

Does power setting impact surgical outcomes of holmium laser enucleation of the prostate? A systematic review and meta-analysis

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Introduction The aim of this article was to enumerate the differences in immediate and postoperative outcomes for holmium laser enucleation of the prostate (HoLEP) performed with low-power (LP) or high-power (HP) laser settings through a systematic review of comparative studies.

Material and methods We performed a systematic literature review using MEDLINE, EMBASE, and Cochrane Central Controlled Register of Trials. Potential clinical differences among LP and HP HoLEP were determined using the PICOS (Patient Intervention Comparison Outcome Study type) model, where outcomes were surgical time, operative efficiency, postoperative catheterization time, length of hospital stay, blood transfusion, incontinence rate, maximum urinary flow rate (QMax) and International Prostatic Symptom score (IPSS). Retrospective, prospective nonrandomized, randomized studies, and meeting abstracts were considered.

Results A total of five studies were included for meta-analysis. No significant differences between LP and HP HoLEP were evidenced in terms of intraoperative variables (surgical time, surgical efficiency); postoperative outcomes (length of stay, length of catheterization); postoperative complications; functional results (IPSS; Qmax). Urinary incontinence rate did not differ between the two groups (OR 0.95, 95% CI 0.362.47, p = 0.91).

Conclusions The study shows equal outcomes in outcomes from HoLEP performed with LP or HP energy settings. Even if further comparative studies are still needed to increase the level of evidence, those results encourage a further clinical adoption of LP HoLEP.

Key Words: holmium laser <> low-power laser <> high-power laser <> benign prostatic hyperplasia

INTRODUCTION

Progressive worsening of lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH) is one of the most common health issues for the ageing male [1].

For several decades, transurethral resection of prostate (TURP) has been recognized as the gold-standard endoscopic treatment for symptomatic (BPH) requiring surgery and those who failed medical therapy and may have complications of outlet obstruction such as bladder stones, urinary retention, or renal insufficiency [2].

In the last two decades, transurethral laser surgery has gained popularity and interest among urologists, mainly for its advantages in terms of reduced blood loss and catheterization time compared to standard TURP. Holmium laser enucleation of the prostate (HoLEP), first introduced by Gilling et al. in 1998 [3], has proven to be a minimally invasive and size-independent technique. The complete enucleation of the adenoma and the simultaneous coagulation of the capsular surface, combined with tissue mechanical morcellation, allow to perform the procedure in all prostate volumes, overcoming the limits of TURP. Therefore, HoLEP is considered a technique of reference for surgical treatment of BPH, offering long-term functional results superior to TURP and comparable to open simple prostatectomy, but with reduced treatment morbidity and complication rate [4].

HoLEP is commonly performed using the standard power setting of 80–100 W with 2 J and 40–50 Hz, with occasional power reduction for coagulation (75 W, 1.5 J and 50 Hz) and apical preparation (30 W, 0.6 J and 50 Hz) [3, 5]. Thus, this requires holmium machines with multiple high-power sockets and multiphase connectors capable of emitting high power (HP).

The relatively high equipment costs, together with a steep learning curve, are generally considered limitations in widespread adoption of HoLEP [6].

However, low-power (LP) machines (i.e., 20, 30 and 50 W) are also available on the market, and several studies showed safety and efficacy of HoLEP performed with a LP compared to standard HoLEP. Moreover, a lower initial investment and no need for dedicated sockets, often not available in operating theaters, may be a potential advantage in comparison to HP units, where the same machine can be used for lithotripsy and BPH surgery.

The first report of HoLEP performed with a maximum power of 50 W is by Rassweiler et al. [7] in 2008, showing the feasibility of the procedure at 25 W (2.0 J, 12 Hz). However, there are still few reports about HoLEP performed with LP settings in comparison with HP ones.

The hypothesis of this paper is that energy settings in holmium laser may not be the only criteria for improving efficacy and efficiency of enucleation. However, there is still a paucity of data on whether LP settings can be equally effective for laser enucleation whilst HP lasers in enucleation have been well investigated in recent times. Therefore, this study aims to systematically review the outcomes of HoLEP for BPH in studies comparing LP vs HP machines and to discuss the potential advantages of one technique over the other.

MATERIAL AND METHODS

Aim of the review

The present study aimed to systematically review the perioperative parameters, complications, and functional outcomes after LP HoLEP as compared to standard (HP) HoLEP for BPH.

Literature search

This study was performed according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework. A comprehensive literature search was performed on 27th January 2022, using EMBASE, MEDLINE, and Cochrane Central Controlled Register of Trials (CENTRAL). Medical Subject Heading (MeSH) terms and keywords such as ‘benign’, ‘prostate hypertrophy’ or ‘prostatic hyperplasia’ or ‘prostate adenoma’, ‘BPH or ‘BPO’ or ‘BPE’ or ‘BOO’, ‘holmium’ or ‘Holmium Lasers’, (‘power’ or ‘energy’ or ‘Watt’ or ‘Joules’ or ‘Hz’ or Hertz’) and (‘holmium’ or ‘HoLEP or ‘Ho-LEP’) were used. No date limits were imposed. The search was restricted to English papers only. Animal and pediatric studies were also excluded. The review protocol was submitted for registration in PROSPERO (receipt # 316564).

