Critical Analysis

SIGMUM
Surgical Interest Group of Monash University Malaysia

Review & Meta-analyses

01

June 2022 Journal Club #2 - Urology

Objectives & Hypotheses

Are the objectives of the study clearly stated?

YES!,

To compare the efficacy and safety of transurethral enucleation and resection of prostate for treatment of benign prostatic hyperplasia

Background Information

Definition

➢ **Benign Prostate Hyperplasia (BPH):**
Non-malignant growth or hyperplasia of prostate tissue and is a common cause of lower urinary tract symptoms in men.

➢ Histologic diagnosis characterised by **proliferation of the cellular elements of the prostate**, leading to an **enlarged prostate gland**.

Epidemiology

➢ 50% of men over the age of 50 shown to have evidence of BPH and the association with the development of LUTS shown to increase with age in a linear fashion.

➢ Studies have shown BPH prevalence to be as high as 70% in those between 60 and 69 years of age and more than 80% in those over 70 years.
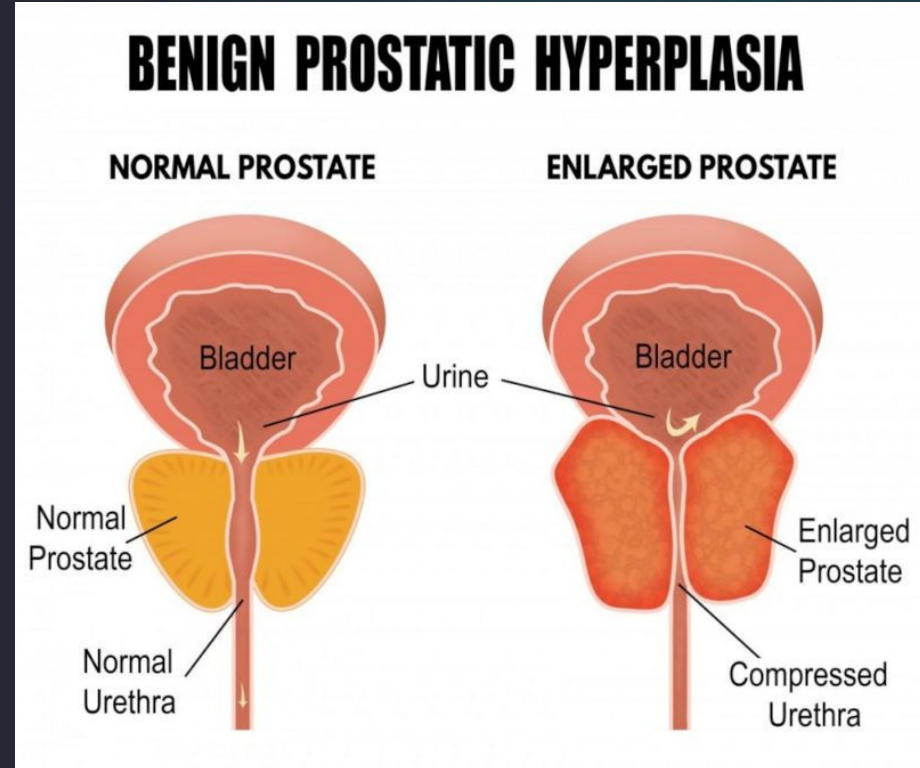
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Methodology

DESIGN

Were the search methods used to locate relevant studies comprehensive?

- **Yes**. Quality assessment of included studies in the meta-analysis was measured by using the Cochrane System!

Was this the right sample to answer the objectives?

