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Review Article

Is retrograde intrarenal surgery a safer and more efficient alternative treatment to percutaneous nephrolithotomy in terms of higher stone-free rates and shorter hospital stay among adults with kidney stones 20 mm or greater?

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ABSTRACT

This review aims to evaluate whether retrograde intrarenal surgery (RIRS) is a safe and efficient alternative treatment to percutaneous nephrolithotomy (PCNL) for stones 20 mm or greater in terms of stone-free rate (SFR) and shorter hospital stay due to lower complications. Research conducted in the years 2007–2017 was considered relevant. Numerous search engines were used to acquire the eight papers included in this meta-analysis. From the eight key papers that were considered, one was a meta-analysis, one was a prospective clinical controlled trial (CCT), and the other six were retrospective CCTs. All studies found higher SFRs in PCNL but the difference was statistically significant in only two of the included studies. This improvement was not reported in any of the studies, including the meta-analysis. As a result, this reflects an inconsistency in the evidence produced. When evaluating hospital stay, all researchers found a statistically significantly shorter stay in the RIRS group compared to the PCNL group, this being potentially attributed to higher rates in minor complications. Due to the inconsistencies evaluated from the key papers, it was concluded that study results ought to be interpreted with caution. RIRS seems to be a safe and effective surgical procedure for selected patients as RIRS offers a comparable initial SFR success as PCNL. This is a cautious statement, drawn in view of inconsistent evidence regarding its superiority over PCNL in this regard. Furthermore, consistent evidence is available, demonstrating its ability to significantly reduce hospital stay without increasing complications. Therefore, RIRS may be considered an alternative to PCNL in selected patients. With that being said, more research is required on this evaluation given that a definite conclusion cannot be reached.

Keywords: Retrograde intrarenal surgery, Holmium laser lithotripsy, Percutaneous nephrolithotomy, Percutaneous nephrolithotripsy, Renal stone

INTRODUCTION

The main aim of this review was to evaluate whether retrograde intrarenal surgery (RIRS) is a safe and efficient alternative treatment to percutaneous nephrolithotomy (PCNL) for stones that are measured at 20 mm or greater, to achieve a favorable stone-free rate (SFR) (which is the main goal of urinary tract stone treatment) and a shorter hospital stay (which indicates a lower rate of complications).

The European Association of Urology guidelines recommend the minimally invasive procedure; PCNL is a first-line surgical treatment for stones that measure at 20 mm or larger. Yet, PCNL is associated with various postoperative complications. This has great implications toward using

RIRS as an alternative to PCNL to reduce post-operative complications.

MATERIAL AND METHODS

Evidence acquisition

Search strategy

Relevant trials were obtained from the following sources: PubMed, Cochrane Library, Academic search complete, Cumulative Index of Nursing and Allied Health Literature Plus with full text, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, E-Journals, American Doctoral Dissertations, eBook Collection (EBSCOhost), MEDLINE Complete, and Google Scholar while hand searching of relevant congress abstracts. The retrieval time involved studies between the years 2007 and 2017.

The following keywords related to kidney stones were used: "Kidney stone," "Kidney calculus," "Nephrolith," "Renal calculus," "Renal stone," "Adult," "Grown-up," "subject," "RIRS," "Flexible ureteroscopy," "Holmium Laser Lithotripsy," "Flexible ureterorenoscopy," "Ureteroscopic treatment," "PCNL," "Percutaneous nephrostomy," "Percutaneous nephropyelostomy," "Percutaneous treatment," "shorter hospital stay," "higher SFRs," and "faster hospital discharge."

Inclusion and exclusion criteria

The selected studies were included based on the following set of inclusion criteria: (1) Publications had to be written in English as this was the language, the authors are most confident with; (2) publications had to be peer-reviewed; (3) humans were considered as the species the population studied, yet both male and female patients were taken into consideration, omitting any limitations the gender difference may pose to the study; (4) reports of at least one of the following outcomes: SFRs, mean operation time, complication rates, and mean hospital stay; (5) renal stones >2 cm in diameter; (6) include patients that were 18 years of age or older (since according to the WHO [2017]), adulthood starts from 18 years of age; (7) compare "RIRS with PCNL" as two independent interventions; (8) include all varieties of PCNL, including mini-PCNL or ultra-mini PCNL; and (9) not take into consideration stone position as long as nephrolithiasis is being studied.

Data extraction

The investigator independently screened the documents according to the inclusion and exclusion criteria. Both quality and content were appraised. The following data from each study: First author, year of publication, baseline patient characteristics, intervention, and outcome measures were extracted. The "assessing risk of bias" table recommended in the Cochrane Handbook 5.2 to assess the risk of bias of the RCT articles was included in the study. For clinical controlled trial (CCT) articles, the quality assessment The PRISMA 2009 Checklist was used for this study. The studies included in this meta-analysis are listed in [Table 1].