Selection criteria

The PICOS (Patient Intervention Comparison Outcome Study type) model was used to frame and answer the clinical question. P: Adults undergoing HoLEP for BPH; Intervention: LP HoLEP; Comparison: HP HoLEP; Outcome: surgical time, operative efficiency, postoperative catheterization time, length of hospital stay, re-catheterization, blood transfusion and incontinence rate, and International Prostate Symptom Score (IPSS), maximum peak flow (Q_{max}) and post-void residual urine (PVR) at last follow-up; study type: randomized, prospective non-randomized and retrospective studies. Patients were assigned in two groups according to the amount of power used. For the HP group HoLEP performed at 100 W, whilst the LP group comprised surgery performed at 30 W, 40W, and 50 W [1].

Study screening and selection

Two independent authors screened all retrieved records through Covidence Systematic Review Management®. A third author solved discrepancies. Studies were included based on PICOS eligibility criteria. Retrospective, prospective non-randomized,

and randomized studies were accepted. Meeting abstracts were also accepted. Case reports, reviews, letters to the editor, and editorials were excluded. The full text of the screened papers was selected if found relevant to the purpose of this study.

Statistical analysis

We aimed to perform a meta-analysis (MA) comparing the perioperative parameters and postoperative outcomes between two amounts of power energy used in HoLEP (LP vs HP). Surgical time, postoperative catheterization time, postoperative length of stay, postoperative IPSS, Qmax, and PVR were pooled using the inverse variance of the mean difference with a random effect, 95% CI, and p-values. Incidence of postoperative re-catheterization rate, blood transfusion and incontinence rates were estimated using the Cochran-Mantel-Haenszel method with the random effect model and reported as odds ratio (OR), 95% confidence intervals (CI), and p-values. Analyses were two-tailed and the significance was set at $p < 0.05$ and a 95% CI. OR less than one (1) indicates a lower risk in the LP group. Study heterogeneity was assessed utilizing the I^2 value. Substantial heterogeneity was defined as an I^2 value $> 50\%$ or a Chi^2 p-value < 0.10 . Meta-analysis was performed using Review Manager (RevMan) 5.4 software by Cochrane Collaboration [14]. The quality assessment of the included studies was performed using the Cochrane Risk of Bias tool, using RoB 2 for randomized studies and ROBINS-I for non-randomized ones [15].

RESULTS

The literature search retrieved 842 papers. After removing 6 duplicates, 836 studies were left for screen-

ing. A further 819 records were excluded following the title and abstract screening because they were irrelevant for this study. The full texts of the remaining 17 studies were screened and 12 papers were further excluded. Finally, 5 studies were accepted and included for meta-analysis. Figure 1 shows the 2020 PRISMA flow diagram.

Study characteristics and quality assessment

Table 1 shows the study characteristics. Five studies compared LP vs HP HoLEP, including 1109 patients (555 in the LP group and 554 in the HP group).

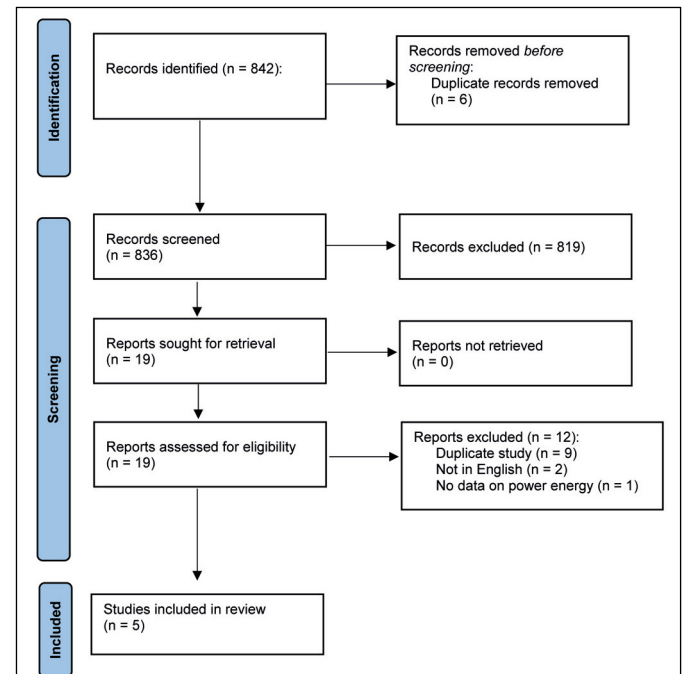


Figure 1. Identification of studies via databases and registers.

