Review Article

Holmium Laser Prostate Enucleation (HOLEP) Versus Trans-Urethral Resection of Prostate (TURP) in Treatment of Symptomatic Prostatic Enlargement; A Health Technology Assessment

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Abstract:

Introduction: Our aim was to compare the cost effectiveness of holmium laser prostate enucleation (HOLEP) versus trans-urethral resection of prostate.
Materials and Methods: We searched all available databases for any controlled trials comparing HOLEP and TURP from January 2000 to February 2009. Two independent reviewers studied and appraised the selected evidences. Then, effectiveness and cost effectiveness of HOLEP was evaluated.
Results: We identified four randomized controlled trials and one systematic review according to the inclusion criteria. Most of the studies had moderate quality of evidence with limited sample sizes. Overall success rate of HOLEP was comparable with TURP; but, some secondary outcomes such as pick flow rate twelve months after the surgery was better in HOLEP. A comparison between the original costs and those obtained from sensitivity analysis showed that the cost parameters were sensitive to the number of the patients treated. Increasing the number of the patients from 200 to 300 changed the study's results in favor of the new techniques.
Conclusion: Since the holmium and thulium laser sets are sensitive to the number of the patients and multipurpose, they potentially can be applied for stone fragmentation. Thus, utilization of these equipments will divide the costs between two groups of the services. In economic terms, these properties lower overhead costs and justify the purchasing of these equipments.
Keywords: Lasers, Solid-State; Prostate; Holmium laser; Therapy; Symptomatic Prostatic Enlargement; Assessment, Biomedical Technology

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Introduction

Benign prostatic hyperplasia (BPE) is defined as enlargement of the prostate gland(1). It is quite common and affects the patients' quality of life due to lower urinary tract symptoms(2,3). Safarinezhad et al showed that 30 of each 100000 Iranian men suffer from symptomatic BPE. Lost life years

(LLY) for BPE was 30174 and disability due to BPE and disability-adjusted life year (DALY) were measured to be 55 and 45.3, respectively(4). Prevalence of symptomatic BPE is reported to be 36% in Iranian men aged 60 to 69 years according to the subjective information of the international prostate symptom score (IPSS), ultrasound, and digital rectal exam(5). Various treatment options are introduced for symptomatic BPE. Transurethral resection of prostate (TURP) is the gold standard surgical method when the medical therapy fails. Despite relatively low TURP- related morbidity, unimproved symptoms might be due to lack of technical skills of the inexperienced urologists. Some other sources of energies have been reported as alternative for prostate enucleation. There is no Iranian evidence based review about the cost effectiveness of the Lasers in prostate surgeries. Laser therapy has been introduced as an effective approach with fewer side effects and faster recovery time(6). Three sources used for symptomatic BPE include neodymium, holmium, and thulium laser, or potassium-titanyl phosphate (green light). The scarcity of the resources along with more external effects have led health policy makers to frequently focus on the health economics. That is, considering fairness and equity aspects of the services, techniques used in health economics have rendered appropriate ways to contain interventions' costs and making appropriate decisions. As advances in medical technologies take place, the more and more expensive equipments, drugs, and procedures will enter into the market with their advantages and disadvantages. Considering the fact that the government should at least provide the minimum needed services, applying a criterion that helps in adopting rational decisions is necessary. Economic evaluations of the health interventions direct the health resources to their best usages. Since the import costs of the equipments and technologies in Iran account for a large part of health expenditures and also these costs are directly related to the human's life, determining the effectiveness and cost-effectiveness of these technologies in the foregoing area is an important issue. This study addresses the same issue attempting to determine costs and outcomes of using laser technology (thulium laser and holmium) in treatment of BPE and compares it with the current method of TURP.

