ENDOUROLOGY
Systematic Review

Is Thulium laser enucleation of prostate an alternative to Holmium and TURP surgeries - A systematic review?

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ABSTRACT

To assess efficacy and safety of Thulium laser enucleation of prostate (ThuLEP) for benign prostatic hyperplasia. It is a systemic review based on a comprehensive search of PubMed, Cochrane, and Google scholar databases from inception to 31 March 2020. All studies in English evaluating ThuLEP as well as those comparing it with Transurethral resection of prostate (TURP) and Holmium Laser enucleation of prostate (HoLEP) were enrolled. The primary outcome was to evaluate operative, postoperative, and functional outcomes (IPSS, QoL, Qmax, PVR) in patients undergoing ThuLEP. Secondary outcome was to compare operative, postoperative, and functional outcomes with TURP and HoLEP in comparative studies. Fourteen studies with a total of 2,562 patients were included in this review. 2,034 underwent ThuLEP, 349 underwent TURP, and remaining 139 had HoLEP. We found that ThuLEP is safe as well as efficacious in all age groups as well as across all prostate sizes and with all four functional outcomes (IPSS, QoL, Qmax, PVR) revealing marked improvement at 3, 6, 12, and 24 months. Compared to TURP and HoLEP, Thulep is non-inferior in terms of operative and functional outcomes and, in fact, is associated with lesser catheterization duration as well as shorter hospital stay. Further, Thulium fiber laser (TFL) has advantages of being light weight, having high frequency, less fiber degradation, and less energy consumption, making it cost effective for operational and maintenance purpose. ThuLEP is a safe, efficacious, and cost-effective procedure for BPE.

Keywords: Enucleation; holmium; LASER; prostate; thulium; transurethral resection.

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Introduction

Benign prostatic enlargement (BPE) often leads to urinary obstruction often referred to as Benign Prostatic Obstruction (BPO). The symptom complex developing as a result of this enlargement is termed as Lower Urinary Tract Symptoms (LUTS). LUTS is the most common urological problem among men, affecting about a third of men over age 50.[1,2] In addition to LUTS, these patients can have other symptoms as well, including retention of urine (acute and chronic), visible or non-visible hematuria, infections in urinary tract, stone formation in bladder, bladder wall weakness and damage, kidney dysfunction, and issues with continence.[3] For standardization of symptoms, International Prostate Symptom Score (IPSS) index is commonly used.[4] There is no ideal treatment, each patient's treatment is determined by factors, such as IPSS, BPE complications, and most importantly patient preferences. Research has revealed that majority of BPE patients receive pharmacological management in the form alpha blockers, 5-Alpha reductase inhibitors (5-ARIs), and other medications.[5] However, there is good population of men who end up having surgical interventions. Transurethral resection has been the reference "gold standard," but due to its complications and issues with larger volume prostates, many alternatives have been developed and assessed.[6] In order to overcome these issues, many alternative procedures have been evolved, which have been able to reduce complications, shorten hospital stay, and accelerate patient recovery without compromising efficacy. The new methods are broadly divided into three types according to their treatment principles: resection methods (resection of prostate tissue piece by piece), vaporization methods (vaporization of excessive prostate tissue), and enucleation methods (peeling the enlarged prostate from the prostate capsule).[7] Among these new treat-

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ments, enucleation methods have shown better Qmax and IPSS values than vaporization and resection methods.[7]

Lasers have been used in BPE treatment from last 15 years, recent advances in technology, more clinical experience, and more advanced devices have challenged the supremacy of TURP.[8] Among lasers, HoLEP has equivalent outcomes to TURP and open prostatectomy with reduced complications. With refinements in technique and better learning, HoLEP is often considered as a true gold standard for surgical management of BPH.[6] The Ho:YAG laser is a non-continuous pulsed laser with pulse duration of 350 ms. Energy is produced at a wavelength of 2,140 nm with prostatic tissue penetration of about 0.4 mm. In 2005, the high-power Thulium laser was introduced in treatment of prostatic hyperplasia.[9]