Table 1. Characteristics of included studies comparing low-power vs high-power holmium laser enucleation of the prostate

Author, year of publication	Type of study	Type of paper	Type of enucleation	Energy setting low-power	Energy setting high-power	Enrolled patients, Low-power vs high-power (total)	Mean PV (\pm SD), ml Low-power vs high-power	Mean age (\pm SD) Low-power vs high-power
Cracco 2017	Retrospective	Meeting abstract	En bloc	40 W (2.2 J; 18 Hz)	100 W (2 J; 50 Hz)	102 vs 214 (316)	45.8 (36) vs 55.3 (38.9)*	67.7 (8) vs 69.4 (7.5)
Cracco 2020	Retrospective	Meeting abstract	En bloc	40 W	100 W	326 vs 212 (538)	51.2 (34.1) vs 44.4 (32.2)	NR
Elshal 2018	RCT	Full text	2-lobe and 3-lobe	50 W (2 J; 25 Hz)	100 W (2 J; 50 Hz)	61 vs 60 (121)	137.6 (58) vs 137.6 (58)	66.4 (7) vs 67.0 (7)
Gilling 2013	Prospective not-randomized	Meeting abstract	NR	50 W	100 W	20 vs 20 (40)	NR	68.48 (10-41) vs 65.88 (8.81)
Shah 2021	RCT	Full text	2-lobe and 3-lobe	50 W (2 J; 25 Hz)	50 W (2 J; 50 Hz)	46 vs 48 (94)	75.17 (51.27) vs 78.58 (47.40)	67.4 (11.2) vs 68.9 (2.0)

RCT – randomized controlled trial; W – Watt; J – joule; Hz – Hertz; PV – prostate volume; NR – not reported; * – adenoma volume

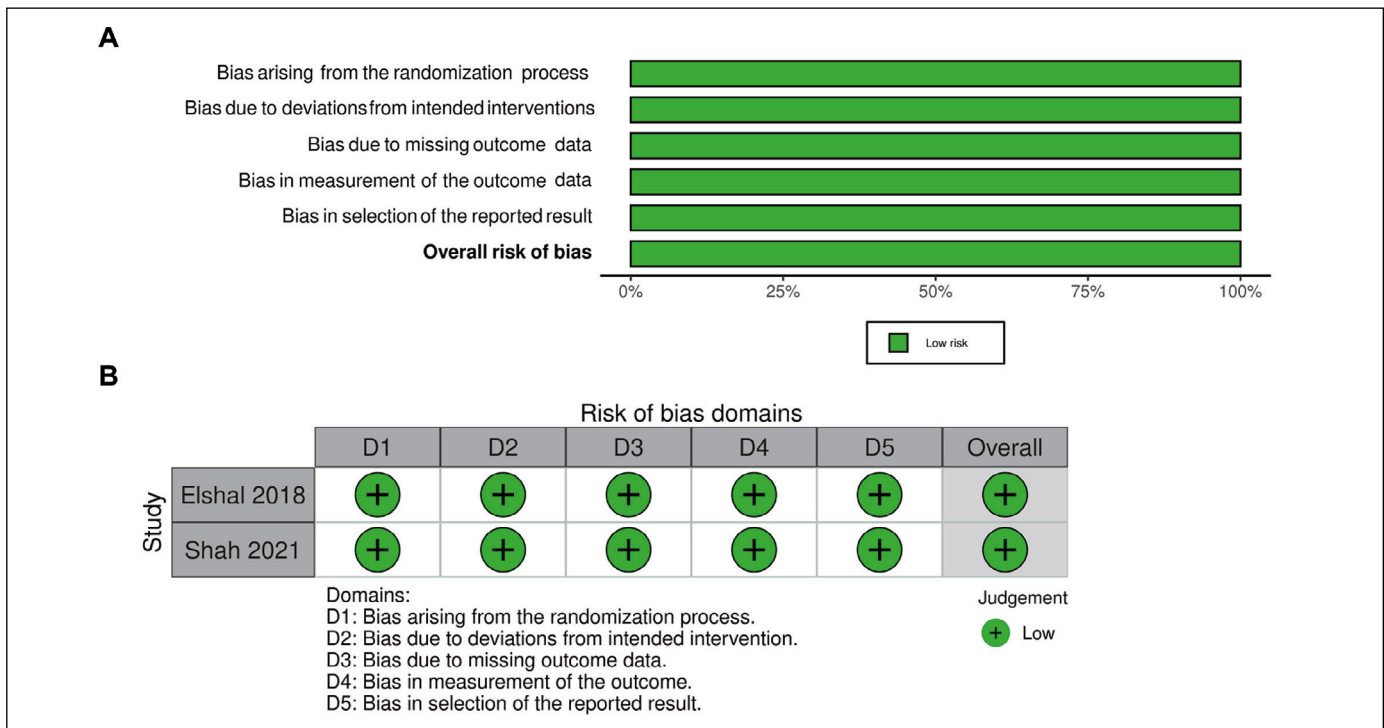


Figure 2. Risk of bias in non-randomized controlled trials (ROBINS-I). **A.** Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. **B.** Risk of bias summary: review authors' judgements about each risk of bias item for each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

Figure 2 shows the risk of bias assessment for prospective and randomized studies that showed an overall low risk of bias.

Figure 3 shows the risk of bias among retrospective and prospective nonrandomized studies. Two studies demonstrated a critical overall risk of bias, and the remaining one exhibited a moderate risk. The most common risk factors for quality assessment were the risk of bias due to measurement of outcomes, and in selection of the results, followed by bias due to confounding, and selection of participants.

