REVIEW PAPER

UROLITHIASIS

Does Moses technology improve the efficiency and outcomes of standard holmium laser lithotripsy? A systematic review and meta-analysis

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Introduction Retrograde ureteroscopy with holmium laser lithotripsy (HLL) is a standard treatment for urolithiasis. Moses technology has been shown to improve fragmentation efficiency in vitro; however, it is still unclear how it performs clinically compared to standard HLL. We performed a systematic review and meta-analysis evaluating the differences in efficiency and outcomes between Moses mode and standard HLL.

Material and methods We searched the MEDLINE, EMBASE, and CENTRAL databases for randomized clinical trials and cohort studies comparing Moses mode and standard HLL in adults with urolithiasis. Outcomes of interest included operative (operation, fragmentation, and lasing times; total energy used; and ablation speed) and perioperative parameters (stone-free rate and overall complication rate).

Results The search identified six studies eligible for analysis. Compared to standard HLL, Moses was associated with significantly shorter average lasing time (mean difference [MD] -0.95, 95% confidence interval [CI] -1.22 to -0.69 minutes), faster stone ablation speed (MD 30.45, 95% CI 11.56–49.33 mm^3/min), and higher energy used (MD 1.04, 95% CI 0.33–1.76 kJ). Moses and standard HLL were not significantly different in terms of operation (MD -9.89, 95% CI -25.14 to 5.37 minutes) and fragmentation times (MD -1.71, 95% CI -11.81 to 8.38 minutes), as well as stone-free (odds ratio [OR] 1.04, 95% CI 0.73–1.49) and overall complication rates (OR 0.68, 95% CI 0.39–1.17).

Conclusions While perioperative outcomes were equivalent between Moses and standard HLL, Moses was associated with faster lasing time and stone ablation speeds at the expense of higher energy usage.

Key Words: urolithiasis ‹› laser lithotripsy ‹› holmium laser ‹› Moses ‹› efficiency ‹› outcomes

INTRODUCTION

The prevalence of urolithiasis has been steadily increasing worldwide [1]. Current guidelines recommend ureteroscopy (URS) as first-line therapy in patients with mid or distal ureteral stones who require intervention [2]. For patients undergoing URS, holmium laser is the current lithotrite of choice due to its safety profile and high fragmentation efficiency [3]. Advanced holmium lasers offer a wider range of pulse energy, frequency, and width settings to improve efficiency [4, 5]. Most recently, further pulse

modulation permitted the introduction of Moses technology [6], a composite mode where a first pulse generates a vapor cavity and delivers a more efficient second pulse to the target [5].
Preclinical in vitro and in vivo evidence indicates that Moses technology reduces stone retropulsion and increases ablation volume [6, 7]. However, it is still unclear how holmium with Moses mode (HMM) compares to holmium standard mode (HSM) laser lithotripsy clinically. We hypothesized that HMM may improve clinical outcomes for holmium laser lithotripsy. We sought to systematically review the literature and perform a meta-analysis to determine whether HMM improves efficiency and perioperative outcomes compared to HSM laser lithotripsy.

MATERIAL AND METHODS

Aim of the review

The objective of the present study was to review the differences in operative characteristics, laser efficacy parameters, and short-term outcomes between HMM and HSM laser lithotripsy for the management of urolithiasis. The outcomes of interest included: operative time, fragmentation time, lasing time, total energy used, ablation speed, stone-free rate (SFR), and overall complications.

Literature search

This study was conducted in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework. An exhaustive literature search was performed by a librarian (S.H.) on April 1, 2022, using the MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases. Medical Subject Heading (MeSH) terms and keywords such as 'urolithiasis', 'urinary calculi', 'kidney stone disease', 'laser lithotripsy', 'holmium', 'Ho-YAG', 'Moses', 'pulse modulated laser' were used. No date or language limits were utilized. The search was restricted to clinical studies in human adults with urolithiasis. In vitro studies, or studies using pediatric or animal subjects were excluded. The search strategy is presented in the supplementary material. Additional studies were also obtained through forward and backward citation chaining. The review protocol was registered in PROSPERO (CRD42022328865).

