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Effect of intraprostatic epinephrine on intraoperative blood loss reduction during transurethral resection of the prostate

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Abstract
Objective To determine whether the use of intraprostatic epinephrine during transurethral resection of the prostate reduces intraoperative blood loss.
Methods A random, double-blind, prospective study was carried out on twenty-three patients that underwent transurethral resection of the prostate. Patients were divided into two groups: (1) group receiving intraoperative intraprostatic injection of epinephrine (thirteen patients) and (2) group receiving intraoperative intraprostatic injection of saline solution as placebo (ten patients). Blood loss was quantified with the following formula: irrigation solution hemoglobin × 1000/intraoperative presurgical serum hemoglobin. The variables analyzed were blood loss, resection time, presurgical prostate volume, and grams of resected tissue. Student́s t test and Pearson correlation were used for their analysis.
Results There were thirteen patients in the epinephrine group and ten patients in the placebo group. Mean blood loss in the epinephrine group was significantly lower than in the placebo group (127.48 mL ± 77.0 mL vs. 336.63 ± 185.6 mL, 95% CI, 45–234, $P < 0.001$). There were no statistically significant differences in mean resected grams or mean resection time between the two groups. One patient in the epinephrine group presented with intraoperative hypertensive crisis (7.7%).
Conclusions Intraprostatic epinephrine injection can be used to reduce blood loss during transurethral resection of the prostate in selected patients. Cardiovascular monitoring should be carried out during its application. Resection time and grams of resected tissue continue to be the most influential factors in relation to blood loss in patients undergoing this treatment modality.

Keywords Transurethral resection of the prostate · Blood loss · Intraprostatic epinephrine

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Introduction

For more than 60 years, transurethral resection of the prostate (TURP) has been the criterion standard for

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treating patients with lower urinary tract symptomatology secondary to obstructive prostatic hyperplasia. During the last 20 years, this procedure has been the recipient of medical development and in particular minimally invasive treatments such as thermotherapy with transurethral microwaves or procedures with laser.

Intraoperative and perioperative mortality has been substantially reduced during the last 30 years and presently varies at under 1% [1]. The most frequent intraoperative complication continues to be blood loss. Even with the technological improvement in endoscopic resection equipment that has reduced procedure morbidity there is still a considerable transfusion rate. Reich et al. [2] presented a series in which transfusion was required in 2.9% of patients. Blood loss risk is associated with preoperative infections and acute urine retention secondary to congestive prostate gland, prostate volume, and resection time [3].

Methods

An experimental, double-blind study with random assignation to two groups was carried out to compare the effect of intraprostatic epinephrine administered prior to TURP with a control group that received saline solution. This study was carried out at the *Hospital General de México OD* from November 2009 to May 2010 after patients had signed informed consent forms. The subjects participating in the clinical trial were randomly distributed into two groups. Saline solution samples and the samples of epinephrine diluted in saline solution were previously prepared by the same urology resident who was not involved in the study or the surgical procedures carried out on the study patients. The samples were identified with a consecutive number to which both the surgeon and patient were blinded. Only the urology resident registering the content of each container saw the numbers. In the first group, called the case group, intraprostatic epinephrine was administered at a dose of 200 mcg diluted in 20 mL of saline solution. In the second group, called the control group, 20 mL of saline solution was administered. Patients with diagnosis of obstructive benign prostatic hyperplasia that were surgery candidates and patients programmed for TURP were included in the study.

Patients with a past history of high blood pressure, heart disease, blood dyscrasia, anticoagulant medications, treatment in the last 3 months with 5-alpha reductase inhibitors, genitourinary cancer, urinary tract lithiasis, and urological surgery within the last 3 months were excluded from the study. Anesthetic procedure utilized subarachnoid block. TURP was carried out with ACMI (Southborough Massachusetts, United States) resecting equipment.

Initially, cystoscopy was carried out with a 21-F sheath with 30° optic for examination of the urethra, prostatic locule, and bladder. After revision, 10 cc of study substance was applied with Williams endoscopic needle at the prostatic floor level. Then, 5 cc were placed in each lateral lobe. Prostate tissue resection with sterile water for irrigation solution was carried out using continuous flow resector with 26-F sheath.