Methodology

Search Strategy

A systematic search was conducted in MEDLINE via Pub med (including Clinical Queries), Cochrane, TRIP database, Psycoinfo, NHS Economic Evaluation Database, NIHR HTA, NHS Centre for Reviews and Dissemination (CRD), Health star database, Dissertation Abstracts Online (UMI) via ProQuest, and Google Scholar. We searched EMRO-WHO website for epidemiological studies and Iranian Ministry of Health websites for economic studies in Iran. We also searched Iranian (Persian) ophthalmology websites for patient views studies. The last search was performed in February 2009. We limited publication date from 2000 to February 2009 and performed the search using holmium laser AND prostate (HOLEP) and thulium laser AND prostate keywords. Accordingly, we searched Pub med (including Clinical Queries) for both MESH terms and free language keywords including "lasers, solid-state" (subject heading), "prostate" and "thulium laser". We limited the search to Meta-analyses and randomized control trials as well as "Title /abstract" field. In Cochrane Library database we searched for keywords in "Title, abstract and keyword" fields. We searched Google Scholar for "HOLEP", "prostate", "thulium laser" and "health technology assessment" in "Medicine, Pharmacology, and Veterinary Science" subject area. In other databases, we searched for above keywords.

Two independent reviewers studied the selected randomized controlled trials, systematic reviews, and meta-analyses. A critical appraisal was done by CASP international tool. For any disagreements, third party was invited to solve the problem. Two prevalence study of BPE in Iran also included obtaining the burden of diseases.

Cost Analysis

In order to economically evaluate the alternatives, the process of surgery, regarding the perspective of the study, we determined through literature review, interview, and observation. Cost analysis was performed after considering the personnel cost, consumables, depreciation, and utilities. Sensitivity analysis was conducted for different scenarios. This study was originally conducted

as a health technology assessment to assess new laser technologies in BPE treatment from the four points of view; safety, efficiency, effectiveness, and economy. This article addressed economic aspect of the foregoing study. Finally, a comparison was made between the laser and surgery (traditional) methods. Cost-effectiveness(7) was used as the principal option in economic evaluation. The different procedures using laser technologies were compared with the traditional procedure (TURP). Patient preferences were used to analyze quality (utility) of life. All costs and outcomes were taken from the perspective(8) of Ministry of Health and Medical Education (MOHME). The study was designed and conducted in three phases: determining effectiveness, cost analysis, and comparison of the costs and outcomes.

Standard costing method was used in cost analysis. Firstly, the process of each intervention was portrayed on the basis of the interview, Delphi method, and focus group method and decision tree were used in the modeling(9). All inputs in the process of an intervention including labor time, consumables required, equipments, utilities and setting, running and training costs were then valued(8). The depreciation cost was calculated using direct line method(10). At the end of the cost analysis stage, the total cost and unit cost of each intervention were estimated. To include indirect costs, the patients' and their families' time off costs, considering minimum settled salary by Iran Ministry of Labor and Social Affairs, were used. Since estimating intangible costs was difficult, they were not included in this study(8). To cope with the uncertainty and generalization issues, one-way sensitivity analysis has been done for some variables(11,12).

End Points

In HOLEP, laser is inserted in the urethra with a cystoscope and delivers heat to the prostate to destroy the tissue. The approach begins from the points 5 and 7 of the bladder neck with 60-80 w through the end fibers. Prostate adenoma is completely ablated. Primary end points of the surgery are lower urinary tract symptom relief and urinary flow rate improvement. Secondary end points are intra- and post-operative complications including bleeding, transfusion rate, TUR syndrome, urinary incontinence, urinary retention, loss of ejaculation, quality of life, duration of surgery, length of hospitalization, and reoperation.

Results

A total of 88 articles were identified, of which, 67 were excluded on the basis of the titles and abstracts and 21 articles were left according to the inclusion and exclusion criteria. These articles were evaluated by clinical librarians and expert evaluators. Also, systematic reviews and RCTs were evaluated through CASP international worksheet. Eventually, 11 titles were excluded, leaving 7 to be reviewed (Figure 1). Meanwhile, 5 RCTs and one related systematic review were selected for evaluation of effectiveness. One recent RCT about HOLEP had open prostatectomy instead TURP in control arm, which was excluded(13-17). Total number of the patients in HOLEP group was 277 in comparison with 270 in TURP group(18).