Data analysis

Effect size and statistical analysis methods were chosen according to the type of data and the purpose of the assessment. For continuous variables (mean operation and hospital stay), if results had the same units of measurement, the weighted mean difference was used, otherwise, the standardized mean difference was used. For categorical variables (SFR and complication rate), statistical analysis was carried out using relative risk (RR) and 95% confidence interval (CI). Heterogeneity among the studies was assessed using χ^2 statistics ($P = 0.10$), fixed effect models were calculated for homogeneous data, and random-effects analysis was performed for heterogeneous data. The population ratio of each study was expressed using forest plots.

RESULTS

How the results were presented

In the eight key studies chosen; all researchers used *P*-values to establish accuracy of results whereby $P < 0.05$ implies strong evidence against the null hypothesis. A large $P > 0.05$ implies weak evidence against the null hypothesis, resulting in no significant differences between the intervention and control groups.[1] As all key studies had relatively small sample sizes, the probability of detecting small differences between the PCNL group and the RIRS group was decreased. The margin of error in all studies was set at 95% CI. The CI provides a range of values that are likely to be found in the population of interest.[1] Only Zheng *et al*. in the meta-analysis presented RR.[2] A forest plot [Figure 1] was included to indicate the size of studies used. The CCTs reported measured SFR and duration of hospital stay and *P*-values.

Discussion of findings related to initial SFR outcomes

In all the studies, researchers opted to present data of the SFR by providing the initial and final SFR values. Initial SFR values represent the success of SFR after one single procedure of either PCNL or RIRS, depending on the group. In the final SFR, values represent the success of SFR after a single procedure of PCNL or RIRS, as well as other additional procedures such as extracorporeal shock wave lithotripsy.

Table 1: Name of studies and designs included in this meta-analysis.

Name of study	Authors of study	Date	Study design
RIRS versus mPCNL for a single renal stone of 2–3 cm: Clinical outcome and cost-effective analysis in Chinese medical setting	Pan *et al.*	2013	RCT
A randomized controlled study to analyze the safety and efficacy of percutaneous nephrolithotripsy and retrograde intrarenal surgery in the management of renal stones more than 2 cm in diameter	Bryniarski *et al.*	2012	RCT
Percutaneous nephrostolithotomy versus flexible ureteroscopy/holmium laser lithotripsy: Cost and outcome analysis	Hyams and Shah	2009	CCT
Comparison of percutaneous nephrolithotomy and retrograde flexible nephrolithotripsy for the management of 2–4 cm stones: A matched-pair analysis	Akman *et al.*	2012	CCT
Management of renal calculi: Retrograde ureteroscopic holmium laser versus percutaneous nephrolithotripsy	Yang *et al.*	2013	CCT
Comparative efficacy analysis of flexible ureteroscopic lithotripsy and percutaneous nephrolithotomy for the treatment of renal calyceal stones	Zhu *et al.*	2013	CCT
Comparative efficacy analysis of percutaneous nephrolithotomy and flexible ureteroscopic lithotripsy for the treatment of kidney stones	Xiao *et al.*	2013	CCT
Comparison of percutaneous nephrolithotomy and flexible ureteroscope for the management of 2–4 cm renal stones	Cao *et al.*	2013	CCT

RIRS: Retrograde intrarenal surgery, CCT: Clinical controlled trial, mPCNL: Minimally invasive percutaneous nephrolithotomy, RCT: Randomized controlled trial

