Original Article

Prophylactic Intravenous Furosemide for Reducing Hyponatremia Risk in Monopolar Transurethral Prostate Surgery: A Randomized Clinical Trial

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Abstract

Background: Transurethral resection of the prostate (TURP) is the gold standard surgical treatment for benign prostatic hyperplasia (BPH). Despite its widespread use, monopolar TURP carries a risk of significant complications, particularly transurethral resection (TUR) syndrome leading to hyponatremia and fluid overload. The study evaluates whether prophylactic furosemide prevents hyponatremia and TUR syndrome in monopolar TURP.

Methods: This study was a triple-blind randomized clinical trial conducted in Al-Zahra and Khorshid educational hospitals of Isfahan, Iran, in 2022-2023. Patients undergoing monopolar TURP, were divided into two groups: those receiving preoperative furosemide and a control group. The primary outcomes were changes in serum sodium levels and the incidence of hyponatremia. Secondary outcomes included fluid balance, complication rates, and recovery times. Continuous data were analyzed using *t* test/Mann-Whitney U, categorical data with Fisher's exact test, and time-based changes with repeated measures ANOVA. Normality was checked via Kolmogorov-Smirnov, and power analysis determined sample size.

Results: The furosemide group demonstrated a significantly lower incidence of hyponatremia than the control group (P=0.008). Additionally, serum sodium levels were significantly higher in the furosemide group after surgery (P=0.011), while potassium levels were lower (P=0.003). Mild hypokalemia was observed as a manageable side effect, primarily in patients with baseline potassium levels below 4.1 mmol/L.

Conclusion: Preoperative administration of furosemide effectively reduces the risk of TUR syndrome during monopolar TURP. Furosemide effectively reduces hyponatremia but may increase hypokalemia in some cases, limiting its clinical utility during monopolar TURP. Patient-specific assessment and further research are needed to ensure its safe and effective use.

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Keywords ● Transurethral resection of prostate ● Hyponatremia ● Furosemide ● Water-electrolyte imbalance ● Postoperative complications

What's Known

- Hyponatremia is a significant complication of monopolar transurethral resection of the prostate (TURP) because of hypotonic irrigant absorption, resulting in transurethral resection (TUR) syndrome.
- Prevention strategies include hypertonic saline, bipolar TURP, and vasopressin. Furosemide loop diuretics can be useful, but randomized data for their prophylactic administration in preventing hyponatremia are lacking.

What's New

- Our triple-blind randomized clinical trial evaluates furosemide in the prevention of hyponatremia for monopolar TURP.
- We demonstrate that it substantially lowers the risk of hyponatremia with no serious complications and enhances fluid management. This trial addresses a valuable gap, calling attention to furosemide as a safe, effective option to enhance surgical outcomes in TURP.

Introduction

Benign Prostate Hyperplasia (BPH) is a common disease in the elderly. The number of global patients has increased from

about 51 million cases in 2000 to more than 94 million cases in 2019, with a prevalence rate of about 2,500 cases per hundred thousand.[1, 2] BPH compresses the urethra and increases the resistance to urine flow from the bladder, leading to lower urinary tract symptoms (LUTS). These symptoms can include obstruction-related symptoms such as hesitancy, straining, weak stream, and sensation of incomplete emptying, as well as irritative symptoms including frequency, urgency, and urge incontinence.[2] Voiding and storage LUTS can be treated using various pharmacological and surgical methods. Aggressive treatment is typically used when pharmacological therapy is ineffective and patients decline medication or in cases of frequent or resistant urinary retention, overflow incontinence, resistant gross hematuria, bilateral hydronephrosis with or without renal failure, frequent urinary tract infections, or bladder stones. Invasive treatment involving transurethral resection of the prostate (TURP) is the gold standard in these cases and is the most common surgery performed on male patients over 60 years of age.[3] However, during the surgery, the irrigation of distilled water in closed body spaces may cause the movement of fluids and electrolytes, leading to complications such as transurethral resection syndrome (TUR syndrome).[4] TUR syndrome occurs due to the absorption of the irrigation fluid used during the procedure, leading to hyponatremia and fluid overload. Approximately 17.5% of hospitalized patients have hyponatremia, a common electrolyte problem. A blood sodium level below 135 mEq/L is referred to as hyponatremia.[5, 6] Symptoms of TUR syndrome can include nausea, vomiting, headache, confusion, seizures, and even coma.[7] In developing countries, monopolar TURP is more commonly used than bipolar TURP. The use of distilled water as an irrigating solution in monopolar TURP can lead to syndrome due to the absorption of large volumes of hypotonic fluids, resulting in hyponatremia and fluid overload.[8, 9]

