Review Article

Treatment outcomes of bladder stones in children with intact bladders in developing countries: A systematic review of >1000 cases on behalf of the European Association of Urology Bladder Stones Guideline panel

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Keywords
Bladder stones; Bladder calculi; Urolithiasis; Children

Abbreviations
CL, Open cystolithotomy; ESWL, Extracorporeal shock wave lithotripsy; PCCL, Percutaneous cystolithotripsy; TUCL, Transurethral cystolithotripsy

Introduction
Bladder stones (BS) are still endemic in children in developing nations and account for a high volume of paediatric urology workload in these areas. The aim of this systematic review is to comparatively assess the benefits and risks of minimally invasive and open surgical interventions for the treatment of bladder stones in children.

Methods
This systematic review was conducted in accordance with Cochrane Guidance. Database searches (January 1970–March 2021) were screened, abstracted, and assessed for risk of bias for comparative randomised controlled trials (RCTs) and non-randomised studies (NRSs) with >10 patients per group. Open cystolithotomy (CL), transurethral cystolithotripsy (TUCL), percutaneous cystolithotripsy (PCCL), extracorporeal shock wave lithotripsy (ESWL) and laparoscopic cystolithotomy (LapCL) were evaluated.

Results
In total, 3040 abstracts were screened, and 8 studies were included. There were 7 retrospective non-randomised studies (NRS’s) and 1 quasi-RCT with 1034 eligible patients (CL: n = 637, TUCL: n = 196, PCCL: n = 138, ESWL: n = 63, LapCL n = 0). Stone free rate (SFR) was given in 7 studies and measured 100%, 86.6%-100%, and 100% for CL, TUCL and PCCL respectively. CL was associated with a longer duration of inpatient stay than PCCL and TUCL (p < 0.05). One NRS showed that SFR was significantly lower after 1 session with outpatient ESWL (47.6%) compared to TUCL (93.5%) and CL (100%) (p < 0.01 and p < 0.01 respectively). One RCT compared TUCL with laser versus TUCL with pneumatic lithotripsy and found that procedure duration was shorter with laser for stones <1.5cm (n = 25, p = 0.04).

Conclusion
In conclusion, CL, TUCL and PCCL have comparable SFRs but ESWL is less effective for treating stones in paediatric patients. CL has the longest duration of inpatient stay. Information gathered from this systematic review will enable paediatric urologists to comparatively assess the risks and benefits of all urological modalities when considering surgical intervention for bladder stones.

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Introduction

Bladder stones (BS) are endemic in children in developing nations and account for a high volume of paediatric urology workload in these areas [1]. BS can be classified as primary, secondary or migratory and have a peak incidence at 3 years of age for children [2,3]. Primary BS occur in children with no other urinary tract pathology and are associated with poor hydration, recurrent diarrhoea and a diet deficient in animal protein [4]. Secondary BS occur in children with lower urinary tract dysfunction [4].

Conventional open cystolithotomy (CL) has been considered as the gold-standard surgical procedure for managing paediatric BS due to the associated high stone-free rate (SFR) and availability of long-term published data [5–7]. However, recent advances in minimally invasive technologies and endoscopic techniques have improved the urological armamentarium for definitively managing bladder stones in children [8]. Transurethral cystolithotripsy (TUCL), percutaneous cystolithotripsy (PCCL), extracorporeal shock wave lithotripsy (ESWL) and laparoscopic cystolithotomy (LapCL) may provide feasible and safe-alternatives to CL [5]. These minimally invasive techniques may be less morbid and have a shorter duration of inpatient stay and urinary catheterisation than CL, but it is unclear whether this is at the expense of inferior SFRs [8]. Investigation into the treatment of bladder stones in children is therefore likely to inform patient and physician decision making leading to improved patient management. Therefore, the aim of this systematic review is to comparatively assess the benefits and risks of interventions for the treatment of BS in children.