Selection criteria

The PICO (Population, Intervention, Comparison, Outcome) model was used to formulate and answer the clinical question. The study population was human adults undergoing retrograde ureteroscopy (either semi-rigid or flexible) plus laser lithotripsy for urolithiasis with HSM as the intervention and HMM as the comparator. Noncomparative single-arm studies were excluded. The outcomes of interest were operative time, fragmentation time, lasing time, total energy used, stone ablation speed, SFR, and overall perioperative complication rate.

Study screening, selection, and data extraction

Two independent authors (G.S. and B.L.) screened all the retrieved records using the covidence systematic review management software. Discrepancies were resolved by a third author (A.F.). Studies were included based on the PICO eligibility criteria. The study types considered were randomized controlled trials (RCTs), prospective nonrandomized, and retrospective studies. Grey literature (meeting abstracts and poster presentations) was also considered. Reviews, case reports, case series, editorials, and letters were not considered. The full text of screened papers was included if found relevant to the objective of the study. The search was further expanded by citation chaining. All data was ex-

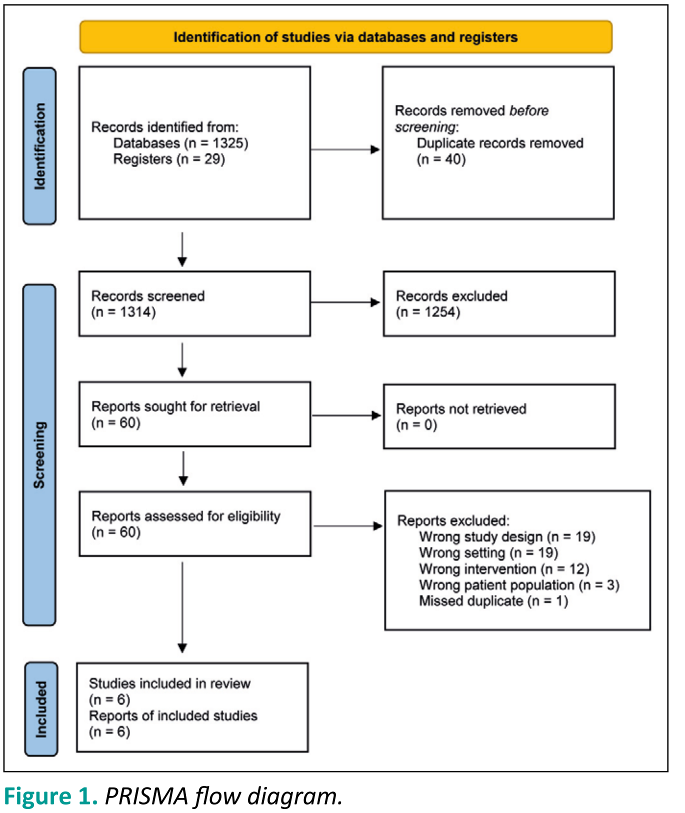

Figure 1. *PRISMA flow diagram.*

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses; n – number tracted into an Excel template by two independent authors (G.S. and B.L.) and checked for accuracy by a third author (C.R.). Continuous data were recorded as mean and standardized deviation. If median and interquartile range were reported instead, these were converted to mean and standardized deviation using the method by Hozo et al. [8]. Binary outcomes were reported as the number of events over

Table 1. *Characteristics of studies comparing HMM and HSM laser lithotripsy*

Study	Moses mode vs standard mode			
	Study type	Patients, n (total)	Mean age, year (SD)	Follow-up, months
Mullerad et al., 2017	Prospective	23 vs 11 (34)	54.6 (16.1) vs 51.9 (11.8)	NR
Mekayten et al., 2019	Retrospective	169 vs 462 (631)	49.82 (15.9) vs 50.62 (15.9)	1–1.5
Ibrahim et al., 2020	RCT	36 vs 36 (72)	57.4 (11.9) vs 54.7 (13.6)	3
Knoedler et al., 2021	Retrospective	110 vs 66 (176)	58.7 (13.2) vs 56.8 (14.8)	0.03–11.9
Wang et al., 2021	Retrospective	114 vs 102 (216)	49.91 (12.86) vs 47.97 (11.6)	1
Pietropaolo et al., 2021	Mixed	38 vs 38 (76)	53.8 (5.8) vs 58.1 (14.5)	2–4

SD – standard deviation; RCT – randomized clinical trial; NR – not reported; HMM – holmium with Moses mode; HSM – holmium standard mode

