. Image 1 was taken "standing at rest" while image 2 was taken "standing with standardized Valsalva". The first image shows that the lowest point of the bladder floor reaches 24.1 mm below the pubococcygeal line (PCL) while the patient is at rest. With Valsalva this distance increases to 36.23 mm for a pelvic floor "excursion" of 12.13 mm.

A sample of two post-operative T2 weighted MRI images developed from the same patient as in Figure 3. Again, the first sagittal image shows the patient while "standing at rest". The

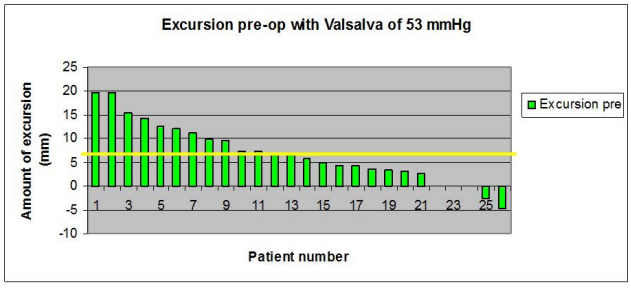
second sagittal image shows the patient while "standing with Valsalva". The most dependent portion of the bladder in image 1 protrudes 9.31 mm past the PCL while in image 2 the protrusion is measured at 14.18 mm for an excursion of 4.87 mm. Comparison of the pre-operative to the post-operative result indicates a pre-op to post-operative "reduction of excursion with Valsalva" of 7.26 mm.

Figure 3. *Sample of Two Post-operative T2-Weighted MRI Images*



A wide range of pre-operative pelvic floor excursion results were obtained. The greatest degree of excursion prior to surgery with Valsalva was 19 mm and the least amount of excursion was positive 4 mm — that is 4 mm less protrusion with Valsalva than at rest (Figure 4).

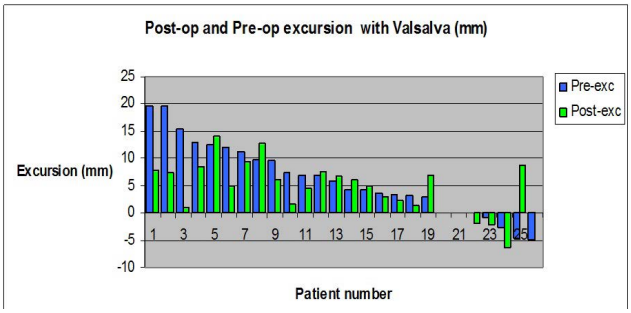
Figure 4. *Histogram Showing Pelvic Floor Excursion Results with Valsalva in mm for All 27 Subjects*



Histogram showing pelvic floor excursion results with Valsalva in mm for all 27 subjects. The greatest amount of excursion prior to Monarc^{R}-TOT was 19 mm and the least amount of excursion was +4 mm. The pre-operative average excursion distance with standardized Valsalva's maneuver was 6.83 mm.

When the same measurements were taken three months after Monarc^{R}-TOT an average excursion with Valsalva of 4.41 mm was recorded. The average "reduction of excursion attributable to surgery was therefore 2.43 mm (Figure 5). Interestingly, eight patients had more pelvic floor excursion following surgery than before surgery. The cause of this result is not immediately apparent.

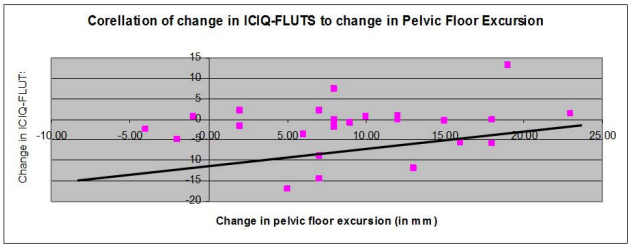
Figure 5. *A Histogram with Direct Comparison of Pre-operative and Post-operative Pelvic Floor Excursion with Standardized Valsalva's Maneuve*



A histogram with direct comparison of pre-operative and post-operative pelvic floor excursion with standardized Valsalva's maneuver is presented. Prior to surgery an average excursion with Valsalva of 6.83 mm was recorded. Following surgery this drops to 4.41 mm for an average reduction of 2.43 mm attributable to Monarc^{R}-TOT surgery. It is notable however, that eight of twenty-seven patients had more pelvic floor excursion after surgery than before.

To compare and correlate the ICIQ-FLUTS results with the upright MRI results directly a Spearman's rank correlation test was used. This statistical procedure was performed by making a comparison of pre-operative/post-operative change in pelvic floor excursion results with the pre-operative/post-operative change in ICIQ-FLUTS results. The Spearman's rank correlation equation ($rs=1–6\ \Sigma d^2/n(n^2–1)$) was used and the statistical operation was performed using Excel^{R} (Figure 6).

Figure 6. *A Scatter Graph (with trend line) Comparing the Change in Pelvic Floor Excursion (vertical axis in mm) to the Change in the ICIQ-FLUTS Result (horizontal axis)*



A scatter graph (with trend line) comparing the change in pelvic floor excursion (vertical axis in mm) to the change in the ICIQ-FLUTS result (horizontal axis). Spearman's rank correlation rs=0.18206. The result indicates a moderate positive correlation and is statistically significant ($p<0.001$).

DISCUSSION

Almost as soon as MRI became clinically available efforts were made to use the imaging technique to investigate the female pelvis.[24-26] The advantages of MRI include lack of ionizing radiation, a clear

depiction of the soft tissues of the pelvic floor, and multiplanar imaging capability. Conventional MRI produces static T1-images and spin echo T2-weighted images. Although useful, standard MRI is limited by its long image acquisition time and by the requirement that the patient be in the supine position.

Using the above-mentioned techniques, the functional anatomy of the female pelvic floor was examined, and studies also began to use MRI to evaluate the soft tissue changes associated with GSUI. In 1995 several studies used conventional MRI to investigate anatomical changes associated with incontinence and prolapse surgery. One study used classical supine MRI to evaluate postural changes occurring in the pelvic floor of healthy continent women.[27]

The development of ultra fast MRI image acquisition (single-shot fast spin echo SSFSE and single-shot turbo spin echo HASTE) and the use of single shot sequencing with a cinematic (or dynamic) display added an additional improvement in the understanding of functional anatomy of the female pelvic floor.[28,29] The introduction of dynamic MRI in 1999 generated great interest as the interaction of anatomical pathology and the pathophysiology of GSUI became clearly visible for the first time.[30] In 1999 Drs. Comiter and Raz developed a standardized nomenclature for grading pelvic prolapse and pelvic floor relaxation in dynamic MRI imagery and this diagnostic system has been widely adopted.[31]

A practical application for MRI in the setting of incontinence has however not yet been developed. While interesting and less invasive, the techniques of supine MRI and dynamic MRI have not been generally adopted as routinely useful.[32]

In the present study upright MRI is used in combination with standardized testing to investigate a cohort of GSUI patients before and after Monarc^{R}-TOT surgery. Twenty-seven human subjects with known GSUI were recruited and investigated prospectively with upright MRI. Pre-operative and post-operative MRI data was collected and compared with a psychometrically valid symptom score. Data were carefully collected over a two-year period and appropriate statistical tests were used to demonstrate a significant positive correlation between the changes in patient's incontinence symptoms and the changes in pelvic floor movement.

This study marks the first time that psychometrically valid symptom score improvements and objective pelvic floor anatomy improvements have been definitively linked as being due to the same surgical intervention in GSUI patients.

This result is significant as it demonstrates that the reductions in pelvic floor excursion achieved by Monarc^{R}-TOT can be objectively linked to the positive clinical outcomes recorded by ICIQ-FLUTS. The symptom improvements long known to be due to trans-obterator tape suspension are thus demonstrated to be objectively correlated to anatomical changes generated by the surgery.

CONCLUSION

In conclusion, upright MRI investigation using this methodology may prove to be useful as a less invasive alternative to urodynamic testing in a subgroup of patient's prior GSUI surgery. As open positional and upright MRI systems become more widely available these methods may prove to be useful clinically for some GSUI patients.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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A Comparison of Continuous Wound Infiltration Plus Patient Controlled Analgesia *Versus* Epidural Analgesia after Open Renal Surgery

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ABSTRACT

Aim

Open nephrectomy is associated with significant post-operative pain. Epidurals have been a core method for provision of analgesia, however, there is increased use of novel analgesic strategies with comparative analgesia but potentially fewer side effects. This pilot study aims to assess the feasibility of a randomised control trial comparing continuous wound infusion (CWI) to epidural analgesia for open renal surgery. Objectives included estimation of recruitment rates, failure rates and complications and refining design of a randomised control trial.