Evidence acquisition

Search strategy

We conducted a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and the Cochrane Handbook for Systematic Reviews of Interventions [9,10]. Medline, Embase, and Cochrane controlled trials databases and clinicaltrial.gov were searched between January 1st 1970 and March 31st 2021 for relevant English language publications. The published a priori protocol includes the search strategy [11] (Supplementary file 1). Following deduplication, review authors (N.D., Y.R. and J.D.) independently screened the abstracts for eligibility. The full-text articles were then retrieved and scrutinised independently by review authors (N.D., Y.R. and J.D.). For any incompletely reported data, study authors were contacted. Disagreements were resolved by discussion or by consulting another review author (C.T., A.N. or A.S.).

Types of study design included

Study designs were limited to randomised controlled trials, non-randomised comparative studies and comparative observational studies comparing any treatments of bladder stones with ≥10 patients per arm [6]. Animal studies, case reports, letters and conference abstracts were excluded.

Types of participants included

Boys and girls ≤18 years of age, of any ethnicity, with single bladder stones or multiple bladder stones were included. Recurrent or first time stone formers, and patients with all stone sizes and compositions were eligible. Patients with pre-existing bladder augmentation or diversion were excluded. Mixed populations which accounted for <10% of the cohort were accepted.

Types of interventions included

Open cystolithotomy (CL), transurethral cystolithotripsy (TUCL), percutaneous cystolithotripsy (PCCL), extracorporeal shock wave lithotripsy (ESWL) and laparoscopic cystolithotomy were evaluated. Any technique or lithotripsy modality was accepted for all interventions [11].

Types of outcome measures included

The primary outcome was stone-free rate measured at any time point up to 3-months post-operatively, using any modality. The secondary outcomes were re-treatment rate (including second session ESWL), recurrence rate (after 3-months being stone free post-operatively), unplanned procedures and need for unplanned secondary intervention. Intra-operative complications (i.e. bladder perforation, trauma to surrounding organs and blood transfusion) were recorded. Requirement and duration of catheterisation, length of hospital stay, stone composition, duration of procedure and ionising radiation exposure were also measured.

Post-operative early complications were classified according to the Clavien-Dindo classification system by the review team where sufficiently reported [12], or details were obtained by contacting the authors [12]. Post-operative complications were measured up to 4-weeks from bladder stone treatment. Late complications, defined as occurring >4 weeks after bladder stone treatment, were also measured.

Assessment of risks of bias

The risk of bias for RCTs was assessed in accordance with Cochrane guidance [10]. Extra domains were used to assess confounders in NRSs: a pragmatic approach informed by methodological literature [13]. We assessed whether each prognostic confounder was considered, whether the confounder was balanced between the intervention and the control group, and whether, if necessary, the confounder was controlled for in the analysis. A list of the most important potential confounders for harm and benefit outcomes was developed a priori with clinical content experts (the European Association of Urology Bladder Stone Guideline Panel): stone size, aetiology, gender, and previous open surgery [11]. In the a priori protocol the presence of an indwelling catheter was prioritised as a potential...
confounder; however no studies included catheterised patients. Therefore, this confounder was replaced with age which was deemed more appropriate by the authors.

Data analysis

We report data at available time points and reported p-values where available, or if unavailable, we calculated these using RevMan 5.3. We did not impute missing data and in the case of incompletely reported data, we contacted the authors. For dichotomous outcomes, we report risk ratios (RRs) and 95% confidence intervals (CIs). For continuous outcomes, we report the mean difference (MD) and median values with standard deviation and/or range and corresponding 95% CIs and p-values, where available.

Evidence synthesis

Description of the included studies

A total of 3040 abstracts were screened and 12 full-text articles were assessed. Eight studies were included. There were 7 retrospective NRS’s and 1 quasi-RCT (patients were consecutively allocated into a group) with 1034 eligible patients in total (CL: n = 637, TUCL: n = 196, PCCL: n = 138, ESWL: n = 63, LapCL n = 0) [1,8,14–19]. Reasons for exclusion are listed in Fig. 1 and risk of bias for included studies are summarised in Fig. 2.

