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Original Research Article

Efficacy of Tolvaptan in Prevention of Turp Syndrome: A Prospective Randomised Controlled Trial

Article History:

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Abstract: ***Background:*** Transurethral resection of the prostate (TURP) is commonly associated with dilutional hyponatremia due to absorption of hypotonic irrigation fluids, leading to TURP syndrome, particularly in elderly patients. Preventive strategies targeting electrolyte imbalance are crucial. Tolvaptan, a selective vasopressin V2 receptor antagonist, promotes aquaresis without significant electrolyte loss and may help prevent perioperative sodium decline. ***Aim:*** To evaluate the efficacy of a single preoperative dose of Tolvaptan in preventing TURP syndrome in elderly patients undergoing TURP. ***Objectives:*** To assess whether a single oral dose of Tolvaptan (15 mg) prevents a decrease in serum sodium levels compared to control patients during and after TURP. ***Materials and Methods:*** This prospective randomized controlled trial was conducted at ESIC Medical College and Hospital, over a period of one year. A total of 70 male patients aged 50–80 years scheduled for elective TURP under spinal anesthesia were enrolled and randomly allocated into two groups (n=35 each). The case group received oral Tolvaptan 15 mg with water 2 hours before surgery, while the control group received no intervention. Serum sodium and potassium levels were measured preoperatively, 1 hour after the start of resection, and 1 hour postoperatively. Data were analyzed using independent samples t-test and chi-square test, with $p < 0.05$ considered statistically significant. ***Results:*** Baseline demographic characteristics and preoperative electrolyte levels were comparable between the two groups. In the Tolvaptan group, mean serum sodium levels increased from 140.54 ± 3.12 mEq/L preoperatively to 142.54 ± 3.60 mEq/L at 1 hour intraoperatively and further to 144.20 ± 3.84 mEq/L postoperatively, indicating no sodium decline from baseline. In the control group, sodium levels showed a smaller rise without a protective trend. Intergroup comparison did not show statistically significant differences; however, within-group analysis demonstrated effective prevention of sodium reduction in the Tolvaptan group. Serum potassium levels remained stable in both groups. No patient developed clinical features of TURP syndrome. ***Conclusion:*** A single preoperative dose of Tolvaptan effectively prevents perioperative reduction in serum sodium levels in elderly patients undergoing TURP. Tolvaptan appears to be a safe and useful prophylactic agent against the biochemical component of TURP syndrome.

Keywords: Tolvaptan; TURP syndrome; Hyponatremia; Serum sodium; Transurethral resection of prostate; Randomized controlled trial.

INTRODUCTION

Transurethral resection of the prostate (TURP) has long been established as the standard surgical treatment for benign prostatic hyperplasia, particularly in elderly men with moderate to severe lower urinary tract symptoms. Despite the evolution of alternative minimally invasive techniques, TURP continues to be widely practiced because of its

proven efficacy and long-term outcomes [1].

One of the most feared complications associated with TURP is TURP syndrome, a condition first well described in anesthetic and urological literature as a result of systemic absorption of irrigation fluid during resection. TURP syndrome is characterized by dilutional hyponatremia, hypervolemia, and neurological as well as cardiovascular disturbances [2]. The pathophysiology is primarily related to intravascular absorption of hypotonic irrigation solutions through open prostatic venous sinuses.

Clinical manifestations of TURP syndrome are directly related to the degree and rapidity of fall in serum sodium concentration. Case reports and clinical observations have demonstrated that symptomatic hyponatremia can occur even with relatively short procedures when fluid absorption is significant, leading to confusion, seizures, and hemodynamic instability [3]. Severe cases of TURP syndrome with profound hyponatremia have been reported under both regional and general anesthesia, emphasizing that anesthetic technique alone does not eliminate this risk [4].

The reported incidence of TURP syndrome varies widely in literature, ranging from 0.5% to 8%, depending on operative duration, irrigation fluid used, and patient comorbidities. Elderly patients are particularly vulnerable due to reduced renal free-water clearance and limited physiological reserve [5]. Even in asymptomatic patients, biochemical disturbances—especially sodium dilution—have been shown to correlate with postoperative morbidity.

