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ORIGINAL ARTICLE

Intra-Prostatic Injection of Epinephrine during Transurethral Resection of Prostate Reduces Blood Loss and Need for Blood Transfusions - A Randomized Controlled Trial

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ABSTRACT

Aim: To assess the role of Intraprostatic injection of epinephrine intra-operatively in patients undergoing TURP in decreasing blood loss and the need for subsequent blood transfusions.
Design: A double-blind, randomized controlled trial.
Place and duration of study: The Kidney Centre Postgraduate Training Institute, Karachi, from March till August 2020.
Methodology: A total of 40 patients were chosen at random and divided into two groups of equal size. One group got an intra-prostatic injection of epinephrine, whereas the other received a standard saline injection. Both groups were evaluated in terms of prostate volume (ml), resected tissue (gms), surgical resection time (minutes), pre and post-operative Hemoglobin (HB), and Hematocrit (HCT) levels. Intra-operative blood loss was then quantified using the last two variables. Transfusion requirement in both groups was also recorded.
Results: Mean +*Age* of patients in Group A and Group B was 66.30+9.24years and 65.65+7.43years, respectively, with no significant difference between both groups (*p*=0.808). Median and IQR *Prostatic volume* in Group A and Group B was 68.0, 15, and 64.0,21, suggesting no statistically significant difference between the two groups (p=0.372). Mean + S.D Loss of HB of patients in Group A and Group B was 1.15 + 0.42 and 1.87+1.04, respectively, with a significant difference between both groups (p=0.007). Mean + S.D of post-op HCT patients in Group A and Group B was 3.16+1.50 and 4.81+2.79, revealing a significant difference between the two groups (p=0.026). No patients in Group A needed blood transfusions, whereas six patients in Group B had blood transfusions, indicating a statistical distinction between the two groups (p=0.001).
Conclusion: The use of intra-prostatic injection of epinephrine leads to reduced blood loss and subsequently reduced operative time, irrigation fluid usage, and blood transfusion during TURP. It also allows a greater amount of prostatic tissue to be resected.
Keywords: Transurethral resection of Prostate, Epinephrine, Blood transfusion, Hemoglobin, Hematocrit.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a frequent scenario in senior men that results in a mix of storage/irritative and voiding/obstructive symptoms. It leads to a persistent decrease in detrusor effectiveness in emptying the urinary bladder and aggravates lower urinary tract symptoms[1]. Older man is far more likely to develop BPH; 50% do so in their 50s and 60s, while in their 70s, 90% of men have symptoms attributable to a hyperplastic prostate. As a result, this illness is both a community and health concern, with significant healthcare and societal financial implications[2,3].

As per the European Association of Urology, patients with moderate - to - severe symptoms should consider medical therapy, such as alpha-1-adrenoceptor antagonists, as a first-line treatment. The medications help relieve bladder-related symptoms while improving urine flow (Qmax). Patients with huge prostate glands (more than 80 gms), who are not responding to medicinal therapy, may be considered for operative intervention.

Among the surgical options, Transurethral resection of the prostate (TURP), has established itself as a standard procedure for treating patients with LUTS caused by obstructive benign prostatic hyperplasia (BPH). Other options include Transurethral incision of the prostate (TUIP), Transurethral vaporization of the prostate (TUVP), Transurethral vaporization-resection of the prostate (TUVRP), Transurethral microwave thermotherapy (TUMT), Transurethral needle ablation (TUNA), Interstitial laser coagulation of the prostate (ILC), and Holmium Laser Enucleation of the Prostate (HoLEP)[4].

Surgical options, specifically TURP, can prevent problems such as urinary discomfort, urinary tract infections, and urosepsis, resulting in shorter hospital stays, lower expenses, and improved overall quality of life[5]. However, 15–20% of TURP patients may encounter significant complications such as hematuria, bladder neck stricture, urinary incontinence, retrograde or an ejaculation, and transurethral resection syndrome. 10–15% of patients may also require a repeat operation within ten years[5]. However, blood loss continues to be one of the most common complications. In fact, according to a published case series, blood transfusions were required in roughly 2.9% of cases of TURP[6,7].

Various methods and drugs have been used peri-operatively to minimize this blood loss. One example is the use of intra-prostatic injection of epinephrine before tissue resection, which may influence a reduction in perioperative blood loss during TURP.

