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TRANSURETHRAL RESECTION OF THE PROSTATE – HOW TO REDUCE MORBIDITY

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*Till Frida,
Siri, Tyra-Myra och Lotten*

Ohyran bet
Grå och fet.
Natten räckte
I evighet.

(Helmer Grundström)

ABSTRACT

Transurethral resection of the prostate (TURP) is the gold standard method for surgical treatment of benign prostatic hypertrophy. Despite the more recent introduction of medical therapies for benign prostatic hypertrophy (BPH), the high efficacy of TURP still makes it one of the most common surgical operations worldwide and approximately 6,000 such operations are performed every year in Sweden. However, this surgical technique is not without problems with per- and postoperative bleeding events and TUR syndromes being the most serious ones. The overarching goal of this Thesis was to explore if morbidity in TURP could be further reduced, either by pharmacological or surgical interventions.

Study I was a double-blind, randomized, placebo controlled, multicentre study comprising 214 patients. The aim was to determine whether pre-treatment with dutasteride reduces surgical blood loss or postoperative complications in patients who undergo TURP. Placebo was compared with dutasteride 0.5 mg/day 2 weeks before and after TURP, or 4 weeks before and 2 weeks after TURP. Despite significant suppression of intraprostatic DHT, pre-treatment with dutasteride did not result in any significant reduction in blood loss during or after TURP or complications afterward compared to placebo. **Study II & III** comprised 202 patients with BPH scheduled for TURP. After randomization to either bipolar or monopolar surgery, 185 patients were evaluated with respect to blood loss (Study II) and postoperative outcome (Study III). In Study II bipolar surgery resulted in significantly lower blood loss (235 ml vs. 350 ml, $P < 0.001$) and transfusion rates (4% versus 11%, $P < 0.01$). The latter probably explained by the 81 % difference in blood loss for the 75th percentiles (472 ml vs. 855 ml). In Study III, bipolar surgery was followed by a 16–20% higher percentage of the patients reporting ongoing improvement at 3 and 6 weeks after the surgery ($P < 0.05$). There were fewer readmissions in the bipolar group than in the monopolar (5 vs. 13, $P < 0.05$). No differences between the groups with respect to hospital stay and catheter duration was recorded. Both bipolar and monopolar TURP resulted in marked and sustained improvements of IPSS, bother score, and TM. **Study IV** was an experimental exploration of the *in vitro* degree of vaporization in bipolar and monopolar resection, something previously poorly investigated. Samples of chicken muscle and lamb kidney were resected and then desiccated. Results showed that more muscle than kidney tissue was vaporized. The fraction of vaporized tissue was significantly higher in the bipolar technique. In muscle, the differences between monopolar and bipolar were 17% ($P < 0.05$) and 26% ($P < 0.001$) respectively, depending on the type of irrigation used. For kidney, the differences were 27% ($P < 0.01$) and 34% ($P < 0.01$) respectively.

In **conclusion**, no significant reductions in blood loss during and after TURP or complications afterward with dutasteride compared with placebo are observed. Bipolar TURP significantly reduces the total surgical bleeding, with as much as 81% for the largest haemorrhages, as well as the need for erythrocyte transfusions. Postoperative readmissions are fewer and postoperative recovery is faster in bipolar TURP. Bipolar TURP, results in equally long lasting good results in TM/IPSS and QoL, as in standard monopolar technique. Vaporization stands for a further 50% tissue removal during conventional resection and is significantly higher in bipolar standard loop resection. Bipolar resection devices work satisfactorily in Ringer's Acetate in an *in vitro* setting.

LIST OF PUBLICATIONS

This Thesis is based on the following manuscripts, which will be referred to in the text by their Roman numerals.

- I. Robert G. Hahn, **Tim Fagerström**, Teuvo L.J. Tammela, Oncko Van Vierssen Trip, Hans Olav Beisland, Annette Duggan and Betsy Morrill. Blood loss and postoperative complications in transurethral resection of the prostate after pre-treatment with dutasteride.
BJU Int 2007; 99: 587-594.
- II. **Fagerström T**, Nyman CR, Hahn RG. Bipolar transurethral resection of the prostate causes less bleeding than the monopolar technique: a single-centre randomized trial of 202 patients.
BJU Int. 2010; 105: 1560-4.
- III. **Fagerström T**, Nyman CR, Hahn RG. Complications and clinical outcome 18 months after bipolar and monopolar transurethral resection of the prostate.
J Endourol. 2011; 25: 1043-9.
- IV. **Fagerström T**, Nyman CR, Rosvall, J, Hahn RG. Degree of Vaporization in Bipolar and Monopolar Resection.
Submitted

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LIST OF ABBREVIATIONS

AMI	Acute Myocardial Infarction
BPH	Benign Prostatic Hyperplasia
Ch	Charrière
DHT	Dihydrotestosterone
EAU	European Association of Urology
5-ARI	5- α -Reductase Inhibitor
g/L, g/l	grams/litre
Hb	Haemoglobin
IPSS	International Prostate Symptom Score
mL, ml	Millilitre
MVD	MicroVessel Density
NSAID	Non Steroidal Anti-Inflammatory Drugs
PT/INR	Prothrombin Time/International Normalized Ratio
TM	Timed Micturition
TRUS	TransRectal UltraSound
TUIP	TransUrethral Incision of the Prostate
TUMT	TransUrethral Microwave Thermotherapy
TUNA	TransUrethral Needle Ablation
TURBT	TransUrethral Resection of Bladder Tumour
TURis	TransUrethral Resection in saline
TURP	TransUrethral Resection of the Prostate
UTI	Urinary Tract Infection
VEGF	Vascular Endothelial Growth Factor

1 INTRODUCTION

TURP is one of the most common surgical procedures in the world. In Sweden alone, about 6,000 such operations are performed every year. This is in spite of a decrease during the last two decades due to the introduction of more efficient pharmacological therapies as well as a range of minimally invasive techniques.¹ This decrease in the number of TURP procedures can also be seen in Western Europe and in the U.S.,² whereas it is increasing in Japan and other Asian countries, and trends in Africa point in the same direction.²⁻⁶ TURP is still referred to as “the golden standard” in treating BPH. An impressive amount of clinical and experimental studies during the last fifty years has contributed to maintaining this position, showing undisputable evidence for this technique in terms of efficiency, safety and reliability.^{7,8} Although there still are potentially dangerous drawbacks of this method, urologists worldwide favour this technique to others. An important reason for this is probably that the technique still contains a great deal of surgical craftsmanship and challenge.

Over the years, there have been improvements regarding different aspects of the technique. Stricter criteria for surgery have been employed, resulting in fewer complications. New irrigating solutions and better monitoring have also contributed to the patient’s safety, but this is only valid for the monopolar technique. It was not until the mid-1990s, when bipolar TURP emerged in the market, that one really could talk about a major change in the way of treating BPH. Suddenly, the surgical procedure was based on a completely new electrical principle facilitating the use of ion-containing irrigating fluids and with this a reduced risk of TUR-syndrome, symptoms from absorption of irrigant, as we know it.

On one hand, we wanted to see whether pre-treatment with a new 5-ARI really could make a change in surgery-associated haemorrhage in monopolar TURP by testing it in a large, well-designed study. On the other hand, we also wanted to assess the aggressively marketed new bipolar technique, which at the time did not have much scientific support in terms of randomized trials. Nonetheless, it was said to present a safer procedure for the patient with no, or reduced, need to monitor saline absorption, as well as a reduced blood loss.

This Thesis aims to summarize the evolution of TURP since the first operations with primitive instruments, over the long era of monopolar TURP with non-ionic irrigants to the present situation, where we face a future consisting of the bipolar technique with an improved safety profile and even further possibilities to increase safety in terms of new irrigants with new markers of absorption.

2 HISTORICAL REMARKS

What we now face in terms of bipolar resection of the prostate can be considered as the fourth generation in surgical procedures concerning the relief of symptoms associated with BPH. The first generation is the open prostatectomy,⁹ the second is the monopolar technique, which has gained the status of the golden standard, and the third generation is the range of different minimally invasive techniques, including effective drug treatments introduced in the 1990s.

At the beginning of the twentieth century, urologists used different kinds of techniques and instruments in order to treat the enlarged prostate. However, open prostatectomy was by this time considered to be the method of choice to achieve any sustainable results. Urologists experimented with a number of concealed knives, cold punches and different electrical devices.¹⁰

It was not until 1926, when Maximilian Stern tried out the new radio-frequency valve diathermy generator invented by Wappler, that loop resection became a real possibility. It was then described that the current created a halo around the Tungsten loop, which cut the tissue during its advance in the gland. Haemostasis was not great, though, and eventually manufacturers combined the old spark-gap technique with the new diathermy, providing variable current outputs necessary for both coagulation and cutting.

McCarthy added his faroblique telescope to the device, and the Stern-McCarthy resectoscope was a fact. This was an instrument that was sturdy and reliable and served as the template for instruments of today. The procedure developed rapidly during the 1930s, and prostates were not considered to be large unless 30 g had been removed.

Nesbit published detailed recommendations on how to perform a TURP in 1943,¹¹ but the method decreased in popularity in favour of open prostatectomy during World War II and the years thereafter. This was probably because of the fact that the electrical equipment was needed elsewhere, the introduction of better antibiotics and the comfort in the field of open surgery that the homecoming surgeons experienced. In addition to this, Terence Millin, one of the pioneers in hot wire resection, confided that his TUR percentage had decreased from 80% in 1940 to less than 10% at the time for his retirement. Progression was now slow but gained speed when three inventions of Harold Hopkins found their way into the pre-existing method. First was the rod-lens telescope, developed in collaboration with Karl Storz. The second was the flexible glass fibre light, providing excellent illumination. The third was the coordinated flexible glass cable, which made it possible for a pupil to watch the operation and thus gave good opportunities for education.

3 TECHNOLOGICAL DEVELOPMENT

INSTRUMENTS AND ELECTRICITY

After various attempts to relieve patients from infravesical obstruction with different types of sounds, concealed knives and punches, a definite step towards the present technique was taken by Bottini at the end of the 19th century.¹² He devised an instrument, not unlike a lithotrite, that was heated by direct current and caused the blade to burn a channel through the bladder neck. The procedure was blind, but there was no blood loss until the slough came away.

When discovering that high-frequency alternating current did not excite nerve or muscle tissues, urologists began to use electric cystoscopes to cauterize neoplasms of the bladder and later to burn a channel through the prostate, even though this was a time-consuming and inefficient procedure that demanded repeated sittings.¹³⁻¹⁵

The next step was to use the cold punch to cut away tissue and the diathermy to stop the bleeding. At the same time, development of loop resection was tried but not very successful because of the fact that it is difficult to cut tissue with only a hot wire at hand.

Further development has already been described, and the Stern-McCarthy resectoscope is the prototype of all the present-day instruments.

Today, several different instrument systems are available by different manufacturers. There are no great differences between the instruments, more a matter of ergonomic and economic features. All systems also have a wide range of interchangeable equipment, providing readiness for different urological tasks.