- **Yes**, all selected RCTS have similar inclusion criteria, which are patients with lower urinary tract symptoms (LUTS) caused by BPH, patients with International Prostate Symptom Score (IPSS) ≥ 8, and maximum urinary flow rate (Qmax) ≤ 15 mL/s.
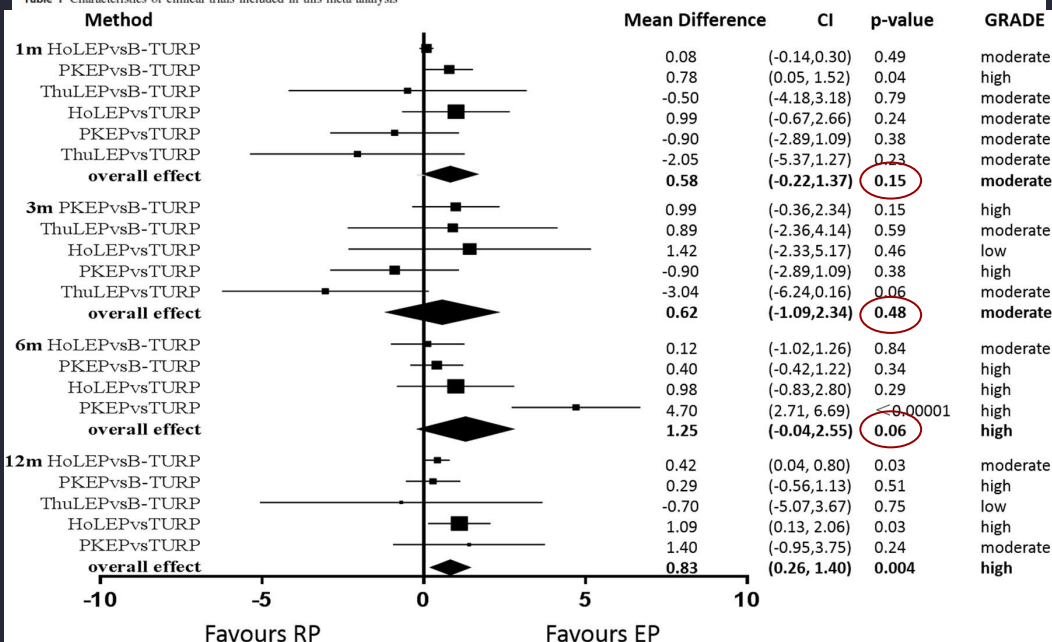
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Recruitment of Participants

Is the study large enough to achieve its objectives?

Long-term Efficacy: NO!

Safety: YES!

Table 1 Characteristics of clinical trials included in this meta-analysis

Method	Mean Difference	CI	p-value	GRADE
1m HoLEPvsB-TURP	0.08	(-0.14,0.30)	0.49	moderate
PKEPvsB-TURP	0.78	(0.05, 1.52)	0.04	high
ThuLEPvsB-TURP	-0.50	(-4.18,3.18)	0.79	moderate
HoLEPvsTURP	0.99	(-0.67,2.66)	0.24	moderate
PKEPvsTURP	-0.90	(-2.89,1.09)	0.38	moderate
ThuLEPvsTURP	-2.05	(-5.37,1.27)	0.23	moderate
overall effect	0.58	(-0.22,1.37)	0.15	moderate
3m PKEPvsB-TURP	0.99	(-0.36,2.34)	0.15	high
ThuLEPvsB-TURP	0.89	(-2.36,4.14)	0.59	moderate
HoLEPvsTURP	1.42	(-2.33,5.17)	0.46	low
PKEPvsTURP	-0.90	(-2.89,1.09)	0.38	high
ThuLEPvsTURP	-3.04	(-6.24,0.16)	0.06	moderate
overall effect	0.62	(-1.09,2.34)	0.48	moderate
6m HoLEPvsB-TURP	0.12	(-1.02,1.26)	0.84	moderate
PKEPvsB-TURP	0.40	(-0.42,1.22)	0.34	high
HoLEPvsTURP	0.98	(-0.83,2.80)	0.29	high
PKEPvsTURP	4.70	(2.71, 6.69)	<0.00001	high
overall effect	1.25	(-0.04,2.55)	0.06	high
12m HoLEPvsB-TURP	0.42	(0.04, 0.80)	0.03	moderate
PKEPvsB-TURP	0.29	(-0.56,1.13)	0.51	high
ThuLEPvsB-TURP	-0.70	(-5.07,3.67)	0.75	low
HoLEPvsTURP	1.09	(0.13, 2.06)	0.03	high
PKEPvsTURP	1.40	(-0.95,3.75)	0.24	moderate
overall effect	0.83	(0.26, 1.40)	0.004	high

-10   -5   0   5   10

Favours RP   Favours EP

Lack of data

The majority of studies included were HoLEP vs. TURP which had a major effect on the overall (short-term) outcome

Lack of longer-term results.

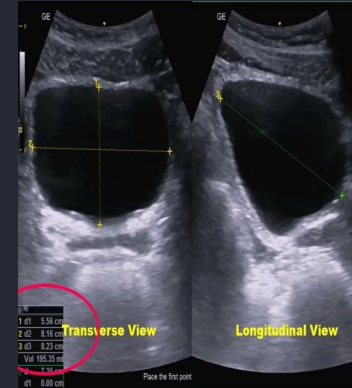# **Evaluation of Study**

Were all appropriate outcomes considered?