Meta-analyses of low-power vs high power holmium laser enucleation of the prostate

Meta-analysis from 2 studies (163 cases in LP and 274 cases HP HoLEP) showed that the mean surgical time did not differ between the two groups (MD -1.82 minutes, 95% CI -7.48 -3.84, $p = 0.53$). Study heterogeneity was substantial ($I^2 79\%$) (Figure 4A). Meta-analysis of 3 studies (209 cases in LP and 322 cases in HP HoLEP) showed that mean surgical efficiency did not differ between the two groups (MD -0.06 g/minutes, 95% CI -0.16 -0.04, $p = 0.23$). Study heterogeneity was not significant ($I^2 0\%$) (Figure 4B). Meta-analysis from 2 studies (107 cases in LP and 108 cases in HP HoLEP) showed that mean post-

operative catheterization time was similar between the two groups (MD -0.09 hours, 95% CI -4.19 -4.0, $p = 0.96$). Study heterogeneity was not significant ($I^2 0\%$) (Figure 4C).

Meta-analysis from 2 studies (107 cases in LP and 108 cases in HP HoLEP) showed that postoperative length of stay was similar between the two groups (MD 10.92 hours, 95% CI -11.94 -33.78, $p = 0.35$). Study heterogeneity was substantial ($I^2 96\%$) (Figure 5A).

Meta-analysis from 2 studies (495 cases in LP and 486 cases in HP HoLEP) showed that re-catheterization rate did not differ between the two groups (OR 0.83, 95% CI 0.06–10.82, $p = 0.89$). Study heterogeneity was substantial ($I^2 96\%$) (Figure 5B).

Meta-analysis from 3 studies (209 cases in LP and 322 cases in HP HoLEP) showed that transfusion rate did not differ between the two groups (OR 0.57, 95% CI 0.17–1.92, $p = 0.36$). Study heterogeneity was not significant ($I^2 0\%$) (Figure 5C).

Meta-analysis from 2 studies (107 cases in LP and 108 cases in HP HoLEP) showed that postoperative Qmax was similar between the two groups (MD -3.56 ml/sec, 95% CI -8.98-1.85, $p = 0.20$). Study heterogeneity was moderate ($I^2 56\%$) (Figure 6A).

Meta-analysis from 3 studies (209 cases in LP and 322 cases in HP HoLEP) showed that postoperative IPSS was similar between the two groups (MD 0.38