Elderly patients who undergo TURP, transcervical endometrial resection, or TUR of bladder tumors are at risk of developing TUR syndrome. As age increases, the functional capacity of organs decreases, reducing reserve and the ability to bear stress. Elderly patients may be impaired in balancing sodium and water due to low plasma renin activity, low urine and blood aldosterone levels, and decreased response to antidiuretic hormone. Additionally, concomitant diseases can further reduce organ reserve and increase the risk of complications. Therefore, it is crucial to take measures to prevent TUR syndrome in these patients.[10] Preventing TUR syndrome and its complications minimizes postoperative morbidity, reduces hospital stays, and enhances recovery.[11] Several factors have been considered to reduce the risk of TUR syndrome, including prostate size, proper patient positioning, reducing surgery duration, adjusting fluid bag height, surgeon experience, vasopressin injection, low-pressure irrigation, and bipolar TURP. However, despite implementing these measures, some patients may still experience this potentially fatal complication.[10]

Diuretics blocking the Na-K-2Cl transporter (NKCC) are essential in treating fluid overload, particularly renal disease and heart failure.[12] Treatment options for hyponatremia, such as water restriction or the use of hypertonic saline with loop diuretics, have limited efficacy.[13] Loop diuretics produce hypotonic urine (sodium concentration ~60 mEq/L), and their net effect is a gradual increase in serum sodium concentration while decreasing total body water.[14] Among the medications that inhibit NKCC in the loop of Henle (furosemide, bumetanide, torsemide, ethacrynic acid), furosemide is the most used drug.[12] Furosemide has a half-life of approximately 2 hours and a total duration of therapeutic effect of 6 to 8 hours.[15] The rapid onset of action and short half-life of furosemide make it a suitable drug for preventing perioperative complications. Administering furosemide acutely in patients without severe underlying diseases, such as heart and kidney diseases, can help avoid possible complications.[16] Furthermore, furosemide administration increases urinary flow into the bladder, enhancing visualization of ureteral orifices and thereby reducing the risk of iatrogenic injury during the procedure.[17]

This study addresses a critical gap in the literature regarding the management of hyponatremia during TURP, particularly in the context of monopolar TURP. Despite its routine use and effectiveness for treating BPH, especially in developing countries, monopolar TURP with distilled water as an irrigating solution carries a significant risk of complications, notably TUR syndrome. Reducing these complications is crucial to improving patient safety. Preoperative interventions, such as the administration of furosemide, offer a promising strategy for preventing hyponatremia, maintaining fluid balance, and enhancing overall surgical outcomes. Current approaches have shown limited efficacy, particularly in elderly patients who are more vulnerable to these complications. By investigating the prophylactic

effects of furosemide, this study seeks to provide an alternative solution that can reduce the incidence of TUR syndrome, improve patient outcomes, and address a critical need in the management of hyponatremia during TURP.

Patients and Methods

Trial Protocol and Studied Patients

This study was a triple-blind randomized clinical trial conducted in Al-Zahra and Khorshid educational hospitals of Isfahan, affiliated with Isfahan University of Medical Sciences, in 2022 and 2023. The study received approval from the Research Ethics Committee of Isfahan University of Medical Sciences (code: IR.MUI.MED.REC.1401.002) and the Iranian Registry of Clinical Trials (code: IRCT20211208053328N2).