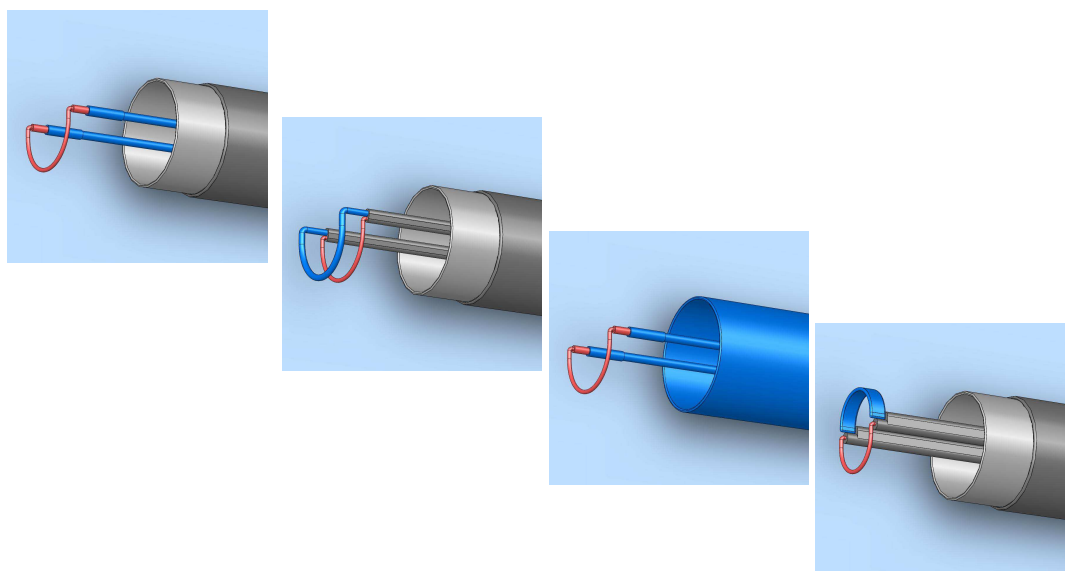
Telescopes are available in different angles starting from 0°. Historically, most resectionists have used the 30° lens, a tradition that has its explanation in the early instruments, where there was a tiny lamp at the end of the telescope and the lens had to be slightly angled in order to provide any vision at all.

The first sheaths were made of Bakelite, then of fibreglass and similar plastics. These materials often cracked and split. Nowadays, all sheaths are made of steel, often with special surface treatments to spare the urethra. The tip of the sheath is insulated by a plastic or ceramic beak. A further development of the sheath was made by Iglesias,¹⁶ which allows a continuous flow of irrigating fluid, preventing a build-up of pressure in the bladder.

Diathermy in transurethral resection has been continuously refined during the years, from the first trembling pursuits in the beginning of the 1900s to the advanced machinery of today.

The general principle for both monopolar and bipolar diathermy is the high-frequency alternating current, which does not allow nerve or muscle stimulation since the cell membranes are not given enough time to depolarize. In practice, frequencies between 300 kHz and 5 MHz are used. This makes it possible to pass very large currents through the body without causing nerve or muscle excitation, thus providing the opportunity to exploit the heating effect at the points of contact with the tissue.

The main difference between monopolar and bipolar techniques is that the former requires a neutral electrode to “collect” the current going through the patient’s body to form a closed circuit. The neutral electrode must be of standardized size and attached properly not to cause electrical burns. The bipolar technique, on the other hand, does not need such a device since the returning current goes via the ion-containing irrigating fluid, through the instrument itself, and is collected in different ways (Pic. 1).



Picture1. Different ways to collect the returning current, as designed by different manufacturers, were the blue colour represents the returning pathway.

This feature also facilitates operation in patients with cardiac devices, such as different kinds of pacemakers, since the risk of electrical interference is minimal.

In monopolar TURP, cutting is performed with a pure continuous sine-wave current, which produces a spark that makes the cells explode. The thin design of the loop facilitates this reaction and no coagulation occurs. Coagulation is achieved by short bursts of sine-wave current, heating the tissue rather than exploding it. When applying the current in a large electrode, there is a risk of cooking the deeper layers of the gland and damaging the sphincter.

Using bipolar systems, coagulation takes place at a much lower peak voltage of 65–120V compared with monopolar systems of 500–800V depending on the system used. Investigators propose that this lower peak volume of energy will cause fewer irritative symptoms post-resection than standard monopolar TUR systems.^{17,18} In the third study of this Thesis we also found that the postoperative recovery was faster in terms of self-reported IPSS. High-frequency current generated by a bipolar instrument tends to remain superficial – Gyrus (manufacturer) reports a 0.5–1mm depth of penetration compared with the 3–5mm depth seen in monopolar systems, something that also has been shown in independent studies.^{19,20} The superficial depth aids in avoiding unintended stimulation of nearby nerves as seen during monopolar resection,^{21,22} even though it cannot be completely avoided.

In bipolar electro surgery, the generator produces a high initializing voltage spike that establishes a voltage gradient in a gap between the bipolar electrodes. When the loop is sufficiently close to tissue, the high bipolar voltage spike arc between the electrodes converts the conductive sodium chloride solution into a non-equilibrium vapour layer or ‘plasma’ containing energy-charged sodium particles. Once formed, this plasma can be maintained at lower voltages. With tissue contact, there is disintegration of tissue via molecular dissociation as the current flows to the nearby return electrode. Energetic species of the charged ions from the plasma result in disruption of carbon–carbon and carbon–nitrogen bonds. There is also electron impact dissociation of water molecules into excited fragments of H^+ - and OH^- -ions. Bottom line is the rupture of cell membranes, which translates into visible cutting.¹⁸

IRRIGATING SOLUTIONS

In transurethral resection, the irrigating solutions are used to dilate the operation field and to wash away debris and blood in order to gain good vision. Since isotonic electrolyte solutions are incompatible with the original monopolar technique, sterile water was first employed for irrigation in TUR. In 1947, it was documented that an uptake of more than three litres led to overt symptoms of absorption, and the condition was called TUR syndrome, first being discovered in such an operation.^{23,24} This led to intense work to make the irrigation safer, and various non-electrolyte solutes were added to the fluids to prevent haemolysis-induced renal failure in case of absorption. Today, a variety of nonhaemolytic, nonelectrolytic solutions are commercially available. Although haemolysis disappeared in the 1950s, other types of serious adverse effects still appear, linked to the type of fluid used and, of course, to the fact that the volume absorbed in itself can cause severe life-threatening and even fatal TUR syndromes.²⁵

Glycine is marketed as a 1.5% solution, which is slightly hypo-osmotic. Glycine is an amino acid; elimination takes place by cleavage in the liver, yielding ammonia. Absorption may give rise to hyper ammonemic encephalopathy and also to visual disturbances and transient blindness due to its properties as a neurotransmitter. When

absorbed, it creates a hyperosmotic diuresis which in turn results in an absolute sodium loss.

Mannitol is an isomer of glucose, sold in 3% or 5% solutions. Mannitol is excreted unchanged in the urine and causes osmotic diuresis. Circulatory symptoms in absorption are as common as for glycine, but neurological symptoms are rare.²⁶

Sorbitol is metabolized into fructose and glucose and may result in lactic acidosis.²⁷ If a patient is intolerant to fructose, life-threatening reactions can appear. In commercial solutions, sorbitol is often combined with mannitol in different ratios. Compared to glycine, no difference in symptomatology has been revealed.²⁸

Sterile water, as mentioned above, may cause haemolysis and renal damage if absorbed and is thus recommended only for cystoscopic procedures without electrocautery.

Despite these facts, sterile water is still used for transurethral resections worldwide.²⁹⁻³¹ When bipolar electrocautery for TUR emerged on the market, it became possible to use electrolyte-containing solutions; therefore, the pattern of side effects has been changed in ways that are still partially unknown. Some authors claim that the risk of TUR syndrome has now been eliminated.^{28,32}

Normal saline is the only irrigating solution used for this modality so far, but there is evidence indicating that other fluids could also be of interest (as shown in Study IV of this Thesis). An infusion of saline may give rise to mental changes and swelling discomfort,³³ as well as hyperchloraemic metabolic acidosis due to the high chloride content.³⁴

MONITORING

Alongside technical improvements regarding the instruments for resection, a similar development has taken place when it comes to monitoring the patient. The anaesthesiologic equipment is now highly advanced and allows for a complete surveillance of the patient's well-being. Several techniques, both invasive and non-invasive, are now at hand for the anaesthesiologist, a field of knowledge which is best discussed elsewhere.

However, there are two issues that deserve a more detailed discussion in this Thesis. In TURP, bleeding is the most common incident, and the uncontrolled absorption of irrigation fluids is the most feared one.

Bleeding in TURP is an easily overlooked issue since adequate measurement methods are rarely applied.³⁵⁻³⁸ It is not uncommon to hear from urologists that "in my hands" haemorrhage is not a problem. Of course, with experience and a good technique, bleeding is less likely to cause problems; nevertheless, it is always important to have a clear view of the patient's status during an operation, especially when the patient might be fragile due to concomitant medical conditions.

Different methods of assessing blood loss are available. They are more or less likely to determine true blood loss. Different ways of visually estimating blood loss have been applied, methods which have been shown to underestimate the true blood loss by as much as 100%.³⁹ The level of potassium after haemolysis has also been used.⁴⁰ Probably the most widespread way to estimate blood loss to this day is by measuring the decrease in blood Hb-concentration.⁴¹⁻⁴⁴ In Study II of this Thesis we showed that precision was poor in assessing blood loss from the fall in blood Hb-levels. The problem with these methods is that they indirectly calculate the blood loss, and with proven drawbacks, they are frequently not more than very gross estimates and often utterly inaccurate. They also give the opportunity to estimate blood loss only postoperatively.

In the 1970s, a photometric method of quantitatively determining blood loss was developed. This was done with a recalibrated photometer,^{39,45} according to the formula:

$$\text{Blood loss (l)} = \frac{\text{Low Hemoglobin concentration (g/l)} \bullet \text{irrigant volume (l)}}{\text{Preoperative blood Hb concentration (g/l)}}$$

When developing the Low Hemoglobin Photometer, an easily handled portable device could be used in the operating room. This created the possibility to continuously follow the volume of the blood loss during surgery, which made it easier to decide *if*, and in that case *when*, to give the patient a blood transfusion. The method was proven to be valid in a number of studies with a strong correlation to transfusion rates.⁴⁶⁻⁴⁸ This method is routinely applied in Södersjukhuset and in many parts of Sweden, but seldom in other parts of the world, where the habit of measuring Hb drop postoperatively clings on.

Early in the era of transurethral resection, it was clear that massive absorption of sterile water led to severe damage and death. At first, there were no other means of estimating absorption than by the volumetric fluid balance, which can easily be misinterpreted by the addition of blood and urine to the returning irrigant, spillage on the floor and inter-bag volume differences.