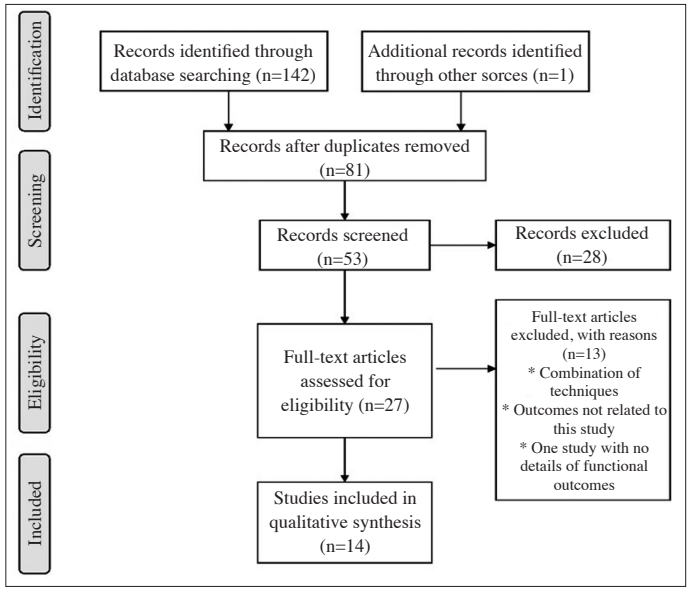

Figure 1. Preferred Reporting items for Systemic reviews and Meta-analyses flow sheet for study selction

Main Points:

- ThuLEP is a safe and efficacious alternative to HoLEP and TURP for all age groups and prostate sizes.
- Thulep is non-inferior in terms of operative and functional outcomes and, in fact, is associated with better post-operative results in terms of lesser catheterization duration as well as shorter hospital stay.
- All four functional outcomes (IPSS, QoL, Qmax, PVR) revealed marked improvement at 3, 6, 12, and 24 months.
- Thulium fiber laser (TFL) has advantages of being light weight, having high frequency, less degradation, and less energy consumption making it cost effective for operational and maintenance purpose.

This literature review will focus on critical analysis of Thulium Laser Enucleation of prostate (Thulep) for BPE. Firstly, this study looked into outcomes of ThuLEP procedure, including demographic characteristics, pre-operative, operative and post-operative variables, evaluating functional outcomes along with long term safety and durability. Secondly, this study compared outcomes of ThuLEP with HoLEP (Holmium Laser Enucleation of Prostate) and TURP in comparative studies to decrease bias. Further, it is important to mention that in our study, only ThuLEP procedures were taken into consideration unlike some other reviews, which have combined the usage of ThuLEP and Thulium Laser Vapoenucleation of prostate (ThuVEP).[10] To the best of our knowledge, as such, this is the first review that discusses ThuLEP exclusively.

Methodology

Search strategy and selection criteria:

PubMed, Cochrane, and Google scholar databases from inception to 31 March 2020. We searched with terms "BPH," "prostatic hyperplasia," "benign prostatic hyperplasia," "prostate enucleation," "Thulium laser," "Holmium laser," "transurethral resection of prostate".

143 articles matched initial search. After removing duplicates, 28 were excluded (language other than English, abstract-only studies) while 53 were screened. Further, SQR3 (Survey, Question, Read, Recite, and Review) technique was used and 14 relevant articles were selected.[11] Figure 1 represents the PRISMA Flow chart.

Outcome measures

The outcome measures for analysis included:

- Patient characteristics (age, high-risk patients),
- Operative characteristics (prostate volumes, surgical operative times, enucleated tissues weight, and enucleation time),
- Post-operative characteristics (pain, catheterization duration, and hospital stay), and
- Functional outcomes (Qmax, IPSS, QOL, PSA, and PVR).

Data extraction

During the first stage, pre-operative data included age of patient in years, prostate volume in mL, IPSS, Qmax in mL/sec, post-void residual (PVR) in ml, prostate-specific agent (PSA) in ng/mL, and hemoglobin in g/dL, and these data were collected and tabulated into two groups.

First group included eight ThuLEP only studies (Non-comparative), Table 1.[12-19] Second group included six Comparative studies only, Table 2.[20-25] It is important to note that out of these six comparative studies, only in four studies patients were randomized. In one study, matching pair analysis was used and in another patient inclusion and exclusion criterion was used for grouping of patients.