Patients diagnosed with BPH who did not respond to pharmacological treatment and required TURP under epidural anesthesia were included in the study. Patients were required to provide written informed consent to participate. Those with abnormal renal function (estimated Glomerular filtration rate (eGFR)<60 mL/min/1.73 m^2), previous diuretic treatment, the inability to induce epidural anesthesia at T6 level for any reason, and surgery duration exceeding 90 min were excluded from the study.

Randomization and Blinding

This study employed a computer-generated simple randomization method to allocate participants into two groups: the furosemide group and the control group. The allocation sequence was generated using www.randomizer.org, ensuring an unbiased and unpredictable assignment process.

To maintain allocation concealment, the randomization sequence was generated by an independent researcher who was not involved in patient recruitment, treatment administration, or data analysis. The assignment was performed before patient enrollment, and group allocation was kept confidential from both the participants and the research team involved in patient management.

Triple-blind status was meticulously maintained throughout the study. Patients were blinded by administering both furosemide and saline in identical intravenous bags, without revealing the content of the injection. The surgical team involved in performing and monitoring the procedure remained unaware of group assignments, as an external anesthesia team member prepared and administered the intervention. Furthermore, data collectors and the statistician were provided only with coded data, ensuring that analysis and outcome assessment were conducted without knowledge of the patient's group allocation. This triple-layer blinding helped reduce potential biases at multiple levels of the study.

Interventions and Outcome

After entering the study, each patient underwent the necessary procedures and protocols to prepare for surgery. The standard anesthesia protocol was used for each patient at the discretion of the anesthesiologist to minimize the interactions between anesthetic drugs and renal function. Epidural anesthesia was performed in all patients at the T6 level. TURP was performed in all patients by one surgeon, and the resectoscope used in the TURP procedure was manufactured by Richard Wolf GmbH, Knittlingen, Germany. Patients in the furosemide group received 40 mg of furosemide (Aburaihan Pharmaceutical Company, Iran) as an intravenous bolus immediately before the induction of anesthesia. Additionally, if more than an hour has passed since the start of the surgery, another 20 mg dose is prescribed during the operation. Patients in the control group received normal saline (Shahid Ghazi Pharmaceutical Company, Iran) in the form of an intravenous bolus immediately before the induction of anesthesia. Normal saline was chosen as the control intervention due to its isotonic properties and minimal impact on electrolyte balance, making it suitable for establishing a physiological baseline for comparison with furosemide. It is widely used in surgical settings as standard intravenous (IV) fluid, ensuring that the control patients receive typical care without confounding pharmacological effects. Placebo effects were minimized by administering both furosemide and saline in identical IV bags and maintaining blinding among patients and surgical staff. This design ensured that observed effects on electrolyte levels and other outcomes could be attributed to furosemide's pharmacological action, rather than psychological or placebo effects. Blood samples were collected at the same laboratory before surgery, one hour, 24 hours, and 48 hours after surgery to measure the required factors.

Before the intervention, the patient's age, prostate volume (PV), and prostate-specific antigen (PSA) were recorded, along with the initial values of systolic (SBP) and diastolic blood pressure (DBP), sodium (Na), potassium (K), creatinine (Cr), and hemoglobin (Hb). The SBP and DBP values, Na, K, Cr, and Hb, were recorded one hour, 24 hours, and 48 hours after the surgery. Additionally, the

medical staff assessed the patients for possible complications, such as nausea, vomiting, need to pack cells, fever, hypokalemia, hypertension, and bradycardia after surgery.

Statistical Analysis

Data analysis was done using IBM SPSS 28 (IBM Corp., Armonk, NY, USA). After using the Kolmogorov-Smirnov test, the median [IQR] and mean (SD) were used to describe continuous variables, and the number (%) was used to describe categorical variables. Man-Whitney U test, independent *t* student test, Fisher's exact test, and repeated measures ANOVA were performed to compare the effect of the intervention. The variables of age, PV, duration of surgery, and baseline value of each variable were entered into the repeated measures ANOVA equation as covariates. A P value less than 0.05 was considered statistically significant (two-sided).

