

STUDY PROTOCOL:

Bipolar transurethral enucleation (BipolEP) vs bipolar transurethral resection of the prostate: A prospective interventional multi-center randomized controlled trial

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Title of trial	Bipolar transurethral enucleation (BipoLEP) vs bipolar transurethral resection of the prostate: A prospective interventional multi-center randomized controlled trial
Medical condition	Lower urinary tract symptoms due to benign prostatic enlargement
Objective(s)	The primary objectives of this study is (i) to demonstrate that the I-PSS at 12 months shows non inferiority for enucleation. Our hypothesis is that enucleation and bipolar TURP might be comparable in improving LUTS. The secondary objectives is to show increased tissue resection per minute for the enucleation (superiority) (ii).
Intervention(s)	<p><u>Experimental intervention:</u></p> <p>Bipolar transurethral enucleation of the prostate (BipoLEP)</p> <p><u>Control intervention:</u></p> <p>Bipolar transurethral resection of the prostate (TURP)</p> <p><u>Follow-up per patient:</u></p> <p>Dysuria visual analogue scale (at 1 month) I-PSS, QOL, Qmax and PVR (at 1, 4 and 12 months) IIEF-15 and PSA (at 4 and 12 months) TRUS for prostate size at 4 months</p>
Key inclusion and exclusion criteria	<p><u>Key inclusion criteria:</u></p> <ul style="list-style-type: none"> - Age greater than 50 years - Refractory LUTS secondary to BPH - I-PSS greater than 15 - QOL score 3 or greater - Qmax less than 15 ml per second or patients with acute urinary retention secondary to BPH in whom trial of voiding failed - Prostate size on preoperative TRUS of 40 to 150 ml <p><u>Key exclusion criteria:</u></p> <ul style="list-style-type: none"> - Patients with neurological disorder - Active urinary tract infection, active bladder or prostate cancer
Outcome(s)	<p><u>Primary efficacy endpoints:</u></p> <ul style="list-style-type: none"> • IPSS improvement at 12 months <p><u>Key secondary endpoint(s):</u></p> <ul style="list-style-type: none"> • Tissue resection per minute <p><u>Assessment of safety:</u></p> <ul style="list-style-type: none"> • Assessment of possible adverse events after applying BipoLEP and compare to TURP (e.g. bladder perforation, urethra stricture, incontinence). • Comparison of peri- and postoperative complications according to the classification of Clavien-Dindo

	<ul style="list-style-type: none"> Blood loss (hemoglobin prior and postoperative)
Trial type	Prospective, interventional, multi-centre, randomized trial
	<p><u>Concept</u></p> <p>The study is designed as a comparison of two kinds of treatment: Group BipolEP: Bipolar transurethral enucleation of the prostate Group TURP: Bipolar transurethral resection of the prostate</p> <p>Two primary endpoints are chosen: (1): IPSS after 12 month [-] (2): Tissue resection [g/min]</p> <p>The use of a gate keeping approach makes it unnecessary to adjust the type I error. Primary endpoint (1) will be investigated by a non-inferiority approach (type I error = 5% one-sided), primary endpoint (2) by a superiority approach (type I error = 2.5% one-sided).</p> <p><u>Hypotheses:</u></p> <p>(1): H-0₁: Compared to group TURP, IPSS after 12months in group BipolEP is higher (non-inferiority range = 3) H-1₁: Compared to group TURP, IPSS after 12months in group BipolEP is not higher (non-inferiority range = 3)</p> <p>(2): H-0₂: Compared to group TURP, tissue resection in group BipolEP is not increased H-1₂: Compared to group TURP, tissue resection in group BipolEP is increased</p> <p><u>Statistical Methods:</u></p> <p>Group Comparisons:</p> <p>Primary Endpoint (1): Data (if appropriate, in logarithmised version) will be checked for normal distribution (Kolmogorov-Smirnov with Lilliefors significance correction, type I error = 10%). Hypotheses (H-0₁, H-1₁) will be investigated either by a parametric or by a non-parametric one-sided test of equivalence (equivalence range one-sided = 3; type I error = 5% one-sided).</p> <p>Primary Endpoint (2): Data (if appropriate, in logarithmised version) will be checked for normal distribution (Kolmogorov-Smirnov with Lilliefors significance correction, type I error = 10%). Hypotheses will be investigated either by the t-test for independent samples or by the Mann-Whitney U-test (type I error = 2.5% one-sided). Hypotheses (H-0₂, H-1₂) will be tested only if H-0₁ hypothesis is rejected.</p> <p>Further Variables: All other variables will be analysed by usual parametric and non-parametric tests for univariate comparisons of independent samples.</p> <p>Two-sided 95% confidence intervals: For selected variables, two-sided 95% confidence intervals will be calculated.</p> <p>Type I error adjustment: No adjustment for the type I error will be made. Therefore – apart from hypotheses testing – the results of inferential statistics will be descriptive only.</p> <p><u>Sample Size Justification:</u></p>
Statistical analysis	