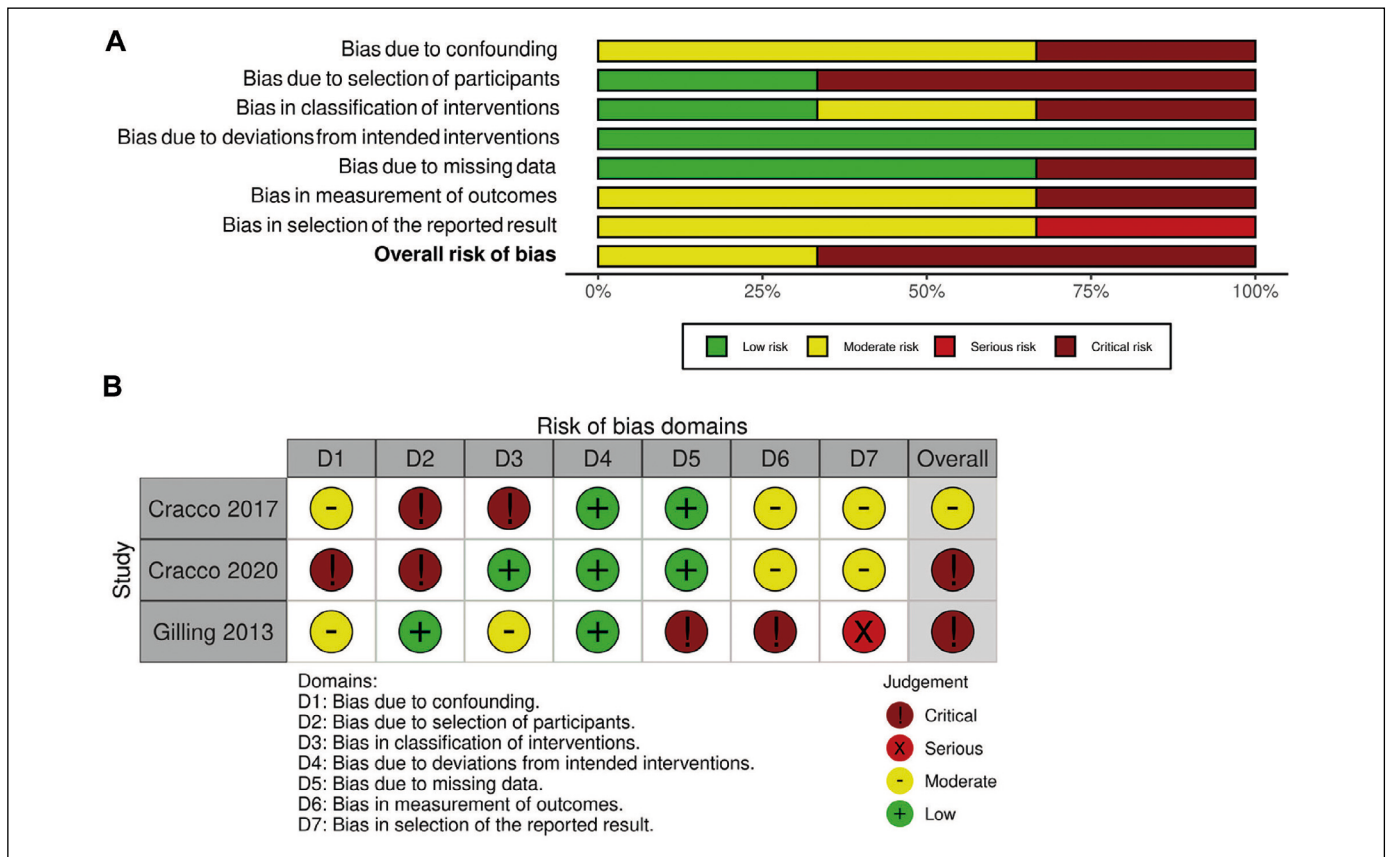


Figure 3. Risk of bias in non-randomized controlled trials (ROBINS-I).

points, 95% CI 0.17–1.92, $p = 0.36$). Study heterogeneity was not significant ($I^2 0\%$) (Figure 6B).

Meta-analysis from 3 studies (209 cases in LP and 322 cases in HP HoLEP) showed that urinary incontinence rate did not differ between the two groups (OR 0.95, 95% CI 0.36–2.47, $p = 0.91$). Study heterogeneity was not significant ($I^2 0\%$) (Figure 6C).

Data on postoperative PVR was available only in one study, making meta-analysis not feasible.

DISCUSSION

The first report of holmium laser application for prostate tissue resection was provided by Gilling et al. in 1998, using a laser power setting of 60 W [8]. The subsequent comparative studies that showed the potential advantages of HoLEP over TURP reported a power setting of 80–100 W [9]. Therefore, HoLEP is traditionally performed at 80–100 W. In a recent editorial, Scoffone et al. [10] reported that, by reducing the power output from 50 to 20 W, they reduced the laser photothermic effect on the capsule without compromising enucleation efficiency and efficacy. This was confirmed by other authors who showed that HoLEP is equally efficient with LP

[11, 12, 16]. The ‘in-vitro’ study by Cecchetti et al. [13] was able to clearly document the interplay of different holmium laser settings and the effect of generated temperatures and shockwaves on soft tissues. They demonstrated that the lowest threshold for plasma formation and shockwave noise for soft tissue ablation was observed at an energy level of 1.4 J and frequency of 10 Hz. Hence, it was purposed that 14 W power was enough to achieve tissue ablation and higher power settings had no additional benefit on ablation and postulated that this increased energy may clinically translate into the postoperative irritative symptoms (i.e., dysuria, urgency and frequency), as suggested by some authors, [10] even if this has not been fully demonstrated.

The most important comparison between LP and HP HoLEP is probably related to the operative efficiency. Our metanalysis shows that perioperative outcomes did not differ between HP and LP. Indeed, surgical efficiency and surgical time were similar, demonstrating that LP energy is enough to complete enucleation with the same time and efficiency compared with HP.

The major evidence of LP HoLEP effectiveness can be found in the single-series retrospective study by