Methods

Participants were randomised using randomisation software. Patients received standardised anaesthesia as per the study protocol. Patients randomised to the CWI group had a wound infiltration catheter inserted at the end of surgery. In the epidural group, patients had an epidural sited prior to surgery. Primary outcomes evaluated were visual analogue pain scores. Secondary outcomes included intravenous fluid use, hypotensive episodes, patient mobilisation, evidence of post-operative ileus, respiratory morbidity, demands on medical and nursing care, length of hospital stay and patient acceptability as assessed by the Quality of Recovery (QoR-15) questionnaire.

Results

Pain scores were similar for both groups with marginally higher mean scores in the wound infiltration group on post-operative day 1 and 3. Supplementary analgesia rates were comparable for both groups with tramadol use being higher in the wound infiltration group.

Conclusion

Collecting outcome data for an appropriately powered randomised controlled trial is feasible. Recruitment was challenging due to the increased minimally invasive laparoscopic or robotic nephrectomies and consideration of a multicentre study is warranted. The two analgesic techniques appear broadly comparable in efficacy and time to discharge. CWI potentially presents safety advantages compared to epidural analgesia.

INTRODUCTION

The open approach to radical and partial nephrectomy remains a commonly practiced procedure despite considerable advances in minimally invasive surgery. Renal surgery may be associated with severe and prolonged post-operative pain. A multimodal approach to analgesia has been shown to be beneficial as part of en-

hanced recovery protocols.[1] Epidurals have traditionally been core in providing post-operative analgesia to this patient cohort. Whilst epidurals still have a clear role in certain patient groups there has been a shift away from their routine use across many types of major surgery, with the acknowledgement that there is a less definitive mortality benefit than previously accepted.[2] The 3rd National Audit Project from the Royal College of Anaesthetists demonstrated that whilst overall serious complications following central neuroaxial blockade were low, the majority occurred in the peri-operative setting as opposed to obstetric or chronic pain environments.[3] Adverse events associated with epidural use can be divided into procedural risks at insertion, and consequences of administered medication. Epidural opioids are often combined with local anaesthetic solutions for infusion *via* epidural catheter and can lead to side effects such as nausea, vomiting, pruritus and respiratory depression.[4] These concerns have led to increased interest in novel analgesic strategies with comparative analgesic properties but potentially fewer side effects.

The infusion of local anaesthetic into the surgical wound has been shown to be a simple, safe procedure that results in comparable analgesia to that provided by epidural, with favourable side effect profiles.[5,6] Meta-analysis examining novel local anaesthetic wound infiltration in patients undergoing colorectal surgery concluded that these techniques reduced pain scores, reduced opiate requirements and increased recovery indices compared with placebo or routine analgesia.[7] Similar benefits have been demonstrated in open abdominal vascular surgery,[8] open hepatic surgery[9] and open nephrectomise.[6,10]

The pilot study aims to assess feasibility of a randomised control trial comparing continuous wound infusion (CWI) plus patient controlled analgesia (PCA) to conventional analgesic approach *via* epidural for open renal surgery. Objectives included estimation of necessary recruitment rates, testing appropriateness of outcome measures, estimation of procedural failure rates, incidence of respiratory and gastrointestinal complications and use data to refine the randomised control trial design.

METHODS

Ethical approval was received from the National Research Ethics Committee (South West, 13/SW/0160). This pilot study was designed to test the feasibility of collecting specific outcome data pertaining to the two aforementioned analgesic strategies, epidural analgesia and continuous local anaesthetic infiltration *via* wound catheter plus patient controlled analgesia for patients undergoing open renal surgery.

Patients were identified by the clinical team and once verbally informed about the study, were given written information and opportunity to discuss the project with a team member. Fully informed patients were invited to participate in the trial, and written consent was obtained. Participants were block randomised by a team member, independent to the data acquisition and analysis process, using the Stats Direct v3.1 (Altrincham, UK) statistical software package and randomisation function.

Male and female adult patients requiring open renal surgery were included in the study. Radical nephrectomy was approached *via* a loin incision and transperitoneal approach. Extraperitoneal access was used for the partial nephrectomies. Exclusion criteria included patients unsuitable for an epidural (localised skin sepsis at proposed site of injection, coagulopathy), unsuitable for a CWI catheter and those listed for laparoscopic surgery.

Both patient groups received a standardised anaesthetic as per the study protocol. Arterial and central venous pressure (CVP) monitoring were established as clinically indicated. At induction, patients were administered Midazolam 2 mg, Propofol 2-3 mg/kg, Remifentanil and Atracurium 0.5 mg/kg. Intermittent positive pressure ventilation was commenced with an FiO_2 of 0.6 to 0.7 and Isoflurane at 0.7-1.0 monitored anesthesia care (MAC) for anaesthetic maintenance. A remifentanil infusion (50 mcg/ml) was initiated. Patients were administered 1 to 3 litres of crystalloid intra-operatively with boluses as required. Post-operative fluid administration was guided by clinical indication. Those undergoing partial nephrectomies received intraoperative Mannitol 0.5 g/kg. All patients received Cyclizine 50 mg and Ondansetron 4 mg intra-operatively and further antiemetic as required. Patients received intravenous morphine boluses in recovery, if required, followed by regular Paracetamol 1 g 6-hourly and Tramadol 50-100 mg 6-hourly if required. Patients in the CWI group all received patient controlled analgesia (PCA). Patients in the epidural arm received opioid within the standard epidural bag mix, and therefore did not have a PCA.

For those randomised to the CWI group, a wound infiltration catheter was inserted at the end of surgery. Partial nephrectomies received a 15 cm Baxter painfusor catheter and total nephrectomies received a 22.5 cm Baxter painfusor catheter. The surgeon inserted the catheter into the deep wound space and flushed with 1 ml of 0.25% Bupivacaine to check catheter integrity. The catheter was inserted through an introducer needle, approximately 7 cm from one end of the incision and placed along the full length of the wound. The entry site was chosen to facilitate patient comfort and nursing access and the 7 cm distance was necessary to create an adequate subcutaneous tunnel and avoid leakage of the anaesthetic infusion from the entry point. After insertion, the introducer needle was split and removed. The catheter was positioned after closure of the peritoneum or transverse muscle, being placed between the deep muscle layer and internal oblique. If the deep muscle layer was not robust enough for secure suturing, a tunnel was created with blunt or sharp dissection between the transverse and internus layers. Care was taken to avoid including the catheter in the suture when closing the internal and external oblique layers. Finally, the subcutaneous space and skin were closed. The catheter was threaded and secured with a 'Lockit' dressing. These patients received subcutaneous wound infiltration of 29 mls of 0.25% bupivacaine prior to commencement of the CWI. The painfusor then infused 0.25% Bupivacaine at a rate of 5 mls/hour for 96-hours.

In the epidural group, patients had an epidural sited at the appropriate level by the anaesthetist prior to surgery. A test dose was given but the epidural was not subsequently used intra-

operatively. At the end of surgery, the epidural was bolused with 0.25% Bupivacaine + 100 mcg Fentanyl (volume) and a standard epidural mix of 0.125% Bupivacaine with Fentanyl 4 mcg/ml was commenced at a rate of 1 to 10 mls/hour. The epidural then stayed *in situ* for as long as it was deemed necessary.

Primary outcomes evaluated were pain scores (visual analogue pain scores).

Secondary outcomes included intravenous fluid management (administered volumes of intravenous crystalloid, colloid and blood, and total fluid output), hypotensive episodes, patient mobilisation, antiemetic use and evidence of post-operative ileus (presence of clinical features including absent bowel sounds, associated abdominal distention, nausea or vomiting, respiratory morbidity (reduced SpO_2, length of hospital stay and patient acceptability as assessed by the Quality of Recovery (QoR-15) questionnaire.[11] Demands on medical and nursing care were assessed using the patient's post-operative observation chart and whether a patient's deranged physiology had prompted any primary or urgent reviews, having triggered an early warning score, or a medical emergency team (MET) call respectively.

The QoR-15 questionnaire is an 11-point numerical rating scale (0-10) questionnaire for 15 items related to patient function, incorporating dimensions of support, comfort, emotions, physical independence and pain. Patients score function pre- and post-operatively (at 24-hours) for each item.

Data was collected for 25 consecutive eligible patients.