Dilutional hyponatraemia caused by absorption can be measured quite easily at the end of an operation. A good estimate is that a decrease in serum sodium of 5-6 mmol/l corresponds to an uptake of 1 litre of fluid.^{49,50} This method is useless when assessing absorption in bipolar surgery, a fact that oddly enough has been neglected in several studies comparing bipolar and monopolar TURP.⁵¹⁻⁵⁵ However, the addition of glucose to a concentration of 5% in the saline might serve as a replacement to serum sodium concentration measurements.⁵⁶

There has been at least one attempt to tag the irrigant with radioactive isotopes, but this was not in use on a larger scale.⁵⁷

TURP – How to reduce morbidity

The ethanol method is now the most accurate and well-documented way to measure fluid absorption.^{50,58,59} It is increasing in use, but still the vast majority of studies dealing with the evaluation of TURP from different points of view do not apply this method. Ethanol is added to the irrigating fluid to a concentration of 1%. The body concentration can then be measured in the exhaled breath, using a hand-held alcolmeter. The method has a superior sensitivity, detecting approximately 100 ml absorption. It is also non-invasive. Another advantage, like the volumetric method, is that this makes it possible to determine the amount of fluid absorbed *during* the surgical procedure, thus giving early warnings to stop the operation before a clinically significant absorption occurs, preventing TUR syndrome. Ethanol can also be added to saline when monitoring bipolar TURP.

The addition of nitrous oxide to the irrigating solution has also been tried with promising results experimentally as well as clinically, but it is not in general clinical use yet.⁶⁰⁻⁶²

4 COMPLICATIONS

TUR SYNDROME

Symptoms of massive absorption and TUR syndrome occur in between 1-8% of TURPs,^{7,50,63,64} when at all reported. Most comparable studies are not capable of answering questions in this matter because of sample sizes that are too small.

Absorbed fluids find their way in to the body either intravascularly through damaged veins or by extravasations through perforated tissues, such as the prostatic capsule or the bladder wall. In the former, absorption usually starts in the middle or at the end of the procedure and continues until the operation is stopped.⁶⁵ It has also been shown that longer operations and larger resections result in more cases of TUR syndrome.^{7,65}

There seems to be a dose-dependent increase of symptoms associated with absorption, best described when using glycine. Typical symptoms during surgery are prickling and burning sensations in the face and neck, chest pain, restlessness, and headache. Bradycardia and arterial hypotension suggest volume overload and might progress to pulmonary oedema. In the postoperative period, patients may present with nausea and continuous hypotension, followed by vomiting and low urine production.^{26,66,67} Transient cognitive dysfunction is associated with smaller absorbed volumes.⁶⁸ If the absorption is extended to 1-2 litres, apparent confusion with a risk of coma is evident.^{69,70} Abdominal pain is a common first sign of extravasation, which is further associated with a higher incidence of arterial hypotension and poor urinary output.⁷¹ Mild TUR syndromes are incomplete and easily overlooked. A drop in arterial pressure at the end of surgery combined with postoperative nausea is the most common presentation. Severe TUR syndrome is rare and occurs in perhaps 0.1–0.5% of operations. A French review of 24 severe cases of TUR syndrome displayed a mortality rate of 25%.⁷²

The pathophysiology of the TUR syndrome is complex. When employing non-ionic irrigants, absorption can result in a cardiovascular disturbance with an initial increase in hemodynamic pressure due to hypervolemia with symptoms such as chest pain, dyspnoea and acute pulmonary oedema. This phase levels off within 15 minutes and is followed by a decrease in cardiac output, lowered arterial pressure and hypovolemia explained by hypokinesia of the heart.⁷³ Bradycardia and ST-depression may also be evident because of both the fluid overload and the specific toxicity to the heart muscle by the irrigants themselves,^{73,74} with glycine being the worst one.^{74,75}

Dilutional hyponatraemia, (<120 mmol/l), which is made worse by osmotic diuresis, can create brain oedema and lowered consciousness postoperatively.

Swelling of the kidneys is followed by low urinary output, and there is a risk of renal impairment and anuria. The causes of death in TUR syndrome are typically cardiovascular collapse or cerebral herniation.

The experience of TUR syndromes in surgeries employing saline is still not comprehensive, but cerebral oedema is not caused by saline irrigation. However, symptoms of fluid overload can still occur. There is also data in dogs suggesting that the excess of chloride ions might induce a decrease in the glomerular filtration, which in turn can cause a delayed diuretic response to fluid overload.⁷⁶

The best way to prevent TUR syndrome is to have a good surgical technique, sealing bleeders when they appear, avoiding open venous sinuses and, if possible, limiting the operation time, even though there is also a risk of massive absorption in the early phase of the operation. Keeping the pressure low in the bladder is also a factor that affects the incidence of absorption; this can be achieved with either a continuous flow resectoscope or a suprapubic trocar, or by frequent intermittent emptying of the bladder. Altering the height of the fluid bags does not have any effect in preventing a TUR syndrome.^{77,78}

Treatment of TUR syndrome in surgeries involving ion-free solutions include initial volume replacement with colloids and infusion of hypertonic saline if symptoms have developed or if serum sodium has fallen to below 120 mmol/l. Diuretics have a role if pulmonary oedema or renal failure develop but should be carefully used until the patient is haemodynamically stable. Massive extravasation into the intraperitoneal or periprostatic spaces can be treated with surgical drainage and accompanying correction of electrolytes.

HAEMORRHAGE AND TRANSFUSION

Bleeding, to various extents, is the most common reason for difficulties during surgery as well as for danger to the patient. Attempts to limit blood loss have been made by refining the surgical technique, improving electrocautery devices, experimenting with preoperative drugs such as 5-ARIs⁷⁹⁻⁸¹ and selecting and preparing the patient. Still, the amount of bleeding depends on the length of the resection, the amount of the resected tissue and the surgeon's experience.

Erythrocyte transfusions are administered to 0-23% of patients in monopolar TURP studies.⁸²⁻⁸⁴ In a review of bipolar TURP studies, the transfusion rate was found to be 0-11%⁸⁶. Mamoulakis *et al.* reported in their meta-analysis that there was a significant difference in transfusion rates in favour of the bipolar technique.⁸⁶

The photometric method of assessing blood loss is infrequently used; therefore, it is difficult to compare the findings of our group to the results of others where either the loss of blood Hb or the visual estimation method was used. Accessible data on blood loss with the photometric method,⁴⁶⁻⁴⁸ suggests a haemorrhage of approximately 15

ml/g of resected tissue. This figure is reproduced in both Study I and II (monopolar group) of this Thesis. Added to the lower transfusion rates, the 11.4 ml/g haemorrhage in Study II clearly indicates that bipolar resection decreases perioperative blood loss in TURP. The rates of haemorrhage-associated complications such as AMI are available for monopolar surgery thanks to a series of large studies from the late 20th century and have gradually decreased.^{7,8,87-89} Data for comparison to bipolar surgery are not yet substantial enough, but there are no indications of any higher rate of complications linked to blood loss in previously published papers on bipolar TURP.

OBTURATOR SPASM

More of a problem in bladder resections, but nevertheless also occurring in TURP, an obturator jump can cause severe damage to the patient. Especially when a tumour is located on the lateral wall, low frequency diathermy currents can stimulate the obturator nerve, resulting in a spasm of the adductor muscles. If the legs are fixed in stirrups, this adduction will lead to an elevation of the pelvis, and there is a major risk for bladder perforation. Obturator jumps in TURP are not as frequent, but when occurring, the surprise effect is potent. Steps to prevent this can be taken, including general anaesthesia with complete muscle relaxation, turning down the current, and applying a local blockade of the obturator nerve.^{90,91}

With bipolar devices, it seems that the incidence of obturator jumps has decreased.^{22,92,93} The explanation for this is that the return current takes another path in a more local circuit.

INFECTIONS

The rate of infection following TURP is usually low, ranging in between 0-22% in monopolar series,^{84,94} with the mean number of cases being around 4%. Preoperative bacteriuria (indwelling catheter, bladder stone), prolonged operation duration (>70 min), long preoperative stay (>2 days) and discontinuation of catheter drainage (due to tamponade evacuation) are all considered as risk factors.

Urosepsis is the most serious infectious complication after TURP, often demanding intensive care efforts, but fortunately it is not common. Other manifestations are febrile or non-febrile lower UTI, and epididymitis.

Several large meta-analyses have found that a general preoperative antibiotic prophylaxis significantly decreases the incidence of bacteriuria, lower UTI and febrile infections including septicaemia.^{95,96} This is considered as strong evidence by the Swedish Council on Health Technology Assessment of 2010,⁹⁷ where a general antibiotic prophylaxis in TURP is advocated. The same point of view is expressed in the updated EAU guidelines of 2011,⁹⁸ where it is shown that antibiotic prophylaxis decreases the relative risk for bacteriuria and septicaemia by 65% and 77%, respectively.

In those analyses of bipolar TURP compared to the monopolar technique, there is no evidence of an altered panorama or frequency of infections, even though it seems as if trends point to a lower incidence.⁹⁴

CATHETER TIME AND HOSPITALIZATION TIME

It is generally difficult to assess the length of postoperative catheterization and subsequent in-patient hospitalization in bipolar TURP compared to monopolar. This is mainly due to insufficient or lack of reporting protocols for catheter removal. There are examples of removing the catheter on a fixed day,⁴⁴ prolonged catheterization for large glands,⁵⁴ and removing the catheter after urine is completely clear.^{53,99-104}

The length of catheterization is subject to different factors, such as clinical routines, interest of caregivers and, inevitably, the amount of blood in the postoperative irrigation.

In the literature for both bipolar and monopolar TURP, the length of catheterization varies from less than one day up to four days or more.⁹⁴

In centres such as our own department, where we routinely remove the catheters as soon as possible, differences in catheterization and hospitalization times are seldom seen. In other centres where longer catheterization is practiced, differences are detectable and in favour of the bipolar technique.⁸⁶ The difference in hospitalization follows the catheterization times; once the catheter is out, the patient is discharged shortly hereafter.

READMISSIONS AND REOPERATIONS

The rate of re-TUR in different monopolar series is 0-6.6%.⁸⁴ Madersbacher *et al.* showed that the accumulated re-TURP rate after 1, 5 and 8 years was 2.9%, 5.8% and 7.4 % respectively.¹⁰⁵ In agreement with this, Wasson *et al.* present a 5-year risk for reoperation following transurethral resection of 5%.¹⁰⁶ Reoperations also include TUIP because of bladder neck contractures, reported to occur in 2-9% of the patients.¹⁰⁷ Bipolar complications of these kinds are likely to be at the same levels, according to reported data.⁹⁴ This is also true for the incidence of urethral strictures, an issue that has caused a great deal of debate.

In the beginning of the bipolar TURP era, a few studies reported higher stricture rates compared to monopolar operations.^{36,37,54} The method was therefore seriously questioned, and warnings were given. Stricture rates in these selected series were about 3-6%, which is not statistically different from monopolar groups. The overall stricture rates in historical monopolar series have varied from 2.2 to 9.8%.⁸⁴ Reasons for this seemingly higher stricture rate were thought to emanate from the path of the bipolar current, causing electrical damage to the urethra. Recently, a number of large studies have not been able to reveal any true differences between the two techniques.^{86,108}

It seems that there is still reason to believe that by using narrow instruments and enough lubrication and limiting the time of operation, one can keep the strictures to a minimum.

