The industrial revolution for the management of benign prostate obstruction: Worldwide publication trends for surgical and medical therapies over the past 2 decades

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Introduction Research for management of benign prostate obstruction (BPO) for adult males remains a cornerstone of urology research. This landscape has witnessed the rise and fall of multiple therapies, both surgical and medical. Our aim was to formally evaluate the publication trends for these interventions over the past 20 years.

Materials and methods A systematic search was performed in a Cochrane style. Data was analysed using the independent t-test and Pearson's correlation coefficient (SPSS version 24). To observe changes in trends more effectively, data was sub-divided into two time periods: 1997 to 2006 and 2007 to 2016.

Results Over the past 20 years, 4236 papers have been published interventions for BPO (Surgical, n= 2177 and medical, n= 2059). For surgical treatments, these included articles on monopolar TURP (n=340), bipolar TURP (n=260), HoLEP (n=293) and Greenlight laser (n=395). For medical therapies, these included alpha blockers (848), 5-alpha reductase inhibitors (n=618) and PDE5I (n=91). Between the two time periods the change was +18.8% (p=0.108) for monopolar TURP, +497.1% (<0.001) for bipolar TURP, -54.5% (p<0.001 for prostatic stents and -81.9% (p<0.001) for TUMT. There was over 290% rise in number of publications related to BPO laser surgery (p<0.001). For medical interventions, the change was

+11.5% (p=0.397) for alpha blockers, -1.9% (p=0.867), +49.0%(0.122) for phytotherapy, +2075% (p<0.001) for PDEI and +2375.0% (p<0.001) for combined alpha blocker and anti-muscarinics.

Conclusions Interventions for BPO have undergone a high volume of research. In particular, minimally invasive laser surgeries and combined medical therapies have seen significant expansion.

INTRODUCTION

A multitude of longitudinal community and epidemiologic studies have confirmed the consensus that benign prostate hyperplasia (BPH) holds a status of ubiquity [1,2]. Indeed, the natural history of this disease process renders one third of men over 60 years old liable to develop moderate to severe lower urinary tract symptoms (LUTS) as a result of benign prostatic obstruction (BPO) [3]. The rationale and demand to develop effective therapeutic strategies is therefore irrefutable. To this end, the field of urology has witnessed a high volume of valuable research and productivity into BPO related medical and surgical innovations, which has been published and disseminated worldwide. This 'industrial revolution' for BPO treatments has pioneered new solutions in both pharmacotherapy and surgery. Novel medical remedies have included the introduction of phosphodiesterase inhibitors (PDEIs) and phytotherapy [4,5]. Meanwhile, surgery has fully embraced the minimally invasive approach, which has included the inauguration of laser treatments as well as non-ablative strategies such as Urolift [6]. The advancements of robotic surgery have also supplemented the range of treatments patients can be offered [7]. While this inexorable rise has continued, formal evaluation of such bibliographic trends has remained under-reported. It was our objective to complete such a task and thereby gain greater insight into the temporal changes in research and practice patterns in BPO treatments over the past 20 years.

MATERIALS AND METHODS

Evidence acquisition: Criteria for including studies for this review
Inclusion criteria
• Articles published in any language
• Primary and secondary research articles
Exclusion criteria
• Studies with no published abstract
• Case reports
• Review articles
• Animal studies
• Laboratory studies

Search strategy and study selection

A sensitive search protocol was developed by the author team and then implemented by two of the authors independently. This was performed in accordance with Cochrane methodology and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [8]. The devised strategy was then applied to the online bibliographic database PubMed to identify all original studies on BPO treatment published between January 1st 1996 to December 31st 2016. Screening and identification of eligible studies also followed a dual approach.

Data Extraction and analysis

Data was extracted by two authors (RG and AP) and any discrepancies or disagreements were resolved by the senior author (BKS). Analysis was performed using the independent t test and Pearson's correlation coefficient (SPSS version 24). To observe and analyse changes more effectively, data was sub-divided into two, 10-year time periods, 1997 to 2006 and 2007 to 2016.