RESULTS

This pilot study included 25 participants; 13 patients in the epidural group and 12 in the CWI group. One CWI patient was excluded due to incomplete data collection. There was a total of 15 males and 9 females with characteristics as per Table 1. Due to the nature of this feasibility trial, the groups were not powered to provide tests of statistical significance, but to inform of a randomised controlled trial. There were no recorded complications from either analgesic technique for any of the 25 patients.

Table 1. *Patient Characteristics for Patients Undergoing Open Nephrectomy, Receiving Analgesia via an Epidural or Wound Catheter. Values Displayed as Mean (SD) or Number (Proportion)*

	Epidural Group (n=13)	CWI Group (n=11)
Age (median years)	72 (8.5)	59 (13.1)
BMI (kg.m-2)	25.8 (4.2)	26.6 (4.2)
ASA		
1	2 (15%)	4 (33%)
2	8 (62%)	4 (33%)
3	3 (23%)	4 (33%)
Length of stay (days)	7.2 (3.8)	7.2 (4.6)
ICU admission	2 (15.4%)	5 (42.7%)
Haemoglobin (mean)		
Pre-operative (g.L-1)	133.9 (15.1)	126.4 (18.0)
Post-operative (g.L-1)	102.5 (18.7)	109.1 (15.2)

Pain scores (Table 2) were similar for both groups. Marginally higher mean scores are noted for the wound infiltration group on post-operative days one and three. Administration of additional supplementary analgesia had comparable rates for both groups, with tramadol use being higher in the wound infiltration group.

Mean blood pressure in both groups was comparable apart from day one, when the mean systolic blood pressure was 19

Table 2. *Mean Maximal Pain Scores and Supplementary Analgesia. Values Displayed as Means (SD) and Frequencies (Proportions)*

Day	Epidural						Wound Catheter					
	Pain Score	Supplementary Analgesia					Pain Score	Supplementary Analgesia				
		Paracetamol	NSAID	Codeine	Tramadol	Oramorph		Paracetamol	NSAID	Codeine	Tramadol	Oramorph
0	3.5 (3.8)	13 (100%)	0 (0.0%)	0 (0.0%)	4 (30.8%)	1 (7.7%)	3.8 (3.1)	11 (91.7%)	2 (16.7%)	0 (0.0%)	7 (58.3%)	0 (0.0%)
1	2.3 (2.9)	13 (100%)	0 (0.0%)	1 (7.7%)	4 (30.8%)	0 (0.0%)	4.7 (2.4)	12 (100%)	0 (0.0%)	1 (8.3%)	5 (41.7%)	2 (16.7%)
2	3.1 (3.4)	13 (100%)	0 (0.0%)	1 (7.7%)	4 (30.8%)	2 (15.4%)	3.4 (3.3)	12 (100%)	0 (0.0%)	2 (16.7%)	7 (58.3%)	2 (16.7%)
3	2.2 (2.4)	11 (100%)	0 (0.0%)	1 (7.7%)	6 (46.2%)	4 (30.8%)	3.1 (2.6)	12 (100%)	0 (0.0%)	0 (0.0%)	6 (50.0%)	2 (16.7%)

Table 3. *Patient Mobility. Values Displayed as Frequencies (Percentage)*

Day	Epidural			Wound Catheter		
	Total Fluid In	Total Fluid Out	Fluid Balance	Total Fluid In	Total Fluid Out	Fluid Balance
0	4807.3 (907.2)	1260.5 (752.5)	3547.7 (781.0)	6539.2 (1903.3)	1130.4 (793.6)	3929.3 (1764.0)
1	3532,2 (1798.4)	2073.7 (1046.6)	1384.9 (1899.9)	2831.4 (782.9)	1980.3 (1207.3)	1046.1 (1334.6)
2	3106.5 (1041.5)	2756.8 (1305.6)	369.0 (1197.6)	2657.8 (1272.2)	2802.6 (1028.9)	60.3 (1076.9)
3	2484.6 (1225.6)	2732.7 (1390.6)	-163.1 (1386.0)	3143.6 (1171.3)	1908.4 (1200.4)	478.2 (1799.3)

mmHg lower in the epidural group and below 90 mmHg systolic. The highest mean systolic pressure was on day 3 in the epidural group at 149/79 mmHg. The differences of upper and lower systolic blood pressure between two groups were otherwise within a 10 mmHg range. Mean diastolic values were within 10 mmHg for both groups on all days.

Fluid balance analysis (Table 3) demonstrated similar values for both groups on days 0, 1 and 2. On day three the wound catheter group had a positive net fluid balance of 478.2 ml. Intravenous fluid administration was of greater volume (more than 3000 ml) in the wound catheter group on days 0 and day 3. The epidural group received larger volumes (more than 3000 ml)of fluid on days 1 and 2.

Table 4 shows the comparisons of number of patients sitting out and subsequently mobilising for each post-operative day. This showed an overall broad agreement between the two groups, however there was a tendency for more patients to sit out and mobilise at an earlier point in their post-operative period within the wound infiltration group.

Table 4. *Patient Mobility.Values Displayed as Frequencies (Percentage)*

Day	Epidural		Wound Catheter	
	Sat Out	Walked	Sat Out	Walked
0	1 (7.7%)	1 (7.7%)	0 (0.0%)	0 (0.0%)
1	7 (53.8%)	3 (23.1%)	9 (75.0%)	4 (33.3%)
2	11 (84.6%)	6 (46.2%)	10 (83.3%)	9 (75.0%)
3	11 (84.6%)	10 (76.9%)	10 (83.3%)	10 (83.3%)

Antiemetic use was higher in the CWI group, particularly on days two and three. On the third day three, 33.3% of CWI patients were still using one or more antiemetics compared to 15.4% of the epidural patients. More patients in the wound catheter group experienced post-operative ileus, with 50% of patients still experiencing symptoms on day three, compared to 38.5% patients in the epidural group.

No medical emergency team (MET) calls were required for either the CWI or epidural groups. post-operative early warning score (EWS), which would require the patient to have a timely medical review, were slightly higher for the epidural group on days two and three. The frequency of anaesthetic review was higher in the epidural group.

The quality of recovery 15 (QOR-15) (Appendix 1) highlighted that scores had baseline similarity indicating that the randomisation process was effective, and groups were evenly matched. Lower scores were given post-operatively for both epidural and wound catheter groups across all variables. Moderate and severe pain, nausea and vomiting and feelings of sadness or depression were higher in the epidural group compared to the wound catheter group 24-hours post-operatively.

Resource costs were assessed to inform health economics. CWI consumables were more expensive consumables at £ 73.25 per patient compared with epidurals at £ 20.15. The cost of the drug was in addition to this.

DISCUSSION

This study builds upon previous research investigating local anaesthetic use *via* wound catheter infiltration as part of a multimodal analgesic strategy in open renal surgery. It is not possible to draw any conclusions from the data due to the study being a pilot however, it does allow for a descriptive analysis of each group to be reported and also for assessment of the trial protocol thus informing the design of a future appropriately powered randomised control trial.

Due to the reduced patient numbers, numbers the groups were not matched, with patients in the epidural arm having a greater median age. Both groups had a similar body mass index. There was no discernible difference in mean length of stay for the two groups suggesting wound catheter use did not have a detrimental effect on discharge time due to suboptimal analgesia. A higher proportion of patients in the wound catheter group were admitted to intensive care post-operatively because of premorbid comorbidities or intraoperative complications rather than post-operatively from the ward, where analgesic technique could have contributed to the clinical course.

Intravenous fluid administration and balance results were unexpected. It was anticipated that fluid administration for the epidural group would have been significantly larger than the wound catheter group. However, the wound catheter group received comparatively more fluid on day 0, less on days 1 and 2 and more again on day 3. It is accepted that differences may occur post-operatively due to variation in clinician practice.

Safety data for both groups demonstrated similar mean early warning scores for day 0 and marginally higher values for the epidural groups at day 1-3. Similarly, there were no medical emergency calls for patients within the CWI group throughout the study compared to a mean of less than 1 for patients in the epidural group suggesting that the CWI technique was indeed safe and in this small cohort suggested a tendency to a lower rate of post-operative adverse events compared to the epidural group.

Analysis of mobility between the two groups suggested that a greater proportion of patients in the wound infiltration group had sat out by day 1 and walked by day 2, but rates were broadly similar by day 3. Pre-operatively, the patient information leaflet stated that 'part of the outcome was to test whether these techniques may be better than the other, not just in terms of pain relief, but also the ability for you to move around after your operation'. This is unlikely to have led to any bias in motivating patients in one analgesic group to mobilise earlier than the other.