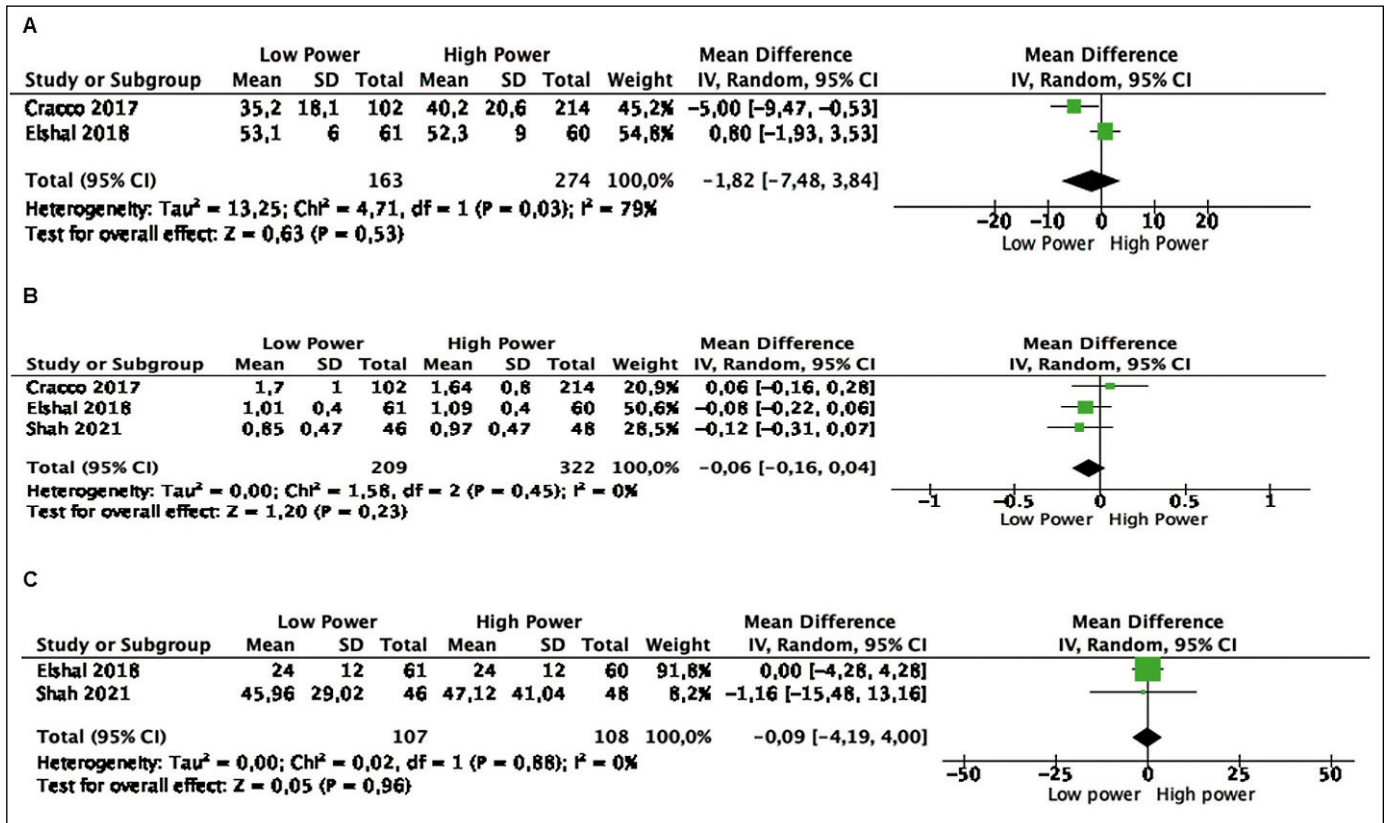


Figure 4. Meta-analysis forest plot. A. Surgical time (minutes); B. Surgical efficiency (grams/minute); C. Postoperative catheterization (hours).

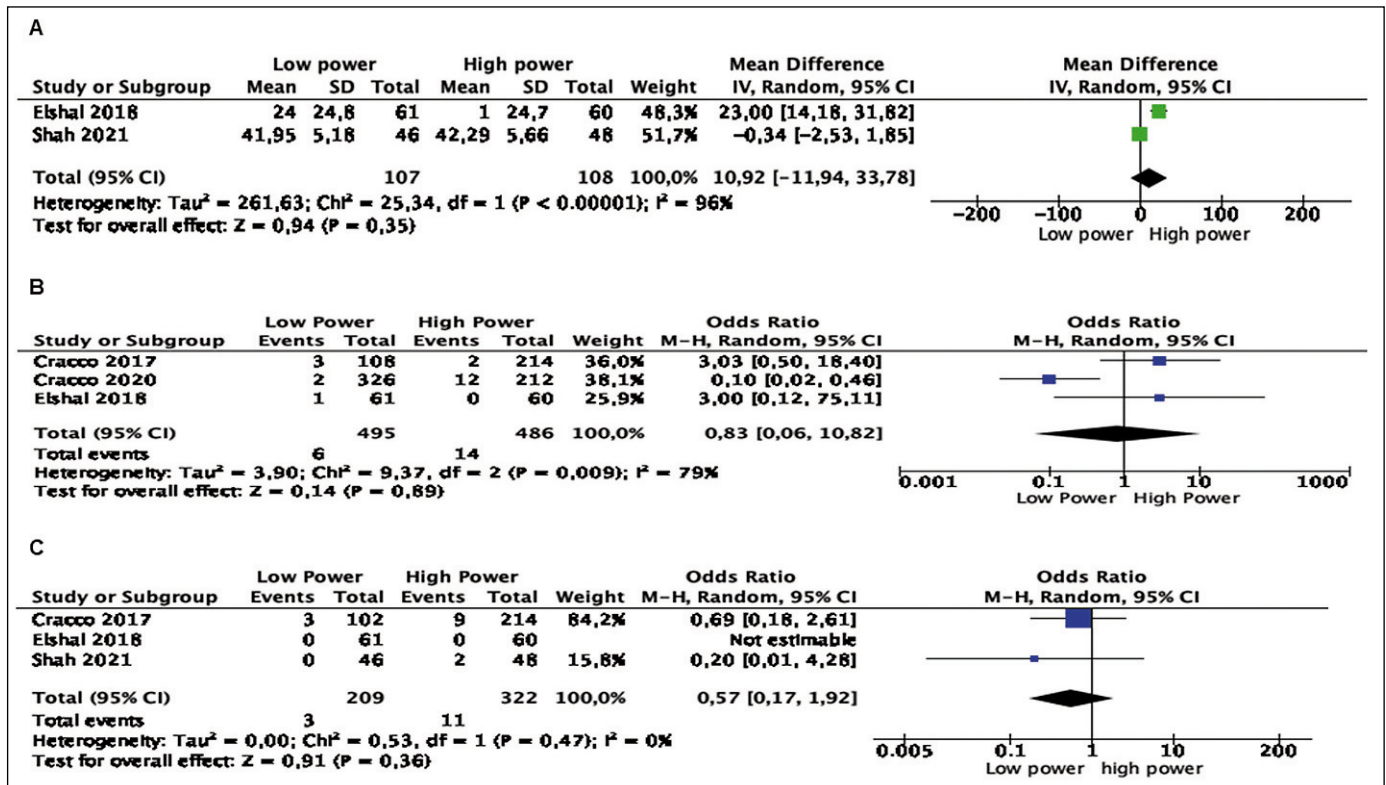


Figure 5. Meta-analysis forest plot. A. Postoperative stay (hours); B. Re-catheterization rate; C. Blood transfusions rate.