RESULTS

Overall number of papers on BPO treatments

Over the past two decades, 4236 original articles have been published on treatments for BPO (surgical, n= 2177 and medical, n= 2059). For medical therapies, these included alpha blockers (n=848), 5-alpha reductase inhibitors (5-ARIs) (n=618), PDE5-Is (n=91), phytotherapy (n=127), combined alpha blockers/5-alpha reductase inhibitors (n=218), combined alpha blockers/PDE5-Is (n=28) and combined alpha blocker/anti-muscarinics (n=103). For surgical treatments, these included articles on monopolar TURP (n=340), bipolar TURP (n=260), TUIP (n=47) simple prostatectomy (n=104), TUMT (n=268), TUNA (n=60), prostate stents (n=64), HoLEP (n=293) and Greenlight laser (n=395).

Although there was a significant increase for both medical and surgical papers respectively when comparing the period of 1997 to 2006 (n=1619) to 2007 to 2016 (n=2528) ($p<0.001$, 95% CI: 31.5 to 59.4), there was no difference between the numbers of medical and surgical papers published ($p=0.69$, 95% CI: -24.6 to 16.5).

Medical therapies

Comparing the volume of papers published between these two time periods, there were non-significant increases of +11.5% ($p=0.397$) for alpha blockers, +49.0% ($p=0.122$) for phytotherapy,and + 29.5% ($p=0.089$) for combined alpha blockers/5-ARIs (Table 1, Figure 1). While there were significant increases in studies published in the following: +2075% ($p<0.001$) for PDE5-Is, +733.3% ($p=0.003$) for combined alpha blockers/PDE5-Is, +2375.0% ($p<0.001$) for combined alpha blockers/anti-muscarinics. For studies on 5-ARIs, there was a non-significant drop by -1.9% ($p=0.867$).

These increases were reflected in trend analyses with Pearson's correlation done for each group [Table 4].

Surgical therapies

Between the two time periods there was a rise of +18.8% (p=0.108) for monopolar TURP, +497.1% (p<0.001) for bipolar TURP and +73.7% (p=0.117) for open simple prostatectomy. Overall, there was over 290% rise in number of publications related to BPO laser surgery (p<0.001) and this included +245.9% (p<0.001) for HoLEP, +702.4% (p<0.001) for Greenlight, +2266.6% (p=0.002) for Thulium and +750.0% (<0.001) for Diode laser (Table 2 and 3, Figure 2). Although from 1997 to 2006, the largest number of laser publications was on HoLEP (n= 61), between 2007 to 2016, Greenlight became the laser receiving the most new articles (n=337). However, there was a significant drop of -54.5% (p<0.001) for prostatic stents, -81.9% (p<0.001) for TUMT, -63.6% (0.004) for TUNA and -80.3% (p=0.002) for Nd:YAG laser. Urolift emerged in the latter decade as a new surgical option (n=31).

DISCUSSION

Key findings

Both medical and surgical treatments for BPO have been the subject of large volumes of research over the past 2 decades. There has been a significant increase in the volume of publications in the past decade compared to the previous in both medical and surgical treatments.

Advances in surgical and medical treatments

While TURP has remained the gold standard for over 30 years and its efficacy for small to medium sized prostate burdens is well established, the search for new techniques has remained ongoing [9]. Since HoLEP was first described in 1996, it has become an active an area of research along with the other new laser technologies [10]. Its success is largely related to the enucleation technique, which allows large prostates to be treated [11]. Alongside HoLEP, Greenlight laser technology has gained notable attention. Ow et al. recently reported an increase in year on year of GreenLight laser use in a tertiary centre [12]. This was largely owing to its suitability in high risk anti-coagulated patients. There is also now growing evidence to support its use in larger prostates [13]. Stents, TUMT and TUNA have far less research interest in recent years and this would likely reflect its diminishing use in clinical practice. Recent study by Gill et al. recorded patients undergoing tissue eliminating procedures to record higher levels of discontinuing alpha blockers and 5-ARIs than those patients undergoing tissue necrosing procedures such as microwave (TUMT) and radio frequency ablation (TUNA) [14].
While HoLEP has become an established intervention for large prostate burdens (>80cc), it is interesting to see our results support the ongoing place of open simple prostatectomy as a surgical option [15,16]. This ongoing attention may be related to its continued application particularly in poorer healthcare communities [17].
Despite a high volume of drug research, a recent meta-analysis concluded there to have been very limited advances in pharmacotherapy for LUTS secondary to BPO [18]. The authors analysed data from 48 studies and found none of the newer medications or combination therapies yielded superior outcomes compared to alpha blockers alone.