Antiemetic use was higher in the CWI group. All patients

that were in the CWI group concurrently had a morphine PCA device and it may be that the addition of opioid led to higher rates of nausea and vomiting. In a repeat study, the use of plain epidurals and concurrent PCA analgesia could be considered and be more directly comparable. The standard practice in our institution; however, is to use epidurals pre-mixed with opioids, and therefore, a decision was taken to test the novel CWI technique with our established standard of care.

The QOR survey used is a validated tool used to assess pre and post-operative function. It is however validated for use in day case patients and therefore has limited impact in our study. A similar survey, looking at longer-term function in addition to the immediate post-operative period, would be preferential in a future trial. This would be informative when looking at the items 'looking after personal hygiene' and 'communication with family and friends', which scored low values immediately post-operatively. Moderate and severe pain scores, nausea, vomiting and feelings of sadness or depression all scored higher in the epidural group; this would be interesting to explore in further detail with larger case numbers, over a longer period.

The study demonstrated that recruitment of patients in a larger scale randomised control trial might be challenging due to change in urological practice. During the study 'robotically-assisted minimally invasive surgery' was introduced at our institution resulting in a reduction in the number of open procedures, thus limiting otherwise eligible patients to participate. Despite this, the open approach for nephrectomy still has a place in certain clinical circumstances and as such, continuous infiltration of local anaesthetic *via* wound catheter has the potential to provide a useful alternative to epidural analgesia in these cases.

Strengths of this study include demonstration of the safety profile of the CWI and the large quantity of data collected that could inform future research design. Specific weaknesses include lack a suboptimal matching of patients, due to small number recruited, and that the use of PCA with the CWI may have confounding effects on primary outcome. Also, a QOR tailored to major surgery and the more protracted post-operative period would be more suitable and potentially capture useful differences.

CONCLUSION

In conclusion, this pilot study suggests that collecting relevant outcome data for an appropriately powered randomised controlled trial is feasible. Recruitment was more challenging than anticipated due to the increase in minimally invasive nephrectomies being undertaken and consideration of a multicentre study may be warranted. A large quantity of heterogeneous variables was collected for this study and in planning for a formal randomised controlled trial, a few of these key variables would have to be chosen to formulate appropriate metrics to answer the research question. This study has suggested that the two studied analgesic techniques are broadly comparable in terms of efficacy and time to discharge, which is useful in terms of CWI not being inferior. It does, however, have implications in planning an adequately powered randomised controlled trial, which would need to be run over multiple centres in order to recruit the necessary volume of patients. The CWI technique potentially presents safety advantages such as ease of siting and not requiring the same level of nursing expertise to look after the patient in the post-operative period, compared to epidural analgesia.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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APPENDIX

Appendix 1. *Quality of Recovery 15 (QOR-15) Questionnaire Results for Patients Undergoing Open Nephrectomy with Epidural or Wound Catheter. Data Displayed as Median Values and Interquartile Ranges*

	Epidural				Wound Catheter			
	Pre-operative QOR		Post-operative QOR		Pre-operative QOR		Post-operative QOR	
	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range
Able to breathe easy	9.5	9-10	10	8.75-10	10	9.5-10	10	8.5-10
Able to enjoy food	10	7-10	7	3.75-10	10	10-10	9	4.25-9.75
Feeling rested	7.5	5.75-10	7	5-8.25	10	7-10	9	5.75-10
Good sleep quality	7.5	5.75-10	5	2.75-6.25	8	5.5-10	8	2.25-10
Unaided personal hygiene	10	10-10	6	1.5-8.25	10	10-10	3	0.25-9.75
Communication with family/ friends	10	10-10	10	9.75-10	10	10-10	10	10-10
Support from hospital staff	10	10-10	10	9.75-10	10	10-10	10	8-10
Resuming usual activities	10	8-10	0	0-0	10	9-10	0	0-2
Feeling in control	8.5	6-10	6	5-8.25	10	10-10	7	5-8
General well-being	7.5	6-10	8	3-10	10	8-10	6	5-7.5
Moderate Pain	10	5-10	5	4.5-6.75	10	7-10	5	3.25-5
Severe Pain	10	10-10	10	7.75-10	10	10-10	8	4.25-9.75
Nausea and vomiting	10	7.5-10	10	6.75-10	10	10-10	10	2-10
Anxiety or worry	5	2.5-6.5	9	6.75-10	8	5.5-10	10	3.25-10
Sadness and depression	9.5	4.75-10	10	10-10	10	9.5-10	10	6.75-10

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Case Report

Prostate Cancer Cutaneous Metastasis: A Case Report

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ABSTRACT

Prostate cancer is the second most common cancer in men. It can be located, present local extension and finally metastasize. Cutaneous metastasis is an infrequent event that is associated with a poor prognosis. We present a clinical case of advanced undifferentiated prostate cancer with cutaneous metastases diagnosed by a punch biopsy and confirmed by immunohistochemistry.

Keywords
Prostate cancer; Cutaneous metastases; Immunohistochemistry.

INTRODUCTION

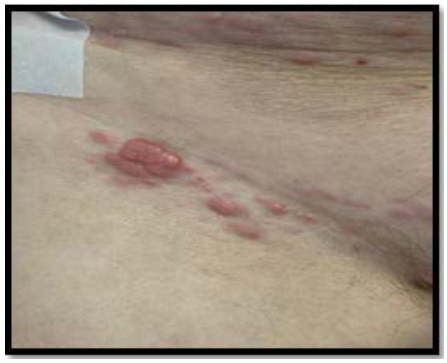
Prostate cancer (CaPR) is the most common genitourinary cancer in men and the second leading cause of cancer death after lung cancer.[1] Cutaneous metastases (MTSc) of internal cancers are rare, ranging from 0.6% to 10%.[2,3] The most frequent sites of metastasis (MTS) are bones and lymphatics, being rare in the liver and lung.[4] A literature review reveals 35 English case reports of MTSc from CaPR.[5,6] We present a CaPRMTSc case.

CASE REPORT

A 60-year-old man, with medical history of diabetes, ex-smoker was presented and diagnosed with prostate cancer (Gleason Score 5+5) in 2016, with baseline prostate-specific antigen (PSA) 14 ng/ml. Complete androgen blockade was performed with luteinizing-releasing hormone (LHRH) analog and antiandrogen and prostate radiotherapy due to localized oncological pathology through staging studies. At 9-months, he presented a biochemical relapse, the restaging computerized tomography (CT) scan showed multiple intercavo aortic and bilateral iliacs lymphadenopathies, and a hypodense image in the sacral bone, which may correspond to secondary disease. The bone scintigraphy showed hyperuptake in the sacral bone. Chemotherapy (CTX) was performed with Docetaxel (18 sessions) with good biochemical and clinical response, with decrease in lymph node images and decrease in the size of the sacral lesion in the first 3-months. Eight-months after the start of CTX, bone progression was evidenced in the ribs, sternum and cranial calotte, as well as liver and lung metastases with a rise in PSA to 20 ng/ml. It was decided to start enzalutamide therapy continuing with androgen blockade.

Four-months later, the patient was consulted for 2-month evolution nodular, violaceous, raised, non-pruritic formations, on an erythematous base in the right inguinal region and suprapubis (Figure 1). Lesions were evaluated by dermatology department and punch biopsy was decided. Histopathological results revealed epidermis with atrophy, dermis with infiltration by medium-sized cells, with a high nucleo-cytoplasmic ratio, anisocariosis and few cytoplasms with imprecise limits. Immunohistochemistry was per-

Figure 1. *Nodular Formations on an Erythematous Base in the Right Inguinal Region and Suprapubic*



formed and showed positive staining for PSA, concluding in lesions compatible with metastasis of acinar carcinoma of the prostate (Figures 2, 3 and 4).