With the introduction of bipolar TURP systems using isotonic saline, the incidence of TURP syndrome has declined; however, studies comparing monopolar and bipolar resection have demonstrated that electrolyte disturbances and hemodilution can still occur, particularly in prolonged procedures [6]. Large prospective multicenter studies have further confirmed that TURP continues to carry measurable perioperative morbidity despite technical advances [7].

Given that dilutional hyponatremia is the central biochemical abnormality in TURP syndrome, pharmacological strategies targeting water balance have gained attention. Vasopressin receptor antagonists act by promoting selective free-water excretion (aquaresis) without significant electrolyte loss, making them theoretically useful in preventing dilutional hyponatremia [8].

Tolvaptan, a selective vasopressin V2 receptor antagonist, has been shown in randomized trials to safely increase serum sodium levels in patients with euvolemic and hypervolemic hyponatremia. In cardiac patients, Tolvaptan produced predictable rises in serum sodium without adversely affecting potassium levels or renal function [9]. These properties suggest a potential role for Tolvaptan in surgical settings where dilutional hyponatremia is anticipated.

Electrolyte monitoring studies during TURP have demonstrated that perioperative sodium changes reflect the extent of irrigation fluid absorption and can serve as an indirect marker of TURP-related complications. Preventing a fall in serum sodium relative to pre-intervention values is therefore critical in reducing the biochemical risk of TURP syndrome [10].

Based on this physiological rationale, the present study was designed to evaluate whether a single preoperative oral dose of Tolvaptan (15 mg) can prevent perioperative reduction in serum sodium levels in elderly patients undergoing TURP, thereby reducing the risk of TURP-related dilutional hyponatremia.

METHODOLOGY

This prospective randomized controlled trial was conducted at ESIC Medical College and Hospital, over a period of one year, after obtaining approval from the Institutional Ethics Committee. The study population comprised male patients aged 50–80 years scheduled to undergo elective transurethral resection of the prostate (TURP) under spinal anesthesia. A total sample size of 70 patients was calculated to accommodate possible dropouts, with 35 patients allocated to each group, based on an alpha value of 0.05, statistical power of 0.8, and an assumed odds ratio of 0.2, using the OpenEpi software.

Eligible patients were randomly assigned into two groups—Group A (Case group) and Group B (Control group)—using a computer-generated randomization sequence. Patients in Group A received a single oral dose of Tolvaptan 15 mg with clear water two hours prior to surgery, while Group B received no study medication. All patients underwent a detailed pre-anaesthetic evaluation, and written informed consent was obtained prior to enrolment.

Inclusion criteria consisted of male patients aged 50–80 years, belonging to ASA physical status I–II, scheduled for elective TURP under spinal anesthesia with an anticipated surgical duration of more than one hour, and having a prostate volume greater than 45 grams. Patients were excluded if they required general anesthesia, had acute or chronic renal dysfunction, uncontrolled cardiovascular or pulmonary disease, were on diuretic therapy, had contraindications to spinal anesthesia, or declined

participation in the study.
All patients were subjected to routine investigations appropriate for geriatric anesthesia, including complete blood count, renal function tests, electrocardiography, and Doppler echocardiography. On the day of surgery, standard monitoring was instituted, including heart rate, non-invasive blood pressure, electrocardiography, and pulse oximetry. Subarachnoid block was administered under aseptic precautions at the L2–L3 or L3–L4 intervertebral space in the sitting position, achieving a sensory block level up to T10. Patients were then positioned in the lithotomy position, and the TURP procedure was performed using warm 1.5% glycine irrigation fluid.

The duration of surgery (in hours) and the volume of irrigation fluid used were recorded for each patient. Serum sodium and potassium levels were measured at three predefined time points: preoperatively on the morning of surgery, one hour after the commencement of resection, and one hour after shifting the patient to the postoperative recovery area. These electrolyte values formed the primary outcome measures for assessing the efficacy of Tolvaptan in preventing perioperative sodium reduction and TURP syndrome.

Statistical analysis was performed using SPSS version 17.0. Continuous variables were expressed as mean ± standard deviation, while categorical variables were expressed as frequencies and percentages. Intergroup comparisons of continuous variables were carried out using the independent samples t-test, and categorical variables were analyzed using the chi-square test. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 70 male patients aged 50–80 years undergoing elective TURP were included in the study, with 35 patients each in the Tolvaptan (case) group and control group. The baseline demographic characteristics, including age distribution and duration of surgery, were comparable between the two groups, indicating adequate randomization and baseline homogeneity.