Power calculation was used to calculate the total sample size required for detecting a statistically significant difference between sodium levels in the furosemide and control groups. The 95% confidence level (α=0.05, two-tailed, $Z\alpha$=1.96) and 80% statistical power (β=0.2, $Z\beta$=0.84) were applied, and the total sample size required was calculated. With a hypothesized effect size of 0.5, an expected mean difference (E) of 5 units, and a standard deviation (S) of 7.5 units, the analysis found that at least 34 patients per group (a total of 68) would need to be available to have adequate power. As an allowance for equal allocation, a ratio of 1:1 was employed, and 35 participants were randomly allocated to each of the intervention and control groups. This design methodology helped to ensure that the research had adequate statistical power to reveal meaningful differences and a manageable sample size.

Results

The study included 70 participants (figure 1), with an average age of 66.6 years and a standard deviation of 8.9 years. The participants were divided into the furosemide (35 participants) and the control (35 participants) groups. Table 1 presents the demographic and clinical characteristics of the patients in the study. Based on the findings of table 1, it can be inferred that the two groups are matched regarding age, PV, PSA, Na, K, Cr, S, and Hb.

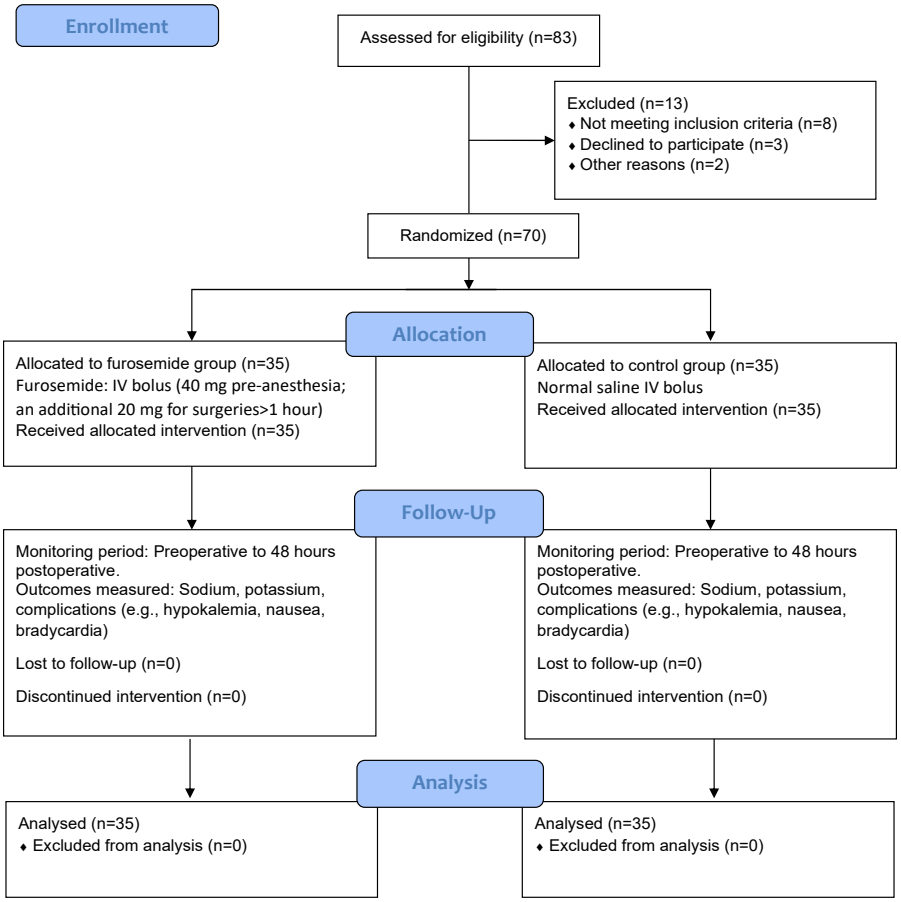

Figure 1: The CONSORT diagram outlines participant flow through enrollment, allocation, follow-up, and analysis, including eligibility assessment, exclusions, and group distribution.