Study characteristics

Characteristics of the 8 included studies are summarised in Table 1. Measured characteristics included procedural aspects, gender, age, stone size and length of follow-up. In total, 637 patients underwent CL (conventional CL: n = 501, ‘drainless’ and ‘catheterless’ CL: n = 136), 196 patients underwent TUCL, 138 patients underwent PCCL and 63 patients underwent ESWL. Three studies compared 3 interventions, 3 studies compared 2 interventions, 1 study compared energy modalities for TUCL and 1 study compared outcomes of CL with no catheter or pelvic drain (i.e. ‘tubeless CL’) with conventional CL (i.e. with catheter and pelvic drain). Mean stone size is detailed in Table 1. Mean stone size ranged from <1 cm for ESWL [1], from 1.2 ± 0.66 cm - 3.8 ± 0.77 cm for TUCL [14,17], from 1.8 ± 0.8 cm–2.6 ± 1 cm for PCCL [8,17] and from 2.9 ± 1.2 cm–3.1 ± 1.6 cm for CL [8,17]. Due to the absence of any randomised controlled trials and the heterogeneous nature of the available literature, a meta-analysis was not performed.

Outcome data

Outcome data are summarised in Table 2. SFR was measured in 7 studies and was assessed using direct visualisation, X-ray, ultrasound (US), or a combination of X-ray and US. SFR was defined as the absence of any visible residual fragments with these diagnostic modalities. In one study by Rizvi et al., stone free was defined as a stone fragment <3 mm fragment post ESWL [1]. Additional recorded outcome data included bladder stone re-treatment rates, recurrence rates, duration of catheterisation, duration of procedure and duration of inpatient stay where applicable. Four studies reported on bladder stone composition [1,8,18,19] (Table 1). No study reported quality of life, satisfaction, cost, or ionising radiation exposure outcomes.

PCCL versus TUCL

Four NRS’s compared PCCL with TUCL [8,14,17,19]. No significant differences were found for SFRs, unplanned procedures, recurrence rates, duration of urethral catheterisation, minor post-operative complications, major post-operative complications, or urethral stricture rates between both treatment modalities; however the overall incidence of urethral strictures were higher with TUCL (Table 2). One study demonstrated a significantly longer duration of inpatient stay with PCCL (median 1.3 ± 0.7 days for TUCL versus median 2.5 ± 0.7 days for PCCL, p < 0.01) [8]. In another study, an indwelling suprapubic catheter was required for ≤8 days in the PCCL group [19]. The duration of the procedure was significantly longer with TUCL (36.3 ± 5.3 min versus 30.54 ± 5.3 min, p < 0.01) in one study [8].

TUCL versus CL

Three NRS’s compared TUCL with CL [1,8,17]. In one study, TUCL (n = 77) had a significantly lower SFR compared to CL (n = 307) (93.5% versus 100% respectively, p = 0.02) [1]. A greater peri-operative complication rate for CL was also reported in this study (11.5% [n = 9] versus 29% [n = 89], p = 0.003), however no specific details for complications were available (Table 2). Two NRS’s found that TUCL was associated with a shorter duration of inpatient stay (median 1.3 ± 0.7 days for TUCL versus median 3.6 ± 1 days for CL, p < 0.01) and median 2.6 days for TUCL versus median 4.8 days for CL, p < 0.05) [8,17]. In one study, the duration of the procedure was significantly longer with TUCL (36.3 ± 6 min versus 26 ± 6.3 min, p < 0.01) [8]. No significant differences were found for recurrence rates, unplanned procedures and incidence of post-operative urethral stricture disease (Table 2).