The introduction of bipolar TURP also seems to reduce the need for immediate postoperative interventions such as bladder evacuation due to clot retention and secondary coagulation as reported by Ahyai *et al.*⁹⁴

MORTALITY

There has been a gradual reduction in immediate postoperative mortality over the years. From the beginning of the TURP era, Perrin *et al.* reported a mortality rate of about 5%.¹⁰⁹ Various works then outline the stepwise decrease in mortality^{7,110,111} until more recent studies, where the 30-days mortality is close to or equal to zero.^{8,89,112} The debate as to whether TURP is associated with an increased long-term mortality was thoroughly summarized by Sandfeldt in his Thesis from 2001.¹¹³ Here, the direct reasons for the slightly elevated risks were not clearly demonstrated, but indices pointed towards a significant incidence of comorbidities among the TURP patients. Other works have stressed that there are no real differences in either long- or short-term mortality when compared to unoperated age-matched control groups.^{106,114}

The decrease in mortality is attributed to a better technique, improved instruments, more thorough patient selection, improved antibacterial medication, safer irrigants, more careful monitoring and improved postoperative care.

5 ALTERNATIVE TREATMENT METHODS

MINIMALLY INVASIVE TECHNIQUES

A range of different minimally invasive methods have found their way into the arena of treating BPH. Why? one could ask, since TURP has proven to be a very efficient treatment option with a long-lasting reduction of symptoms that is performed in a more and more safe fashion with fewer and fewer complications. But when examining the aspect of day-care, the concept of TURP has been less successful, and it is in contrast to this that we must view the new techniques which, to a higher degree, focus on performance in an out-patient setting.

Vaporization

Vaporization was first described in 1995 by Kaplan *et al.*¹¹⁵ By adding more energy than in the regular TURP, it was possible to vaporize the adenoma of the prostate with special loops and rollers. The method was time-consuming, though, and it was also associated with a higher degree of postoperative retention, impotence and incontinence.¹¹⁶

The method has experienced a renaissance since the introduction of the bipolar technique, where vaporization is an option with all major bipolar systems, by the use of specific electrode designs. There are an increasing number of studies showing that this modality produces positive results comparable to TURP both in symptom relief and complication rates.^{94,117,118} Vaporization advocates often point out that the method is virtually bloodless, but it is not always clear how this is monitored. However, results indicate shorter postoperative catheterization, fewer blood transfusions and shorter hospital stays.^{43,52,119}

An important issue to bear in mind when discussing vaporization is that this technique does not provide a histological specimen. Incidental prostate cancer is discovered in roughly 1 out of every 10 TURPs.^{120,121} Not all of these are clinically relevant, but the possibility of cancer must be carefully considered and discussed with the patient whenever choosing between methods that may be unable to give a correct diagnosis.

Lasers

Different kinds of lasers have been used, but the two most widespread methods are KTP (Potassium-Titanyl-Phosphate, “green light laser”), which reduces prostate volume by coagulation, and the Holmium laser that either evaporates or cuts through the tissue in an enucleative way. When enucleating the prostate with the Holmium

laser, a morcellator is needed to disperse the tissue in order to pass it through the urethra.

Several comparisons to TURP have been made, and both methods are successful in lowering IPSS-scores (KTP < Holmium < TURP), but overall complication rates are higher in both laser methods than in either bipolar or monopolar TURP.⁹⁴

However, lasers are also undergoing development, and different combination lasers are emerging, designed for both coagulation and vaporization as well as for stone disintegration in the upper urinary tract.

TUMT

Early transrectal microwave treatments were outranged when transurethral antennas were developed. New cooling systems with intricate thermo sensors were applied in order to protect the rectal wall and the urethra while heating the prostate up to 70° C. Today the devices provide the performer with dynamic reports of cell kill and temperatures of the treated area, supplying a custom-made treatment. Heating of the prostate results in a coagulative necrosis of the prostatic tissue, that is later resorbed, thus decreasing the prostate volume.

Outcomes after TUMT are comparable to those after TURP regarding symptom relief and rates of complications.^{122,123} However, flow improvement is lower and retreatment rates are higher, as several studies show a range from 19.8% to 84.4% after 5 years. Low-energy TUMT displays more disappointing results than the high-energy version.¹²⁴⁻¹³¹ TUMT is said to be a good and safe treatment for those unfit for other surgical procedures, unless the patient has a prominent middle lobe.¹²⁹ Common complications include urinary retention, infections, perineal discomfort and urinary urgency. An advantage of this method is that it is truly a day-care intervention, since it can be done under local anaesthesia.

TUNA

Like the TUMT procedure, TUNA delivers heat to the prostate. This is achieved by inserting needles transmitting radio-waves creating heat-induced coagulation necrosis. Retreatment rates are much higher than in TURP,¹³² and improvements in symptoms and flow significantly lower. It has similar side effects as TUMT. Long-term evaluations are not yet available.

PHARMACOTHERAPY

With an increasing proportion of ageing men in the Western world, the need for efficient treatments of BPH has led to the development of different pharmacological regimes. Drugs are now considered the first line treatment for mild to moderate symptoms due to BPH and have proven to be very efficient in postponing or even avoiding surgery. Two separate mechanisms of action are predominant, and combinations of these are frequently used.

Alpha blockers

Alpha blockers were originally developed as anti-hypertensives. They also lower the tone of the smooth muscles in the urinary tract by blocking different subsets of the α_1 -receptor and thus reducing the dynamic component of the bladder outlet obstruction. The effect of alpha blockers is dose-dependent, with increasing side effects, such as hypotension, vertigo and headache.

Alpha blockers decrease IPSS by 3-4 points and increase flow by 2-4 ml/s. The chance of being catheter-free following an episode of acute urinary retention increases by about 50 % if an alpha blocker is given 2-5 days before removing the catheter.¹³³ In the large MTOPS-study, ¹³⁴ alpha-blockers alone reduced the risk for surgical intervention for two years and then leveled with the placebo arm.

5-Alpha Reductase Inhibitors

In castrated patients, the prostate ceases to grow. This indicates the need for androgens in the growth of the prostate. Testosterone is converted into the active metabolite dihydrotestosterone (DHT) by the two iso-enzymes of the enzyme 5-alpha reductase. Finasteride blocks 5-alpha reductase 2, while dutasteride is a dual blocker.

Both drugs have shown long-term effects in preventing progression and improving symptoms.¹³⁵⁻¹³⁷ Side effects include loss of libido, erectile dysfunction and gynecomastia. Combinations of 5-ARIs and alpha blockers have shown even better results than for either of the drugs alone.¹³⁴

6 OBJECTIVES OF THE STUDIES

PAPER I

To determine whether 2-4 weeks of pre-treatment with dutasteride, a dual 5 α -reductase inhibitor, reduces surgical blood loss and/or postoperative complications in patients with benign prostatic hyperplasia who undergo transurethral resection of the prostate.

PAPER II

To compare bipolar resection with the conventional monopolar TURP with respect to perioperative parameters, such as blood loss, transfusion rate and speed of resection.

PAPER III

To compare bipolar resection with the conventional monopolar TURP, focusing on peri- and postoperative complications, re-admission rates, reoperations, speed of recovery and long-term outcome.

PAPER IV

To determine and compare the *in vitro* degree of vaporization in bipolar and monopolar resection in different kinds of tissue, different fluid environments and with different kinds of loops.

7 ETHICAL CONSIDERATIONS

Ethical permits Paper I: 140/03 (KI, Forskningskommitté Syd, Huddinge
Universitetssjukhus F59)

Papers II and III: 2005/576-31/1 (Regionala etikprövningsnämnden i
Stockholm)

All patients gave their written informed consent before entering the studies. Participating in the studies did not delay the scheduled surgery. Additional blood samples were taken for research purposes, but not to an extent that would affect them haemodynamically. Each patient could terminate his participation without further notice. In study I, participating patients were subject to more out-patient visits than in the normal clinical routine. In study III, the patients were asked to fill in forms of IPSS/QoL and timed micturition four times postoperatively, which is three times more than in the clinical routine.

In study IV, no ethical permit was necessary, since the studied tissues were derived from neither humans nor experimental animals.

8 STUDY SUMMARIES

MATERIALS / PATIENTS AND METHODS

Study Designs

Study I was a randomized double-blind, placebo-controlled multicenter study in which 214 men with a prostate volume of ≥ 30 mL were enrolled. The 23 recruitment centres were located in Sweden, Denmark, Finland, Norway, the Netherlands and the UK. Patients were scheduled for monopolar TURP within a period that allowed 28–32 days of preoperative treatment with study medication. Exclusion criteria included history or evidence of prostate disease other than BPH, previous prostate surgery, treatment with any 5ARI within 12 months, requirement for treatment with aspirin or NSAIDs during the restricted periods and severe medical conditions. The patients were randomized in a 1 : 1 : 1 ratio to one of three treatment groups, where group 1 received daily placebo for 4 weeks before and 2 weeks after TURP, group 2 received placebo for 2 weeks followed by 0.5 mg of dutasteride daily for 2 weeks before and 2 weeks after TURP, and group 3 received dutasteride 0.5 mg for 4 weeks before and 2 weeks after TURP.

The primary endpoint was the evaluation of total blood loss during TURP. Secondary efficacy outcomes included measures of late bleeding 4 to 14 weeks after TURP, and the incidence of clot retention, transfusions, acute urinary retention, UTI and urinary incontinence after TURP. Throughout the study period, all patients completed a diary, recording bleeding events and clots. Every patient visited his urologist repeatedly during the 20 weeks of study participation. Blood loss was measured for each bucket used to collect irrigating fluid, using the Low Hemoglobin system (HemoCue, Ängelholm, Sweden).^{39,47,48} Serum concentrations of testosterone and DHT were measured on three occasions. The resected prostate chips were also assessed for these hormones. Areas of the prostatic urethra and prostatic nodular hyperplasia were fixed until incubated with a monoclonal immunohistochemical antibody. After mild staining with haematoxylin-eosin, the MVD was determined by microscopy. A central laboratory was responsible for all measurements in order to reduce inter-site variability for each laboratory variable.

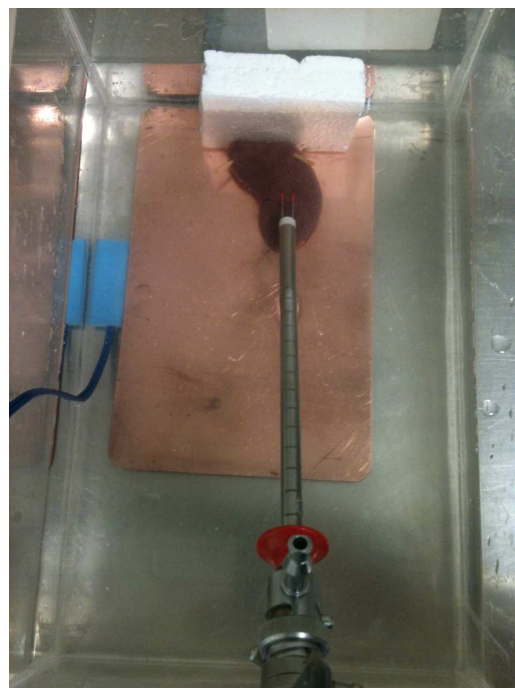
In *Study II* and *III*, 202 patients were randomly allocated between 2005 and 2008, using a random numbers table, to either TURP using a bipolar system or conventional monopolar technique. Inclusion criteria were a TRUS prostatic volume of 30 - 100 mL and symptomatic BPH that required surgery. Exclusion criteria were evident prostate or bladder cancer, core biopsy of the prostate within 3 months before surgery, signs of neurogenic bladder dysfunction or urethral strictures.