YES!, however

Cost-benefit outcome

Prostate specific antigen (PSA)

Prostate volume

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In-depth Analysis

- Measurement and Observation

- Presentation of Results

- Interpretation

Measurement and Observation

Is it clear what was measured, and what the outcomes were?

- **YES!**

2 Types of outcome

Efficacy outcome
- IPSS
- Qmax
- Quality of life (QoL)

Safety outcomes
- Perioperative outcomes
  - Hemoglobin loss
  - Operative time
  - Hospital stay
  - Blood transfusion
- International Index of Erectile Function-5 (IIEF-5)
- Clavien classification of surgical complications
- Early and late complication

Presentation of Results

Were differences between studies adequately described?

OPERATIVE TIME
Shorter in resection group than enucleation group

- Enucleation group included enucleation & morcellation
- Fear of bladder mucosal injury
- Complexity of technique

GRADE 1 COMPLICATIONS

Higher rate in HoLEP than B-TURP

- Greater incidence of bladder mucosal injury during morcellation in enucleation

URGE INCONTINENCE

Higher rate in PKEP than B-TURP

- High energy applied to the capsule
- Depends on surgical technique

Analysis

Were the results of primary studies combined appropriately?

YES!

- **Weighted averages** of estimates across the studies were done
  - Larger studies = More weightage
- **Heterogeneity test** was done
- **Random-effects model** was used
- **Forest plots** were provided that combined all the results
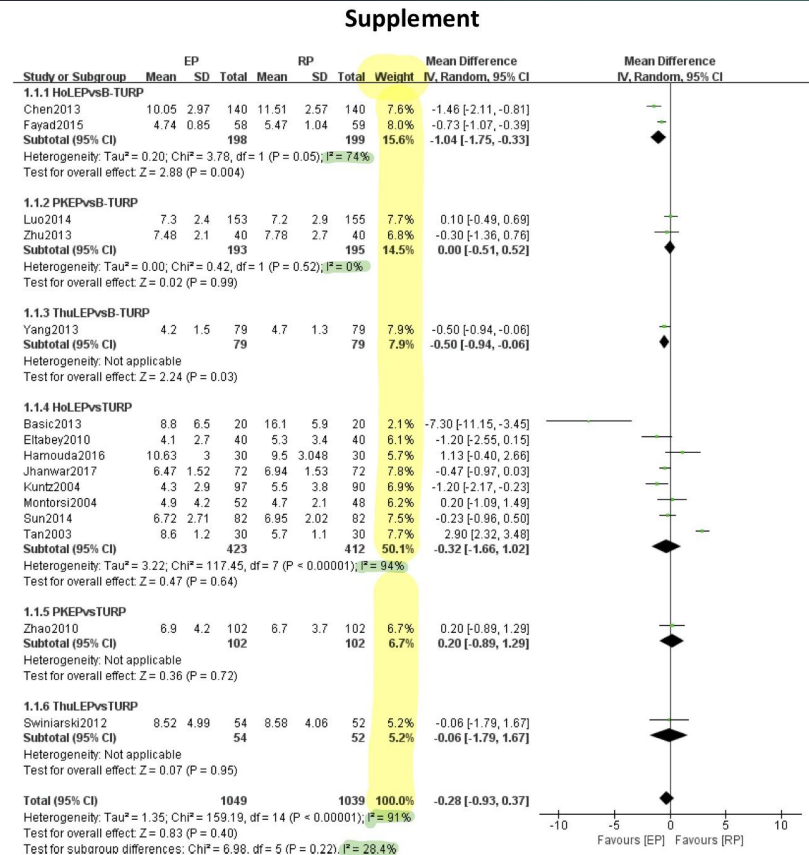
Supplement Figure 1. Forest plot of IPSS at 1m postoperatively

IPSS = international prostate symptom score; HoLEP = holmium laser enucleation of the prostate; TURP = transurethral resection of the prostate; B-TURP = bipolar transurethral resection of the prostate; PKEP = plasma kinetic enucleation of prostate; ThuLEP = thulium laser enucleation of the prostate; EP = enucleation of prostate; RP = resection

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Discussion

Is the discussion biased?

- All results were presented including the results that reported no significant differences.
- Admitted to having lack of data to produce longer term follow-up data
- All sources were cited accurately including the results of study
- Unexpected differences in the results were explained
- Secondary outcomes of sexual dysnfunction studied in few RCTs which found no significant difference were also reported
- Publication bias was explained
  - Zhang et al reported enucleation had shorter operative time than resection
  - Small sample size in Tan et al and Dragoslav et al caused deviation in hemoglobin loss, IPSS and Qmax results
- Funnel-plot were used to estimate risk of publication bias
  - All outcomes showed symmetry except operative time, hospital stay, Hb loss and grade I complications

Interpretation

Are the author's conclusions justified by the data?