PCCL versus CL

Three NRS’s compared PCCL with CL [8,15,17]. Two studies demonstrated that PCCL was associated with a significantly shorter duration of inpatient stay (median 2.5 ± 0.7 days for PCCL versus median 3.6 ± 1 days for CL, p < 0.01 and median 2.6 days for PCCL versus median 4.8 days for CL, p < 0.05) [8,17]. The duration of the procedure was significantly longer with PCCL (30.54 ± 5.3 min versus 26 ± 6.3 min, p < 0.01) in one study [8]. No significant differences were found for SFR, unplanned procedures, major postoperative complications and incidence of post-operative urethral stricture disease (Table 2).

ESWL

One large NRS (n = 447) compared outcomes for outpatient ESWL (n = 63), TUCL (n = 77) and CL (n = 307) [1]. Patients were assigned into the following cohorts according to stone size: ESWL for stones <1 cm, TUCL for stones 1.1–3 cm and CL for stones >3 cm. ESWL was performed using an EDAP LT02 (Technomed, Lyon, France).
piezoelectric lithotriptor with a storage shock wave of 35–45 Watts and power of 1134 bars. SFR was characterised by ultrasonography or plain film x-ray and was significantly lower in the ESWL cohort (47.6%) compared to the TUCL (93.5%) and CL (100%) cohorts (p < 0.01 and p < 0.01 respectively). In the ESWL group, ‘stone free’ was defined as a stone fragment <3 mm after treatment.

TUCL: Laser versus pneumatic lithotripsy
One small quasi-RCT compared energy modalities for TUCL [18]. Laser and pneumatic lithotripsy were compared in 25 consecutively enrolled patients. No significant differences were noted for SFR (100% with both modalities), intraoperative complications, unplanned procedures and major complications. Duration of inpatient stay and duration of procedure were similar with both modalities (p = 0.05 and p = 0.81). However, the procedure duration was shorter with laser lithotripsy for smaller stones (i.e. <1.5 cm) (49.4 min versus 44.6 min, p = 0.04).

CL: ‘Tubeless’ versus traditional
One large NRS (n = 176) compared ‘tubeless CL’, with no urethral catheter or pelvic drain (n = 136) to traditional CL, with a urethral catheter and pelvic drain (n = 40). SFR and length of follow-up was not available to compare despite contacting the authors [16]. Duration of inpatient stay was shorter with tubeless CL (median 2 days versus median 6 days, p < 0.01) and the incidence of urethral stricture disease was lower with tubeless CL (0% versus 2.5% respectively, p = 0.16). The incidence of unplanned procedures and major complications was higher with tubeless CL (p = 0.22 for both). Notably, all patients requiring an unplanned postoperative procedure had prior surgery or a previous urine infection.

Complications
Postoperative complications were measured up to 4-weeks and are summarised in supplementary tables A and B.
according to their incidence rates. There were no reported Clavien-Dindo 4 or 5 complications. Clavien-Dindo grade 1 and grade 2 complications for TUCL included haematuria (8.3–23%) [5,18], treatment with antipyretics (8%) [19], irritative voiding symptoms (18.5%) [8] and UTIs (25%) [18]. Clavien-Dindo grade 3 complications for TUCL included impaction of stone fragment in urethra causing acute urinary retention requiring urethoscopic lasertripsy (7.7%) [18]. Clavien-Dindo grade 1 and grade 2 complications for PCCL included irritative voiding symptoms (5.1%) [8], treatment with antipyretics (22.2%) [19], UTIs (5.6%) [19], wound infection (5.1%) [8] and conservatively managed urine leak (2.6–3.7%) [8,17]. Clavien-Dindo grade 3 complications for PCCL included laparotomy for intraperitoneal bladder rupture (7.4%) [17]. Clavien-Dindo grade 1 and grade 2 for CL included irritative voiding symptoms (6.3%) [8], wound infection (1.5–5.0%) [16,17] and UTIs (7.5%) [16]. Clavien-Dindo grade 3 complications for CL included laparotomy for haematoma evacuation (0.7%) [16], urinary catheterisation under general anaesthesia due to high drain output (5.9%) [16] and reoperation for urine leakage (1.3%) [8].