Table 1. Pre-operative characteristics from Thulium-only studies

	Study	Number of patients	Age in years	Prostate volume in ml	IPSS	QOL	Qmax (mL/sec)	PVR in mL	PSA (ng/mL)	Hb
1	Chang et al.[12] (Retrospective)	125	71.85	106.8	27.9	-	9.9	329.7	4.5	-
2	Raghuvanshi and Vartak[13] (Prospective)	109	70	120.5	30	-	-	-	1.85	11.75
3	Saredi et al.[14] (Prospective)	100	70	59	26	4	8.8	70	4.16	14.6
4	Castellani et al.[15] (Prospective)	412	69.8	58	26	4.4	8.1	-	2.9	-
5	Raber et al.[16] (Prospective)	139	67.8	66.9	21.2	4.4	9.6	131	4.5	-
6	Vartak and Salvi[17] (Prospective)	236	72.5	70	21	-	11.2	-	3.8	-
7	Rausch et al.[18] (Prospective)	234	72.88	84.8	-	-	10.17	-	7.29	-
8	Iacono et al.[19] (Prospective)	148	68.2	108.8	21.1	4.38	-	-	9.53	-

Hb: Hemoglobin; IPSS: International Prostate Symptom Score; PVR: Post-Void residual; PSA: Prostate Specific Antigen; ThuLEP: Thulium Laser enucleation of Prostate; QoL: Quality of Life; Qmax: Maximum Flow rate

Table 2. Pre-operative details from comparative studies (ThuLEP vs HoLEP)

	Study	Procedure Type	Number of patients	Age in years	Prostate volume in mL	IPSS	QOL	Qmax (mL/sec)	PVR in mL	PSA (ng/mL)	Hb
9	Pirola et al.[20] (Retrospective)	ThuLEP	117	70	75	20	5	7	90	3.8	13.5
		HoLEP	117	70	75	21	5	7	130.5	5.4	14
10	Zhang et al.[21] (Prospective)	ThuLEP	71	74.2	45	24.6	-	7	64.6	-	-
		HoLEP	62	74.2	45	22.8	-	7	64.6	-	-
Pre-operative details from comparative studies (ThuLEP vs TURP)											
11	Hou et al.[22] (Retrospective)	ThuLEP	135	70	53.5	25.5	4.8	7.8	125	5.7	-
		TURP	141	68	48.4	24.6	4.6	10	118	4.8	-
12	Bozzini et al.[23] (Prospective)	ThuLEP	102	72.5	89.7	19.7	-	7.5	120	3.2	14.2
		TURP	106	70.7	81.9	18.6	-	6.9	112.9	3.6	14.7
13	Swinarski et al.[24] (Prospective)	ThuLEP	54	68.3	62.03	20.38	4.7	7.73	166.2	3.37	14.2
		TURP	54	69.3	66.5	20.85	4.9	8.57	152	3.73	14.4
14	Xia et al.[25] (Prospective)	ThuLEP	52	68.9	59.2	20.8	4.7	8.0	93.1	-	-
		TURP	48	69.3	55.1	20.8	4.5	8.3	85	-	-

Hb: Hemoglobin; HOLEP: Holmium laser enucleation of prostate; IPSS: International Prostate Symptom Score; PVR: Post-Void residual; PSA: Prostate Specific Antigen; ThuLEP: Thulium Laser enucleation of Prostate; TURP: Transurethral Resection of Prostate; QoL: Quality of Life; Qmax: Maximum Flow rate

This was followed by extracting intra-operative details, including total surgical time in minutes, enucleation time in minutes, morcellation time in minutes, and enucleated adenoma weight in grams. Post-operative parameters included hospital stay, catheterization time, prostate volume in mL, IPSS, Qmax in mL/sec, PVR in mL, PSA in ng/mL, Hemoglobin drop in g/dL, and overall complications. These details are summarized in Tables 3 and 4 (a, b).[12-25]

Results

Based on primary outcomes, the results from patients who underwent ThuLEP procedure for BPH are as under:

1. Age: This review found that mean age of patients was around 70 years. However, many studies have revealed ThuLEP is safe in elderly population even in the range of 90 years as well.[12,13,22]
2. High-Risk Patients: ThuLEP can be used in patients having high risk American Society of Anaesthesiologists (ASA) grades for surgery. In one study, 109 patients with ASA Grade 3 or 4, in age group of 60 and 70 years, having comorbidities, such as ischemic heart diseases, hypertension, and diabetes mellitus, underwent ThuLEP with good results.[14]