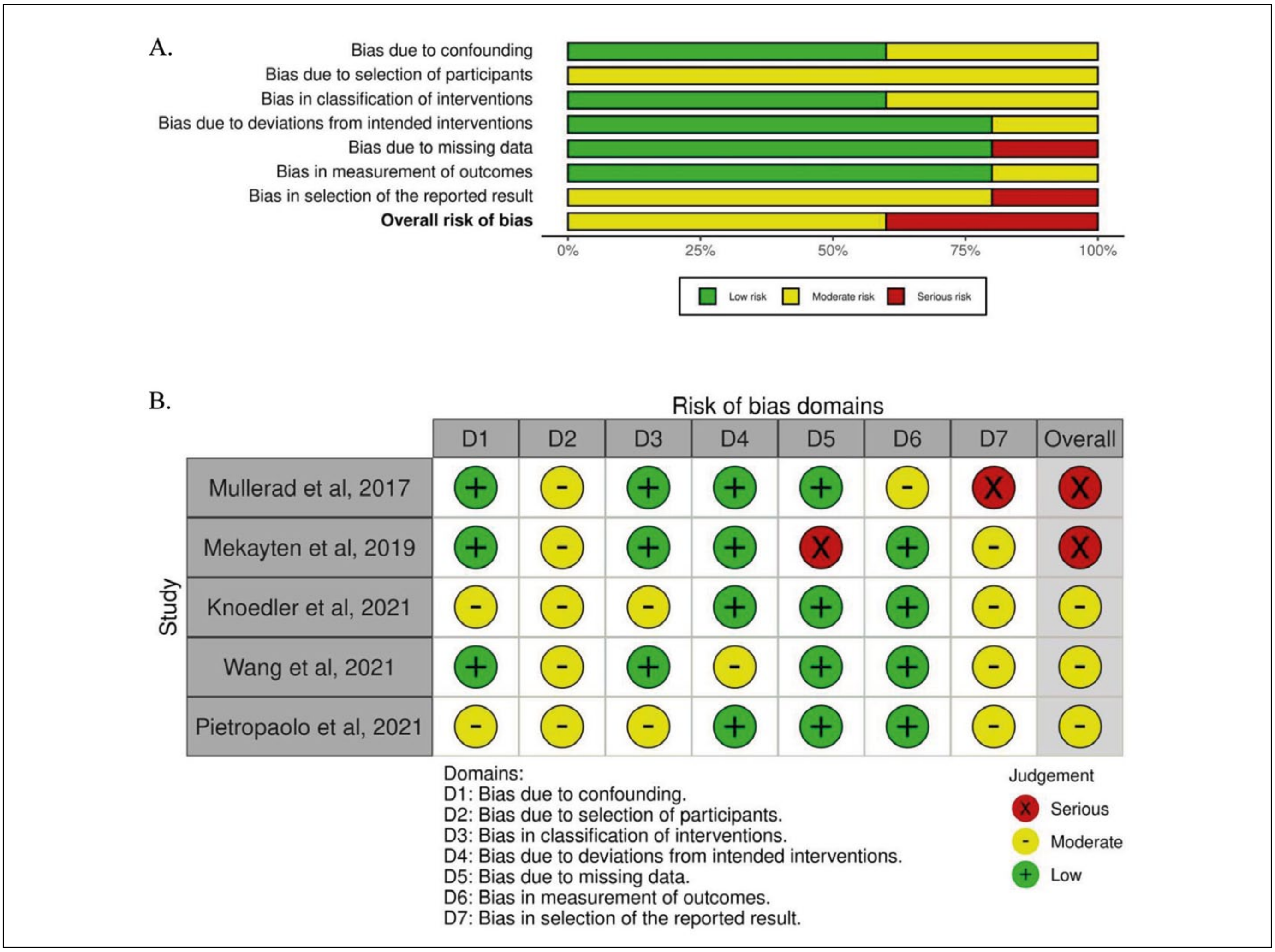

Figure 2. *Risk of bias in non-randomized controlled trials (ROBINS-I).* ***(A)*** *Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.* ***(B)*** *Risk of bias summary: review authors' judgements about each risk of bias item for each included study.*

the sample size (n) for that outcome in each treatment arm. Authors were contacted if data was not reported in the manuscript or supplementary files.