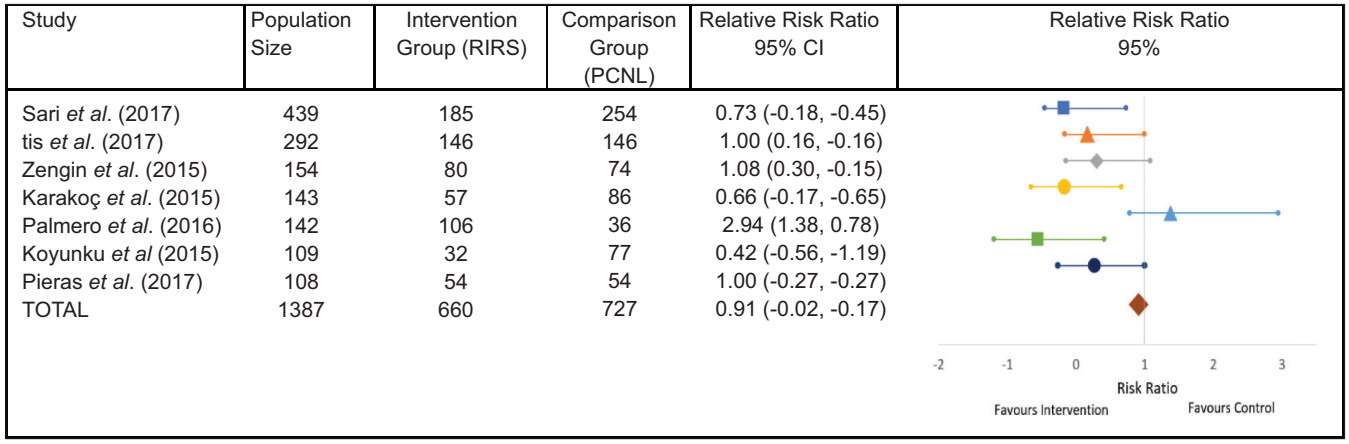

Figure 1: Forest plot sho wing population size in the included studies. RIRS: Retrograde intrarenal surgery, PCNL: Percutaneous nephrolithotomy.

In the meta-analysis, Zheng *et al.* pooled the results of SFR obtained in the included studies, in the form of a forest plot.[2] Pooling all of the results obtained a RR of 0.95 (at 95% CI, 0.88–1.02) and $P = 0.15$. Therefore, this indicated that there was no statistically significant difference in SFR values between the PCNL and the RIRS group. This is because the *P*-value obtained was more than 0.05 and the range of values in the CI included the value of one. The occurrence in the CI indicates statistically insignificant results. All the individual studies included in the meta-analysis except for the one conducted by Pan *et al.* failed to identify a significant difference in SFR between groups. One factor which may have contributed to this result is the fact that the authors of the meta-analysis used a random effect model to make up for the heterogeneity in the results obtained from the included studies. The use of these models is known to produce

conservative results.[1]

From the seven acquired CCTs below, when comparing the efficacy of both treatments, it was found that following a single procedure, SFR was higher with PCNL than RIRS. This difference reached statistically significant levels in the studies conducted by Sari *et al*. and Atis *et al*. who obtained $P = 0.001$ and 0.040, respectively.[3,4] The latter denoted a marginally significant difference. On the other hand, the studies conducted by Koyunku *et al*., Palmero *et al*., Zengin *et al*., and Pieras *et al*. did not find the difference as being statistically significant, reaching $P = 0.26$, 0.402, 0.061, and 0.1, respectively.[5-8] As a result, all of these *P*-values are higher than 0.05.

In non-randomized CCT, Karakoç *et al*. do not report SFR results but report the number of patients with residual stones.[9] The fewer stone fragments reported, the more successful the intervention is. Karakoç *et al*. reported only statistically significant results on residual stones between the two groups due to $P \leq 0.001$.[9] All researchers in their studies have reported that two of the limitations in their study are the enrollment of small sample size and being single-center trials. In the study conducted by Pieras *et al*., even though a power calculation was utilized to calculate the minimum sample size required as well as having more participants than the required sample size, the SFR results were still insignificant and the sample size was still small ($n = 108$).[8] The presence of significant results in Sari *et al*. and Atis *et al*. can be deduced from the presence of recruiting the largest sample sizes of 439 patients and 292 patients, respectively, when compared to other studies.[3,4]

As shown in [Table 2], each researcher of the CCTs measured SFR differently. Only Atis *et al*. defined SFR as the complete absence of residual fragments.[4] The other researchers also considered the presence of clinically insignificant residual fragments as SFR. Palmero *et al*. included fragments <4 mm while Sari *et al*. included fragments <3 mm.[3,6]

On the other hand, Koyunku *et al*. considered fragments 2 mm or less while Zengin *et al*. considered fragments <2 mm.[5,7] Karakoç *et al*. and Pieras *et al*. did not define SFR.[8,9] Hence, one cannot correlate results for generalizability as SFR was measured differently from study to study.

Discussion of findings related to a hospital stay

In the meta-analysis, similar to what they did for SFR, Zheng *et al*. pooled the results of hospital stay in the form of forest plots.[2] Yet instead of RR, a mean difference was calculated for a hospital stay. A mean difference of −2.10 days with $P < 0.0001$ at 95% CI (−3.08−−1.11 days) was reported by the researchers on the pooling of results. This indicates a statistically significant difference between the two groups whereby hospital stay was less in RIRS than in PCNL. The mean difference is denoted with a minus sign because it is <0, hence, favoring RIRS. Post-operative complications are directly proportional to increased hospitalization regardless of age.[10] Zeng *et al*. also reported a statistical difference in bleeding rate, intraoperatively and postoperatively, whereby the PCNL group had a bleeding rate of 6.87% while that of RIRS was 0.5% with $P = 0.01$. This statistical difference in bleeding rate may have contributed to the statistically significant difference in-hospital stay.

