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| protocol  |
| A randomised controlled trial comparing mini-PCNL with flexible ureteropyeloscopy for urinary tract calculi  |
| Protocol Number (Mandatory field)?:Version: #1Date: 28/03/2018 |
|  |
| **Author/s:**Niall Davis, Damien Bolton, Greg Jack**Sponsor/s:**None |

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| **CONFIDENTIAL**This document is confidential and the property of The Austin Hospital. No part of it may be transmitted, reproduced, published, or used without prior written authorization from the institution.**Statement of Compliance**This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95). |

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| **STUDY SYNOPSIS**  |  |

|  |  |
| --- | --- |
| Title: | A randomised controlled trial comparing mini-PCNL with pyeloscopy for urinary tract calculi |
| Short Title: | Mini-PCNL versus pyeloscopy for urinary tract calculi |
| Design: | Randomised controlled trial |
| Study Centres: | 1 |
| Hospital: | The Austin and Repatriation Hospital, Heidelberg 3084, Melbourne, Victoria |
| Study Question: | Is one treatment modality associated with a greater post-operative stone free-rate and complication rate compared to the other modality? |
| Study Objectives: | This study aims to comparatively evaluate clinical outcomes of mini-PCNL and pyeloscopy for treating urinary tract calculi in a single session. Both surgical techniques are recognised as established treatment modalities for proximal ureteral and intra-renal calculi by the European Association of Urology (EAU) and American Urological Association (AUA) guidelines. The objective of this randomised controlled trial will be to comparatively evaluate both techniques for treating urolithiasis. Secondary outcome measurements will be to compare operative duration, and inpatient stay for both techniques. |
| Primary Objectives: | To compare stone-free rates (SFRs) and complication rates for both techniques |
| Secondary Objectives | To compare operative duration and inpatient stay with both techniques |
| Inclusion Criteria: | Any renal stone (single or multiple) or proximal ureteral stone ranging from 0.5cm-3 cm in diameter. |
| Exclusion Criteria:  | Patients undergoing any other surgical procedure during same admission, pregnancy, patients <18 years of age, renal malformation, uncorrected coagulopathy.  |
| Number of Planned Subjects: | At least 70 patients in total, with 35 patients randomised to each arm in a 1:1 ratio |
| Investigational product: | Not applicable |
| Safety considerations: | Not applicable. Both surgical techniques are established and routinely performed in The Austin Hospital for treating urinary tract calculi |
| Statistical Methods: | In a preliminary analysis of our stone database, the response within each treatment group was normally distributed, and the standard deviation was 9. The true difference of surgical success rate was 6.5%. Type I error probability was 0.05 associated with the test of this null hypothesis. Therefore, we need to study 31 subjects in each group to be able to reject the null hypothesis that the surgical success rates of mini-PCNL and pyelsocopy groups are equal with a probability of 0.8. The follow-up rate of patients is estimated at 10%. Finally, the sample size is 35 cases in each group. |
| Subgroups: | None |

## **Glossary of Abbreviations & Terms**

|  |  |
| --- | --- |
| **Abbreviation** | **Description (using lay language)** |
| Mini-PCNL | Micro-invasive percutaneous nephrolithotomy |
| PCNL | Percutaneous nephrolithotomy |
| FURS | Flexible ureteropyelsocopy |

## **Study Sites**

### Study Location/s

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Site** | **Address** | **Contact Person** | **Phone** | **Email** |
| The Austin Hospital & Heidelberg Repatriation Hospital | 145 Studley Road, Heidelberg 3084, Melbourne, Victoria | Niall Davis and Greg Jack | 0432038324 | Nialldavis2001@yahoo.comGregory.jack@austin.org.au |

## **Introduction/Background Information**

### Lay Summary

Mini-PCNL and flexible ureteropyeloscopy are commonly used modalities for treating ureteral and renal stones. Both treatment options are invasive and are associated with complications. There are only a few studies that compare these two treatment modalities. Both modalities are associated with reasonable postoperative stone free rates with minimal complications. Immediate stone free rate is higher with mini-PCNL but comparable in both modalities at 1 month. Pyeloscopy is associated with favourable pain scores and lower haemoglobin drop. We aim to compare both techniques to definitively investigate whether one modality is superior than the other.