Strengths, limitations and future directions

This review provides formal confirmation of trends observed by the urology community worldwide. To our knowledge, this is the first such evaluation of its kind. In order to truly demonstrate worldwide trends and reduce bias, our review included non-English publications also. Our search application was limited to PubMed only and therefore non-indexed articles will exist, which this review does not capture. An exhaustive review of such material was considered beyond the scope of this article. Nonetheless, the authors feel confident that bibliographic patterns are accurately captured by use of PubMed alone [19]. This review also primarily covers surgical intervention but does not cover radiological interventions such as prostate artery embolization (PAE) [20]. The Rezum system and iTind are both other novel interventions, which have emerged in recent years, however their formal roles in current practice are yet to be determined beyond the research setting [21].

While robot technology has made a profound impact on uro-oncological surgery, its application has also extended to benign prostate disease. Its role as an alternative to open simple prostatectomy has received increased attention as has its use in aquablation [22,23]. In the field of new medical treatments, new intra-prostatic injections are currently being studied in the trial setting [24,25]. These include intraprostatic onabotulinum toxin A and Fexapotide triflutate (NX-1207)[26,27].

CONCLUSION

Medical and surgical treatments for BPO have undergone a high volume of research over the past 20 years. In particular, minimally invasive laser surgeries such as Greenlight have seen significant expansion as well as combined medical therapies such as blockers and anti-muscarinics. While others such as TUMT and TUNA have stopped attracting research interest. There are now of plethora of management options available but these should be tailored to the individual needs of the presenting patient.

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Attached tables:

1. JonesTable1.docx
   Caption/remarks: *Table 1. Changes in medical treatments over time*

2. JonesTable2.docx
   Caption/remarks: *Changes in surgical treatments over time*
3. JonesTable3.docx
   Caption/remarks: *Trends in laser treatments*
4. JonesTable4.docx
   Caption/remarks: *Summary of trends analysis*

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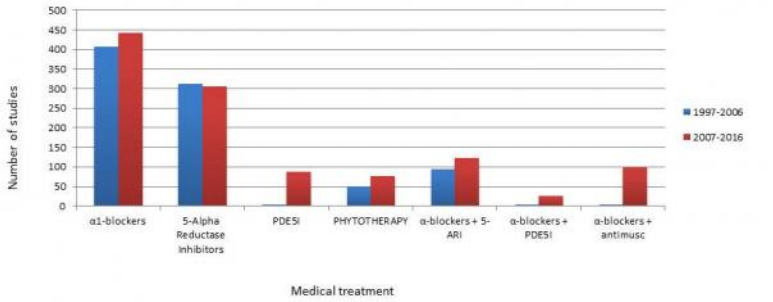
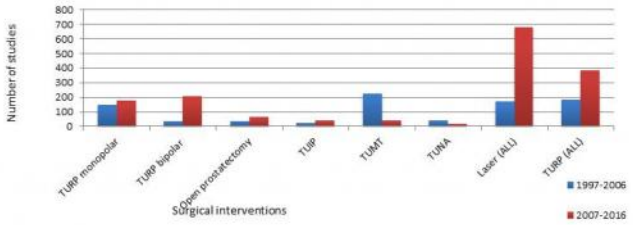
ATTACHED FIGURES



JonesFig1.jpg
Trends in medical treatments over time



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Trends of surgical interventions over time