Monopolar TURP was performed with a Storz resectoscope, using factory-made irrigating fluid containing mannitol 3% and ethanol 1%. Bipolar TURP was performed with the Olympus TURis system with normal saline solution as the irrigant. To offer the same possibility to early detect and quantify fluid uptake in both groups, ethanol was added to the saline to the same concentration as in the electrolyte-free irrigating fluid⁵⁰. Anticoagulation treatments were discontinued prior to surgery. No selection of patients to any particular surgeon occurred. General antibiotic prophylaxis was not applied.

In **Study II**, the main outcome measure was blood loss; peri-, postoperative and total, as determined by the Low Hemoglobin method. Secondary outcome measurements included operating time, bleeding velocity, blood lost per g resected tissue, resection radicality and transfusion rate. Factors that could affect results, such as preoperative medication, indwelling catheter, surgical treatment and the surgeon's experience, were assessed in subgroup analyses.

In **Study III**, the postoperative course of the same cohort was investigated. We recorded complications, comprising infections and haemorrhage leading to re-admissions and prolonged hospital stay, as well as reoperations. IPSS/QoL- and TM-forms were collected preoperatively and at 3 and 6 weeks and at 6 and 18 months after surgery.

Study IV was an experimental *in vitro* study, in which ten samples each of chicken muscle and lamb kidney were resected in an isolated container with a fixed volume of irrigating fluid. After weighing, the specimen was placed in a plexiglass basin filled with 1500 ml of irrigating fluid at room temperature and fixed to a piece of Styrofoam (Pic. 2).



Picture 2. Arrangements set up for monopolar resection of a kidney in the container.

Ten cuts in each sample were made. Bipolar resection was performed with the Olympus TURis system set at either 280 W (medium loop) or 290 W (large loop) for cutting. Saline and acetated Ringers solution were used as irrigants. Monopolar resection was performed with a Storz 24 Ch resectoscope with a standard loop, set at 130 W for cutting. Mannitol 3% was used as irrigant. Container irrigant was changed after every five samples.

As tissue chips may absorb irrigating fluid to an unpredictable extent, we desiccated reference samples in an incubator to determine the normal water content of the tissues. This generated a factor for each tissue, which was used to calculate fresh weights from desiccated samples. Fresh, wet and dry weights of the resected samples were recorded.

During the period in the incubator, the samples were weighed repeatedly until no further weight loss was registered. The difference between the fresh weight of the uncut sample and the sum of the fresh weights (calculated based on its expected “normal” water content) of the resected tissue and the remains represented the amount of vaporized tissue.

Statistics

For *Study I*, the power calculations were based on the study by Donohue *et al.*, which showed a benefit of *finasteride* treatment in reducing perioperative blood loss compared with placebo.¹³⁸ The study had > 90% power to detect a difference in pair-wise comparisons between each active group and placebo in the primary endpoint using a t-test and a general linear regression model with effects for treatment and country. Multiple stepwise regression analysis was used to identify significant effects in the blood loss model. Complications after TURP were compared using Fisher’s exact test.

Study II and *III* were designed to detect a difference in total blood loss of 30% between the groups, and this was considered the primary endpoint. The other measurements in study II, as well as the parameters studied in paper III, were considered as secondary endpoints. The Mann-Whitney U test was used to evaluate numerical variables with a skewed distribution. Categorical variables were analyzed using the χ^2 test. Factors of importance to the blood loss were identified by stepwise multiple regression. Two-way ANOVA was used, controlling for factors associated with absorption.

In *Study IV*, all parameters showed a normal distribution. Means were compared with independent samples’ t-test. Factors of importance for vaporization were analyzed with one-way and three-way ANOVA.

RESULTS

Study I

Of the 214 patients enrolled, 197 completed the study. (Fig 1)

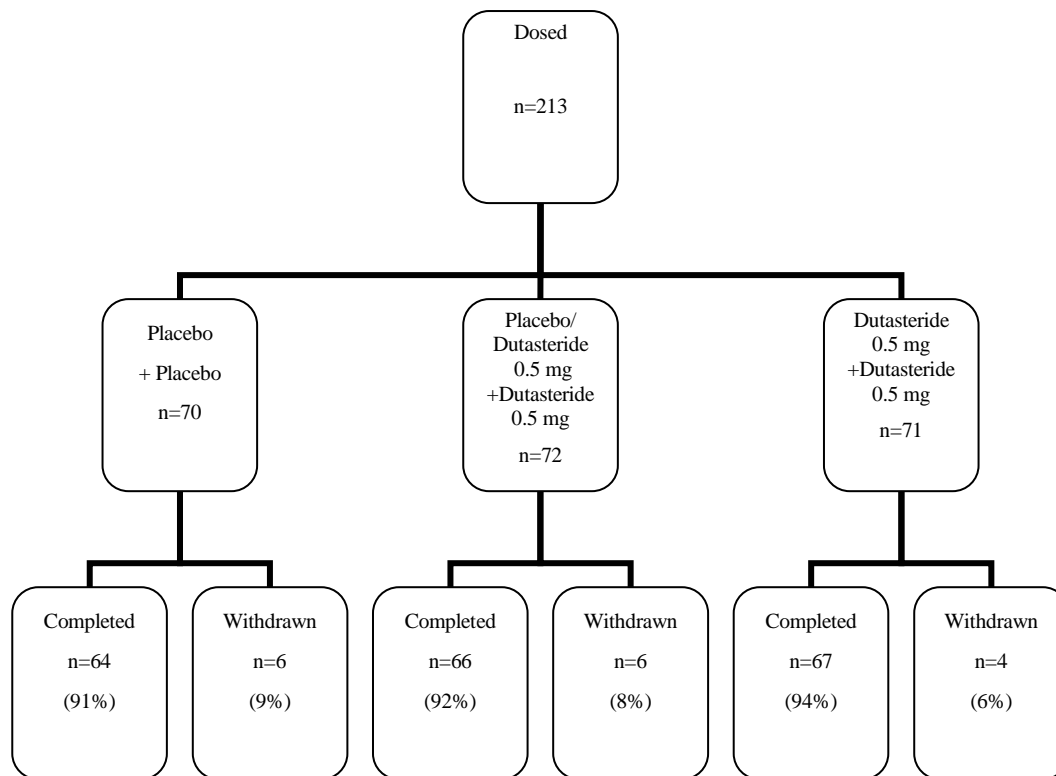


Fig 1. Disposition of randomized patients

The mean operative duration was 45 min, during which 25 g of prostatic tissue was resected. There were no statistically significant differences among the treatment groups in the primary endpoint of Hb loss during surgery. As expected, resection weight and operating time were significant effects in the blood loss model ($P < 0.004$ and < 0.001 , respectively), but correction of the Hb loss for these variables showed no significant differences among the groups. Blood transfusions were given to 1–3% of the patients in each group. Two patients required further surgery during the initial hospitalization. After initial discharge, an additional three patients were re-admitted as inpatients and one as an outpatient. Mean initial hospital stay was 3.1–3.3 days. Excessive and/or severe bleeding occurred in relatively few patients per group. No statistically significant differences among the groups with respect to perioperative bleeding, defined as excessive bleeding, clot retention (requiring intervention), or the occurrence of bloody urine and/or clots in the urine as reported by the subject on the diary card, were found. In patients treated with dutasteride, no alterations of the MVD in the prostatic urethra or regions of nodular hyperplasia were seen, the serum concentration of DHT

was decreased by 86-89 %, while the serum testosterone levels were increased by 13-15 %, and the concentration of intraprostatic DHT was 10 times reduced. These findings were all expected.

Study II & III

Of 202 randomized patients, 185 eventually were evaluated, 98 patients in the bipolar and 87 patients in the monopolar group. There were no relevant differences in base-line parameters between the groups (Table 1.).

	Operation Technique						<i>P</i>
	Bipolar (n=98)			Monopolar (n=87)			
	Mean	SD	n	Mean	SD	n	
Age (yr)	69.5	7.2	98	72.7	8.4	87	0.007
Prostate volume (ml)	55.6	18.2	98	58.2	17.6	86	ns
Hemoglobin pre-op (g/l)	141.0	13.1	98	141.8	14.0	87	ns
PT-INR	1.1	0.1	98	1.1	0.1	87	ns
IPSS pre-op (points)	21.7	6.9	31	20.4	7.6	32	ns
Botherscore pre-op (points)	3.9	0.9	31	3.7	1.1	32	ns
Time Micturition pre-op (s/1:st dl)	24.5	14.4	21	27.7	17.9	20	ns
Indwelling Catheter (n)			33			34	ns
5-ARI treatment (n)			23			25	ns

Table 1. Baseline Data Study II and III

Operation time tended to be longer in the monopolar group, and resection speed was slightly higher in the bipolar group. Resection weight showed no difference between the groups.

Per operative, as well as total, blood loss was significantly smaller in the bipolar group ($P<0.001$), a difference that remained when correcting for operating time and resection weight. The Hb drop and transfusion rate were significantly lower in the bipolar group ($P<0.001$ and $P<0.01$ respectively), a fact that has its explanation in the markedly lower 75th percentile for blood loss in the bipolar group (472 ml versus 855 ml, respectively, Fig 2.)

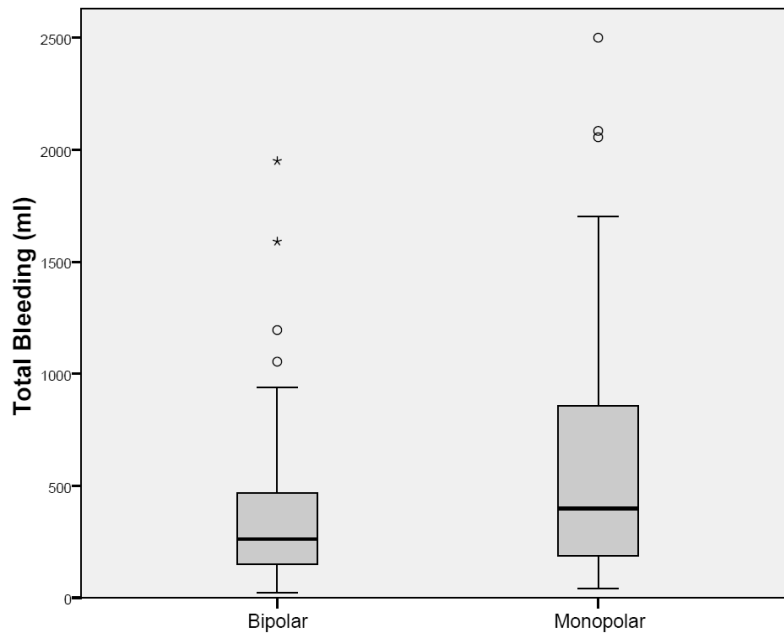


Figure 2. Total blood loss in ml expressed as box-plots with the median, 25th–75th percentile, and outliers.