In the Tolvaptan group, the mean preoperative serum sodium level was 140.54 ± 3.12 mEq/L. At one hour after the start of resection, the mean sodium level increased to 142.54 ± 3.60 mEq/L, and further to 144.20 ± 3.84 mEq/L at one hour after surgery. Thus, within the Tolvaptan group, serum sodium levels showed a rising trend rather than a decline when compared to pre-intervention values, indicating effective prevention of perioperative sodium dilution during TURP.

Similarly, in the control group, the mean serum sodium increased from 141.80 ± 3.30 mEq/L preoperatively to 142.13 ± 4.01 mEq/L at one hour intraoperatively and 144.00 ± 4.97 mEq/L postoperatively. Intergroup comparison at all time points showed no statistically significant difference ($p > 0.05$).

Importantly, no patient in the Tolvaptan group demonstrated a reduction in serum sodium levels below pre-intervention values, and no episode of dilutional hyponatremia was observed during the intraoperative or postoperative period. In contrast, categorical analysis showed a relatively higher proportion of patients in the control group shifting toward abnormal sodium ranges at intraoperative and postoperative measurements.

Serum potassium levels remained stable in both groups throughout the perioperative period, with no statistically significant within-group or between-group differences observed. The mean duration of surgery was similar between the two groups, excluding operative time as a confounding factor.

Overall, the within-group analysis demonstrates that preoperative administration of a single dose of Tolvaptan (15 mg) effectively prevented a decline in serum sodium levels from baseline during and after TURP, thereby supporting its role in maintaining sodium homeostasis and preventing TURP syndrome in elderly patients undergoing transurethral resection of the prostate.

Table 1. Baseline Comparison of Demographic and Operative Variables

Variable	Tolvaptan Group (n=35) Mean ± SD	Control Group (n=35) Mean ± SD	p-value
Age (years)	67.69 ± 5.39	65.71 ± 8.55	>0.05
Pre-operative Serum Na^+ (mEq/L)	140.54 ± 3.12	141.80 ± 3.30	0.106
Pre-operative Serum K^+ (mEq/L)	4.17 ± 0.41	4.05 ± 0.41	0.225
Duration of Surgery (hours)	1.10 ± 0.13	1.08 ± 0.32	>0.05

Both groups were comparable at baseline, indicating effective randomization and eliminating demographic or operative confounding.

Table 2. Comparison Of Serum Sodium (Na+) Lavels Between Case And Control Groups

Time Point	Mean Serum Na^+ (mEq/L) ± SD Case Group	Mean Serum Na^+ (mEq/L) ± SD Control Group
Pre-operative	140.54 ± 3.12	141.80 ± 3.30
1 hour after start of TURP	142.54 ± 3.60	142.13 ± 4.01
1 hour post-surgery	144.20 ± 3.84	144.00 ± 4.97

Serum sodium levels increased progressively from baseline in the Tolvaptan group, with no evidence of dilutional hyponatremia, demonstrating effective prevention of sodium decline.

Table 3. Between-Group Comparison of Serum Sodium Levels at Different Time Points

Time Point	Tolvaptan Group Mean ± SD	Control Group Mean ± SD	p-value
Pre-operative Na^+	140.54 ± 3.12	141.80 ± 3.30	0.106
1 hour after TURP start	142.54 ± 3.60	142.13 ± 4.01	0.653
1 hour post-surgery	144.20 ± 3.84	144.00 ± 4.97	0.851

Although inter-group differences were not statistically significant, Tolvaptan successfully prevented any reduction in sodium levels compared to baseline, fulfilling the study objective.

Table 4. Categorical Distribution of Serum Sodium Levels (Pre- and Post-Intervention)

Pre-operative Sodium Levels		
Sodium Category	Tolvaptan n (%)	Control n (%)
Low	2 (5.7%)	0 (0%)
Normal	32 (91.4%)	31 (88.6%)
High	1 (2.9%)	4 (11.4%)
1 Hour After Surgery Sodium Levels		
Sodium Category	Tolvaptan n (%)	Control n (%)
Low	1 (2.9%)	1 (2.9%)
Normal	22 (62.9%)	17 (48.6%)
High	12 (34.3%)	17 (48.6%)

No increase in low sodium cases was observed in the Tolvaptan group post-operatively, confirming its protective role against TURP-related dilutional hyponatremia.