Figure 2. *(A) Hematoxylin and Eosin (H&E) Examination of Skin Punch Biopsy 400x. (B) Prostate Specific Immunohistochemical Staining at 400x (visualization: cytoplasmic)*

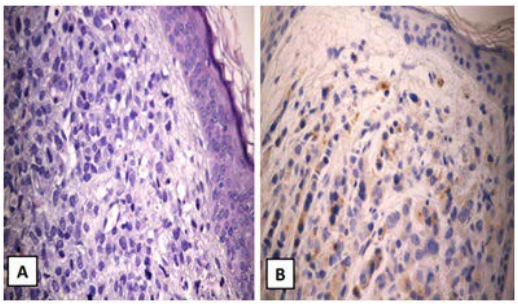


Figure 3. *Hematoxylin and Eosin (H&E) Examination of the Skin Punch Biopsy 100x. Inset Image Shows the Same Sample at 400x*

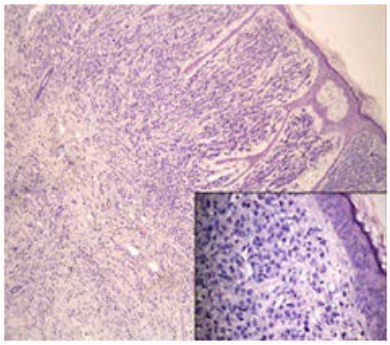
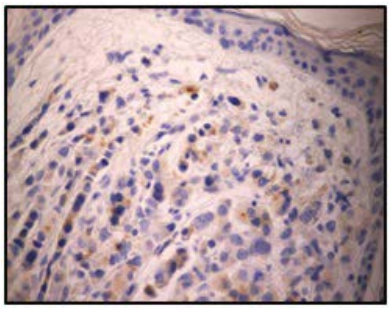


Figure 4. *Prostate Specific Immunohistochemical Staining of the Same Skin Sample at 400x (visualization: cytoplasmic)*



Chemotherapy was started, receiving 2 cycles of cabacitaxel without evidence of clinical response. The patient died 4-months after detection of the MTSc.

DISCUSSION AND CONCLUSION

CaPRMTSc is an infrequent entity and less than 100 cases were reported in the literature until 2016. An incidence of 0.09% of MTS in CAPR skin is recorded, which can increase taking into account the refractoriness and final stage of pathology[7-10]

In recent years, case reports of skin involvement has increased. This could be due to both the relative increase in the elderly, the world's population and the development of new treatments for CaPR that extend the survival rate.[8]

CaPR can metastasize through four different mechanisms: local spread of the disease, implantation through a surgical scar, lymphatic spread, and hematogenous spread.[9]

Cutaneous involvement has a poor prognosis as in other malignancies. It is considered an advanced disease marker with an average survival of 6-months.[4,8,11,12] Therefore, a skin extension should be suspected when appearing new skin lesions in a patient with an aggressive oncological diagnosis.

When skin involvement appears, they are usually nodular lesions that involve the supra pubic region, anterior aspect of the thigh, inguinal region, and few reports of facial, neck, chest and umbilical region involvement.[8,10,13,14]

In the literature review, Pistone et al[15] shows a patient with a history of prostate cancer who develops two tumors in chest and neck, after eight years of the diagnosis of the neoplasm, which were compatible with skin metastases. On the other hand, Rodriguez-Lojo et al[14] presents two cases of cutaneous metastases of the prostate, of which only one of them appeared in the skin of the chest as subcutaneous infiltration after eleven-years. In both cases, the presentation time of the metastasis was different from ours, which was 2-years possibly due to the tumor undifferentiation, however, according to our case, the patients died within a few months of the diagnosis of skin metastasis.

Unlike our report, Champoñan-Relaiza et al[16] presented a case of skin lesions in the chest and neck without a previous diagnosis of prostate cancer. When performing a skin biopsy, positive cell staining was shown for specific prostate antigen.

In our case, it is an aggressive, undifferentiated CaPR, which was evidenced by the Gleason Score (5+5), with early refractoriness to the established treatments.

Prostate specific antigen and prostate specific acid phosphatase (PSAP) are sensitive and specific immunoreactives for CaPR, however in certain cases they can be negative due to the great undifferentiation that the tumor could present.[9,13,17] Thus, immunohistochemistry become essential for diagnosis in these cases.

To conclude, urologists and dermatologists should bear consider a differential diagnosis when examining nodular lesions or skin rash in oncological patients, knowing that it may represent as the first manifestation of an oncological disease and are largely associated to a bleak forecast.

CONSENT

The authors have received written informed consent from the patient.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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UROLOGY AND ANDROLOGY

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Case Report

Nested Type Urothelial Carcinoma in the Upper Urinary Tract

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ABSTRACT

We report an atypical clinical case of an infrequent subtype of upper tract urothelial carcinoma (UTUC), with a nested variant. It is an infrequent histological subtype with poor prognosis. Laparoscopic left nephroureterectomy and adjuvant chemotherapy (AC) with good outcomes were performed.

Keywords
UTUC; Adjuvant chemotherapy; Nested variant urothelial carcinoma (NVUC).

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) includes any malignant tumors derived from the urothelium between the level of the renal pelvis and the distal ureter.

The vast majority of tumors from the upper tract are of urothelial origin (>90%). They can present as carcinoma *in situ* (CIS), as papillary or sessile lesions, and as solitary lesions or in a multifocal pattern.[1]

Urothelial carcinomas (UC) appear in the renal pelvis, ureter, or urethra much less frequently than in the bladder. In 2004, the World Health Organization (WHO) added histological variants of UC, which included lymphoepitheliomatoid cells, sarcomatoid, plasmacytoid, microcystic, micropapillary, nested, and small cell, each with different biological behaviors.

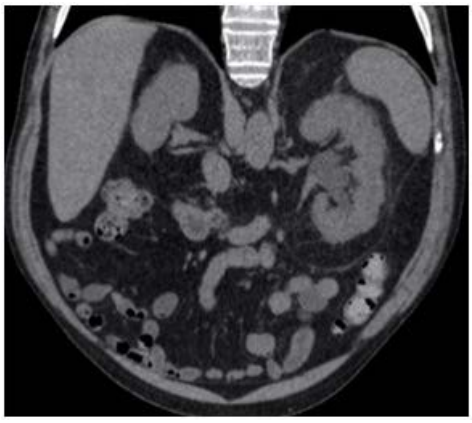
The nested variant urothelial carcinoma (NVUC) is an uncommon histological type described as an invasive form of UC,[2,3] with an estimated incidence of 0.3%.[4] It is characterized by a nested pattern, with a low-grade histological appearance with aggressive biological behavior,[5,6] islets of atypical, soft urothelial cells that strongly simulate von Brunn's nests and invade the lamina propria or deeper.[2,3]

CLINICAL CASE

A clinical case of a 70-year-old man with a medical history of hypertension and a former tobacco user is presented.

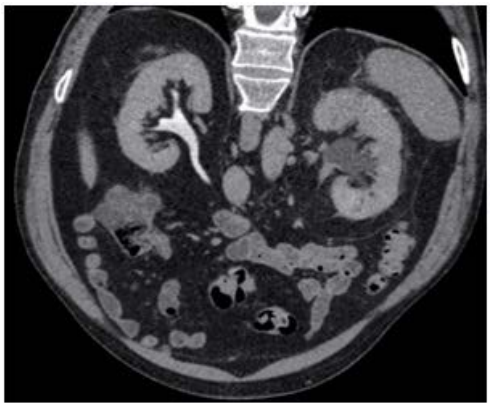
He was admitted to hospital with colic-type left lumbar pain associated with a single episode of gross hematuria without clots. He had experienced a similar clinical episode 2-months before which was self-limiting, so he did not consult. Urine analysis

Figure 1. *Unenhanced CT Scan*



showed microhematuria. Abdominal ultrasound reported a 16 mm diameter left pelvicalyceal dilation. Abdomen and pelvis computerized tomography (CT) scan showed an enlarged left kidney associated with thickening of the anterior and posterior pararenal fascia and pelvicalyceal dilatation associated with a non-calcified soft tissue density in the region of the pelvis and the left proximal ureter (Figure 1). A contrast enhanced study confirmed the presence of an endoluminal filling defect with a soft tissue density and marked delay of contrast drainage from the left kidney (Figure 2).

Figure 2. *Enhanced CT Scan*



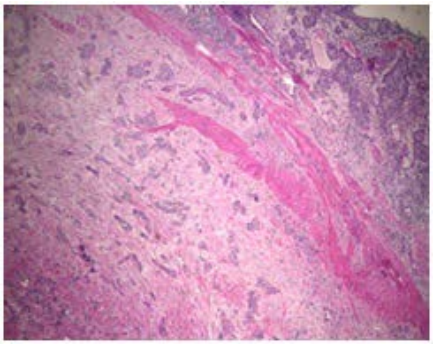
Due to the acute presentation and intense pain, cystoscopy and left ascending pyelography were performed, which demonstrated a 4 cm uretero-pyelicstricture, moderate pelvicalyceal, and marked delay in contrast evacuation. Ureteroscopy revealed the strictured segment with inability to progress a 6 and 4.8 French ureteral catheters. Cytology and distal biopsy of the stenosed area was taken with negative results for atypia. Left percutaneous nephrostomy and nephroscopy were performed with no apparent evidence of injury, but without being able to cross the ureteropelvic junction stricture.