A systematic review performed in 2008 included all selected RCTs related to HOLEP. But, because of significant heterogeneity of the data, they were done a random effect meta-analysis(18). Mean different of the mentioned end points in

Table 1. Outcome of HOLEP versus TURP 12 months after surgery

Outcome	No of trials in meta-analysis (total reporting outcome)	Effect size (95% CI)	P value
Mean symptom score	5 (5)	0.82 (-1.76 to 0.12)	0.09
Duration of operation	5 (5)	16.96* (13.45 to 20.47)	<0.001
Length of hospital stay	4 (4)	−1.05* (−1.20 to −0.89)	<0.001
Reoperation	4 (4)	0.68† (0.32 to 1.44)	0.31
Peak urine flow rat (ml/s)	5 (4)	1.48 (0.56 to 2.40)	0.002
Loss of ejaculation	2 (2)	1.14 (0.95to 1.36)	0.15
Blood transfusion	4 (4)	0.27 (0.07-0.95)	0.04

*Weighted mean difference.
†Relative risk

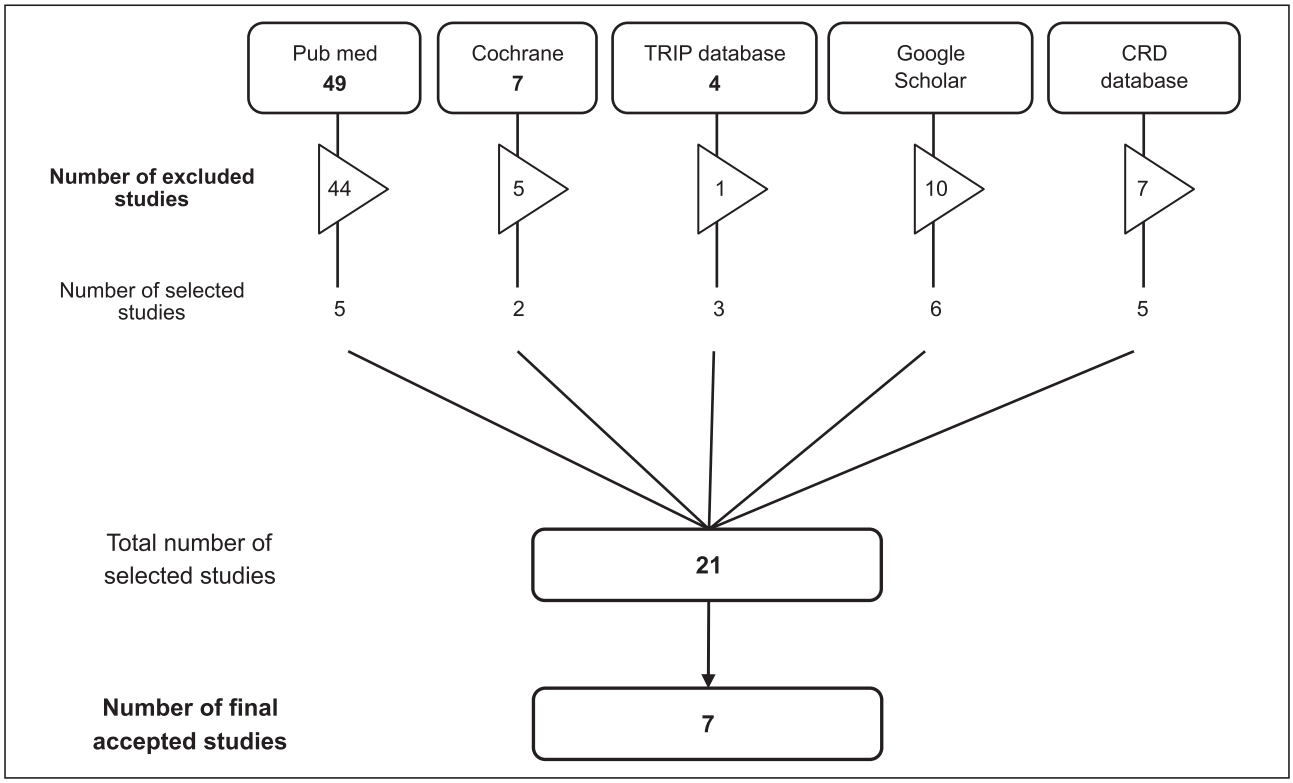

Figure 1. Study selection flow chart

methodology, illustrated in Table 1.