The difference in blood loss remained also when taking subgroups of patients in to account (Table 2.).

	Operation technique				Mann-Whitney U
	Bipolar		Monopolar		
	Bleeding/g/min		Bleeding/g/min		
	n	Median	n	Median	
All patients	98	0.14 (0.10-0.28)	87	0.23 (0.15-0.33)	<0.001
5-ARI	23	0.13 (0.09-0.31)	25	0.23 (0.17-0.34)	0.007
Anticoagulants	4	0.11 (0.09-0.14)	9	0.26 (0.19-0.39)	0.014
Preop indwelling Catheter	33	0.13 (0.08-0.20)	34	0.21 (0.15-0.30)	0.02
Reuter's trocar	19	0.12 (0.08-0.14)	25	0.19 (0.14-0.30)	0.03
Residents	9	0.27 (0.09-0.32)	5	0.12 (0.11-0.14)	0.606

Table 2. Study II, Subgroup analyses. Perioperative bleeding/g/min (blood loss in ml over number of grams resected over length of resection in minutes) expressed as median, 25-75th percentile

Stepwise multiple regressions found three factors of importance for predicting blood loss: operation time, resection weight and the choice of mono/bipolar surgery (all $P < 0.001$).

Absorption of irrigating fluid was detected by the ethanol method in 21 (11%) of the patients, with no difference between the groups, even though there was a trend of fewer absorptions in the bipolar group. All but one of the absorptions occurred at the end of surgery, and ten had a duration of at least 20 minutes. No obturator nerve affection was recorded in either of the two groups. The absorption led to symptoms in three monopolar patients (drop in arterial pressure and decrease in serum sodium, abdominal pain and headache). Two-way ANOVA showed that the incidence of fluid absorption was independently associated with a larger surgical blood loss and 15 minutes longer operation time (both $P < 0.02$).

In all, 131 (71%) catheters were successfully terminated within 24 hours, and an additional 23 (12%) patients had their catheters permanently removed within 48 hours with no inter-group differences. A similar number of patients in the two groups were discharged with an indwelling catheter due to failure to void. Only one patient (monopolar) did not succeed in the removal of his catheter within the follow-up period. The hospital stay was similar in the two groups with a median of 51-52 hours.

The number of readmissions was 14 for monopolar and 5 for bipolar ($P < 0.011$). Readmissions were associated with larger haemorrhage per minute during the resection ($P < 0.03$). Two patients in the bipolar and one in the monopolar group were diagnosed with urethral strictures in the follow-up. Of the six patients (3%) who were reoperated, two were in the bipolar (2%) and four (5%) in the monopolar group. Reoperations in the bipolar group consisted of one urethrotomy and one TUIP, while the monopolar group received one TUIP and three re-TURPs performed at 3, 4 and 12 months after the initial operation because of incomplete resections.

13 patients in both groups had infections that did *not* lead to readmission, while one in each group did. Most infections appeared within 24 hours of surgery.

A detailed analysis of the IPSS forms showed that recovery occurred faster in the bipolar than in the monopolar group, since a larger fraction of the former patients reported ongoing improvement at both 3 and 6 weeks ($P < 0.05$; Fig. 3.). The difference was 20% at 6 weeks ($P < 0.05$). At 18 months, the early differences between the groups had levelled out.

Study IV

In the reference samples, water content was 73% in muscle and 77% in kidney. This means that 1 g of fresh sample corresponded to 0.27 g of dried muscle and 0.23 g of dried kidney. In the resected samples, the degree of vaporization was higher in muscle than in kidney ($P < 0.0001$), and it was also higher when using bipolar resection (Table 3.).

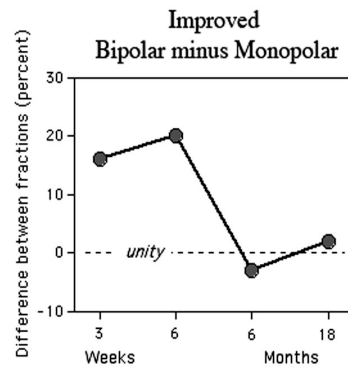


Figure 3. The difference in percentage of “Improved” between the groups.

MUSCLE AND KIDNEY VAPORIZATION DATA					
	Monopolar Standard loop Mannitol	Bipolar Standard loop Saline	Bipolar Standard loop Ringer's Acetate	Bipolar Large loop Saline	Bipolar Large loop Ringer's Acetate
Muscle Vaporization/ resected tissue (%)	45 (12)	62* (18)	71*** (14)	41 (6)	43 (5)
Kidney Vaporization/ resected tissue (%)	22 (12)	39** (15)	56** (28)	23 (10)	22 (9)

Table 3. Mean (SD). Pair wise significance comparisons vs. monopolar technique, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Bipolar and monopolar resection yielded the same degree of vaporization when using the bipolar large loop instead of the standard loop. The uptake of fluid into the resected chips was quite consistent, regardless of which irrigant used, with about 17% in muscle and 12% in kidney. According to one-way ANOVA, the resection method, type of loop and choice of tissue were all factors of importance to the vaporization, while the choice of irrigant was not. Three-way ANOVA showed that the choice of loop ($P < 0.0001$), fluid ($P < 0.03$) and tissue ($P < 0.0001$) were all independently associated with the degree of vaporization. No problems in using the bipolar device in Ringer's Acetate were encountered.

9 DISCUSSION

STUDY I-IV

The most direct and obvious cause of morbidity in TURP is surgical haemorrhage. In most operations, this is not a problem, but in a substantial part bleeding is troublesome. Massive bleeding leads to increased risks of hemodynamic disturbances. There might be a need for transfusions, something that is expensive, not free of risks and could lead to immunologic consequences. Because of this, transfusion is usually considered to be a complication of TURP. There is also a risk that a massive haemorrhage influences the outcome of the procedure. Since there is a considerable number of TURPs performed worldwide every year, there are a corresponding number of patients suffering from haemorrhage-related sequelae.

The main goal of study I and II of this Thesis was to see whether blood loss during TURP could be decreased, either by short-term pre-treatment or with the employment of a new technique.

Despite the 86–89% reductions in serum DHT in *Study I*, neither blood loss during or after TURP, nor the incidence of TURP-associated complications differed significantly among the treatment groups. The DHT reduction would be sufficient for an effect in comparison to other studies with longer treatment including both finasteride and dutasteride¹³⁹. This study is the largest reported that includes 5-ARI and blood loss. The extent of blood loss in the placebo group and a transfusion rate of $\approx 3\%$ were as expected from previous reports.^{7,47} To adjust for variability in operation time⁴⁷ and the amount of resected tissue, the Hb loss was expressed per amount of resected tissue. Still, this did not reveal any intergroup differences.

The thought behind the belief that 5ARIs reduce blood loss during TURP, is that these drugs shrink the prostate by reducing the number of blood vessels. This is supported by a number of studies from the 1990s showing that treatment with finasteride reduces gross hematuria in men with BPH.¹⁴⁰⁻¹⁴⁴ However, studies on finasteride and blood loss in TURP are less consistent. In four published double-blind placebo-controlled studies (including the present), Sandfeldt *et al.*⁴⁸ was *not* able to confirm that 3 months pre-treatment with finasteride would reduce blood loss in TURP. On the other hand, Donohue *et al.* showed that finasteride 5 mg or placebo for only 2 weeks before TURP resulted in losses of 2.7 and 4.7 g Hb/ g resected tissue, respectively.¹³⁸ This was not seen in the present study, and might be explained by the fact that the blood loss in the placebo group was unusually high compared to other studies.⁴⁷ Yet another multicentre study by Boccon-Gibod *et al.*,¹⁴⁵ examining the effects of pre-treatment with dutasteride or placebo for four weeks, did *not* show any differences between treatment groups. Other recent and less robust studies have generated further differing results.^{48,79,80} A few studies have shown a possible benefit by treating with 5-ARI for larger resections with resection weight > 30 g.^{48,146}

The lack of observable effect on prostatic tissue MVD was expected since previous studies have indicated that such an effect appears at a minimum of six weeks of dutasteride treatment.^{147,148}

In **Study II**, bipolar TURP resulted in 34% less bleeding during the operation. When comparing the 75th percentile for blood loss, the difference was as high as 81%. This also resulted in significantly fewer erythrocyte transfusions in the bipolar group. It is our belief that such a reduction is an important advantage, since every step taken to limit the haemorrhage benefits both the patient and the surgeon. In all other recorded perioperative measures, bipolar TURP showed similar results to the monopolar technique.

The postoperative blood loss amounted to only 3.4% of the total blood loss, with no difference between the groups. Thus, it is clear that the great difference in blood loss was limited to the ongoing surgical procedure. The reason for this lower haemorrhage is not fully known, but a possible explanation could be that the coagulation depth of the bipolar device exceeds the diameter of the microvessels in the prostate.²⁰

Most previous assessments of blood loss in bipolar TURP have shown inconclusive results. Some have used the decrease in Hb levels,^{53,149} others visual analogue scales⁹⁹ or indicator dilution.⁵⁴ The common feature for these studies is that they give only an indirect estimation of the blood lost estimations that may be influenced by several unknown factors. Neither do they say anything about the postoperative blood loss, which in this study was found to be low in both groups, a parameter of value in the discussion of when to terminate the postoperative catheterization.

The concept of measuring the blood loss with the Low Hemoglobin Photometer has been proven to be an objective, reliable and easy method.^{39,47} In spite of this, adequate measurement methods rarely are applied in these kinds of studies. To use transfusion rate as an index for blood loss is a poor substitute, since transfusion trigger levels varies between caregivers and involve a subjective evaluation of health status.

The most widespread method to estimate blood loss is to note changes in the patient's Hb levels, something that might be of inferior precision, as shown in this study (Fig 4.). (Other means of measuring blood loss are discussed in the monitoring section of this Thesis)

As in Study I, we were not able to show a decrease in surgical haemorrhage among patients treated with 5-ARIs.

Study III revealed a faster postoperative recovery in the bipolar group, based on the fact that a larger fraction reported early improvements in IPSS and QoL-scores. Bipolar

TURP was also followed by fewer readmissions, especially when caused by late hematuria.