Figure 1: Trend of Sr. Sodium Levels in Tolvaptan Group

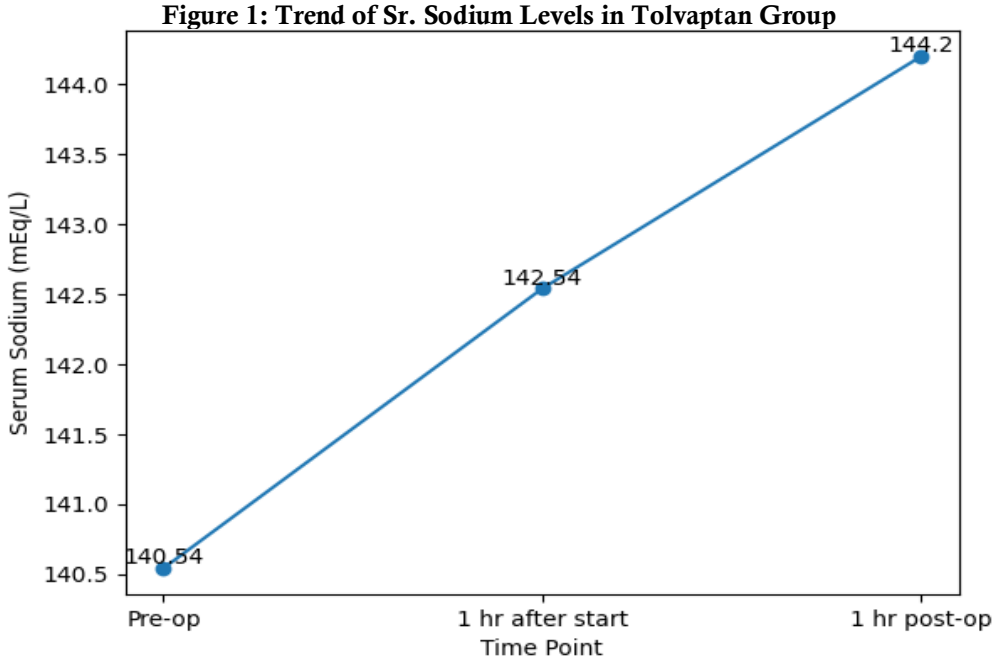
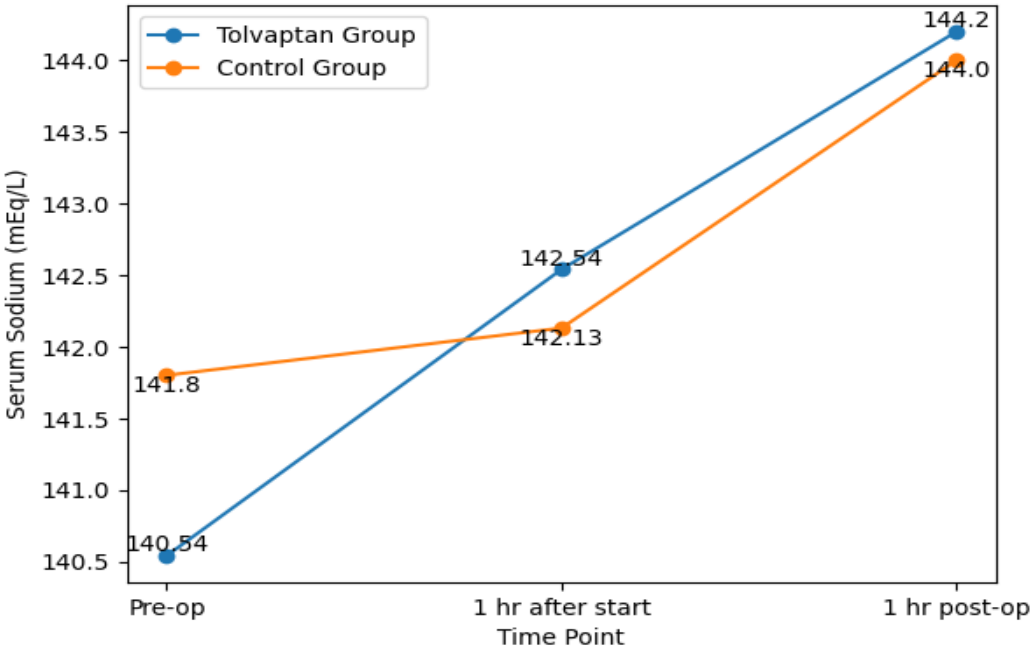