Statistical analysis

Operative time, fragmentation time, lasing time, total energy used, and ablation speed were pooled using a random effect model and reported as the inverse variance of the mean difference (MD), 95% confidence interval (CI), and p value. The frequency of events for binary outcomes (SFR and overall perioperative complication rates) was estimated using the Mantel-Haenszel random effect model and reported as the odds ratio (OR), 95% CI, and p value. All statistical tests were two-tailed, and a $p < 0.05$ was deemed significant. For treatment comparisons, smaller outcome values (i.e. smaller mean values for continuous data, or ORs less than 1 for binary data) were considered desirable, except for stone ablation speed. Odds ratios <1 indicate a lower risk in the Moses mode group. Study heterogeneity was assessed using the I^2 value, and it was considered substantial if >50% or $p < 0.10$ for a chi-square test. Meta-analysis was performed using RevMan v5.4.1 software. Quality assessment of the included studies was evaluated using the Cochrane risk of bias tools [9].

RESULTS

The literature search identified 1354 studies. Forty duplicates were identified and excluded, leaving 1314 studies to be screened. After the primary screening, 1254 studies were deemed irrelevant, leaving 60 full-texts eligible for full-text review. After the secondary screening was completed, 54 studies were excluded. Finally, six studies comparing HSM versus HMM laser lithotripsy were accepted and included in the meta-analysis [10–15]. Figure 1 shows the PRISMA flow diagram.

Study characteristics and quality assessment

A total of 1205 patients were included from six studies: 715 patients receiving intervention with HSM and 490 patients receiving HMM. A summary of the study characteristics can be found in Table 1. Figure 2 shows the risk-of-bias assessment for the five non-randomized studies. There was a serious overall risk of bias for two of the studies and some concerns for three studies. The most common risk factor was bias in the selection of reported results, followed by bias due to participant selection, confounding bias, classification of interventions bias, missing data bias, deviations from intended interventions bias,