In the CCTs which adopted a non-randomized approach as illustrated in [Table 3], CCTs reported a shorter hospital stay in the RIRS group than in the PCNL group. CCTs conducted by most authors found that hospital stay was significantly reduced following RIRS. It was only Palmero *et al*. who did not achieve statistically significant differences in their results.[6] It is important to note that *P*-values were very low, showing that the significant levels were not simply marginal and, as such, the strength of the evidence is high. Complications are directly proportional to increased hospitalization regardless of age.[10] All researchers in the articles reported postoperative complications in both PCNL and RIRS groups using the Clavien-Dindo classification system. As illustrated in [Table 3], none of the studies reported major complications in patients who underwent RIRS or PCNL. Only Sari *et al*. reported the death of one patient in the PCNL group following cardiac arrest (Clavien Grade V).[3] Yet it was not reported whether PCNL was the cause of the cardiac arrest.

Table 2: Summary of the results of the initial SFR reported in CCTs.

Author of articles	Initial SFR of PCNL (%)	Initial SFR of RIRS (%)	*P*-values obtained for differences between groups
Koyunku *et al.* (2015)	96.1	90.6	0.26
Karakoç *et al.* (2015)	91.8	66.6	Not reported
Atis *et al.* (2017)	91.7	74	0.040
Palmero *et al.* (2016)	80.6	73.6	0.402
Zengin *et al.* (2015)	95.5	80.6	0.061
Sari *et al.* (2017)	93.3	73.5	0.001
Pieras *et al.* (2017)	87	76	0.1

RIRS: Retrograde intrarenal surgery, CCT: Clinical controlled trial, PCNL: Percutaneous nephrolithotomy, SFR: Stone-free rate

Table 3: Summary of the results of complications reported in CCTs.

Author of articles	Complications of PCNL	Complications of RIRS	*P*-values obtained for differences between groups
Koyunku *et al.* (2015)	Minor complications: 6.4% transfusion rate: 5.1%	Minor complications: 9.3% Transfusion rate: 0%	Minor complication rates: *P*=0.51 Hemorrhage: *P*<0.01
Karakoç *et al.* (2015)	The researchers report that from a cohort of 86 patients, fever was reported in nine patients while blood transfusion and stone street* were reported in two patients A fall in post-operative fall in hemoglobin (g/dL) of 2.39±1.77 was also reported	The researchers report that from a cohort of 57 patients, the only stone street in two patients was reported. A fall in post-operative fall in hemoglobin (g/dL) of 2.39±1.77 0.48±0.50 was also reported	Fever: *P*=0.12 Blood transfusion: *P*=0.24 Stone street: *P*=0.54 Post-operative hemoglobin: *P*≤0.001
Atis *et al.* (2017)	Minor complications: 6.8% Visual analog scores: 4.69±1.39	Minor complications: 3.4% Visual analog scores: 2.41±1.43	Minor complication rates: *P*=0.18 Visual analog score: *P*=0.0001
Palmero *et al.* (2016)	Peri-operative free complications: 83.3%	Peri-operative free complications: 97.1%	*P*=0.08
Zengin *et al.* (2015)	Complication rates: 13.5%. Mean decrease in hemoglobin level: 1.4±0.9 g/dL	Complication rates of 8.8%. Mean decrease in hemoglobin level: 0.3±0.1 g/dL	Complication rates: *P*=0.520 Mean hemoglobin levels: *P*<0.001
Sari *et al.* (2017)	Complication rates: 8.3%	Complication rate: 3.8%	*P*-value is so small that researchers did not report it
Pieras *et al.* (2017)	Complications rates: 29%	Complication rates: 27%	*P*=0.4

RIRS: Retrograde intrarenal surgery, CCT: Clinical controlled trial, PCNL: Percutaneous nephrolithotomy

As illustrated in [Table 3], even though minor complication rates in PCNL were greater than RIRS, the difference between groups was statistically insignificant. Yet, a statistically significant difference in hemorrhage (Koyunku *et al.*) and post-operative hemoglobin (Karakoç *et al.*) was reported.[5,9] Atis *et al.* also reported statistical differences in pain levels using a visual analog score.[4] All these differences were reported to be higher in the PCNL group than in the RIRS group. It is these differences that may have increased hospital stay in PCNL, leading to statistically significant differences in-hospital stay.