Two weeks later, an exploratory laparoscopy was performed, which showed uretero-pelvic junction with inflammatory characteristics,. The decision was made to perform a segmental resection of the proximal ureter. Frozen section were taken but the pathology report was not definitive.

Due to the extensive involvement of the ureter, renal pelvis, the difficulty of subsequent reconstruction and, eventually, the high clinical suspicion of a neoplastic process, a left nephroureterectomy with a laparoscopic bladder cuff was performed.

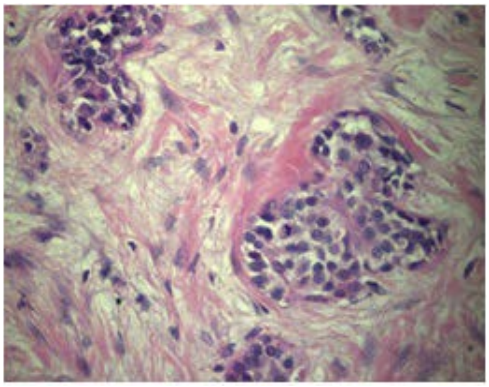
The definitive pathological report was invasive urothelial carcinoma with characteristics compatible with a nested variant (nested), located in the renal pelvis with complete invasion of the wall, including the muscularis and peri-pelvic adipose tissue. The final pathology report showed focal tumor infiltration of the ureteral segment with a distal margin free of tumor involvement. The renal parenchyma was tumor-free, pathological staging was pT3; Nx (Figures 3 and 4).

Figure 3. *H&E 40xPanoramic*



Urothelial epithelium with an increase in the number of its strata with moderate nuclear atypia, irregularly infiltrates the lamina propria with the presence of nests including muscular tunica and adipose tissue.

Figure 4. *H&E 400x*



The nests are confluent with each other, and the smaller ones have angled or blunt contours. Tumor cells have only mild atypia (mild pleomorphism, slightly increased N/C ratios, occasional prominent nucleoli, rare mitotic figures).

One-month later, laparoscopic left retroperitoneal lymphadenectomy was performed. Thirteen lymph nodes were removed with a negative result.

Adjuvant chemotherapy (AC) was performed with cisplatin and gemcitabine due to the high risk nature of the cancer, with a good clinical response.

DISCUSSION AND CONCLUSION

Nested variant urothelial carcinoma is an atypical histological variant with a high potential of malignancy. The vast majority of reported cases refer to their being found in the bladder.[1,7] Approximately 50% are around ureteric orifices.[1,7,8]

Despite its low-grade appearance in morphology, NVUC appears to behave like a high-grade tumor, at least in the bladder.[2,3] The World Health Organization (WHO) has reported that 70% of patients died 4 to 40-months after diagnosis, despite treatment.[2] According to microscopic characteristics, NVUC nests may show

a microcystic or cribriform pattern and rarely small tubules.[8,9] Mild anisonucleosis and relatively soft chromatin are evident with a tendency to increase atypia with increasing invasion at depth. The cytological characteristics of the nested variant are subtle and can be confused with reactive changes, and are therefore lost in urine cytology.[10] Furthermore, the preference of this variant of submucosal growth over exophytic growth may be the reason for the absence of urinary signs and symptoms that lead to a possible delay in diagnosis.

Differential diagnoses that can be made are benign, such as Von Brunn's nests, glandular cystitis, cystitis cystica, and malignant, such as carcinoid or paraganglioma.[8,11]

In their review, Veskimäe et al reported similar oncological outcomes after radical cystectomy in patients with nested variant compared with pure urothelial carcinoma in bladder.[12]

According to European Association of Urology (EAU) 2020 guidelines, the case reported was a high risk UTUC and radical nephroureterectomy with bladder cuff is the standard treatment for those cases, regardless the tumor location.[13] In high risk cases, retroperitoneal lymphadenectomy improves the cancer specific survival and reduces the risk of local recurrence[14] even in clinically[15] and pathologically[16] node negative patients

Recently Birtle et al published the results of the peri-operative chemotherapy *vs.* surveillance in upper tract urothelial cancer (POUT) trial, a phase 3, randomized clinical trial comparing platinum-based peri-operative adjuvant chemotherapy *vs.* surveillance in high-risk UTUC patients. The results showed a statistically significant benefit in favor of chemotherapy, with a 55% decrease in the relative risk of disease recurrence or death (HR 0.45, 95% CI 0.30-0.68; log-rank p=0.0001). However, in the absence of evidence based treatment for with patients with NVUC alone.[4,17,18] radical surgery remains the treatment of choice.[19]

Seisen et al published an observational study of 3,253 patients diagnosed with UTUC, T3/T4 N0, or N+ staging who underwent radical nephroureterectomy, and subsequently studied the follow-up of patients who underwent adjuvant chemotherapy and those who were observed. They showed a greater overall survival for the AC group over the observation (47.41-months *vs.* 35.78-months; p>0.001)[20]

Controlled clinical trials evaluating the role of chemotherapy in UTUC with histological variants are needed.

To conclude, NVUC is a histologically unique tumor, which should not be confused with other tumours, due to its poor prognosis. Currently, the action protocol for this specific diagnosis is not standardized given its low incidence, but in principle, radical surgery would be indicated with patient, clinical, imaging and endoscopic follow-up.

CONSENT

The authors have received written informed consent from the patient.

FINANCIAL DISCLOSURE

There are no funding sources.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Observational Study

Is Supine Mini Percutaneous Nephrolithotomy better than Prone Mini Percutaneous Nephrolithotomy: A Single-Center Experience

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ABSTRACT

Objective
Miniaturized percutaneous nephrolithotomy (mini-PCNL) is the primary treatment modality in stone management. However, prone and supine positioning remains a matter of concern because of associated complications and morbidity. The present study aimed to compare success and complication rates of supine and prone position in patients undergoing mini-PCNL.

Material and Methods
A prospective observational study was conducted in patients (age >18-years) with renal calculi 1-3 cm in size who performed mini-PCNL between September 2017 and February 2019. The stone size was determined by computed tomography (CT) scan and kidney, ureter, and bladder X-ray. Post-operative parameters and complications were compared in both the groups. Statistical significance was defined as $p<0.05$.

Results
A total of 116 patients were enrolled (52 in the supine mini-PCNL group and 64 patients in the prone mini PCNL groups). The mean operative time was significantly lower (44.80 mins) in supine mini-PCNL compared to the prone mini-PCNL (53.93 mins) ($p<0.0074$). The mean hospital stays in supine and prone mini-PCNL group was 2.06 and 2.51-days, respectively ($p=0.01$). A complete stone clearance was observed in supine mini-PCNL group. The incidence of tubeless and totally tubeless procedure was significantly higher in supine mini-PCNL group (90% and 61%, respectively) ($p<0.0001$). No difference in terms of complications is reported between the supine and prone mini-PCNL group.

Conclusion
Supine mini-PCNL and prone mini-PCNL found to be comparable in terms of success rate and complications. However, supine mini-PCNL can be preferred due to its shorter operative time in the patients with renal stones.

Keywords
Percutaneous nephrolithotomy; Prone position; Supine position; Stone free rate.

INTRODUCTION

Since renal calculi was successfully removed by percutaneous nephrolithotomy (PCNL) reported in 1976, it became the standard treatment for large (>2 cm) renal stones.[1] On the other hand, the complications and morbidity associated with the PCNL remains matter of concern.[2,3] During puncture and dilatation of nephrostomy tract, the injury to renal parenchyma could be a major limiting factor of PCNL. It has been overcome by miniaturization of the renal access tract and nephroscope. The miniaturized (mini)-PCNL technique was initially developed for children, subsequently used in adults with a specially designed mini-nephroscope.

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Comparable success rate has been reported with mini-PCNL with standard prone lithotomy position in adults.[4] However, increased morbidity has been reported, mainly due to cardiac and respiratory hindrance.[5] Valdivia et al[6] introduced the supine position and subsequently many variations in the patient positions with advantages and disadvantages. Supine PCNL was reported to be promising initially in terms of complication rate; however, recent meta-analysis does not support these finding.[7-10] Intra-operative and post-operative outcomes, such as length of stay, duration of the operation and blood transfusion could be important to differentiate supine and prone positioning. A meta-analysis by Kumar et al[11] reported lower blood transfusions and less operative time in supine position. However, recently reported meta-analyses did not report difference between the operation time between supine and prone positions.[7-9] The advantages of supine are comfortable patient positioning, lesser radiation exposure of the surgeon, easy access to airways, possibility of simultaneous retrograde access, and low pressure in the renal pelvis.[12] In prone position, the hindrance to access the respiratory system by anesthesiologist could be a limiting factor.