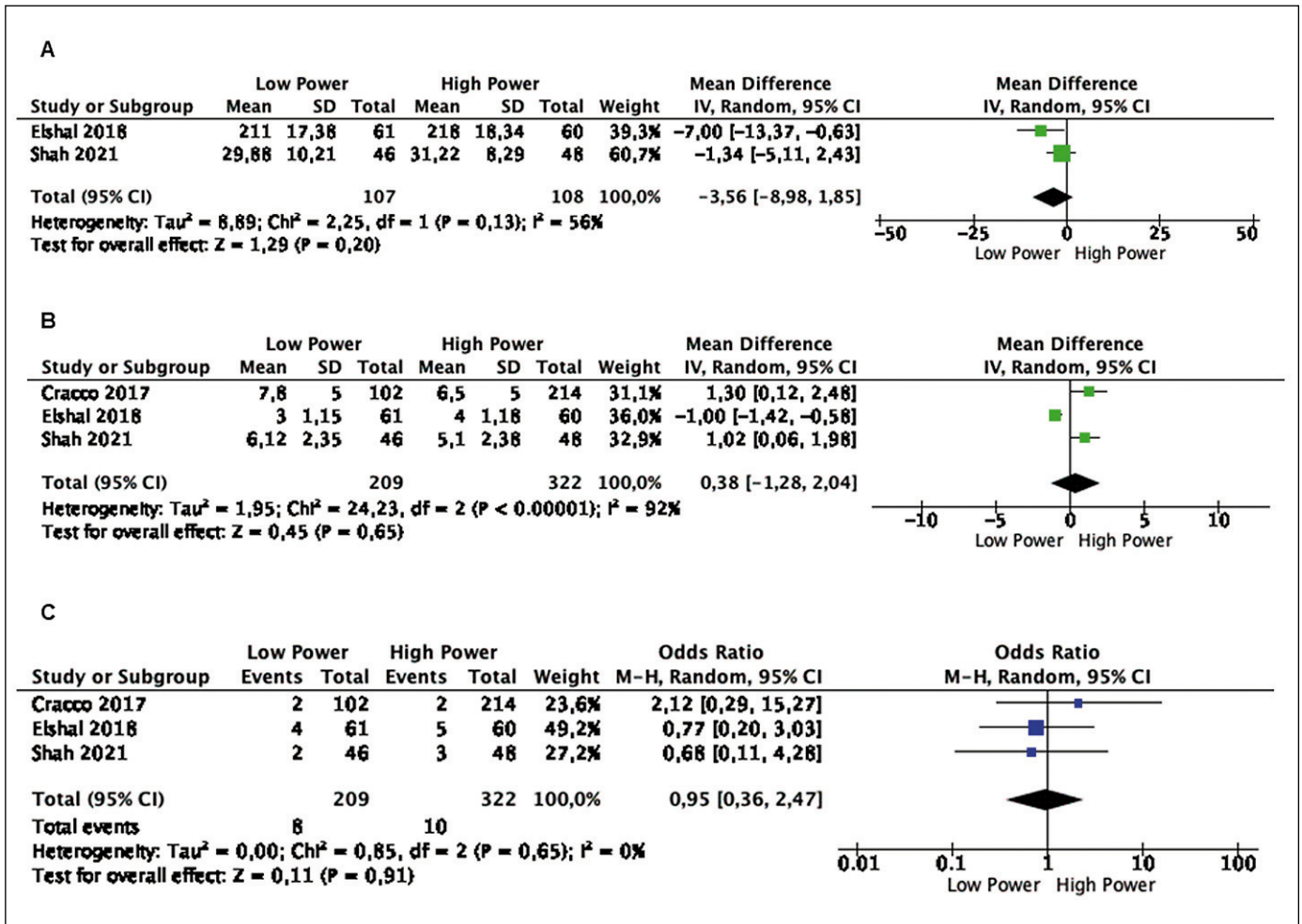


Figure 6. Meta-analysis forest plot. A. QMax (milliliters/second); B. IPSS; C. Incontinence rate.

Minagawa et al. [11]. In this study, 30 W HoLEP was performed by surgeons with different surgical expertise. Forty-four patients were operated on by an experienced surgeon, whereas 30 patients were operated on by 2 less experienced ones. HoLEP was completed successfully in all cases despite the LP setting, without the need to increase the output of the laser in any case, and no patient required blood transfusion. This sustains the hypothesis that HP is not necessary to achieve an effective enucleation with excellent hemostasis. The latter is also confirmed by our meta-analysis that showed no difference in postoperative transfusions rate between the LP and HP groups.

In the randomized controlled trial (RCT) by Elshal et al. [18], the authors performed HoLEP with a high energy setting to cut the prostatic tissue at the bladder neck, while the rest of the enucleation and hemostasis was performed with the low energy setting. They demonstrated comparable enucleation efficiency and procedure times even with low power laser

settings (50 W, 2 J/25 Hz), with a mean enucleation efficiency of 1.42 ± 0.6 and 1.47 ± 0.6 gm/min following LP HoLEP and HP HoLEP.