Quality of life 12 months after the surgery was almost similar; but, the confidence interval was very wide. There was no high-quality report about the rate of urinary retention, incontinence, infection, urethral stricture, or erectile dysfunction in two groups(18). On the other hand, in a prospective trial for thulium laser prostatectomy (ThuLEP), 100 patients were randomized to receive either a TURP (n = 48) or thulium laser prostatectomy (n = 52). Thulium laser prostatectomy associated with significantly better results in comparison with TURP in terms of catheterization time (45.7 ± 25.8 h vs. 87.4 ± 33.8 h, P < 0.0001), hospital stay (115.1 ± 25.5 h vs. 161.1 ± 33.8 h, P < 0.0001), and drop in hemoglobin level (0.92 ± 0.82 g/dl vs. 1.46 ± 0.65 g/dl, P < 0.001); but, it was time-consuming. The quality of the study was moderate and learning curve was not illustrated in this study(19).

Xia et al reported another RCT to compare ThuLEP and TURP in a group of 100 patients. The results showed that ThuLEP was superior to TURP in term of catheterization time (45.7+/-25.8h vs. 87.4+/-33.8h, P<0.0001), hospital stay (115.1+/-25.5h vs. 161.1+/-33.8h, P<0.0001), and drop in hemoglobin (0.92+/-0.82 g/dl vs. 1.46+/-0.65 g/dl, P<0.001), whereas, it required equivalent time to perform (46.3+/-16.2 vs. 50.4+/-20.7 min, P>0.05). Improvement of the symptoms was similar in both groups. Again, this study is suffering from little attention to methodological points(20).

In summary, HOLEP seems to have an acceptable effectiveness in comparison to TURP.

As a result of the study, various cost elements incurred during the process of a prostatic surgery were determined. The activities carried out in each procedure were reviewed and it was indicated that the processes of activities in both procedures were almost similar. The differences between the two methods were attributable to the quality of services (resources used), the length of hospital stay, and the side effects of the surgery. In this study, costing was done based on the government tariffs rather than real costs. Some overhead costs were not included in the analysis due to the similarity of these costs between the two procedures, while there was not any difference in the effectiveness of the two procedures. Thus, the incremental cost effectiveness ratio (ICER) was not calculated

and this study was conducted on the basis of Cost Minimization Analysis (CMA)(8). Table 2 represents the cost analysis of different procedures from the perspective of MOH, thereby unit cost per patient in the sampling of 200 patients.

In order to make a comparison between the costs of the alternatives, the cost difference of each alternative with the current procedure worked out. The unit cost of each alternative shows the cost of performing a surgery using each alternative.

Since holmium and thulium laser sets can be applied for both prostate surgery and stone fragmentation, the purchasing and setting costs of these sets will be cut in half. In fact, following this scenario, some of the overhead costs will be distributed among more patients and this leads to a drop in the unit costs. Obviously, under this scenario, the thulium laser procedure - as shown in Table 3- will be emerged as the most cost effective procedure.

Sensitivity analysis: In this section, the impact of changes in demand on the unit cost of procedures was examined. The objective was to find the threshold level that changed the dominance of an alternative(9). Increasing the number of patients from 200 to 300 changed the study results. A comparison between the original costs and those obtained from sensitivity analysis showed that the cost parameters were sensitive to the number of the patients treated. The impacts of changes in the number of the patients are reported in Tables 4 and 5.

As shown in these Tables, the thulium laser procedure was determined as the most cost-effective way in both uni-purpose and dual -purpose conditions (-772808 cost difference in comparison with the current procedure).