Prostate tissue was cut with Valleylab (a division of Tyco Healthcare Group LP, Boulder Colorado, United States) monopolar electrocauterizer. Continuous cardiovascular monitoring was carried out to evaluate any hemodynamic change that could be related to epinephrine administration. Irrigation solution was collected in a container from which a sample was taken to determine hemoglobin. Grams of resected tissue were quantified on a medical scale, and surgery duration was measured in minutes. Intraoperative blood loss of each surgery was quantified with the formula validated in previous reports in the literature (blood loss = irrigation solution hemoglobin $\times$ 1000/presurgical hemoglobin) [4].

Blinding was opened, and data were analyzed using measures of central tendency and dispersion (means and standard deviation [SD]) as well as Student's *t* test and Pearson correlation for the data of both groups. The SPSS 17.0 © Statistics Program (IBM Chicago, Illinois 60606) was used. Sample size was calculated taking into account variance presented in a reference article by Schelin S. (10) for an 80% potency and 95% CI and for an expected standard deviation of 835.3 in a first group and 150.6 in a second group, producing a result of $n = 12$ for each group. Our sample size was 13 in the group that underwent surgery and 10 in the control group. The latter was a marginal result; however, we do not feel that it could have changed the final results.

The study was in accordance with the General Health Law and its research regulations and with the

International Conference on Harmonisation (ICH) Guidance Documents on good clinical practice.

Results

From November 2009 to May 2010, a total of 23 patients were randomly assigned to two groups. Thirteen patients made up the intraprostatic epinephrine application group and 10 patients made up the saline solution group.

General characteristics of both groups are shown in Table 1.

Mean age in the epinephrine group was 66 years and in the placebo group was 62 years. Mean prostate volume measured by means of ultrasound was 68.9 ± 16.1 cc in the epinephrine group and 65.08 ± 13.4 cc in the placebo group. Mean blood loss in the epinephrine group was significantly lower than that of the placebo group (127.48 ± 77.0 mL vs. 336.63 ± 185.6 mL, with 95% CI, 45–234, $P < 0.05$), There were no statistically significant differences between mean grams resected (14 vs. 26.2) and resection time (40.9 vs. 45.1 min) per group. Blood loss difference between the two groups is shown in Fig. 1.

Pearson correlation with respect to blood loss showed a very significant and direct correlation with resection time for both groups; epinephrine ($r = 0.780$, $P < 0.001$) and placebo ($r = 0.905$, $P < 0.001$).

There was a moderate correlation between grams of resected tissue and blood loss in the placebo group ($r = 0.673$, $P < 0.001$), but not in the epinephrine group. There was no correlation between prostate volume measured by ultrasound and intraoperative blood loss.

Table 1 Demographic characteristics of study groups

Variable	Case group $n = 13$ epinephrine (X ± SD)	Control group $n = 10$ saline solution (X ± SD)
Age (years)	66.23 ± 9.89	62.2 ± 9.75
Prostate volume (g)	68.9 ± 16.1	65.08 ± 13.4
Resected tissue (g)	14 ± 8.2	26.2 ± 23.6
Resection time (min)	40.92 ± 20.3	45.1 ± 21.1
Blood loss (mL)	127.48 ± 77	336.63 ± 185.6

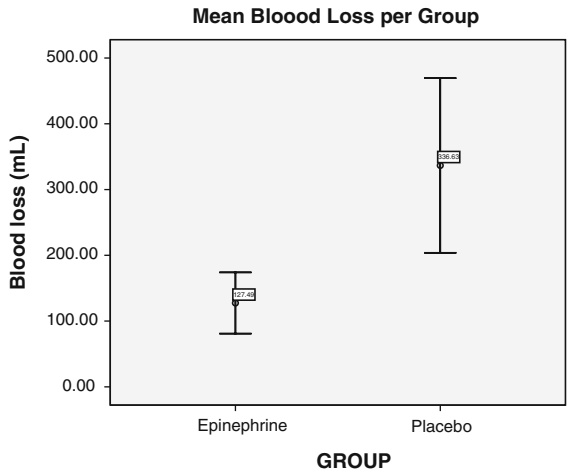

Fig. 1 Shows mean blood loss per group

One patient assigned to the intraprostatic epinephrine group presented with transitory high blood pressure up to 190/110 mm/Hg that was managed with oral nifedipine, resulting in remission at 30 min. This adverse event occurred during surgery after drug application and represented 7.7% of the total population. No other cardiovascular event presented nor did post-TURP syndrome.