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Table 3. Intra- and post-operative details from Thulium-only studies

	Study	Total surgical time (minutes)	Enucleation time/ Morcellation time (minutes)	Enucleation Weight in grams	Hospital Catheterization in days	Stay in days	IPSS	QoL	Qmax In mL/sec	PVR mL	PSA in (ng/mL)	Hb drop g/dL	Complication rate
1	Chang et al.[12] (Retrospective)	-	-	-	-	-	7.35	-	17.92	48.22	-	-	CD-24 %, Mortality=0.8%
2	Raghuvanshi and Vartak[13] (Prospective)	62.5	35/27.5	-	1	2.5	-	-	-	-	-	0.9	41% including one death
3	Saredi et al.[14] (Prospective)	56.5	21.5/ 15	-	1	1	3	1	19	-	1	1.4	CD-14%
4	Castellani et al.[15] (Retrospective)	55	-	-	2	3	4	0.9	13.2	-	1	-	CD-14.1 %
5	Raber et al.[16] (Prospective)	63.7	-	23.8	1.5	-	3.6	1.8	31.2	-	1.2	1.9	CD -3.6%
6	Vartak and Salvi[17] (Prospective)	86.5	53/33.5	-	1.05	1.18	4.2	-	21	-	1.3	0.8	Superficial bladder injury (7.6%), Stricture (3.8%), Bladder neck contracture (1.2%)
7	Rausch et al.[18] (Prospective)	102.54	-	53.68		6.5	5.1	1.07	23.27	12.40	-	-	CD-19.8%
8	Iacono et al.[19]	70.03	50.34/18.23		2.04	2.15	3.90	-	28.67	-	0.94	1.27	UTI (12.8%), Irritating symptoms (6.7%, Re-catheterization (2.7%)

CD-Clavien Dindo classification of post-operative complications[26], Hb: Hemoglobin; HOLEP: Holmium laser enucleation of prostate; IPSS: International Prostate Symptom Score; PVR: Post-Void residual; PSA: Prostate Specific Antigen; ThuLEP: Thulium Laser enucleation of Prostate; TURP: Transurethral Resection of Prostate; QoL: Quality of Life; Qmax: Maximum Flow rate

3. Prostate Volumes: In this review, we found ThuLEP has been safely used in prostates with volumes of 70 mL on an average. However, a recent study has found, in 125 patients with volumes of more than 80 mL, that ThuLEP is safe as well as efficacious.[12]
4. Operative times: Operative times of ThuLEP was around 75 minutes in our review. On an average enucleation time was about 50.75 and morcellation time being 20.72 minutes. It is anticipated that enucleation can be better with TFL as compared with Ho:YAG as laser fiber as it is continuous in former rather than pulsed. However, there was still visible variation in duration of surgeries in different studies, the two main factors responsible for time duration included previous exposure to laser enucleation techniques and, secondly, less experienced surgeons taking more time for enucleation.[14]
5. Enucleated Tissue: Enucleated adenoma weight was on an average around 35 grams.
6. Post-operative pain: A recent study has established that ThuLEP is far more tolerated and needed minimal analgesia in post-op period compared with other procedures; study found that the TURP group required oral analgesics for more than 1 week after surgery (12.2% vs 4.4%, p=0.039).[22]
7. Catheterization Time and Hospital stay: For ThuLEP procedures average Catheterization timing was 1.5 days. This is quite an important factor as it often determines safe discharge of the patient from the hospital. The average hospital stay in hospital was 2.8 days for ThuLEP patients.

Table 4a. Intra- and post -operative details from comparative studies (ThuLEP vs HoLEP)

	Study	Procedure type	Total surgical time (minutes)	Enucleation time/ Morcellation time (minutes)	Enucleation Weight in grams	Catheterization in days	Hospital stay in days	IPSS	QoL	Qmax In mL/sec	PVR in mL	PSA (ng/mL)	Hb drop g/dL	Compli-cation rate
10	Pirola et al.[20] (Retrospective)	ThuLEP	82.7	70.5/12.0	45.6	1	1	3.8	0.36	20.43	11.83	2.6	0.5	20%
		HoLEP	90	75.5/11.5	44	1	2	4.8	1	23	29.83	2.0	0.9	26%
11	Zhang et al.[21] (Prospective)	ThuLEP	37.6	-	37.6	2.4	-	9.0	1.8	21.75	16.25	-	0.5	-
		HoLEP	40.4	-	40.4	2.5	-	9.5	1.8	19.75	18.00	-	0.5	-