Table 1: Baseline characteristics of the study participants

Variable	Furosemide (n=35) mean±SD	Control (n=35) mean±SD	Total (n=70) mean±SD	P value
Age (year)	65.4±9.1	67.8±8.7	66.6±8.9	0.26*
PV (cm³)	57.3±12.6	57.6±12.2	57.4±12.3	0.93*
PSA (ng/mL)	1.8±0.7	1.5±0.7	1.7±0.7	0.17*
SBP (mmHg)	119.5± 3.2	123.3±11.4	121.4±12.4	0.20*
DBP (mmHg)	82.3±10.8	86.5±13.7	84.4±12.7	0.16*
Na (mmol/L)	139.9±2.1	141.0±2.4	140.5±2.3	0.06**
K (mmol/L)	4.0±0.2	4.2±0.2	4.1±0.2	0.38**
Cr (mmol/L)	1.0±0.2	1.2±0.3	1.2±0.2	0.33**
Hb (g/dL)	16.9±18.3	13.7±1.9	15.4±12.9	0.29**
Surgery duration (min)	57.2±14.2	53.3±12.4	55.3±13.4	0.23**

*Independent *t* test; **Mann-Whitney U test; A P value less than 0.05 was considered statistically significant. SD: Standard deviation; IQR: Interquartile range; PV: Prostate volume; PSA: Prostate-specific antigen; SBP: Systolic blood pressure; DBP: Diastolic Blood Pressure

Table 2: Changes in serum electrolyte and hemodynamic parameters over time

Parameter	Groups	1 hour after surgery	24 hours after surgery	48 hours after surgery	Within-group P value**	Between-group P value**
Sodium (Na) (mmol/L)	Control	133.4 (3.4)	133.1 (3.5)	133.7 (3.2)	0.49	0.011*
	Furosemide	134.5 (3.0)	134.1 (2.8)	134.5 (2.6)		
	Between-group P value#	0.008*	0.014*	0.028*		
Potassium (K) (mmol/L)	Control	3.9 (0.2)	3.9 (0.2)	3.8 (0.2)	0.19	0.001*
	Furosemide	3.8 (0.3)	3.7 (0.2)	3.7 (0.3)		
	Between-group P value#	0.001*	0.001*	0.064		
Creatinine (Cr) (mg/dL)	Control	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	0.39	0.73
	Furosemide	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)		
	Between-group P value#	0.91	0.65	0.51		
Hemoglobin (Hb) (g/dL)	Control	12.6 (2.1)	12.4 (2.2)	12.4 (2.0)	0.83	0.51
	Furosemide	12.4 (2.1)	12.3 (2.0)	12.3 (1.9)		
	Between-group P value#	0.49	0.57	0.49		

Adjusted for age, prostate volume, duration of surgery, and baseline count of each variable (Repeated measures ANOVA); *A P value less than 0.05 was considered statistically significant; **Represents overall statistical significance at all time points using repeated measures (Within-group comparisons using paired *t* test); #Shows the statistical comparisons between the groups at particular time points (Between-group comparisons using an Independent *t* test).

Table 3: Postoperative complications observed in frusemide and control groups

Complication	Furosemide (n=35) n (%)	Control (n=35) n (%)	Total (n=70) n (%)	P value*
Nausea and vomiting	4 (11.4)	5 (14.3)	9 (12.9)	>0.999
Pack cell transfusion	1 (2.9)	2 (5.7)	3 (4.3)	>0.999
Fever	0 (0)	1 (2.9)	1 (1.4)	>0.999
Hypokalemia	10 (28.6)	5 (14.3)	15 (21.4)	0.24
Hypertension	2 (5.7)	2 (5.7)	4 (5.7)	>0.999
Bradycardia	1 (2.9)	3 (8.6)	4 (5.7)	0.61

*Fisher's exact test; A P value less than 0.05 was considered statistically significant.