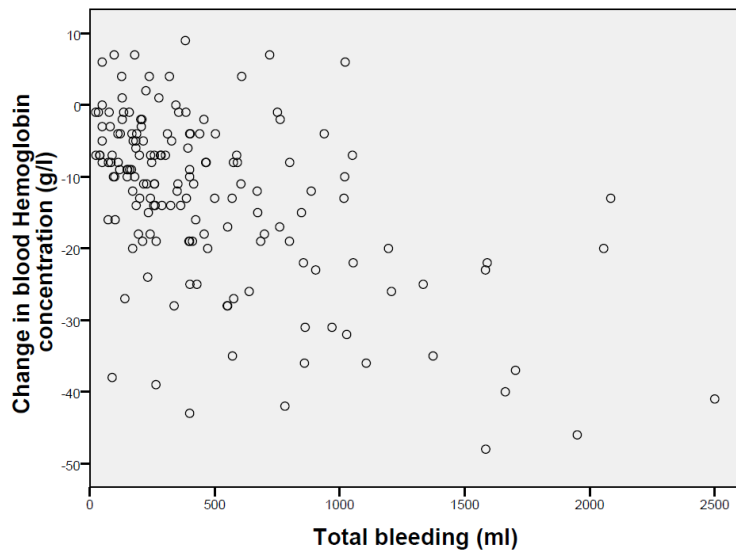


Figure 4. Blood loss as measured in recovered irrigating fluid versus the change in blood Hemoglobin concentration from before surgery until it was completed. The coefficient of determination for the linear relationship (r^2) is 12%.

The result of this study is somewhat difficult to view in perspective, since most of the previous studies comparing these two techniques have rendered inconclusive results, due to too small sample sizes^{85,86} and a mix of techniques.^{37,43,149-151} Readmission rates are seldom reported; therefore, our 10 % rate is tricky to interpret when comparing to other studies. There was a significantly lower incidence of readmissions in the bipolar group (5% vs. 16%). This figure is not easy to compare because of its unique nature in this field.

However, our reoperation rate is comparable to those previously reported.^{37,43,84,94,152} Our practice of not giving all patients antibiotics before surgery might explain why our incidence of infection is slightly higher than that reported by others⁹⁴.

We show a markedly shorter catheterization time than several other studies.^{37,53,54,85} This probably reflects matters of clinical routines and traditions as well as different interests between private and public caregivers. There is little or no evidence supporting a need for prolonged postoperative catheter treatment, in particular as the median postoperative haemorrhage is very low in both methods (shown in Study II of this Thesis).

There is a debate about whether bipolar TURP is associated with a higher incidence of urethral strictures⁸⁵ while several studies suggest that there might not be a real difference between the two methods.^{41,86,108} The number of patients developing strictures within the study period was too low to allow any comparisons between the methods. We believe that in keeping the operation short, limiting the use of wide instruments and trying to shorten the postoperative catheterization, we will continue to

have a low incidence of urethral strictures in comparison to others.⁸⁵ By not applying a general antibiotic prophylaxis, we experienced a higher incidence of infections after TURP.

A potential limitation of both study II and III is that operations were performed by a heterogeneous group of surgeons, including residents. This “every-day” situation is a reality at most urological departments, but in spite of this our team obtained similar results regarding surgical efficiency and postoperative outcome as in previous studies that included operations performed only by highly experienced urologists.^{6,41,44}

The formation of subgroups is another possible limitation; however, analyses of our key findings with respect to the differences in blood loss were not explained by this fact.

Study IV showed that approximately 50 % more tissue disappears than indicated by the weight of the resected tissue in bipolar resection. Thus, one can expect around 1.4-1.7 g of total tissue loss when resecting 1 g, depending on the type of tissue, resection method and choice of loop. When using the bipolar large loop, the results were similar to the monopolar technique. The type of irrigating fluid used is of some but limited importance. With further developments of the bipolar technique, alternative more physiologic irrigants would be of interest. In this context, we demonstrated that the device worked without problems in Ringer’s Acetate, with an even higher degree of vaporization.

Calculations of vaporization are important when comparing resection methods to open surgery in a context of stretching the volume limits of TURP as stated by EAU.⁹⁸ In Study II, we found that the intraoperative blood loss in TURP is substantially lower when employing bipolar resection. When taking vaporization into account, the amount of blood lost per gram of resected tissue is far below any former reported results of TURP-associated bleeding, regardless of the technique used.^{47,48} Even though the degree of vaporization in both bipolar and monopolar TURP has not been thoroughly examined, there are indications of vaporization in other studies. Sandfeldt *et al.* noted a difference in TRUS volume corrected to resection weight, pointing towards a vaporization rate of 35-67%.⁴⁸

Bipolar TURP has proven advantages,^{41,153} not only in regards to blood loss and reduced risk of TUR syndrome, but also when assessing the histological quality in resected specimens where coagulation artefacts are less pronounced.¹⁹ It facilitates a clearer view due to a less-pronounced cautery effect,^{154,155} which is a contradiction to the fact that the coagulation depth in the residual tissue seems to be deeper than in monopolar resection.²⁰

The concept of desiccating tissue to decide the true weight of the specimen and the water content has been used in several other studies,¹⁵⁶⁻¹⁵⁸ but as this study did not deal with prostatic tissue, it is still not clear how the connection to human tissue should be made. This is a limitation of the study, but it also gives a suggestion on a usable concept when proceeding in future studies engaging the human prostate.

GENERAL DISCUSSION

In addition to the argument that bipolar TURP reduces or eliminates the risk of life-threatening TUR syndrome, we now show that this technique results in a substantially reduced surgical haemorrhage, something that might be just as important. Smaller surgical haemorrhage with lower transfusion rates and a reduced risk of shock-related complications such as AMI, faster recovery and fewer readmissions, are all benefits offered to the patients by bipolar surgery. The long-term data confirm that these results are as long-lasting as in monopolar TURP. It also benefits the performing surgeon in terms of visibility and respecting anatomical landmarks. It might also reduce the stress for the performing surgeon, which would be an advantage in a teaching situation.

The impact of reduced bleeding is even more pronounced if surgery in different prostate volume intervals is considered. Table 4 illustrates this explicitly (Table 4.). As shown here, the results for small prostates are not that different, except for a markedly shorter hospital stay in the bipolar group, maybe indicating a more uncomplicated postoperative course. But as larger prostates are operated, clear differences between the two techniques begin to appear. First, one can note that the amount of blood per gram of resected tissue is quite constant in the bipolar group, regardless of prostate size. On the other hand, in the monopolar group, the bleeding rate increases drastically with prostate size. Here we also have the answer to the difference in transfusion rate between the groups. Resection weight, the length of the operation, absorption, infections and reoperations do not seem to differ among the volume groups compared to the totals. Postoperative catheterization is shorter in the bipolar large prostate group. Readmission rates are higher in all monopolar groups, suggesting that this phenomenon is associated to the method rather than the size of the prostate.

The incidence of infections following TURP in study III of this Thesis was higher than previously reported (14% bipolar, 16% monopolar). This was valid for both techniques and was most likely a result of our policy not to apply a general antibiotic prophylaxis. Prophylaxis was given only to those with risk factors or a positive preoperative urine culture. This has led our department, with support of the 2010 antibiotic guidelines of the Swedish Council on Health Technology Assessment,⁹⁷ to change our policy regarding general prophylaxis in TURP.

	Prostate Size							
	All (30-100 ml)		Small (30-50 ml)		Intermediate (51-75 ml)		Large (76-100 ml)	
	Operation technique		Operation technique		Operation technique		Operation technique	
	Bipolar (n=98)	Monopolar (n=87)	Bipolar (n=45)	Monopolar (n=34)	Bipolar (n=39)	Monopolar (n=38)	Bipolar (n=14)	Monopolar (n=14)
Total blood loss (ml)	262	399	207	186	278	507	552	969
Blood loss /resected tissue (ml/g)	11	15	11	11	12	20	11	27
Operation time (min)	60	66	50	54	68	74	82	79
Resected weight (g)	24	24	17	17	27	29	48	41
Transfusion (n)	2	10	0	2	0	3	2	5
Absorption (n)	9	13	3	4	6	7	0	2
Cathetrization time (h)	20	20	20	19	19	19	19	30
Hospitalization (h)	51	52	33	52	52	52	52	56
Readmission (n)	5	14	3	6	2	5	0	3
Infections (n)	13	13	8	5	5	6	0	2
Reoperations (n)	2	4	1	1	1	1	0	2

Table 4. Blood loss, complications and postoperative parameters according to prostate size and choice of surgical method. Expressed in median and count as appropriate.

If one gives a patient with a prostate size of 100 ml and an expected resection weight of 50 g (resection weight taken from interval “large” in table 4) a choice of treatment, different options are available according to the different elements of this Thesis (Table.5).

Extracting data from study I and II, we can say that the bleeding with a conventional monopolar technique would be about 750 ml if 50 grams are resected. When adding a correction for prostate size, bleeding is greater, about 1350 ml for monopolar technique. As stated in study I, no reduction can be seen by pretreating the patient with 5-ARIs. There is, of course, an option in treating the patient with a 5-ARI in order to shrink the prostate and thus decrease the blood loss. Studies show that you have to treat the patient for 1-2 years to get a volume reduction of 20-25%.^{136,159} The same patient now has a prostate volume of about 75 ml, and expected monopolar blood loss is about 600 ml (resection weight 30 g, blood loss 20 ml/g; both extracted from table 4, “intermediate” prostate).

If, instead, bipolar TURP is considered, we can expect a blood loss of 550 ml with no difference if short-term pre-treated. Shrinking the prostate for 12-24 months reduces the blood loss to 360 ml, a difference that is most likely clinically insignificant.

The vaporization rate from study IV of this Thesis is yet another factor to take into account when assessing TURP-related overall blood loss. The reason for choosing the kidney vaporization factor in table 5 is that the water content of the kidney resembles that of the human prostate to a greater extent, as shown in a study by Leissner *et al.*¹⁵⁷ Since the vaporization during TURP of the human prostate is yet unknown, the reasoning regarding this must be considered hypothetical.

In Study IV, we had a significantly higher vaporization in bipolar resection. These figures suggest a vaporization of about 40% in kidneys resected with bipolar instruments and half of that in the monopolar series. The difference was even more pronounced when chicken muscle was resected. If employing these figures in table 5, the amount of removed tissue is greater than indicated by the resection weight. Correspondingly, the blood lost per gram of removed tissue is even smaller. Based on the data from Study II and IV, the amount of blood lost is as low as 7.89 ml/g for the bipolar technique in the largest prostates.

	BIPOLAR	MONOPOLAR
Total Prostate Volume (ml)	100	100
Expected Resection Weight (g)	50	50
Expected Blood loss (ml)	550 (11 ml/g)	750 (15 ml/g)
Expected Blood loss corrected for volume (ml)	550 (11 ml/g)	1350 (27 ml/g)
Resection Weight including Vaporization (g)	70 (40%)	60 (20%)
Expected Blood loss 2-4 weeks Dutasteride Pretreatment (ml)	550	1350
Prostate Volume, after 2 years Dutasteride treatment (ml)	75	75
Expected Resection Weight Prostate Volume = 75 ml (g)	30	30
Resection Weight including Vaporization (g)	42 (40%)	36 (20%)
Expected Blood loss Prostate Volume = 75 ml (ml)	360 (12 ml/g)	600 (20 ml/g)

Table5. Different scenarios of blood loss for a prostate with an initial volume of 100 ml.