Table 4b. Intra- and post-operative details from comparative studies (ThuLEP vs TURP)

12	Hou et al.[22] (Retrospective)	ThuLEP	79.3	-	24.99	-	4.2	4.06	1.4	14.76	-	-	-	11.99 %
		TURP	62.4	-	23.03	-	4.3	3.9	1.3	15.1	-	-	-	5.0%
13	Bozzini et al.[23] (Prospective)	ThuLEP	53.69	-	51.13	1.3	1.7	5.8	-	22.14	31.2	-	.45	17.2%
		TURP	61.66	-	48.84	4.8	5.2	5.7	-	19.87	39.8	-	2.8	24.3%
14	Swinarski et al.[24] (Prospective)	ThuLEP	102.2	74.2/28.1	24.8	2.1	3.6	7.5	1.7	22.44	29.9	-	0.95	-
		TURP	74.2		34.8	2.0	3.5	7.8	1.4	24.9	32.4	-	1.8	-
15	Xia et al.[25] (Prospective)	ThuLEP	46.3	-	21.2	1.9	4.8	4.7	1.2	24.0	14.1		0.92	UTI (3.9%) Ret. Ejacu-lation (55%)
		TURP	50.4	-	34.8	3.6	6.7	4.7	1.1	23.3	15.0		1.46	UTI (8.3%) Ret. Ejacu-lation (965%)

Hb: Hemoglobin; HOLEP: Holmium laser enucleation of prostate; IPSS: International Prostate Symptom Score; PVR: Post-Void residual; PSA: Prostate Specific Antigen; ThuLEP: Thulium Laser enucleation of Prostate; TURP: Transurethral Resection of Prostate; QoL: Quality of Life; Qmax: Maximum Flow rate

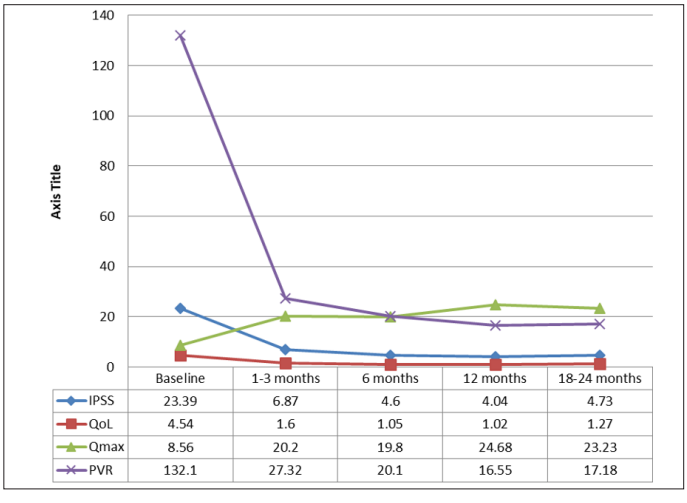

Figure 2. Functional outcomes after ThuLEP
IPSS: International Prostate Symptom Score; PVR: Post-Void residual; PSA: Prostate Specific Antigen; QoL: Quality of Life; Qmax: Maximum Flow rate

8. Functional outcomes: Functional outcomes after calculating averages are summarized in Figure 2. The main reason was variability in studies in their follow up. In some studies, it was 4-6 weeks and in others as far as 24 months. The reasons for variation are 2-fold origin of study determining length of follow up based on local guidelines and practices and secondly determined by the main aim of study. All four parameters IPSS, QoL, Qmax, and PVR show improvement till 12 months and then values usually plateau. This is seen in terms of means as well as values obtained in studies carried for 24 months.[15,18]
9. Complications: We found lot of variation in reporting of complications. On Clavein Dindo reporting most studies reported Grade 3 being maximum[26]. Most common complications included urinary tract infections, irritating symptoms, and re-catheterization. One study reported death of a patient due to myocardial infarction 1-week post-surgery.[13]

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Table 5. Summarized results for all three types of surgeries