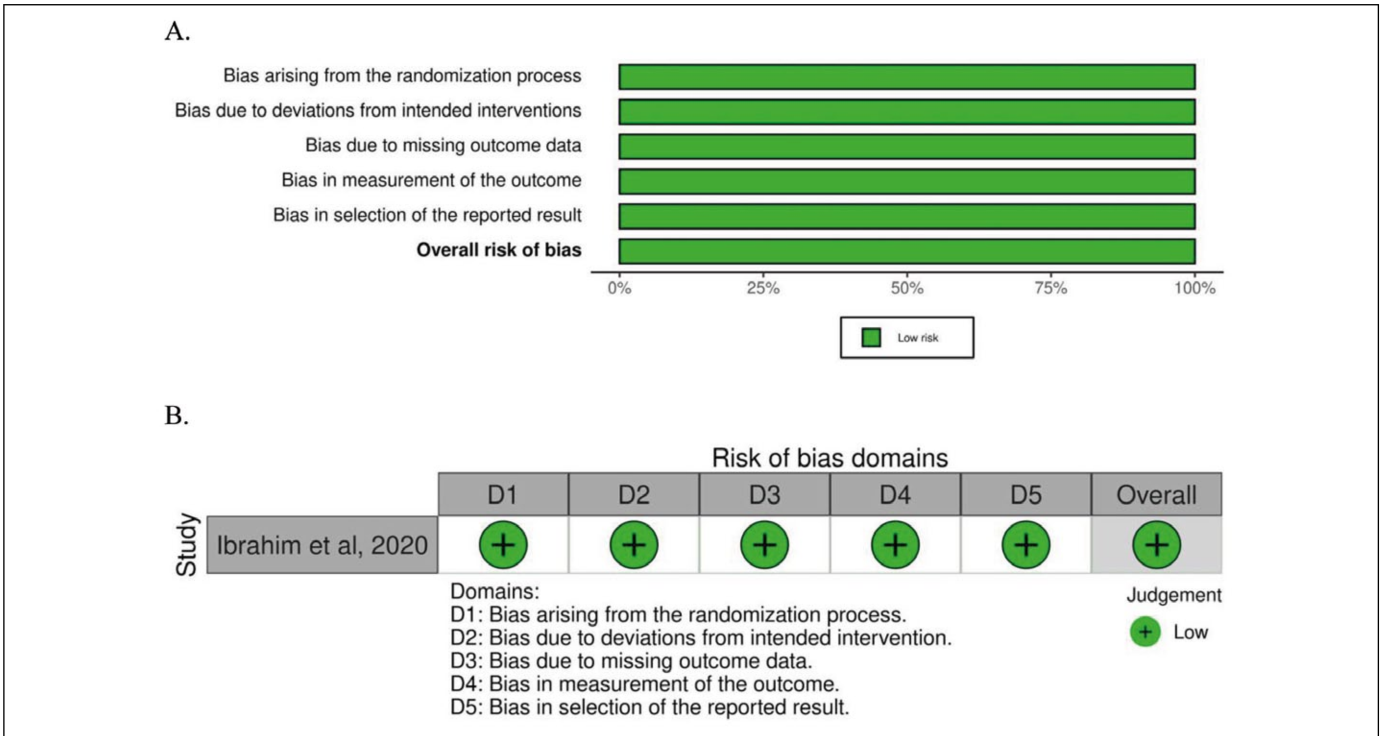

Figure 3. *Risk of bias in randomized controlled trials (ROB-2).* **(A)** *Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.* **(B)** *Risk of bias summary: review authors' judgements about each risk of bias item for each included study.*

and measurement of outcomes bias. For the only randomized prospective trial, the quality assessment showed an overall low risk of bias (Figure 3).

Meta-analyses of holmium standard mode vs holmium with Moses mode

The mean operative time based on three studies (262 HMM and 206 HSM cases) was not found to be significantly different for HMM compared to HSM. However, the mean operative time tended to be lower for HMM (MD -9.89, 95% CI: -25.14 to 5.37 minutes, p = 0.20, I^2 = 93%; Figure 4A). The fragmentation time based on two studies (146 HMM and 102 HSM cases) was found to be similar for HMM compared to HSM (MD -1.71, 95% CI: -11.81 to 8.38 minutes, p = 0.74, I^2 = 81%; Figure 4B).
Average lasing time based on four studies (283 HMM and 215 HSM cases) was found to be shorter for HMM compared to HSM (MD -0.95, 95% CI: -1.22 to -0.69 minutes, p <0.001, I2 = 0%; Figure 4C). The total energy used based on four studies (338 HMM and 575 HSM cases) found the HSM to use more energy (MD 1.04, 95% CI: 0.33 to 1.76 kJ,