Table 2. The unit cost of different procedures used in prostatic surgery, (200 patients)

	Procedures		
	Thulium laser	**Holmium**	**Transurethral resection of the prostate**
Unit cost	4338541	4719261	4325794
The cost difference in comparison with the alternative	12746	393466	0

Note: all costs estimated in Rails

Table 3. The unit cost of different procedures used in prostatic surgery regarding bi-purpose properties of thulium and holmium, (200 patients)

	Procedures		
	Thulium laser	**Holmium**	**Transurethral resection of the prostate**
Unit cost	3728541	4534261	4325794
The cost difference in comparison with the alternative	-597253	208466	0

Note: all costs estimated in Rails

Table 4. The unit cost of different procedures used in prostatic surgery, (300 patients)

	Procedures		
	Thulium laser	**Holmium**	**Transurethral resection of the prostate**
Unit cost	3931874	4595927	4298016
The cost difference in comparison with the alternative	-366142	297911	0

Note: all costs estimated in Rials

Table 5. The unit cost of different procedures used in prostatic surgery regarding dual -purpose properties of thulium and holmium, (300 patients)

	Procedures		
	Thulium laser	**Holmium**	**Transurethral resection of the prostate**
Unit cost	3525207	4472594	4298016
The cost difference in comparison with the alternative	-772808	174577	0

Note: all costs estimated in Rials

Discussion

This review shows that effectiveness of HOLEP in improvement of lower urinary tract symptoms is comparable with TURP(13-18). Although there is a lack of evidence for some of post-operative complications like urinary infection, urinary incontinence, urethral stricture, and erectile dysfunction, according to one of the RCTs peak flow rate, 12 months after surgery in HOLEP group was better than TURP(18). Despite ThuLEP is another version of HOLEP, more controlled studies are needed to confirm its effectiveness(19,20). It is clear that most valid and reliable evidences can be obtained from clinical trials(8,9) and economic evaluations using these data can result in accurate decisions. But, in some situations, conducting a clinical trial is difficult because of the long period

of time required, high costs, and the lack of data. A preferred method in this situation is using the secondary data from previous studies. The main limitation of conducting this study was the absence of data related to different procedures especially for new procedures.

Results of this study showed that if the study's perspective constrained to providers such as hospitals and similar surgery centers, costs such as patients' and their families' time off costs that reduce social productivity will not be included in the analysis and then the traditional method (surgery) will become dominant. But, considering the fact that this study was conducted on the basis of social perspective, these kinds of costs included. Thus, the new procedures that reduce the hospital stays and convalescent period become dominant methods. In addition, taking patients' preferences into account, it is clear that they prefer shorter hospital stays. Also, the existence of third-party (insurance) that shares the in-patient costs provides incentives for patients to demand for new surgical procedures. Since the holmium and thulium laser sets are multipurpose and potentially can be applied for stone fragmentation, utilization of these equipments will divide the costs between the two groups of services. In economic terms, these properties lower overhead costs and justify the purchasing of these equipments.

As indicated in "Results", there was not any significant difference between the effectiveness of interventions and their effect on the patients' quality of life. Therefore, cost minimization analysis (CMA) was used as an appropriate way for adopting most cost-effective procedure. Depending on different perspectives, the way of using laser sets, and threshold level, CMA may give different results.

The study results indicate that neither holmium nor thulium laser sets was cost-effective in 200 patients' scenario and the traditional surgery was determined as dominant procedure. Since the primary cost of procedures account for a large number of costs, it seems that increasing the number of patients undergoing surgery using laser will be rational in terms of economics. While the number of patients increased, the threshold level for cost-effectiveness of thulium laser was determined at 250 patients.

Conclusion

HOLEP is an effective method for treatment of symptomatic BPE. But, well designed control trials are still necessary for evaluation of the secondary outcomes. Since the holmium and thulium laser sets are sensitive to the number of the patients and multipurpose, they can potentially be applied in stone fragmentation. Thus, utilization of these equipments will divide the costs between the two groups of services. In economic terms, these properties lower overhead costs and justify the purchasing of these equipments.

Study Limitations

1- The limits in the availability of related studies
2- The lack of high-level evidences to examine the effectiveness of new lasers
3- The absence of a comprehensive information system in the country which leads to using evidences with low validity instead of gold standard evidences
4- Lack of real prices for technologies
5- Inconsistency in the unit cost of procedures in public and private sectors

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