For this purpose, we are conducting this study to add to the data that intraprostatic epinephrine injection during TURP can improve institutional practices for the benefit of patients undergoing such intervention and, therefore, changes in the future protocols/guidelines might be shaped and innovated accordingly.

MATERIAL AND METHODOLOGY

Settings: From March 2020 to August 2020, a randomized controlled trial was conducted in The Kidney Centre Postgraduate Training Institute, Karachi, for six months. It was an experimental, double-blind trial. Before beginning this study, an ethical clearance from the board was sought (Ref: 74-URO-012020).

All symptomatic males with BPH requiring TURP were included in this study. Exclusion criteria included patients with abnormally high blood pressures, ischemic heart disease, blood dyscrasia, urinary lithiasis, those using anticoagulant medications, or having undergone any urological surgical intervention in the previous three months.
Sampling size: Two equal groups of 20 patients were assigned at random, labeled Group A, the Case group, and Group B, the control group. The analyst was a senior registrar who was in charge of randomly assigning groups to the patients. The surgeries were performed by different surgeons unaware of the drug being administered, as were the patients (double-blind). Group A received an intra-prostatic epinephrine injection (200mcg diluted in 20ml normal saline), while Group B received a 0.9% normal saline injection (20ml). Both groups were compared in terms of prostate volume (mL), resected tissue (gms), resection time (minutes), pre-

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op Hemoglobin (Hb) and Hematocrit (HCT), post-op Hemoglobin (Hb) and Hematocrit (HCT) as well as the need for blood transfusion. All procedures were carried out under General Anesthesia.

Sampling technique: Non-probability consecutive sampling.

Data collection: Before the procedure, the prostatic volume (ml) and pre-operative Hemoglobin and Hematocrit levels were obtained. Cystoscopy was carried out with a 21 Fr rigid cystoscopy sheath with a 30^{o} optical lens to examine the whole urinary tract, especially the urethra, prostate, and urinary bladder. 10ml of the designated solution (epinephrine in Group **A**; normal saline in Group **B**) was injected into the median lobe, while 5ml was given in both lateral lobes of the prostate with a 20G metal needle (making a total infusion of 20 ml). The TURP procedure was carried out five minutes after the injection with a 26 Frresectoscope sheath. Prostatic chips were cut with a monopolarelectrocautery loop. Continuous cardiac monitoring was done to note any rhythmic changes due to epinephrine. The time of prostate resection was noted in minutes, and chips of resected tissue were measured in grams. The patient's Hemoglobin (HB) and Hematocrit (HCT) levels were also collected. Blood transfusion requirement was assessed in both groups as well.

Data analysis: Open EPI sample size calculator was used. Each group had a sample size of 20 patients, and mean blood loss, by comparing pre, and post-op Hb and HCT levels were estimated in Group-A and Group-B at a 95% confidence level and a power of 90%. Age (years), Prostate Volume (ml), Resected tissue (gms), Resection time (minutes), Pre-op HB (gm/dl), Post-op HB (gm/dl), Pre-op HCT (percent), Post-op HCT (percent) had been assessed in the two groups. We considered A p-value of 0.05 as a statistically significant finding.

Variable descriptive analyses were provided as frequencies and percentages. We estimated the mean and variance for normally distributed continuous data, whereas for skewed continuous variables, we computed the median with interquartile range (IQR). The Shapiro-Wilk test was used to determine the data's normality, with a significant difference value of p = 0.05. The t-test was used for regularly distributed continuous data, and the Kruskal-Wallis test was used for continuous asymmetric variables to see if there was a difference between the two groups. The Chi-square test was used to find a connection between two categorical variables with a significance threshold of 0.05. (p-value). IBM SPSS version 20 was used to analyze all data.