A higher degree of vaporization also suggests a more effective procedure in removing prostate tissue, which can be of great importance if discussing whether to expand the volume limits for TURP or not. There are already voices heard suggesting that the bipolar technique is suitable for glands up to 120-130 ml, thus replacing enucleation in this volume interval. However, it must be said that the vaporization rate in the human prostate remains to be shown, something that will be presented in a forthcoming work from our group. Although not statistically significant, there was a higher incidence of re-TURPs in the monopolar group of study III (bipolar 0 vs. monopolar 3).

In patients treated two or four weeks prior to surgery with dutasteride, no alterations of the MVD in the prostatic urethra or regions of nodular hyperplasia were seen, although the serum and intraprostatic concentrations of DHT were sufficiently decreased. Correspondingly, the serum testosterone levels were increased. These findings were all expected.

Dutasteride has been shown to be effective in reducing intraprostatic DHT within 4 weeks, but showed no effect of pre-treatment on blood loss during or after TURP, or on the complication rate.

The role of 5-ARIs in reducing complications is limited to the volume-reducing effects and – possibly – to the use in large glands when regarding blood loss. Even though the drug is well-tolerated, it is not without side effects. In combination with the lack of effect on blood loss, it does not motivate a long pre-treatment period, particularly not when previous works have been unable to discover any benefits of such a regime.

By switching to a modern bipolar system of resection – which in several up-to-date (yet mostly small) studies has been proven to reduce the overall complication rate, especially in terms of blood loss and TUR syndrome – morbidity is likely to be less of a problem. The bipolar systems also have an advantage in that they can be used for TURBT, where the superior cutting qualities are much appreciated. The option of vaporization in most bipolar systems is yet another feature that secures the future survival of this surgical evolution. Versatility is thus provided to an extent that is unchallenged by the other minimally invasive techniques. Future research in this field includes larger comparisons to different minimally invasive techniques, such as lasers and TUMT. Comparisons between the different bipolar systems would also be welcomed. There are slight differences in loops, electrical pathways and general features that might have an influence on the results.

Considering that TURP is increasing in frequency in the developing world, it is tempting to suggest that these countries do not take the detour via the outdated monopolar technique, but go straight on to bipolar systems in order to minimize the risk of complications.

The “physiologic” properties of saline can be debated. In anaesthesiology, rapid infusions of large volumes of saline are never in question. In bipolar resection, ion-containing irrigants other than saline may be used. Ringer’s Acetate is employed to treat shock and replace volume, and the results from study IV in this Thesis indicates

that resection works just as well in this environment. Bearing in mind that accurate monitoring of irrigating fluids rarely is applied; a development with more physiologic irrigants would be welcomed.

Without doubt, the bipolar technique has contributed greatly to making TURP safer for the patient and easier for the surgeon. By decreasing the blood loss, decreasing the rate of short-term reoperation and readmission as well as minimizing the risk of a life-threatening TUR syndrome, the method has been taken up as a new standard in our department, and it is our belief that bipolar TURP should be considered as the new reference standard when comparing techniques for surgical management of BPH.

When adding to this the Ethanol method and the Low Haemoglobin system for monitoring absorption and haemorrhage, we have the best and safest concept seen until this day to perform TURP. This must be the final conclusion of this Thesis and also the answer to the statement outlined in the title.

10 CONCLUSIONS

- ❖ Compared with the placebo, no significant reductions in blood loss during and after TURP or complications afterward with dutasteride are observed despite significant suppression of intraprostatic DHT within four weeks of treatment.
- ❖ Bipolar TURP significantly reduces the perioperative and total surgical bleeding by as much as 81% for the largest haemorrhages.
- ❖ Bipolar TURP significantly reduces the need for erythrocyte transfusion.
- ❖ Postoperative readmissions are fewer and postoperative recovery is faster in patients undergoing bipolar TURP.
- ❖ Bipolar TURP results in equally long-lasting positive results in TM/IPSS and QoL as the standard monopolar technique.
- ❖ Vaporization accounts for a further 50% of tissue removal during conventional resection and is, significantly, even higher in bipolar standard loop resection.
- ❖ Bipolar resection devices work satisfactorily in Ringer's Acetate in an *in vitro* setting.

- With a prostate of 100 ml, 12-24 months of treatment with 5-ARI before a monopolar TURP still does not result in a blood loss in line with the bipolar technique without pre-treatment.
- There is only a marginal profit in blood loss when shrinking a prostate scheduled for bipolar operation.
- With an assumed two-fold vaporization compared to monopolar resection, bipolar surgery is more effective in removing prostatic tissue.
- Bipolar technology has a consistent blood loss regardless of prostate size, while blood loss increases with a larger prostate size and resection weight in monopolar operations.
- If the effect of vaporization is added, blood loss per unit of resected tissue decreases in *both* groups, but the difference becomes even more pronounced *between* the groups, favouring the bipolar technique.

11 SAMMANFATTNING

Bakgrund

Transuretral prostataresektion, TURP, är fortfarande en mycket vanlig och uppskattad ”golden standard” metod för behandling av benign prostatahyperplasi (BPH). Trots att farmakologiska och minimalinvasiva tekniker förekommer som alternativ så utförs ca 6000 TURPar varje år i Sverige. TURP utförs knappast polikliniskt då den operativa morbiditeten i per- och postoperativa blödningar och ”TUR-syndrom”, som orsakas av spolvätskeabsorption, kan kräva särskild uppmärksamhet. Blodtransfusion ges till cirka 10 % av de patienter som genomgår TURP. En möjlighet att operera med en mindre operationsblödning, färre efterblödningar och med en minimering av antalet blodtransfusioner är av stort värde. Förbehandling inför TURP med hormonmodulerande läkemedel i blödningsminskande syfte har utvärderats vid ett flertal tillfällen utan konklusiva resultat. TURP har utvecklats föga på senare år, men nu har ett nytt instrument blivit tillgängligt där resektionen sker med bipolär teknik i fysiologisk koksaltlösning. Det främsta argumentet för bipolär TURP är att användningen av 0.9% NaCl (koksalt) som spolvätska förhindrar det potentiellt farliga TUR-syndromet. Det finns också indikationer på att det blöder mindre vid operation med bipolära instrument. Blödning under operationen kan kvantifieras mer exakt under TURP än vid andra former av kirurgi då allt förlorat blod löses ut i spolvätska.

Syfte

Avhandlingens övergripande syfte var att utvärdera om morbiditeten vid TURP kan förändras med specifika farmakologiska och tekniska interventioner. Detta studerades dels genom att undersöka om förbehandling med en 5-Alfa-reduktashämmare (dutasterid) kunde minska blödningen vid konventionell monopolär TURP, dels genom att jämföra ny bipolär resektion med konventionell monopolär TURP med avseende på blodförlust, per- och postoperativa komplikationer samt långsiktiga resultat. Slutligen undersöktes graden av vävnadsförångning (vaporisering) i en experimentell studie av både mono- och bipolärt instrument där också funktionen av bipolärt instrument testades i en annan spolvätska (Ringer-Acetat).

Delstudie I

Denna dubbelblinda, randomiserade, placebokontrollerade, multicenterstudie omfattade 214 patienter med BPH. Placebo jämfört med dutasterid 0,5 mg/dag 2 veckor före och efter TURP, eller 4 veckor före och 2 veckor efter TURP undersöktes. Resultaten visade en förväntad och adekvat minskning av dihydrotestosteron i serum hos patienter behandlade med dutasterid, men ingen signifikant minskning i blodförlust under eller

efter TURP eller komplikationer efteråt med dutasterid jämfört med placebo. Blodförlust och transfusion i placebogrupperna var lägre än de som tidigare rapporterats i studier där relationen mellan 5 α -reduktashämmare och blodförlust från prostatan studerats.

Delstudie II & III

202 konsekutiva patienter från sjukhusets väntelista randomiserades att genomgå TURP med antingen ett bipolärt system eller ett monopolärt system. I delstudie II låg fokus på att beskriva blodförlust under och efter operation samt transfusionsfrekvens. Delstudie III registrerade peri- och postoperativa mätvärden och komplikationer. TM- och IPSS-formulär insamlades vid 4 tillfällen efter operation. 185 patienter kunde evalueras. Det fanns statistiskt signifikanta skillnader med avseende på den totala blodförlusten, 262 ml för bipolär och 399 ml för monopolär TURP. Nedgång i Hb-koncentration under dagen för operationen var mindre i den bipolära gruppen. Färre patienter i den bipolära gruppen transfunderades med erytrocyter (4 % vs. 11 %), något som kan förklaras av den mycket lägre 75:e percentilen för blodförlust i den bipolära gruppen (472 ml vs. 855 ml). I delstudie III noterades att bipolär kirurgi resulterade i fler patienter som rapporterade en förbättring vid 3 och 6 veckor efter operationen. Det fanns färre återintag till slutenvård i den bipolära gruppen. Inga skillnader mellan grupperna med avseende på sjukhusvistelse och kateterbehandlingstid noterades. Bipolär och monopolär TURP resulterade i markanta och bestående förbättringar av symtomskattning, Quality of Life samt tidsmiktions.

Delstudie IV

Referensprover visade att vattenhalten var 73 % i muskel och 77 % i njure. Mer muskel än njure vaporiserades. Andelen förångad vävnad var signifikant högre vid bipolär teknik. I muskel, var skillnaderna mellan monopolär och bipolär 17 % respektive 26 %, beroende på vilken typ av spolvätska som användes. För njure var skillnaderna 27 % respektive 34 %. Djupare analys av graden av vaporisering, vid användning av bipolär resektion, visade att valet av slynga, typ av vätska och typ av vävnad alla var oberoende faktorer som kunde associeras med graden av vaporisation. Bipolär resektion fungerade problemfritt i Ringer-Acetat.

Konklusion

Förbehandling med dutasterid 2-4 veckor minskar inte blödning i samband med TURP. Bipolär TURP minskar per- och postoperativ blödning med upp till 81 %, reducerar behovet av erytrocyttransfusioner, resulterar i snabbare läkning och färre återintag. Bipolär TURP ger lika långvariga och goda resultat i TM/IPSS och livskvalitet, som konventionell monopolär teknik. Vaporisering står för ytterligare 50 %

vävnadsminskning under konventionell resektion och är ännu högre vid bipolar resektion med standardslynga. Bipolar resektion fungerar tillfredsställande i Ringer-Acetat *in vitro*. Förbehandling under 12-24 månader med en 5-ARI i volymssminskande syfte hos en patient med en prostatavolym på 100 ml inför monopolär TURP, leder inte till en blodförlust i nivå med bipolar teknik utan förbehandling. Det finns endast en marginell vinst i blodförlust med att krympa en prostata planerad för bipolar operation. Bipolar teknik har en konstant blodförlust oavsett prostatastorlek, medan den ökar med större prostatastorlek och resektionsvikt vid monopolär teknik. Om vaporiseringseffekten adderas, minskar blodförlust per borttaget gram vävnad i *båda* grupperna, men skillnaden ökar *mellan* grupperna och gynnar bipolar teknik.

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14 APPENDIX (PAPERS I-IV)