Discussion

Obstructive benign prostatic hyperplasia is the most frequent genitourinary pathology in the adult male population. Its prevalence increases importantly with age, affecting 50% of 50-year-old men and approximately 80% of men reaching 80 years of age [5]. There are multiple medical and surgical treatment alternatives for the disease. Medical treatment includes drugs such as alpha blockers, 5 alpha reductase inhibitors, and phytotherapy. TURP continues to be the treatment of choice for managing obstructive prostatic hyperplasia. Mortality secondary to TURP has gone down over the years with 2.5% in 1962, 1.3% in 1974, 0.23% in 1989, and 0.1% in 2000. These results reflect the improvement in surgical techniques and instrumentation as well as in perioperative management. However, early and late postoperative complications are similar to those that have presented for decades, with rates of, for example, 18% in 1962, 17% in 1974, 18% in 1989, and 11.1% in 2000 [2].

Epinephrine is a drug with vasoconstricting action that stimulates smooth muscle vessel adrenergic receptors causing reduced blood flow [6]. Local epinephrine administration into tissue has been used in many specialties. In orthopedic knee surgery, it is used intraoperatively in arthroplasty, [7] and in gastroenterology, it is used in actively bleeding ulcers [8]. In urology, Scherin reported on a series of non-randomized patients in which intraprostatic epinephrine and mepivacaine injections were used intraoperatively during TURP that resulted in reduced blood loss [9]. At the prostatic level, epinephrine with mepivacaine reduces intraprostatic flow. This has been demonstrated by means of flow measurements made with positron emission tomography [10].

Over the last few years, many ways of reducing blood loss during TURP have been studied, including warming of the irrigation solution [11] and intraprostatic injection with ethanol [12]. Inconclusive results of these measures led to postoperative mechanical practices such as transurethral catheter traction that was shown to be a useful technique for controlling bleeding with loss of the hemostatic effect upon traction release [13].

A group of researchers in Denmark evaluated the instillation of a bovine fibrin glue preparation that was applied to the prostatic locule after TURP and compared the results with a control group. They found there was significant perioperative blood loss reduction with that technique [14]. Since 1981 chlormadinone acetate, an antiandrogen steroid, has been known for its effect on reducing prostatic blood flow in an animal model. It was used in the treatment of hyperplasia and cancer. In 2005, it was used to evaluate blood loss reduction during TURP with reduction secondary to the diminishing of microvascular density in the prostatic tissue [15].

The 5 alpha reductase inhibitor, dutasteride, has been found to reduce intraprostatic dihydrotestosterone in the first 4 weeks of treatment. However, treatment 2 weeks prior to surgery or 4 weeks prior to TURP did not reduce intraoperative blood loss or surgical complications [16]. This led to the study of a combination of dutasteride with *serenoa repens* but no significant differences or treatment advantages were found in relation to blood loss during TURP [17]. Likewise, the effect of treatment with presurgical finasteride compared with placebo has been studied, and no statistically significant differences have been found in relation to blood loss [18].

Many studies have been carried out in different specialties in order to determine epinephrine usefulness during and after surgical procedures in relation to blood loss. Results have varied but the majority of studies have shown blood loss reduction [19–21].

Finally, patients included in the present study were a highly selected population, which was a study limitation. In daily practice, men in this age group that have undergone TURP frequently present with comorbidities. Therefore, the present authors believe further clinical trials are necessary in order to determine whether similar results can be obtained in different populations.

Conclusions

Intraprostatic epinephrine injection can be useful for reducing blood loss during TURP in selected patients. Cardiovascular monitoring is recommended during its application. Blood loss during transurethral resection of the prostate depends on multiple factors, and resection time and grams of resected tissue continue to be two of its most influential variables.

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