Many studies have been published in the literature comparing efficacy and safety of prone and supine positions in the patients undergoing PCNL. But the comparison of supine and prone positioning in patients undergoing mini-PCNL is scanty. A study by Tokatl et al[13] compared the mini-PCNL performed in these two positions. No significant difference has been reported between these two approaches in terms of stone-free rates, complication rates and hospital stay. However, longer operative time has been reported in prone position.

The present study aimed to compare the success and complication rate of supine and prone mini-PCNL in patients with renal calculi 1-3 cm in size.

MATERIAL AND METHODS

This was a prospective observational study conducted at the Department of Urology, Apollo Main Hospitals, Chennai, India, from September 2017 to February 2019. The study protocol was approved by the Institutional Ethics Committee and study procedure was in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent.

Inclusion Criteria

All in-patients, more than 18-years of age with renal calculi of 1-3 cm in size, who underwent mini-PCNL during the study period were included in this study.

Exclusion Criteria

Patients with following conditions were excluded;

1. Complete staghorn calculus.
2. Altered anatomy limiting access to the kidney in the supine position (such as horseshoe kidney, pelvic kidney, retro renal colon, transplant kidney, etc.)
3. Medical comorbidities including coagulation abnormalities, cardiovascular and respiratory conditions which render patients unfit to withstand anesthesia.
4. Active urinary tract infection.
5. Pediatric patients.

After pre-operative assessment for surgical and anesthetic safety, patient underwent one of the two procedures, either supine or prone mini-PCNL as per the surgeon's and patient's preference. Bulls eye technique was used for all prone cases and free hand technique for supine cases. Sheath size used was between 14 Fr, 15.5 Fr, 16 Fr based on stone burden. The criteria for not putting double-J (DJ) stents/nephrostomy is mostly due to low intra-operative bleeding, no procedural complications which was purely surgeon's choice based on the above factors. Operating time was considered from the time of induction of patient till removal of Amplatzs heath after confirmation of stone clearance. Supine mini-PCNL was done by one individual surgeon and prone mini-PCNL was done by another individual surgeon. No multiple surgeons for individual approach.

Demographic details such as age, sex, body mass index (BMI), co-morbidities, date of submission, surgery, and discharge, stone characteristics (size, location and number) were recorded. Pre-operative investigations included evaluation of complete blood count, serum levels of creatinine, blood urea, and coagulation profile. The stone size of the patients was determined by computed tomography (CT) scan and kidney, ureter, and bladder (KUB) X-ray of the intravenous urography series. Intra-operative assessments including stone clearance, operation time, puncture techniques under fluoroscopic guidance, lithotripter and puncture site, complications, usage of nephrostomy, placement of DJ stent and post-operative evaluations including hospitalization time, complications, drop in hemoglobin, secondary procedures for residual fragments were performed in all the patients. Post-operative complications were assessed during the period of 60 days. In post-operative follow-up, patients were assessed for stone clearance by KUB X-ray and stents were removed if deployed.

Statistical Analysis

The sample size was calculated using the software G*Power 3.1.9.2 based on the parameters of Giusti G et al[14] The required sample size calculated was 35 patients in each group. All statistical analyses were performed using statistical package for the social sciences (SPSS) version 16.0. All the numerical variables were presented as mean (standard deviation (SD)) or median (interquartile range). All categorical variables were expressed as number (percentage). Categorical variables were compared with Chi-square (χ) test or Fischer's exact test. Continuous variables were compared with independent sample *t*-test (for normally distributed data) or Mann–Whitney *U* test (for skewed data). Statistical significance was defined as $p<0.05$.

RESULTS

A total of 116 patients were enrolled in this study. Out of these, 52

patients underwent supine mini-PCNL and 64 patients underwent prone mini-PCNL. The mean age of the patients in supine and prone mini-PCNL groups was 47.40 and 47.95-years, respectively (p=0.79). The male to female ratio in supine and prone mini-PCNL groups was 3.9:1 and 2.7:1, respectively. No significant difference was observed in mean BMI between supine (26.71 kg/m^2) and prone mini-PCNL groups (25.40 kg/m^2) (p=0.16). In supine and prone min-PCNL groups, respective mean hemoglobin was 13 gm% and 13.42 gm%, respectively. The mean blood urea levels in prone mini-PCNL group was slightly higher (26.19 mg/dL) compared to the supine mini-PCNL group (23.21 mg/dL). The mean serum levels of creatinine in prone mini-PCNL group was marginally higher (1.33 mg/dL) compared to the supine mini-PCNL group (1.02 mg/dL). In both the groups, no significant difference was observed in the biochemical parameters (hemoglobin, blood urea and serum creatinine). The mean stone size was comparable between supine and prone mini-PCNL groups (15.53 mm and 16.33 mm, respectively) (p=0.43). The respective mean number of stones in supine and prone mini-PCNL group was 1.43 and 1.32. The respective number of patients with left sided procedure in supine and prone mini-PCNL groups were 56% and 44%, while number of patients with right-sided procedure were 44% and 56% (Table 1).

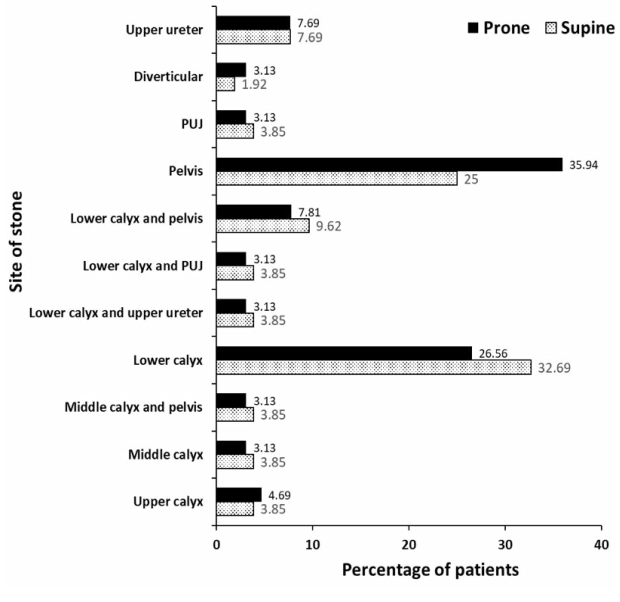
In supine mini-PCNL group the most common site of stone was at lower calyx (32%), followed by renal pelvis (25%), however, in prone mini-PCNL group the most common site of stone was renal pelvis (35%), followed by lower calyx (26%). Diverticular stones were presentin one patient (1.92%) of supine mini-PCNL group, and two patients (3.13%) of prone mini-PCNL

Table 1. *Demographic and Biochemical Parameters*

Parameters	Supine mini-PCNL (n=52)	Prone mini-PCNL (n=64)	p value
Age (years)	47.40 (10.28)	47.95 (12.03)	0.79
Sex, n (%)			
Male	38 (73)	51 (81)	0.16
Female	14 (27)	13 (19)	0.3
BMI (kg/m^2)	26.71 (5.19)	25.40 (4.57)	0.16
Hemoglobin (gm%)	13.00 (2.01)	13.42 (1.93)	0.27
Blood urea (mg/dL)	23.21 (7.37)	26.19 (9.88)	0.08
Serum creatinine (mg/dL)	1.02 (0.57)	1.33 (2.49)	0.39
Stone size (mm)	15.53 (5.67)	16.33 (6.00)	0.43
Number of stones	1.43 (0.73)	1.32 (0.62)	0.39
Laterality of Procedure, n (%)			
Right	23 (44)	36 (56)	0.2
Left	29 (56)	28 (44)	0.2

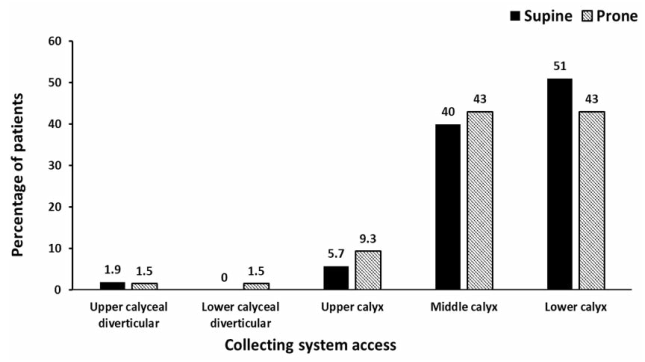
Data shown as mean (SD), unless otherwise specified.
BMI, body mass index; mini-PCNL, miniaturized percutaneous nephrolithotomy.