RESULTS

The study included a total of forty in this randomized controlled trial, with an equal number of patients in each group. The demographical characteristics of both study groups were analyzed and are shown in Table 1. The mean *age* of patients in Group A and Group B was 66.30+9.24 years and 65.65+7.43, respectively, with no significant difference between both groups (*p*=0.808). Median and IQR *Prostatic volume* in Group A and Group B were 68.0, 15, and 64.0, 21, respectively, with no significant difference between both groups (*p*=0.372)**.**

The laboratory parameters were also quantified and compared and are shown in Table 2. Mean+S.D *Pre-op HB* of patients in Group A and Group B was 13.08+0.66 and 12.69+1.03, respectively, with no significant difference between both groups (*p*=0.173)**.** Mean+S.D *Post-op HB* of patients in Group A and Group B was 11.93+0.62 and 10.87+1.54, respectively, with a significant difference between both groups (*p*=0.007)**.** Mean+S.D *Loss of HB* of patients in Group A and Group B was 1.15+0.42 and 1.87+1.04, respectively, with a significant difference between both groups (*p*=0.007)**.** Mean+S.D *Pre-op HCT* of patients in Group A and Group B was 41.63+3.54 and 39.25+4.02, respectively, with no significant difference between both groups (*p*=0.054)**.** Mean+S.D *Post-op HCT* of patients in Group A and Group B was 38.47+3.50 and 34.44+4.34, respectively, with a significant difference between both groups (*p*=0.003)**.** Mean+S.D *Loss of HCT* of patients in Group A and Group B was 3.16+1.50 and 4.81+2.79, respectively, with a significant difference between both groups (*p*=0.026)**.** Median and IQR *Resected tissue* of patients in Group A, and Group B was 41.0, 18, and 30.0, 12, respectively, with significant differences between both groups (*p*=0.017)**.** Median and IQR *Irrigation fluid* of patients in Group A and Group B was 18.50, 6, and 25.0, 10, respectively, with highly significant differences between both groups (*p*=0.001) [Table-2]. *Blood transfusion* was not observed in any patients of Group A, while six patients in Group B were transfused, showing a significant difference between both groups (*p*=0.001) [Table-2].

Table 1: Baseline clinical characteristics

Variables	Groups		*p*-Value
	TURP with Epinephrine	TURP with Normal saline	
Age (years) (mean with S.D)	66.30 + 9.24	65.65 + 7.43	0.808
Prostate size (gms) (median with IQR)	68.00 , 15	64.00 , 21	0.372

Table 2: Laboratory and operative parameters

Variables	Groups		P value
	TURP with Epinephrine	TURP with Normal saline	
Pre-op HB (mg/dL) (mean with S.D)	13.08 + 0.66	12.69 + 1.03	0.173
Post-op HB (mg/dL) (mean with S.D)	11.93 + 0.62	10.87 + 1.54	0.007
Loss of HB (mg/dL) (mean with S.D)	1.15 + 0.42	1.87 + 1.04	0.007
Pre-op HCT (%) (mean with S.D)	41.63 + 3.54	39.25 + 4.02	0.054
Post-op HCT (%) (mean with S.D)	38.47 + 3.50	34.44 + 4.34	0.003
Loss of HCT (%) (mean with S.D)	3.16 + 1.50	4.81 + 2.79	0.026
Resection Time (min)(median with IQR)	30.00, 19	42.50, 19	0.024
Resected Tissue (gms)(median with IQR)	41.00, 18	30.00 , 12	0.017
Irrigation Fluid (litres) (median with IQR)	18.50, 06	25.00, 10	0.001
Blood Transfusion (n)	0	6	0.010

DISCUSSION

BPH is a common clinical condition in the elderly male population and affects their standard of living. Age, race, genetics, food, physical exercise and comorbidities are all factors that influence it[9]. It is caused by prostatic cell proliferation leading to obstructive urinary tract disease resulting in Lower Urinary Tract Symptoms (LUTS). BPH can be treated medically in the majority of the cases, using five alpha-reductase inhibitors. Various surgical procedures have also been developed to manage this disease when medical treatment fails.

Among the surgical options, Transurethral Resection of the Prostate (TURP) continues to be the most common procedure. It is an elective treatment that improves LUTS and eliminates the need for lifelong catheterization in patients worldwide, including the old and fragile[10]. The most common complications associated with this surgery include the inability to urinate (6%), surgical revision (5.6%), substantial UTI (3.6%), Transurethral resection Syndrome

(1.5%), and intraoperative or postoperative blood loss requiring blood transfusions (3%)[11].