### Introduction

The management of nephrolithiasis is evolving rapidly, and a variety of urological technologies are currently available for treating patients with symptomatic stone disease. According to EAU and AUA guidelines, the available treatment options for renal and proximal ureteric calculi are extracorporeal shockwave lithotripsy (ESWL), flexible ureteropyeloscopy (FURS), miniaturised percutaneous nephrolithotomy (mini-PCNL), and conventional percutaneous nephrolithotomy (PCNL) [1, 2]. Percutaneous nephrolithotomy (PCNL) was initially introduced in 1976 and remains the recommended treatment option for removing large renal calculi due its high rate of stone clearance [3]. Morbidities associated with PCNL are bleeding, transfusion, pain, and urine leakage [4, 5]. Mini-PCNL involves a miniaturised nephroscope and offers a nephrostomy tract size < 20Fr [6]. It was initially introduced to decrease complications associated with tract size during conventional PCNL while providing comparable stone-free rates (SFR) [7]. One early meta-analysis of mini-PCNL and conventional PCNL demonstrated that mini PCNL had a greater safety profile with similar SFRs [8]. Similarly, significant improvements in endoscopic technologies such as advancements in fibre optics, ureteroscopedesign, and laser therapies have led to increasing use of FURS for primary treatment of intra-renal and proximal ureteric calculi [9]. The advantages of FURS in this setting are preservation of renal parenchyma and less bleeding; however, FURS may be less effective for clearing larger calculi [9]. Therefore, selecting the optimal modality for treating renal calculi is challenging, as both techniques may be associated with different patient benefits and risk profiles. Despite the evolution of mini-PCNL and FURS techniques into clinical practice, there is a lack of comparative clinical data assessing SFRs and complication rates. The aim of this randomised controlled trial is to comparatively evaluate the outcomes of mini-PCNL and FURS for treating urinary tract calculi in a single session.

### Background information

We have published a systematic review and meta-analysis as part of the background information and research to this randomized controlled trial and have attached it to our application:

[World J Urol.](https://www.ncbi.nlm.nih.gov/pubmed/29450733) 2018 Feb 16. doi: 10.1007/s00345-018-2230-x.

# Miniaturised percutaneous nephrolithotomy versus flexible ureteropyeloscopy: a systematic review and meta-analysis comparing clinical efficacy and safety profile.

[Davis NF](https://www.ncbi.nlm.nih.gov/pubmed/?term=Davis%20NF%5BAuthor%5D&cauthor=true&cauthor_uid=29450733)1, [Quinlan MR](https://www.ncbi.nlm.nih.gov/pubmed/?term=Quinlan%20MR%5BAuthor%5D&cauthor=true&cauthor_uid=29450733)2, [Poyet C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Poyet%20C%5BAuthor%5D&cauthor=true&cauthor_uid=29450733)2, [Lawrentschuk N](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lawrentschuk%20N%5BAuthor%5D&cauthor=true&cauthor_uid=29450733)2, [Bolton DM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bolton%20DM%5BAuthor%5D&cauthor=true&cauthor_uid=29450733)2, [Webb D](https://www.ncbi.nlm.nih.gov/pubmed/?term=Webb%20D%5BAuthor%5D&cauthor=true&cauthor_uid=29450733)2, [Jack GS](https://www.ncbi.nlm.nih.gov/pubmed/?term=Jack%20GS%5BAuthor%5D&cauthor=true&cauthor_uid=29450733)2.

Our systematic review and meta-analysis provides a detailed and accurate comparative analysis on mini-PCNL and FURS. We found that modifications and advancements in equipment design will continue to improve the performance of both techniques. The continuing evolution of both urological technologies, should facilitate high levels clinical efficacy while maintaining high safety profiles. We also found that ongoing randomised controlled trials are necessary to accurately evaluate outcome variables for both techniques as only 3 randomised controlled trials have been published on the topic to date.

## **Study Objectives**

### Hypothesis

Few prospective randomised controlled trials have compared mini-PCNL and flexible ureteropyeloscopy for treating renal and proximal ureteral stones.Furthermore, no specific guideline is available regarding the optimal surgical management of renal stones and proximal ureteral stones. We hypothesise that one modality is associated with a greater stone free rate and lower complication rate compared to the other modality for managing nephrolithiasis

### Study Aims:

To compare stone free rate and surgical parameters between flexible ureteropyeloscopy mini-PCNL and RIRS in the management of renal stones and proximal ureteral stones >5 mm in a single session.

### Outcome Measures

The primary end-point in this study is stone free rate (SFR) in a single session. Before a 3-month follow-up visit, all patients will undergo a low-dose non-contrast CT scan to assess for the presence of residual stone. Stone free status is defined as no residual stones or stones within 3 months postoperatively. The secondary outcomes are intraoperative and postoperative parameters such as operation time, estimated blood loss, hemoglobin drop, analgesic requirement, hospital stay, and complications. Complications will be evaluated according to the Clavien classification of surgical complications.

### **Study Type & Design & Schedule**

Eligible patients with proximal ureteral or intra-renal stones >0.5 cm in size referred to our institute will be considered for this study. The proximal ureter is defined as the portion extending from the ureteropelvic junction to the lower border of the fourth lumbar vertebra. Patients will be preoperatively evaluated with a history, physical examination, and image system (including non-contrast CT of the kidneys, ureters and bladder), The size and location of all stones will be evaluated via non-contrast). The mean Hounsfield unit will be evaluated using an ellipsoid region of interest with axial images of computed tomography.

Preoperative laboratory evaluation will include urinalysis, urine culture, coagulation profile, serum creatinine level, estimated glomerular filtration rate (eGFR) and complete blood count. Patients with a known urinary tract infection will receive specific antimicrobic culture before flexible ureteropyeloscopy or mini-PCNL until the urine culture turned is negative.