DISCUSSION

Kidney stone disease is considered to be the third most common urinary tract disorder. Kidney stones are mineral concretions present in the renal tracts and pelvis which are either free or attached to the renal papillae.[11] Following UTIs and prostate pathophysiology, the urinary stone disease is the third most common urinary tract disorder.[9] When the author collected reports from the National Hospital Information System, it was found that one in eight Maltese people will develop kidney stones at some point in their lives. Punnoose *et al.* claimed that dehydration is the primary cause of stone formation.[12] Buttigieg *et al.* also confirmed that hotter and drier climates increase the risk of kidney stone formation.[13]

Minimally invasive procedures are used in stone treatment to achieve maximum SFR with the lowest morbidity. PCNL is the standard treatment for stones as this procedure is associated with 90% SFRs postoperatively.[5] Yet, according to the Working Group of the CROES PCNL Global Study who evaluated the PCNL complications, PCNL has several disadvantages. This includes acute hemorrhage which is the most common complication which arises mostly from renal parenchyma. Other reported complications include delayed hemorrhage due to arteriovenous fistulas or arterial pseudoaneurysms, visceral injury particularly to the left side of the colon, pleural injury including hydrothorax and pneumothorax, post-operative fever and sepsis, urinoma formation, partial renal loss, and renal lacerations.[10] RIRS reduces complications mainly since, unlike PCNL, it does not involve an incision and most of the complications mentioned require the need to perform an incision.[14] PCNL complications have led to the need to focus on more non-invasive procedures, thus resulting in RIRS being included as an alternative treatment for kidney stones. In fact, despite EUA guidelines, RIRS is becoming widely used to treat

stones that measure over 20 mm, with the hope of reducing complications.[4]

Studies have consistently found a better outcome in terms of SFR in the PCNL group, but this reached statistically significant levels only in two of the retrospective CCTs conducted by Atis *et al*. and Sari *et al*. which happened to have the largest sample sizes.[3,4] The implication is that if the other studies had larger samples, they might also have found PCNL to be statistically better than RIRS. This reflects an inconsistency in the evidence produced.

Several arguments have been raised by the author, particularly in the inability of most studies to find a statistical difference. For example, lack of power in most of the CCTs conducted which was attributed to their small sample sizes may have made it difficult to identify small treatment effects, resulting in type 2 errors. The significant heterogeneity in Zheng *et al*.'s meta-analysis and the relatively small number of studies included also made it difficult for the authors to find a significant difference in the pooled SFRs, especially after using random-effect models to overcome the influence of heterogeneity.[2] These models are known to produce conservative results, especially in small meta-analyses.[1] This may explain the fact that the superiority of PCNL over RIRS in achieving SFR is existent and may hold true; however, it may be particularly small such that very large samples are required to identify this at a statistically significant level. On the other hand, the evidence related to hospital stay consistently showed the superiority of RIRS over PCNL, denoting that the former is associated with significantly fewer complications, and the strength of this evidence was particularly high. One should also keep in mind that the designs used by most of the trials lacking randomization and control issues may jeopardize the validity of results obtained.

While the evidence produced to date points to the need for more research in the area, it raises the question as to whether the better SFR rates obtained in PCNL in the studies included in this review are clinically (and not merely statistically) significant, keeping in mind the other advantages associated with RIRS. Evidently, while more studies are needed to confirm the statistically significant superiority of PCNL, there may be enough evidence to show that RIRS may be a potentially good alternative with better outcomes in terms of postoperative complications.

Therefore, study findings need to be interpreted with caution. RIRS seems to be a safe and effective surgical procedure, particularly for selected patients who may exhibit a greater risk for certain post-operative complications such as bleeding. This is a cautious statement, drawn based on the limited evidence available to date.

CONCLUSION

The evidence available to date sheds light on the potential safety and effectiveness of RIRS as an alternative surgical procedure to PCNL for selected patients. Yet, due to study limitations and inconsistent evidence, no definite conclusion can be drawn. Nonetheless, the synthesized evidence has given direction to practice, particularly in regard to considering the use of RIRS on individuals who may most benefit from its advantages over PCNL. It has also provided direction toward further research in this area, with the hope that this would provide clearer guidelines for clinical decision-making.

Authors contributions

Analysis and Interpretation of data: Rebecca Caruana. Writing of article: Rebecca Caruana. Concept and design: Rebecca Caruana and Sheriseane Diacono. Critical revision of the article for important intellectual content: Rebecca Caruana and Sheriseane Diacono.

Declaration of patient consent

Patient consent is not required as the patient's identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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