To minimize the blood loss, alpha-blockers and five α inhibitors (5-ARIs) have been used as the primary treatment for large-sized prostates before surgery. The major purpose of these drugs is to lower the level of active testosterone, dihydrotestosterone (DHT), minimizing the blood loss by reducing the prostate size[12,13,14].

A study published in the East-Central African journal in 2013 collected data from 228 patients, 128 of whom had undergone TURP. They found that the transfusion incidence in these patients was 58.2%, and the total whole blood transfusion rate was 1.2 units per case. They discovered that this high incidence of blood transfusions in TURP patients could be brought down with careful planning, proper transfusion protocols, surgical expertise, and the use of intraprostatic epinephrine injections[15].

Many agents have been used to achieve hemostasis to reduce blood loss during the Transurethral resection of the prostate. To minimize postoperative blood loss, M. Luke et al. tested BERIPLAST (fibrin sealant) as a local injecting agent during TURP in Sundby Hospital, Denmark. According to the findings, patients treated with fibrin glue in the prostatic cavity had much less post-operative bleeding ($p<0.01$)[16]. Later, in 2016, Mohammad Hatef Khorrami et al had a similar concept and retested the same idea, utilizing fibrin glue injections in the prostatic fossa and saw a tremendous response in TURP patients in terms of reduced blood loss, corroborating the idea that fibrin decreases blood loss post-surgery[17].

The use of tranexamic acid (TXA) to minimize blood loss in patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA) is well accepted[18]. It is commonly used as a potent and reliable drug for decreasing bleeding and transfusion rates in cardiac, orthopedic, gynecological, transplant surgeries, and urological procedures, especially TURP[19]. A few authors asserted that TXA has a dose-dependent effect when administered during B-TURP and found that high-dose TXA significantly reduced the drop-in hemoglobin and ultimately needed for blood transfusions compared to placebo.[20] However, new research is now bringing to light the promising benefits of epinephrine in lowering blood loss in patients, particularly those undergoing total joint arthroplasty (TJA)[21,22]. This, in effect, reduces the need for post-operative transfusions[23,24].

Epinephrine is a hormone, a medicine, and a well-known vasoconstrictor widely used in different body parts, especially the smooth muscles, leading to a decrease in blood flow. Sonny Schelin conducted a trial in Kalmar County Hospital, Sweden, in 2009 in which the prostate gland was injected with Mepivacaine epinephrine (Carbocain-Adrenalin®) before surgery, and different prostate surgery techniques were compared in terms of their pros and cons. He utilized the idea of using Mepivacaine epinephrine and found fruitful results regarding blood loss and resection time as there was excellent visibility and less time consumption for coagulating vessels intraoperatively, saving patients from morbidity and cost of additional procedures[25].

Pre-operatively for tonsillectomy, levobupivacaine, a solitary S-enantiomer of bupivacaine, was employed as a novel amide local anesthetic that resulted in a considerable reduction in intraoperative blood loss.[26] Epinephrine with lidocaine also experimented with different concentrations (1:50,000,1:200,000, and 1:100,000), and surgeons found excellent success in lowering perioperative bleeding with 1:50,000 while comparing to 1:20,000 and no significant difference found when compared 1:200,000 with 1:100,000[27].

In our study, Patients in our Case group A, who received intraprostatic epinephrine injection during TURP before tissue resection was performed, had a significantly lower blood loss than those in the Control Group B, who received normal saline. This comparison was made by measuring and comparing patients' pre-operative and post-operative Hemoglobin and Hematocritlevels in both groups. The patients in Group A did not require any blood transfusion, whereas 6 of the patients in Group B underwent blood transfusion.

Another critical factor to note was that it was possible to remove a greater amount of tissue in patients belonging to Group A due to a lower level of bleeding, better visibility, and lesser time spent in achieving hemostasis. The decrease in peroperative bleeding also led to lesser irrigation fluid being used in Group A than in Group B, with a shorter procedure time overall.

CONCLUSION

To conclude, our study demonstrated that the use of Intraprostatic Epinephrine injection in TURP led to significantly lesser blood loss, a more considerable amount of tissue to be resected, lesser operative time, and decreased need for blood transfusion.

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Patient consent: The trial protocols and procedures were presented to all patients, and informed consent was taken from all patients after explaining the procedure, its adverse effects, outcomes, and alternative procedures. The consent form was available in English and Urdu (native language).
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