	ThuLEP	TURP	HOLEP
Patients	2034	349	179
Age	70.49	69.3	72.1
Preoperative			
	ThuLEP	**TURP**	**HOLEP**
Prostate volume	75.64	62.9	60.0
IPSS	23.39	21.21	21.9
QoL	4.54	4.6	5.0
Qmax	8.56	8.4	7.0
PVR	132.1	116.9	97.5
PSA	4.55	4.04	5.4
Hb	13.65	14.55	14.0
Operative			
Total surgical time	69.12	62.16	65.2
Enucleation time	50.75	-	75.5
Morcellation time	20.72	-	11.5
Enucleated adenoma weight	35.35	35.36	42.2
Post-operative			
	ThuLEP	**TURP**	**HoLEP**
Catheterization time (days)	1.57	3.4	1.75
Hospital stay (days)	2.8	4.9	2.0
IPSS	5.07	5.5	7.15
Qol	1.24	1.26	1.08
Qmax (mL/sec)	21.52	21.04	21.37
PVR (mL)	23.41	29.06	23.9
PSA (ng/mL)	1.34	-	2.0
Hb drop (g/dL)	0.95	2.0	0.7

Hb: Hemoglobin; HOLEP: Holmium laser enucleation of prostate; IPSS: International Prostate Symptom Score; PVR: Post-Void residual; PSA: Prostate Specific Antigen; ThuLEP: Thulium Laser enucleation of Prostate; TURP: Transurethral Resection of Prostate; QoL: Quality of Life; Qmax: Maximum Flow rate

10. Cost: Regarding cost effectiveness, although there are no comparative trails available but there are multiple factors that make ThuLEP a cost-effective procedure. If we look at acquisition costs, TFL fiber cost is about 400 Pounds each, which is comparable to other Laser systems, however, in contrast to them, it can be used many times and amounts to negligible running costs.[27] Similarly, energy consumption is 9 times less than Holep and less maintenance of components decreases cost further.[28] Also less intra-operative morbidity and early post- operative recovery, helps in early hospital discharge, and subsequently leads to a decreased cost.[29]

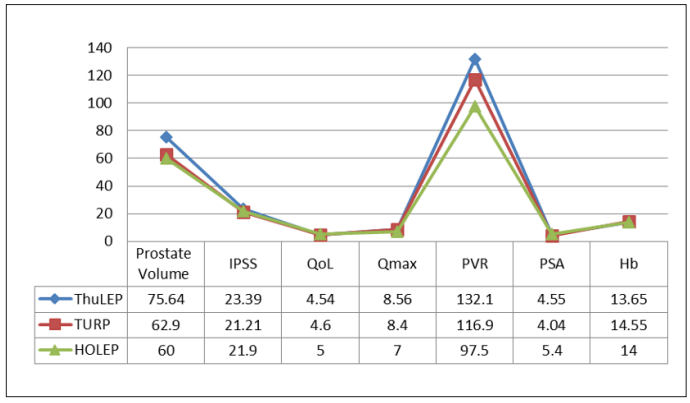

Figure 3. Pre-operative comparison
Hb: Hemoglobin; HOLEP: Holmium laser enucleation of prostate; IPSS: International Prostate Symptom Score; PVR: Post-Void residual; PSA: Prostate Specific Antigen; ThuLEP: Thulium Laser enucleation of Prostate; TURP: Transurethral Resection of Prostate; QoL: Quality of Life; Qmax: Maximum Flow rate

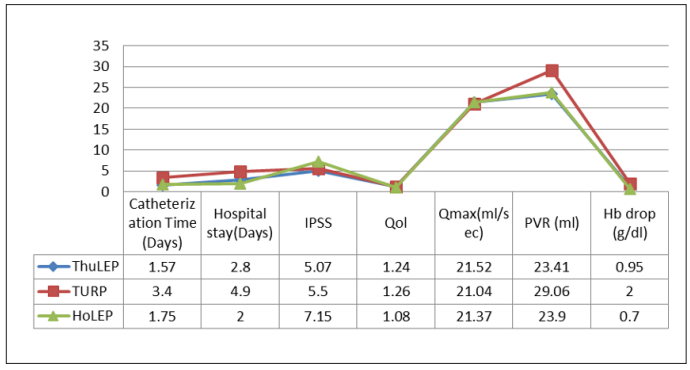

Figure 4. Post-operative comparison
Hb: Hemoglobin; HOLEP: Holmium laser enucleation of prostate; IPSS: International Prostate Symptom Score; PVR: Post-Void residual; PSA: Prostate Specific Antigen; ThuLEP: Thulium Laser enucleation of Prostate; TURP: Transurethral Resection of Prostate; QoL: Quality of Life; Qmax: Maximum Flow rate

Secondary outcomes included comparison with TURP and HoLEP. Table 5 summarizes mean values for all studies for purpose of comparison. Graphical comparison is represented in Figures 3, 4.