According to table 2, it was discovered that there are significant differences between the groups regarding Na and K variables, with P of 0.008 and 0.001, one hour after surgery. These results indicate that the amount of Na in the furosemide group was higher than in the control group, while the amount of K was lower in the furosemide group. These findings suggest that furosemide has effectively reduced hyponatremia, but it has been associated with decreased K levels.

Table 3 shows no significant difference in the incidence of complications after surgery between the furosemide and control groups. Therefore, it can be concluded that using furosemide in patients undergoing surgery does not lead to any complications. However, it is worth noting that hypokalemia is the only complication that may occur in patients treated with furosemide. Nevertheless, all patients who experienced hypokalemia in both groups had only mild cases (ranging from 3.0 to 3.5 mmol/L)

and had K levels below 4.1 mmol/L at baseline. Therefore, it can be said that patients in the upper limit range of K level before the surgery are suitable for receiving furosemide.

Discussion

Our study found that administering furosemide is an effective way to reduce hyponatremia during prostate resection surgery. The results showed that the only possible complication of using furosemide was mild hypokalemia. We recommend using furosemide to prevent hyponatremia in patients with an upper-limit range of plasma K levels (4.2 to 5.0 mmol/L).

Hyponatremia is a common electrolyte disorder, with a prevalence of about 17.5% among hospitalized patients.[5] It is defined as a serum sodium concentration of less than 135 mEq/L. Hyponatremia represents an imbalance in the ratio of total body Na to total body water, where total body water is more than total body Na. Hyponatremia has three types, including hypovolemic hyponatremia, hypervolemic hyponatremia, and euvolemic hyponatremia.[6] In cases of hyponatremia after prostate resection surgery, the cause is the use of distilled water during the surgery, resulting in hypervolemic hyponatremia.[7]

Distilled water and hypotonic serum have advantages, including the achievement of local hemostasis during surgery; therefore, it is used in other cases, such as colorectal cancer surgery and peritonitis, besides TURP.[18-20] However, the use of distilled water in these cases has also been associated with secondary hyponatremia.[21] Common treatments for patients with hypervolemic hyponatremia include fluid restriction, the use of hypertonic serum, and the administration of diuretics.[6, 22]

Different methods for managing hyponatremia in TURP have been suggested in several studies. Seif and others investigated the effectiveness of prophylactic hypertonic saline preloading in preventing hyponatremia in a study conducted on 60 TURP patients. The patients were divided into three groups, each receiving a different amount of saline as fluid therapy. Group 1 received 4 mL/Kg.h Hypertonic Saline (HS) 3% serum, group 2 received 2 mL/Kg.h HS 3% serum, and the third group received 6 mL/Kg.h normal serum. The amount of sodium in the groups receiving hypertonic saline serum after TURP was significantly higher than in the group receiving normal saline serum. Furthermore, the group that received 4 mL/Kg.h HS had a lower sodium reduction than the group receiving 2 mL/Kg.h HS.[23] Their study reported that preloading patients with hypertonic saline reduced sodium levels post-surgery, similar to our findings with furosemide. However, hypertonic saline requires careful monitoring due to the risk of overly rapid sodium correction, which can lead to osmotic demyelination syndrome.[24] In contrast, our study suggests that furosemide provides a gradual and controlled increase in serum sodium concentration while also preventing fluid overload.

A study by Singh and others aimed to investigate whether the use of tolvaptan before TURP surgery could help prevent hyponatremia. The study involved 60 patients aging 45-80 years who underwent spinal anesthesia. The patients were randomly divided into two groups: one group received 15 mg of tolvaptan oral tablets two hours before surgery, while the other group received oral multivitamin tablets two hours before surgery. The study's results showed that a single dose of tolvaptan 15 mg effectively prevented hyponatremia after TURP.[25] Tolvaptan is expensive, requires careful dosage adjustments, and is not widely available in many clinical settings. Our study demonstrates that furosemide, which is widely used, can achieve similar protective effects on sodium balance with fewer challenges.