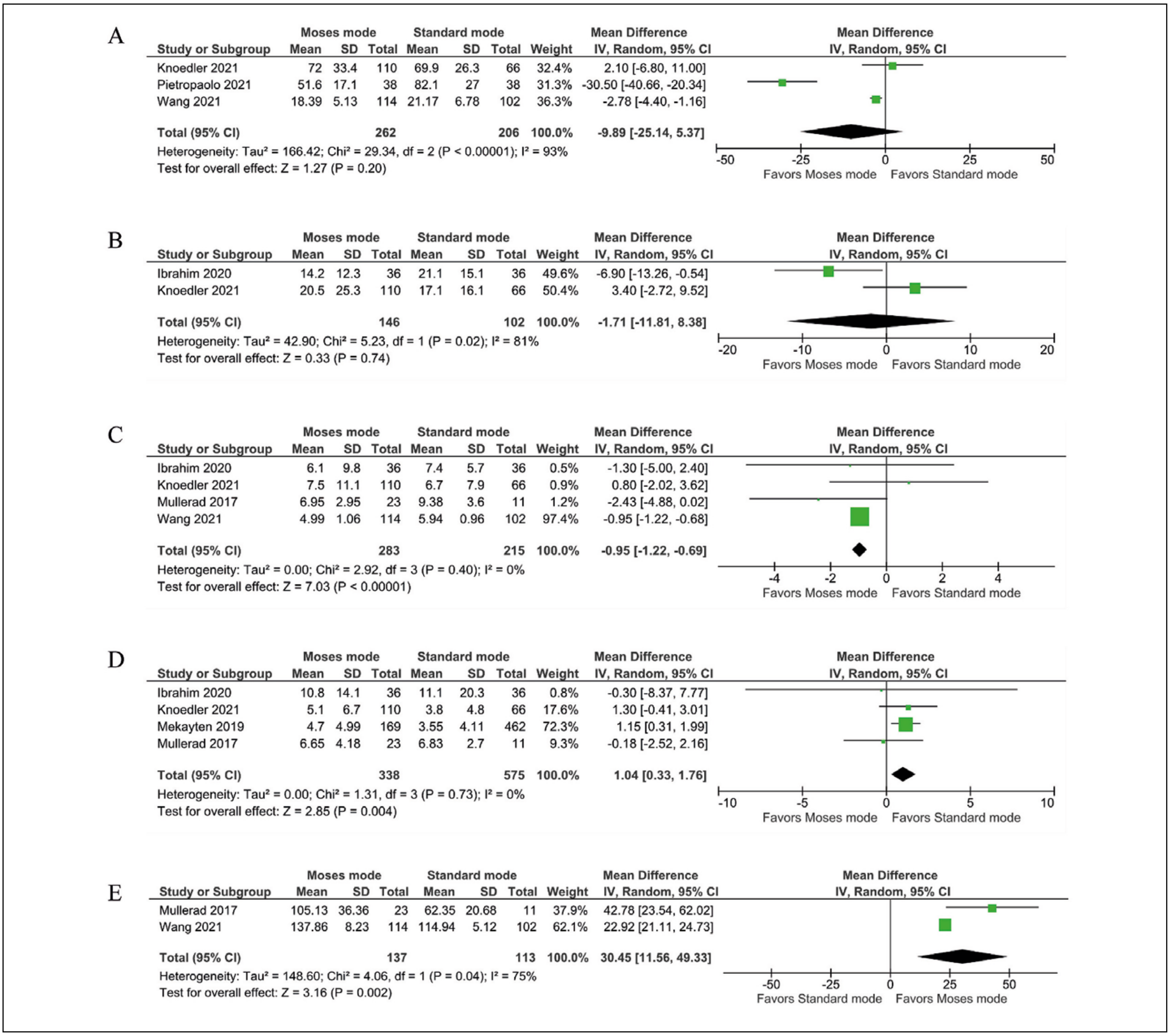

Figure 4. *Forest plots summarizing the differences in operative characteristics between HMM and HSM.* **(A)** *Operative time;* **(B)** *Fragmentation time;* **(C)** *Lasing time;* **(D)** *Total energy used;* **(E)** *Ablation speed.*

SD – standard deviation; CI – confidence interval p = 0.004, I^2 = 0%; Figure 4D). The ablation speed based on two studies (137 HMM and 113 HSM cases) was found to be faster in HSM compared to HMM (MD 30.45, 95% CI: 11.56 to 49.33 mm^3/min, p = 0.002, I^2 = 75%; Figure 4E).

Stone-free rate based on five studies (443 HMM and 687 HSM cases) was found to be similar for HMM compared to HSM (OR 1.04, 95% CI: 0.73 to 1.49, p = 0.81, I^2 = 0%; Figure 5A). Overall complication rates based on five studies (443 HMM and 687 HSM cases) were similar. There was a non-significant trend of lower complication rates for HMM (OR = 0.68, 95% CI: 0.39 to 1.17, p = 0.16, I^2 = 0%; Figure 5B).

DISCUSSION

The holmium laser has been extensively studied and modified over the past several decades [16]. High pulse energy (0.6–1.2 J) has been demonstrated to be better for fragmenting and extracting stones with baskets [17]. Low pulse energy has been demonstrated to be superior for dusting stones which can be passed [18]. High frequency laser settings up to 80–100 Hz have been shown to fragment stones at a faster rate compared to settings of 20 Hz; however, higher frequencies are associated with more retropulsion [19]. Frequency settings are contingent on the location and type of stone in the urinary tract [20]. Long laser pulse duration (1,200 μs) may potentially reduce both laser fiber tip degradation and laser retropulsion compared to standard laser pulse duration (150–350 μs) [21].

Next-generation holmium lasers offer an opportunity for refinement of outcomes and increased efficiency. The publication of the commercially-funded prospective study from Ibrahim et al was impactful in supporting usage of HMM with a 20% reduction in operative time and 33% reduction in laser/fragmentation time compared to HSM [10]. Studies from Wang et al and Pietropaolo et al. found a significant reduction in operative time with HMM [14, 15]. While the mean operative time in our analysis tended to be lower with HMM by roughly 10 minutes compared to HSM, this did not reach statistical significance. Studies from Wang et al. and Mullerad et al. showed a significant reduction in lasing time with HMM [13, 15]. In our analysis, lasing time favored HMM over HSM.