Discussion

This systematic review provides the first detailed analysis on the benefits and risks of different interventions for the treatment of BS in children. CL is usually considered the gold-standard surgical option for managing BS in paediatric patients; however its limitations include a surgical scar, prolonged urinary catheterisation, prolonged inpatient stay, increased risk of wound infection and increased analgesia requirements [5,7]. Therefore, less invasive endoscopic techniques such as TUCL and PCCL may be safe alternatives [20]. The main finding of the present systematic review is that CL, TUCL and PCCL have comparable SFRs. We also noted that CL is associated with a longer duration of inpatient stay and may have a higher complication rate compared to both less invasive modalities. Another important finding is that CL may be safely performed with a ‘tubeless’ approach in high volume centres in carefully selected patients and this can significantly decrease the duration of inpatient stay [16]. Finally, we found that ESWL is less effective for treating BS compared to the other 3 modalities assessed but can be performed in an outpatient environment without the risk of complications [1].

Technological advances in paediatric endoscopic equipment and lithotripsy modalities have led to the evolution of TUCL as feasible surgical option for bladder stone management in children [8]. We found that SFRs were high after TUCL and ranged from 86.6% to 100%. In addition, we also noted the acceptable safety profile of the procedure as there was only 1 postoperative Clavien-Dindo ≥3 complications reported among all analysed studies (i.e. urinary retention due to an impacted urethral stone) [18] and 1 intra-operative complication (i.e. urethral rupture) [17]. Another advantage with TUCL is the relatively short duration of inpatient stay which ranged from 1 day to 2.6 days. Potential disadvantages are technical difficulties when extracting large stone fragments [18] and the association with urethral stricture disease which was 7.4% in one study and a prolonged surgical procedure, particularly for larger BS [8]. Finally, it appears that Ho:YAG laser lithotripsy and pneumatic lithotripsy have similar results with TUCL, but the procedure may be shorter with laser lithotripsy for smaller stones [18].

At present, TUCL is a recognised alternative to CL due to recent endourological technological advances. However, with TUCL, there are legitimate concerns about the development of urethral stricture disease in boys as the narrow calibre and length of the paediatric male urethra can be extremely variable children on similar ages and this needs to be carefully considered [7,21,22]. Tissue ischaemia from
prolonged urethral instrumentation and iatrogenic urethral trauma are risk factors for acquired urethral stricture disease [22]. Urethral stricture disease occurred in 3 studies (Rattan et al. (n = 1), Javanmard et al. (n = 3), Al Mahmood et al. (n = 1)). In the study by Rattan et al., the timeframe at which the stricture occurred was not recorded. Their patient required urethral dilatation at 3-weekly intervals for 3 months. In the study by Javanmard et al. 3 children (2 in the TUCL group and 1 in the PCCL) developed bulbar urethral stricture disease that was managed with urethral dilatation once. In the study by Al Mahmood et al. one patient treated with TUCL developed a bulbar stricture 1-year post-operatively, which was treated with visual internal urethrostomy using a paediatric 13Fr sheath.

PCCL offers a potential simple solution as the paediatric urethra is bypassed. In our systematic review, we found that PCCL was associated with an excellent SFR (i.e. 100%) for each included study. Duration of inpatient stay was longer than TUCL, but still favourable, and ranged from 1 to 3 days. The main disadvantage with PCCL is the potential for perioperative vescicourethral perforation as reflected in one study where the incidence of significant bladder perforation was 11.5% during the perioperative period [17] (Table 2). Another potential disadvantage with PCCL is prolonged suprapubic catheterisation as described in another study where a suprapubic catheter was required for ≤8 days in patients undergoing PCCL [19]. Notably, like TUCL, PCCL has also benefited from miniaturised technological advances. Early studies frequently used larger access sheaths (30-32Fr) and nephroscopes (26Fr) for percutaneous access [17,23]. More recently, the safety profile of the procedure has been improved with the development of less invasive percutaneous equipment and percutaneous access sheaths and nephroscopes are now more refined at 15Fr and 12Fr respectively [14].