 **STUDY TABLE**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Assessment/Procedure** | **Screening in outpatients** | **Day 1 post-op** | **Day of discharge post-op** | **Follow-up (3 months)** |
| **Informed Consent** | **x** |  |  |  |
| **Demographic Information** | **x** |  |  |  |
| **Weight Measurement** | **x** |  |  |  |
| **Non-contrast CT** | **x** |  |  | **x (within 3/12)** |
| **Pain score** |  | **x** | **x** | **x** |
| **Urine collection** | **x** | **x** |  |  |
| **Blood Collection** | **x** | **x** | **x** |  |
| **Vital signs measurement** | **x** | **x** | **x** |  |

### Randomisation

The closed envelope method will be used to randomise the enrolled patients to mini-PCNL or flexible ureteropyeloscopy. Informed consent will be obtained before surgery in the outpatients department.

Study methodology

Patients will be preoperatively evaluated with a history, physical examination, and image system (including non-contrast CT of the kidneys, ureters and bladder), The size and location of all stones will be evaluated via non-contrast). The mean Hounsfield unit will be evaluated using an ellipsoid region of interest with axial images of computed tomography.

Preoperative laboratory evaluation will include urinalysis, urine culture, coagulation profile, serum creatinine level, estimated glomerular filtration rate (eGFR) and complete blood count. Patients with a known urinary tract infection will receive specific antimicrobic culture before flexible ureteropyeloscopy or mini-PCNL until the urine culture turned is negative.

All patients will be asked about the pain severity by visual analogue score (VAS; range: 1-10) 1 hour postoperatively and on the morning of the first operative day. Postoperative usage of analgesics used on an as-needed basis will be recorded. On the first operative day, patients will be checked regarding complete blood count, renal function, and kidney, ureter, and bladder X-ray. In the absence of complications, patients will be discharged 1 day after surgery.

Parameters included in our analysis will be patient demographics (mean age, gender and body mass index), perioperative data (mean stone location and size, operative time, fluoroscopy time, blood transfusion rate, hospital stay, re-treatment rate, auxiliary procedure rate, 3-month SFR on non-contrast CT and stone chemical composition) and complications if any.

## **6.0 Study Population**

### Recruitment Procedure

Eligible patients are consecutive patients who presented to the urology outpatient department with a proximal ureteric and/ or ≥1 intrarenal calculus >0.5cm requiring intervention due to symptoms such as pain or recurrent urinary tract infections., and in whom flexible ureteropyeloscopy or mini-PCNL is planned.

### Inclusion Criteria

Eligible patients are patients with proximal ureteral or intra-renal stones >0.5 cm in size referred to our institute will be considered for this study. The proximal ureter is defined as the portion extending from the ureteropelvic junction to the lower border of the fourth lumbar vertebra.

### Exclusion Criteria

Patients with urogenital anomaly, solitary kidney, age <18 years, or coagulopathy will be excluded.

### Consent

Written informed consent will be obtained from each patient who agrees to participate, by a member of the urology team. The process of obtaining informed consent will be conducted in compliance with the principals of good clinical practice and requirements of the approving research ethics committee and other regulatory requirements as appropriate. Consent to enter the study will be sought from each subject only after a full explanation has been given and time allowed for consideration. Three copies of the consent form will be signed, one each for the patient, the patient’s hospital records and the study records.

# **Participant Safety and Withdrawal**

### Risk Management and Safety

Both procedures are established modalities for treating urinary tract calculi. Risk management and safety will be managed according to the hospital’s established perioperative management protocols for both surgical techniques. Therefore, there will be no additional risks to patients consenting to the randomization process.

### Handling of Withdrawals

Participants are free to withdraw from the study at their discretion. All collected data on withdrawn patients will be maintained electronically for 7 years in The Austin Hospital.

### Replacements

Patients that withdraw will be replaced with consecutive patients referred to the outpatients’ department with urolithiasis that meet inclusion criteria. Replacements will continue until our sample size of 70 is reached.

# **Statistical Methods**

### Sample Size Estimation & Power Calculations

In a preliminary analysis of our stone database, the response within each treatment group was normally distributed, and the standard deviation was 9. The true difference of surgical success rate was 6.5%. Type I error probability was 0.05 associated with the test of this null hypothesis. Therefore, we need to study 31 subjects in each group to be able to reject the null hypothesis that the surgical success rates of mini-PCNL and pyelsocopy groups are equal with a probability of 0.8. The follow-up rate of patients is estimated at 10%. Finally, the sample size is 35 cases in each group.

### Statistical Methods To Be Undertaken

Excel and SPSS, version 12.0 will be used to record study parameters. G\*Power 3.1 (http://www.gpower.hhu.de/en.html) was used to calculate study power. Continuous data, shown as the mean ± standard deviation will be analysed by 1-way ANOVA and the Student’s t-test. Categorical data, shown as the number or percent, will be analysed by the chi-square or Fisher exact test. Statistical significance is considered at p <0.05.

# **Data Security & Handling**

### Details of where records will be kept & How long will they be stored

Data on all patients agreeable to the study will password protected for 7 years. Consent forms, patient data and standard feedback & follow-up forms will be placed in a sealed container along with the device after the procedure and handled only by the lead and co-investigators. Collected electronic data will be password protected and the responsibility of the lead investigator. All electronic data will remain in the grounds of The Austin Hospital

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