Figure 1. *Site of Stone*



group (Figure 1). The most commonly used site of access to reach the stone in supine and prone mini-PCNL groups was lower calyx (51% and 43%, respectively), and middle calyx (40% and 43%, respectively) (Figure 2).

Figure 2. *Collecting System Access*



The mean operative time and mean hospital stay was significantly lower in supine mini-PCNL compared to the prone mini-PCNL group (44.89 *vs.* 53.94 min, p=0.007 and 2.06 *vs.* 2.51 days, p=0.01, respectively). All patients in supine mini PCNL group had 100% stone clearance, however, one patient in prone mini-PCNL group had residual fragments. The number of patients having nephrostomy was significantly lower in supine mini-PCNL group (9%) as compared to prone mini-PCNL group (74%) (p<0.0001). The number of patients with DJ stent placement was significantly lower in supine mini-PCNL group (29%) as compared to prone mini-PCNL group (85%) (p<0.0001). The number of tubeless (no nephrostomy) and totally tubeless (no nephrostomy plus no DJ stent) procedures were significantly higher in supine mini-PCNL group (90% and 61%, respectively) as compared to prone mini-PCNL group (23% and 4%, respectively) (p<0.0001). The mean drop in haemoglobin was significantly lower in supine mini-PCNL group (1.30 gm/dL) compared to prone mini-PCNL group (1.62 gm/dL) (p=0.009). In both the groups, none of the patients reported collecting system injuries or visceral injuries. One patient in supine mini-PCNL had right lower lobe basal atelectasis and underwent 3 units packed red cell blood transfusion for haemoglobin drop from 9.3 gm/dL to 7 gm/dL in post-operative period.

In prone mini-PCNL group, one patient required blood transfusion for significant drop in haemoglobin from 12.3 gm/dL to 7.8 gm/dL. This patient had right renal subcapsular hematoma with multiple pseudoaneurysms as diagnosed by CT Renal angiography in post-operative period. The right renal artery super selective angioembolization was performed to control the post mini-PCNL bleeding. Another patient from prone mini-PCNL group reported residual fragments for which extracorporeal shock wave lithotripsy (ESWL) was performed post-operatively for complete stone clearance (Table 2). Right lower lobe basal atelectasis reported in two patients, one patient each in both the prone and supine mini-PCNL groups.

DISCUSSION

Urolithiasis especially renal calculi are major risk factor associated with increased prevalence worldwide. Mainly, surgical procedure with high stone free rate, minimal risk of hemorrhage and decrease operative time should be considered as a standard treatment for renal calculi. PCNL has an excellent stone clearance rate which is an advantage over the previous minimal invasive procedure. Recently, to decrease renal parenchymal trauma conventional PCNL is shifted to a mini-PCNL with smaller tract size (11-20 Fr). An important topic to address is whether miniaturization affects the outcomes of the procedure comparing between prone and supine positions. The data in the literature concerning this subject are very limited. There are only two studies reporting the comparison between supine and prone mini-PCNL.[13,15]

The present prospective study comparatively assessed the outcome of supine and prone mini-PCNL. In this study the mini-PCNL was preferred over retrograde intrarenal stone surgery

Table 2. *Post-Operative Parameters*

Parameters	Supine mini-PCNL (n=52)	Prone mini-PCNL (n=64)	*p* value
Operative time (min), mean (SD)	44.89 (10.48)	53.94 (22.21)	0.007
Hospital stay in days, mean (SD)	2.06 (0.42)	2.51 (1.23)	0.01
Stone clearance	52 (100)	63 (98)	0.3
Nephrostomy	5 (9)	49 (74)	<0.0001
DJ stenting	15 (29)	55 (85)	<0.0001
Tubeless (no nephrostomy)	47 (90)	15 (23)	<0.0001
Totally tubeless (no nephrostomy+no stent)	32 (61)	3 (4)	<0.0001
Drop in hemoglobin (gm/dL), mean (SD)	1.30 (0.7)	1.62 (0.6)	0.009
Complication			
Bleeding mandating transfusion	1 (1.92)	1 (1.56)	-
Residual fragments	0	1 (1.56)	-

Data shown as n (%), unless otherwise specified.
double J (DJ); miniaturized percutaneous nephrolithotomy (mini-PCNL).

(RIRS) to achieve complete stone clearance, as at the present study site several RIRS are preformed, sometimes unavailability of flexible ureteroscopy for kidney stones (URS) due to repairs. Hence, in the present study only mini-PCNL in both positions were evaluated. Both the procedures were comparable in terms of complications. However, operation time and hospital stay in the supine mini-PCNL were significantly shorter compared to prone mini-PCNL. Though, the reason for shorter hospital stay is not very clear most of the supine cases have no nephrostomy, so that could be one of the possible reasons for being pain free early recovery. The mean age and gender wise distribution of patients in both the groups was comparable and majority of patients were men. This is in accordance with the previous studies which also showed men prevalence in these patients.[13,16]

In the present study, the mean operative time in the supine mini-PCNL group was significantly shorter compared to prone mini-PCNL group. The reduced operation time in the supine mini-PCNL was due to lack of repositioning of supine lithotomy position to prone one which saves the time with less complexity and minimal operation theatre personnel. Even though the mean operation time was significantly shorter in the supine PCNL group than prone PCNL group in the previous studies, the hospital stay did not differ between these two groups.[7-9,13,15,16] In contrast, the present study reported significantly shorter hospital stay in the supine mini-PCNL group. However, a meta-analysis including 20 studies reported similar operation time and hospital stay between both the groups.[10]

In this study, prone and supine mini-PCNL have similar stone clearance rate which is consistent with previous studies.[9,13,17] In contrast, a meta-analysis based on 9 studies involving 4956 patients with prone PCNL and 1457 patients with supine PCNL, showed significantly higher stone free rate in the prone position than supine position.[8] Higher stone free rate in prone position maybe due to the effects of gravity on the irrigating fluid, and an unrestricted range of movement for the nephroscope, the prone position are easier access to the renal upper pole calices, a more distended collecting system for better vision, therefore, better clearance of stones.[18,19]

A retrospective study of 180 patients treated with mini-PCNL either in supine or prone position using nephrostomy tube reported similar success rate with shorter operative time and is only benefit of supine position over prone position. Similar results were obtained in a randomized study of patients with upper urinary tract calculi using prone and supine minimally invasive PCNL. A nephrostomy tube was placed in all the patients with post-operative internal stent.[13] Nephrostomy tube placement and DJ stent placement after mini-PCNL depends upon many factors like intra-operative bleeding, size of the stones and more of surgeons' preference. A study done by Gupta et al. reported ultra-mini PCNL in supine position with a complete tubeless approach for renal stone disease is a safe method for treating low-volume disease.20 The smaller access tract helps to make mini-PCNL tubeless or totally tubeless. In the present study, 47 and 15 procedures were tubeless and 32 and 3 procedures were totally tubeless in the supine mini-PCNL and prone mini-PCNL group, respectively. In both supine and prone mini-PCNL groups most of the patients who does not have nephrostomy or DJ stent, were retained with retrograde catheter (5 Fr open ended ureteric catheter) which was drained into Foleys catheter during their post-operative period.

Regarding the complications, only one patient from each group had required blood transfusion and one patient in the prone mini-PCNL group reported residual fragments. Meta-analysis of nine studies demonstrated lower blood transfusions in the supine position than in the prone position.[7] Whereas, randomized study of 109 patients with upper urinary calculi reported no requirement of transfusion in either groups. A meta-analysis was done to assess the best position for the management of kidney stones; reported patients in the supine PCNL group received less transfusion and had less fever rates.[10] Another recent meta-analysis of 15 randomized controlled trials involving 1474 patients revealed comparable results in overall complications rate and blood transfusion between supine PCNL group and prone PCNL group.[9] A case series of 14 patients who underwent ultra-mini PCNL in the supine position demonstrated only one patient had residual fragments and needed subsequent extracorporeal shock wave lithotripsy.[20]

The present study has few limitations. It is a non-randomized observational study with relatively small sample size. The supine mini-PCNL has been performed by a single surgeon. However, prone mini-PCNL has been performed by different surgeons. This might have attributed to the variation observed in operation time for each patient. This study did not report the need of analgesic requirement and morbidity associated with DJ stent placement.

CONCLUSION

In the treatment of renal calculi of 1-3 cm in size, supine mini-PCNL can be an alternative option for prone mini-PCNL as stone clearance rate and complications were similar in both the groups. However, significantly shorter operative time and hospital stay were benefits of the supine mini-PCNL technique.

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None.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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