Regarding mean postoperative catheterization time, this MA found no significant differences between LP and HP HoLEP (MD -0.09 hours, 95% CI -4.19 -4.0, $p = 0.96$). This is also of utmost importance as it confirms the optimal coagulation effect also achieved with LP. No significant differences were noticed regarding mean hospitalization (MD 10.92 hours, 95% CI -11.94 - 33.78, $p = 0.35$).

With regards to the functional aspect – which is of great importance, especially in the context of benign diseases as BPH, short-term post-operative Qmax, IPSS score and PVR were analyzed. As far as we know, this is the first meta-analysis that analyzed post-operative functional data after LP versus HP HoLEP. LP HoLEP demonstrated to be non-inferior in comparison to HP HoLEP, with similar results in terms of both postoperative improvement of Qmax and IPSS score. Conversely, the MA results support

the hypothesis that using HP machines functional outcomes after HoLEP do not really improve. Data on PVR are only available in one comparative study by Shah et al. [21], in which they reported a similar decrease in both groups at early and long-term follow-up (up to five years).

Gilling et al. prospectively analyzed LP (n = 20 cases) versus HP (n = 20 cases) HoLEP and found no differences between the groups in terms of both postoperative Qmax and IPSS score up to 12 months of follow-up, with a significant and sustained improvement in these parameters for both energies [7]. Therefore, the proposed potential advantages of less postoperative storage symptoms in LP HoLEP were not statistically significant from results analysis.

The trifecta of a good anatomical enucleation includes the ability to perform a complete removal of the adenoma with minimal complications and early catheter removal with successful voiding.

Across the decades, HoLEP has demonstrated to be a safe technique with low complication rate and is referred to as the gold standard after TURP [19, 20, 21]. Moreover, the advent of MOSES technology can further improve HoLEP outcomes, transforming it to a day surgery procedure [22]. While HP and MOSES may only be available in referral centers, LP holmium laser machines are universally available, as frequently adopted for other endourological procedures (i.e., lithotripsy). In our MA we find that the 3 most common issues that concern a urologist, namely need for re-catheterization, blood transfusion and postoperative urinary incontinence, show no difference between both cohorts using LP or HP holmium laser machines. This is a very important revelation as it directly infers that in using a holmium energy source for enucleation, clinical outcomes are influenced more from the surgeon and that expertise plays a more important role than the machine itself [23].

It has been reported that approximately 16.6–29.4% of patients suffered from postoperative urinary incontinence within 6 months after HoLEP, but only 0–3.3% of patients could not fully recover their continence at 12 months [24]. Regarding the complications reported in this MA, similar incontinence rates were noted among the three included studies. Incontinence was mainly reported as transient and stress-induced in all the three works, and this can be reassuring for the patients and adds an important value in the context of preoperative counselling [25].

Anatomical enucleation of the prostate (AEEP) is known to be superior to resection techniques for any prostate size with regards to intra- and postoperative bleeding [26]. A large multicenter study by Romero-Otero et al. [26] reported that HoLEP

has no remarkable impact on blood loss. Mean hemoglobin before and after HoLEP decreased from 14.6 to 12.3 g/dl, and mean hematocrit decreased from 44.3% to 37.7%. Most recently, Ibrahim et al. [27] revealed in their prospective research that perioperative blood transfusion was required in merely 0.8% of patients. Our results also show that the blood transfusion rates were not different between the two groups. Theoretically, using HP setting affords the potential of better hemostasis due to the longer pulse width, however studies have also shown that there is no significant difference. Whilst it would have been of added value to know if patients on anticoagulant therapy show any difference when the energy used differs, this could not be examined as most studies excluded patients with bleeding tendencies or on anticoagulation, which could represent further confounders. However, since both cohorts have negligible blood loss, our MA also confirms the safe hemostatic effect of LP HoLEP.

Further multicentric trials are still needed to evaluate how factors considered important for enucleation, namely size of prostate, surgical technique and surgeon expertise [28], could influence the complication outcomes when different holmium machines are used, as only 1109 patients were included in this MA. The main limitation of this MA consists of the few number of available RCT and comparative studies, even if the actual evidences are in favor of a substantial similarity of results between LP and HP settings. Moreover, most of the comparative studies adopted a two-or three-lobes enucleation; thus, we can not certainly extend those indications for en-block HoLEP. However, from results of the en-block ‘no-touch’ LP HoLEP series by Cracco et al. [17] the incidence of postoperative dysuria appears markedly reduced due to less energy delivery to the capsular plane with consequently fewer thermal effects on the sphincter and at the same time avoiding inadvertent stretching of the sphincteric mucosa throughout apex enucleation.

CONCLUSIONS

Evidence from this MA show that the laser power setting does not relevantly impact on intra- or postoperative variables nor on complication rate. Whilst further comparative trials are still needed to validate the effectiveness of LP HoLEP with different techniques of enucleation, this MA can provide validity to surgeons who have access to LP machines to adopt this technique for HoLEP.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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