Discussion

Lasers have become an essential tool in the armamentarium for urologists. Lately, Thulium laser has been making in roads and replacing Ho:YAG laser. Although both Holmium and Thulium lasers use water as chromophore, the fiber in Thulium Fiber Laser (TFL) is diode pumped, which gives it the capability of operating in either a pulsed mode or a continuous wave mode at around 2000 nm. The continuous wave mode is more suitable for haemostasis and coagulation of tissue, whereas the pulsed mode is more suited for lithotripsy.[30] The continuous mode causes

rapid and improved vaporization thereby ensuring smooth tissue incisions compared to those of the holmium laser. This helps surgeons to accurately remove the adenoma at the level of the surgical capsule by easily distinguishing adenoma.[31] Further with shallow depth of penetration of 0.25 mm, it causes minimal damage to surrounding tissues. This helps in prevention of many post-operative complications, including post-operative dysuria noticed with other lasers.[32] The other advantages of TFL is that its diameter is about 50 mm compared to minimum 200 mm in Ho:YAG, this results in advantages in irrigation, scope deflection, and (in) direct effects on accessibility, visibility, efficiency, and surgical time, as well as offering future miniaturization possibilities.[33] Further, TFL fibers do not degrade easily and have 4 times more absorption coefficient and results in higher ablation efficiency.[34] The TFL machine itself is seven times smaller and eight times lighter than a high-power Ho:YAG laser system(35-45 kg to 250-300 kg) and consumes nine times less energy as its frequency can reach upto 2,200 Hertz (Hz) compared with Ho:YAG, which can reach a maximum of 80-100 Hz. Maintenance is expected to be very low due to the durability of its components.[15]

Our review revealed that ThuLEP is safe for all age groups as well as for all prostate sizes. Comparing it with TURP and HoLEP we established it is non-inferior to both these standard procedures intra-operatively in terms of tissue enucleation and overall surgical duration. The results from our review regarding improvement in functional outcomes and complications are somewhat similar to a previous review in which all forms of Thulium laser procedures for BPH (enucleation, resection, and vaporization) were compared with TURP, BiTURP, and Holmium.[10] In one study comparing ThuLep with TURP, a higher proportion of patients in the TURP group required oral analgesics for more than 1 week after surgery (12.2% vs 4.4%, p=0.039).[25] In our review, the mean catheterization timing for ThuLEP was 1.5 days, which was lower compared with HoLEP at 1.75 days and 3.4 days for TURP. This often gets reflected in early discharge from hospital. It is estimated that such outcomes can bring down cost from conventional surgeries by about 27%.[16]

Regarding cost effectiveness, although there are no comparative trails available but there are multiple factors that make ThuLEP a cost-effective procedure as has been explained and highlighted earlier in results section. Another added benefit is that ThuLep is easy in terms of the learning curve as compared with HoLep, which needs 40-60 cases on an average to become proficient.[35] The first important reason for this that the thulium laser allows for instant conversion to vaporization with the same end-fire fiber, a technique that more urologists are comfortable with.[36] The second reason is that compared to HoLEP, ThuLEP vaporizes more tissue, makes a wider incision and plane between adenoma, and the capsule is always clearly visible.[19]

This review has many limitations, the primary goals of different studies were variable and as such there was quite variability in patient characteristics. Further, the outcome measurements were calculated in different methods and authors had to often calculate averages for outcome measurements. In addition, there was often non-uniformity in reporting complications. Some studies had reported complications using Clavien Dindo classification, while as others had enlisted in percentages.[26]

In conclusion, ThuLep is safe, efficacious, and cost-effective alternative to TURP and HoLEP in all age groups and prostate sizes. To establish its permanent position in management of BPE, more comparative trials will be necessary in future.

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