Tong and others reported a case of severe TUR syndrome in a patient who underwent TURP. The patient showed signs of pulmonary edema and respiratory failure due to hypovolemic hyponatremia, with a sodium concentration of 112.6 mmol/L, indicating severe hyponatremia. The patient was successfully treated with respiratory support and intravenous administration of 20 mg of furosemide, 150 mL of 3% NaCl, and 100 mL of sodium bicarbonate 8.4%. Although this was a case report, it suggests that furosemide can effectively treat TUR syndrome.[26] Similarly, we hypothesize that furosemide may be effective due to a combination of fluid overload and hyponatremia. Our study found that administering furosemide is an effective way to reduce hyponatremia during prostate resection surgery. However, our study differs, as it focuses on the prophylactic use of furosemide rather than its emergency application.

Our study found that the use of furosemide may cause mild hypokalemia as a possible complication. However, the cases who experienced hypokalemia (ranging from 3.0 to 3.5 mmol/L) were mild in both the control and furosemide groups. Research has shown that furosemide, being a loop diuretic medication, can lead to hypokalemia by increasing the amount of urine produced by the kidneys, which

causes the loss of K and other electrolytes from the body.[27] Therefore, patients taking furosemide are advised to monitor their K levels regularly by their healthcare provider and follow dietary or medication recommendations to prevent hypokalemia.[28] Since all patients who experienced hypokalemia had K levels below 4.1 mmol/L at baseline, we recommend using furosemide in TURP for patients with an upper limit range of plasma K levels (4.2 to 5.0 mmol/L).

Alternative approaches to managing hyponatremia during TURP surgery include the use of HS and other diuretics. HS is effective for rapid sodium correction and cerebral protection but requires close monitoring to prevent overcorrection.[29] Thiazide and potassium-sparing diuretics offer milder effects on fluid balance and may reduce hypokalemia risk, though they are less potent than furosemide for managing acute fluid overload.[30] Combination therapy, such as hypertonic saline with furosemide, can be beneficial for severe cases but necessitates intensive electrolyte monitoring to avoid complications.[31] Each approach has distinct advantages and limitations, and selection should be tailored to the patient's clinical profile and risk factors.

The scope of this study was limited to two health centers, which may restrict the applicability of its findings to a broader population. Moreover, only patients with a normal range of plasma K levels were included in this study, and it still needs to be determined whether these findings can be extended to patients with low baseline K levels. Even with randomization attempts, outcomes may be influenced by potential confounding variables, such as individual patient health problems and metabolic variances. In this investigation, we did not consider the patient's metabolic state. Additionally, this study only examined the short-term effects of furosemide administration, and it remains to be determined whether this drug is safe and effective for long-term use in patients undergoing prostate resection surgery. Furthermore, this study did not compare the effectiveness of furosemide with other diuretics or electrolyte replacement therapies, nor did it investigate non-pharmacological interventions such as changes to fluid management protocols or surgical techniques.

Conclusion

This study suggests that furosemide administration is an effective way to reduce hyponatremia during TURP. We recommend using furosemide to prevent hyponatremia in patients with an upper-limit range of plasma K levels (4.2 to 5.0 mmol/L). Further research is needed to fully understand the safety and efficacy of furosemide in this context. Additionally, exploring alternative methods for preventing hyponatremia should also be considered.

Our study suggests furosemide as a promising option for preventing hyponatremia during TURP. Future research should explore its long-term effects, potential adverse outcomes, and impact on recovery. Additionally, alternative strategies, including other diuretics, electrolyte therapies, and non-pharmacological interventions, should be investigated.

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Authors' Contribution

F.Gh: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision; H.B.S: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Visualization; A.A: Data curation, Formal analysis, Investigation, Software; A.B: Conceptualization, Funding acquisition, Investigation, Resources, Supervision, Visualization; M.N: Conceptualization, Funding acquisition, Investigation, Resources, Supervision, Visualization; N.S: Conceptualization, Funding acquisition, Investigation, Resources, Supervision, Visualization. All authors participated in writing the original draft and reviewing and editing the final version. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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