Pulse energy and fragmentation rate are directly related; however, high energy use also means higher retropulsion rates and possibly extended procedural times [3]. Mekayten et al. found a significant difference based on total energy usage [12]; in our analysis, we found a significant difference of around 1 kJ less energy used for HSM. This lower pulse energy for HSM translates into a decreased lithotripsy efficiency, as defined by ablation speed (mm^3/s) [22]. In our analysis, we found a faster ablation speed for HMM of approximately 30 mm^3/s due to its use of a modulated high energy pulse.

Initial studies of HMM from Ghani et al. which included 12 patients showed an improvement in SFRs for renal stones less than 2 cm using HMM [23]. However, SFRs were not assessed by Ibrahim et al.

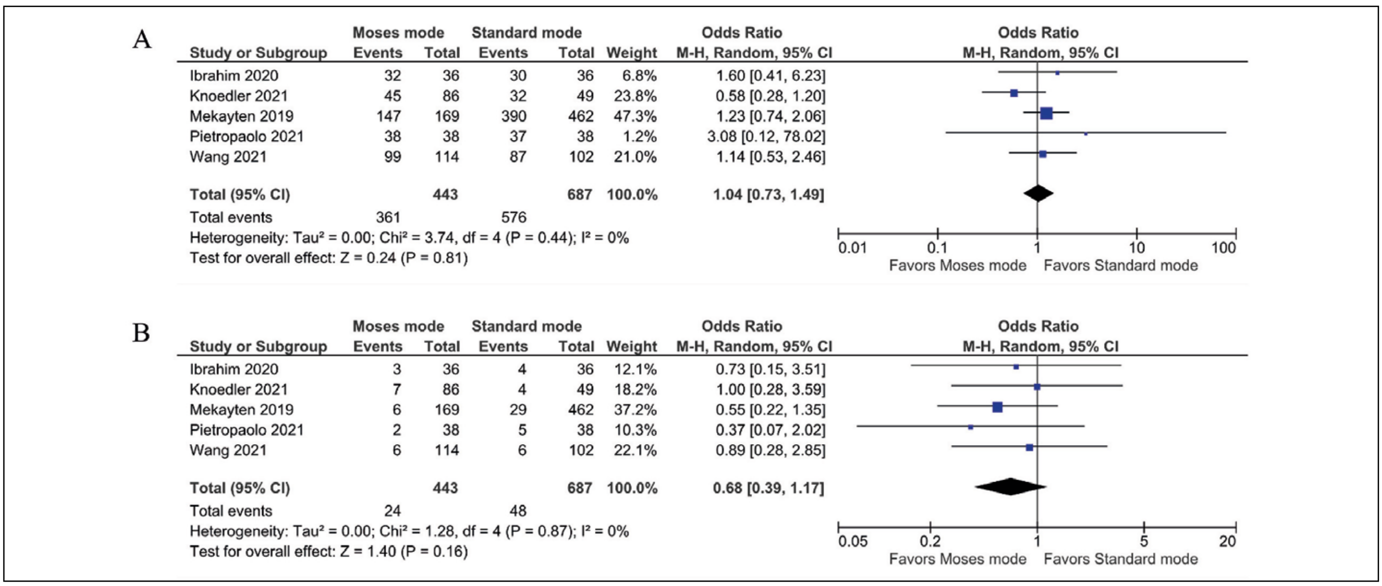

Figure 5. *Forest plots summarizing the differences in perioperative outcomes between HMM and HSM.* **(A)** *Stone-free rate;* **(B)** *Overall perioperative complication rate.*

M-H – Mantel-Haenszel; CI – confidence interval

[10], and while Wang et al. and Pietropaolo et al. found significant differences [14, 15], in our analysis SFRs were not statistically significant. The perioperative complication rates between HMM and HSM were not statistically different. HMM performed better in our analysis over traditional HSM technology particularly in lasing time and stone ablation speed. Due to the few meaningful differences, the higher cost of HMM may not yet justify its widespread adoption [24].

The lack of differences between HMM and HSM may be due to limitations in the studies themselves. The retrospective study by Wang et al. included 114 patients with kidney stones treated with HMM by three fellowship-trained endourologists [15]. The patients were not randomized to either treatment group and the HSM mode used was long-pulse, which has similar characteristics to HMM [25]. The retrospective study by Pietropaolo et al. included 38 patients with both kidney and ureter stones treated with HMM performed by a single urologist. While the patients were not randomized to a treatment group, analysis was performed by a third party [14]. The retrospective study by Mullerad et al. included 23 patients with HMM performed by three urologists which were compared to 11 patients with HSM by two different urologists. Patients with either kidney or ureter stones were included. The patients were not randomized to either treatment group [13].