Similar to PCCL, we found that the SFR with CL was 100% for each analysed study. CL is generally considered the choice of treatment for larger bladder stones (i.e. >4 cm) as it offers excellent SFRs and our systematic review is consistent with this finding [8]. Like PCCL and TUCL, the approach to open CL has evolved to become more minimally invasive with authors describing smaller incision (i.e. 20 mm) due to the distensibility of bladder tissue for removing larger bladder stones [8]. In addition, the conventional approach of leaving a urethral catheter and pelvic drain in situ may not always be necessary as demonstrated by Rattan et al where ‘tubeless’ CL was performed in paediatric patients (n = 136) [16]. In their comparative study, ‘tubeless’ CL was associated with a shorter duration of inpatient stay and a lower incidence of acquired urethral stricture disease. Disadvantages of the ‘tubeless’ approach included a slightly higher incidence of unplanned procedures and major complications. Overall, the main disadvantage of CL is the longer duration of inpatient stay which ranged from 2 days (for a tubeless approach) to 9 days for conventional CL [15,16]. However, with smaller surgical incisions the length of stay decreases to 3.6 days for conventional CL [8]. Another disadvantage is the higher incidence of perioperative complications that was demonstrated in one study where conventional CL was compared with TUCL [1].

Although the present systematic review is the first to comprehensively compare the risks and benefits of
Table 2  Clinical outcomes after treatment of bladder stones in paediatric patients.

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Dichotomous outcomes (SFR, Re-treatment, Recurrence, Complications) are reported as percentage (n). Continuous outcomes (length of hospital stay, procedure and catheterisation) are reported as mean ± SD, range unless otherwise stated and significant p-values are included where applicable.


* Tubeless CL: no drain and no catheter. Traditional CL: retropubic drain and urethral catheter.
interventions for the treatment of BS in children, there are several limitations. There was only one randomised controlled trial available for inclusion so a meta-analysis could not be performed. Notably, the majority of the manuscripts included in this systematic review were published in India over a 30-year period. It is likely that costly endoscopic equipment may not have been available globally at this time, thereby contributing to the high number of paediatric patients undergoing CL in this systematic review. Important outcomes such as ‘SFR’ and accurate classification of ‘perioperative complications’ were either not reported or poorly defined in some studies and this limited standardised comparison between studies [16]. Finally, a high risk of bias was evident in the included studies, therefore caution should be advised when interpreting their conclusions due to low quality data (Fig. 2). However, this is a very robust systematic review involving >1000 patients with extensive outcome data involving multiple institutions. The review also includes international publications over a 36-year period and is therefore representative of current global evidence based treatments for BS in children.

Conclusions

In this systematic review we demonstrate several notable findings. Firstly, we found that the SFR with CL, TUCL and PCCL are comparable and excellent. We also noted that conventional CL is associated with a longer duration of inpatient stay and may have a higher complication rate compared to both less invasive endoscopic techniques. Another important finding is that CL may be safely performed with a ‘tubeless’ approach, in patients with no prior history of UTIs or bladder surgery, and this can significantly decrease the duration of inpatient stay. Information gathered from this systematic review will enable paediatric urologists to comparatively assess the risks and benefits of all urological modalities when considering surgical intervention for bladder stones.

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Ethical approval

Ethical approval was not required as this manuscript is a systematic review of published literature.

Conflicts of interest

All authors confirm they have no conflicts of interest to declare.

References

Management of bladder stones in children


Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpurol.2022.01.007.