	<p>The following scenario was used for the sample size estimation concerning primary endpoint (1):</p> <ul style="list-style-type: none"> • Non-inferiority range = 3 • Type I error = 5% one-sided • Type II error = 10% • IPSS after 12 months in both groups ($Mw \pm SD$) = 4 ± 4 • n (group BipolEP) / n (group TURP) = 1 / 1 • Parametric test <p>The result of the sample size estimation is a requirement of 31 cases per group. Assuming a drop-out rate of 20% and considering the possible need for a non-parametric test a total of 84 inclusions ($n=42$ / group) are chosen as the sample size of the study.</p> <p><u>Analysis Populations:</u></p> <p>Intent-to-treat (ITT) population: All subjects at whom the group-specific treatment (TURP, BipolEP) at least has started will be included in the ITT population. All variables will be analysed.</p> <p>Per-protocol (PP) population: All subjects without occurrence of any drop-out situation (all valid cases) will be included in the PP population. All variables will be analysed. The PP analysis is paramount.</p> <p><u>Handling of Implausible Values and of Missing Values:</u></p> <p>Implausible values have to be identified during the data management process in agreement with the clinical investigator. They will be converted into missing values.</p> <p>Missing Values will be replaced only in the ITT population and only for the two primary endpoints. The replacements will be made according to the worst-case principle (use of the worst assessed value in the study).</p> <p><u>Post-hoc Analyses:</u></p> <p>Analyses of subgroups and other post-hoc analyses can be performed for cause. However, all statistical results will be only descriptive.</p> <p><u>Interim Analyses:</u></p> <p>A priori no interim analysis is intended.</p> <p><u>Presentation of the Results (Descriptive Analysis, Graphs etc.):</u></p> <p>Categorical variables will be presented using counts and percentages. Variables measured on ordinal scales will be presented using counts and percentages (where appropriate) or minimum, 25%-percentile, median, 75%-percentile and maximum and number of patients (where appropriate). Continuous variables will be presented using minimum, 25%-percentile, arithmetic mean, median, 75%-percentile, maximum, standard deviation and number of patients.</p> <p>All results will be presented in the form of tables, selected results additionally in the form of graphs (bar charts, boxplots).</p>
Allcation	<p>For the allocation of treatment to subjects the minimization method will be used (manual see accompanying documents).</p>

	<p>Strata:</p> <ul style="list-style-type: none"> prostate 60 to 80 ml / more than 80 ml catheterized / non-catheterized <p>The minimization procedure will be applied centrally (by the coordinating centre).</p> <p>According to the allocation approach and the multicentre nature of the study minor deviations in defined group BipolEP / group TURP ratio of 1 / 1 cannot be excluded.</p>
Trial duration	<p>First patient in to last patient out (months): 36</p> <p>Duration of the entire trial (months): 36</p> <p>Recruitment period (months): 12</p>
Participating centres	N = 2

Intervention scheme/ Trial flow

1. 1. The Medical Problem

Lower urinary tract symptoms (LUTS) caused by prostatic enlargement (benign prostatic hyperplasia, BPH) are a common problem in elderly men. It is well known that the incidence of LUTS is rising with age and there are reported incidence rates of 38 cases per 1000 man-years at the age of 75-79 years [1]. In the EAU guidelines LUTS is divided in three different groups, mild, moderate and severe, by using the international prostate symptoms score (IPSS). Surgical intervention is recommended for moderate to severe LUTS. However, transurethral resection of the prostate (TURP) is still representing the gold standard [2]. On the other hand the surgical approach is changing from conventional monopolar TURP to minimally invasive surgical techniques such as holmium laser enucleation (HoLEP) or GreenLight lithium borate laser vaporization (PVP) [1] or other minimal invasive techniques. Transurethral enucleation of the prostate (TUEP) has been available as a monopolar current-based enucleation– resection since it was first described by Hiraoka in 1983 [3]. Although it was the blueprint for all other transurethral enucleations to come, it remained a local phenomenon in Japan [4]. Only when enucleation was in focus again with laser technology and the mechanical tissue morcellator, did it come into focus after publication of a paper on holmium laser enucleation of the prostate (HoLEP) in 1998 by Fraundorfer and Gilling [5]. HoLEP is regarded as a standard approach for the treatment of large prostate glands, and the great evidence base is mentioned in support of that. However, only in 2006 there was the first randomized controlled trial on HoLEP versus bipolar enucleation (plasmakinetic enucleation of the prostate, PKEP) published by the same group [6].

Nowadays 15 randomized controlled trials have been published comparing bipolar enucleation with a standard treatment arm (OP or TURP) so far. Numerous studies have demonstrated that bipolar TUEP is an attractive minimally invasive alternative to OP for large BPH, with comparable functional results and significantly lower perioperative morbidity [7-12]. Recently Prof TRW Herrmann introduced a specific electrode which aims to reproduce a wedge to more easily perform anatomic enucleation of the prostate. This technique propagated by its inventor is known as BipolEP.

1. 2 The need for a trial

There is no doubt that BipolEP has huge potentials. BipolEP has shown to be performed effectively and safely with functional outcomes and complications similar to the gold standard for prostatic enlargement, whereas it has the advantages of a shorter catheter period, shorter hospital stays and less blood transfusion compared to open surgery [13].

To the best of our knowledge there is not a randomized trial available compared this new device with TURP. For this reason this trial is needed

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