The retrospective study by Mekayten et al. included 169 patients treated for either kidney or ureteral stones with HMM performed by a single fellowship-trained endourologist. Patients were not randomized, and those who underwent HSM lithotripsy for ureteral stones were treated using short-pulse mode, while those with kidney stones were treated using long-pulse mode [12]. The retrospective study by Knoedler et al. included 110 patients treated with HMM for upper urinary tract stones performed by several fellowship-trained endourologists. Patients were randomly assigned to treatment groups; however, the endourologists were not blinded to laser modality [11].

The prospective study by Ibrahim included 36 patients treated for urolithiasis with HMM and performed by four urologists. While the urologists were experienced, none of them had formal fellowship training in endourology. Patients were randomly assigned to treatment groups with the urologists blinded to treatment. The randomized clinical trial (RCT) by Ibrahim et al. was the only one to compare HMM and short-pulse mode HSM laser lithotripsy. Despite the potential for bias, the relative equality between the two cohorts is reassuring and likely indicates a similarity of treatment outcomes. There is currently one multi-institutional clinical trial (NCT04505956) that is recruiting patients comparing HMM and HSM laser lithotripsy.

Heterogeneity amongst stone characteristics between HMM and HSM may have underpowered our study. Stone sizes varied immensely among the included studies which may have an impact on comparisons between treatment groups with larger stones favoring HMM over HSM. Four of the studies did not assess the composition of the stone altogether. Measurements of stone volume were included in only three studies. More precise comparisons of stone HMM and HSM are necessary.

The future of lithotripsy research is focused on either optimizing current laser settings or developing new laser technology altogether. In a study comparing several laser pulse modulation technologies from Quanta Systems, the Virtual Basket demonstrated improved ablation rates by creating bubbles from the fiber tip compared to either Bubble Blast or Vapor Tunnel [26]. A comparison of holmium software systems from either Lumenis with Moses or Quanta Systems with Virtual Basket has not been explored but would be valuable to explore in the future. Studies have also showed enthusiasm in use of the Thulium laser which offers a continuous laser wave compared to the pulsed wave of the holmium laser [27]. The Thulium laser fiber in small studies has shown improved stone-free rates and reduced intraoperative complications compared to the holmium laser [28]. The new super pulse Thulium laser fiber is particularly adept for dusting [29]. While there is enthusiasm of Thulium laser fiber in clinical practice, further studies are needed to warrant Thulium laser fibers over the holmium standard [30].

CONCLUSIONS

While Moses technology had better operative proficiency based on lasing time and stone ablation speed compared to standard holmium, results were similar in terms of fragmentation time, and SFR. Moses technology tended to have a lower operative time and complication rates, but the results were not statistically significant. Further studies are needed to ascertain the meaningful benefits of laser technology advancements and the clinical benefit they may provide.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

Appendix 1. Systematic search strategy

Databases: MEDLINE, EMBASE, CENTRAL
Patient/Population
("urinary calculi"[mesh] OR "kidney calculi"[mesh] OR nephrolithiasis[mesh] OR urolithiasis[mesh] OR ((kidney[tiab] OR renal[tiab] OR urinary tract[tiab] OR ureth*[tiab] OR ureteral[tiab]) AND (lithiasis[tiab] OR stone[tiab] OR calculi[tiab] OR calculus[tiab])) OR nephroliths[tiab] OR "kidney stone disease") AND lithotripsy[mesh] OR lithotripsy
15090

Intervention/Comparator
("lasers, solid-state/therapeutic use"[mesh] OR "lithotripsy, laser"[mesh] OR "laser therapy"[mesh] OR "lasers/therapeutic use"[mesh] AND (holmium[mesh] OR holmium OR moses[tiab]))OR holmium doped yttrium aluminum garnet laser OR "holmium YAG laser" OR "holmium laser" OR ((laser OR holmium OR moses[tiab])AND (lithotripsy OR ureteroscopy OR endoscopy OR pulse-modulat* OR "URSL" OR "laser stone fragmentation"))
13862
#1 AND #2- 1325 citations

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