<mark>YES….and NO</mark>
- Yes in terms of safety
- No in terms of efficacy

What level of evidence has this paper presented? (using CEBM levels)

Level 1a (Systematic review/Meta analysis of randomised controlled trials)

Implementation

Changes to current practice

Barriers

Future Prospects

Can any necessary change be implemented in practice?

- Enucleation has been **proven to be safer** than resection.
- **More data** is needed to validate its **long-term efficacy**
- **More variables in terms of efficacy** are needed to evaluate efficacy profile **(i.e prostate volume, PSA level, etc.)**
- At this point, it is safe to say **enucleation of the prostate should be the preferred method** compared to resection based on its **superior safety profile, and short term efficacy** (albeit evidence not as strong)
- Need to take into account different techniques in the study
- **Barriers to implementation exist**

Future Prospects

What barriers to implementation exists?

- Current guidelines (eg. European Association of Urology 2019 Guidelines) continues to recommend TURP in men with prostate size of 30-80 mL.

- Lack of mentorship

- Risk of complications

- Steep learning curve

- Unavailability of morcellator, bipolar or laser energy sources

- Lack of support from device company, reimbursement issues

Thank You!

Appendix

Efficacy outcomes of E vs R	Duration (months)				
	1	3	6	12	24
IPSS (n=21)	No difference − 0.28 [− 0.93, 0.37], p = 0.40	No difference −0.26 [−0.90, 0.37], p=0.42	No difference −0.31 [−0.89, 0.28], p=0.30	Lower −0.84 [− 1.32, − 0.35], p = 0.0007	No difference −0.48 [−1.33, 0.37], p=0.27
Qmax (n=19)	No difference 0.58 ml/s [− 0.22, 1.37], p = 0.15	No difference 0.62 ml/s [− 1.09, 2.34], p=0.48	No difference 1.25ml/s [−0.04, 2.55], p= 0.06	Higher 0.83ml/s [0.26, 1.40], p = 0.004	-
QoL (n=11)	No difference0.04 [− 0.27, 0.36], p = 0.78	No difference− 0.07 [− 0.16, 0.03], p = 0.18	No difference− 0.14 [− 0.40, 0.12], p = 0.28	No difference− 0.14 [− 0.37, 0.09], p = 0.24	-

Perioperative outcomes	Results (E vs R)
Operative time (n=22; 2842 pt)	Longer (11.14 min [5.51, 16.78], p = 0.0001)
Hospital stay (n=20; 2629 pt)	Shorter (− 22.11 h [− 28.87, − 15.36], p < 0.00001)
Hb loss (n=20; 2399 pt)	Lower (− 0.62 g/dl [− 0.81, − 0.43], p < 0.00001)
Serum Na loss (n=12; 1729 pt)	Lower (− 0.68 mmol/L [− 1.15, − 0.22], p = 0.004)

Safety outcomes		Results (E vs R)
Grade classification		For Grade I and IV, no significant difference For Grade II and III, less frequency in E than R
Early	Urinary retention	Lower (0.68 [0.48, 0.97], p = 0.03)
	Hematuria (n=7; 700pt)	Lower incidence ((0.37 [0.17, 0.82], p = 0.01)
	Blood transfusion rate (n-19;2315 pt)	Lower (0.26 [0.15, 0.46], p < 0.00001)
	Urge incontinence (n=15; 2026 pt)	No significant difference (1.24 [0.94, 1.65], p = 0.13)
	UTI	Lower (0.52 [0.30, 0.93], p = 0.03)
	Dysuria (n=8; 1009 pt)	No significant difference (0.48 [0.13, 1.71], p = 0.26)
Late	Bladder neck contracture (n=7; 1276 pt)	No significant difference (0.82 [0.35, 1.92], p = 0.64)
	Stress incontinence (n=7; 666 pt)	No significant difference (0.87 [0.38, 2.02], p = 0.75)
	Retrograde ejaculation	No significant difference (1.01 [0.84, 1.22], p = 0.88)
	Urethral stricture	Lower incidence (0.50 [0.30, 0.84], p = 0.009)
	Reoperation	No significant difference (0.61 [0.17, 2.17], p = 0.45)