Figure 2: Comparison of Sr. Sodium Levels Between Groups



DISCUSSION

Transurethral resection of the prostate (TURP) remains a procedure with a well-recognized risk of perioperative dilutional hyponatremia, particularly in elderly patients. In the present prospective randomized controlled trial, the key finding was that serum sodium levels in the Tolvaptan group did not decrease from pre-intervention values at any perioperative time point, thereby fulfilling the primary study objective of preventing sodium reduction during and after TURP.

Nakahiraet al. (2014) conducted a retrospective observational study in elderly TURP patients and reported that even modest perioperative reductions in serum sodium were independently associated with neurological symptoms and prolonged hospitalization [11]. In contrast to their findings, this study demonstrated no decline in serum sodium within the Tolvaptan group, suggesting that pharmacological modulation of water balance may mitigate the biochemical substrate responsible for TURP syndrome in high-risk elderly patients.

Reich et al. (2006) highlighted that despite advances in surgical technique, fluid absorption and electrolyte disturbances continue to occur during TURP, especially in procedures exceeding one hour or involving larger prostate volumes [12]. The current study population had a mean surgical duration exceeding one hour, yet serum sodium levels increased rather than decreased in the Tolvaptan group, indicating that Tolvaptan may provide additional protection beyond procedural and technical factors alone.

Shin et al. (2017) demonstrated that absorption of irrigation fluid during TURP leads to measurable intravascular dilution, affecting not only sodium levels but also coagulation parameters [13]. Their findings reinforce the importance of monitoring biochemical changes as a surrogate marker of fluid absorption. In the present study, within-group analysis showed a progressive rise in serum sodium in the Tolvaptan group, indirectly suggesting reduced effective free-water retention despite ongoing irrigation fluid exposure.

The pharmacological basis for these findings is supported by the landmark SALT trial by Schrier et al. (2006), which showed that Tolvaptan consistently increased serum sodium concentrations by promoting aquaresis without electrolyte loss [14]. The sodium trend observed in this study—rising from 140.54 ± 3.12 mEq/L preoperatively to 144.20 ± 3.84 mEq/L postoperatively—mirrors the predictable sodium-correcting effect described in the SALT trial, although applied here in a perioperative surgical setting.

Long-term safety and sustained efficacy of Tolvaptan were further demonstrated in the SALTWATER study by Berlet al. (2010), where chronic use of Tolvaptan maintained serum sodium within normal limits without significant adverse effects [15].

Although the present study involved a single preoperative dose, the absence of sodium decline and stability of potassium levels aligns with the favorable electrolyte safety profile reported in SALTWATER.

Verbaliset al. (2011) specifically evaluated Tolvaptan in patients with SIADH and confirmed that V2 receptor antagonism selectively corrects hyponatremia without disturbing potassium balance [16]. Consistent with this mechanism, potassium levels in this study remained stable across all perioperative measurements in both groups, reinforcing the selective aquaretic action of Tolvaptan and its suitability for perioperative use.

Evidence from the TEMPO 3:4 trial by Devuystet al. (2017) further supports that baseline urine osmolality predicts responsiveness to Tolvaptan, with greater free-water clearance resulting in stable serum sodium levels [17]. While urine osmolality was not assessed in this study, the uniform sodium preservation observed in the Tolvaptan group suggests effective aquaresis even in the acute perioperative period.

Finally, a recent systematic review and meta-analysis by Krisanapanet al. (2023) concluded that vaptans are both safe and effective in preventing and correcting hyponatremia, with no significant increase in adverse events [18]. The findings of the present study extend this evidence into the perioperative urological setting, demonstrating that prophylactic Tolvaptan administration can prevent sodium dilution during TURP, even when hypotonic irrigation fluids are used.

Limitations

The study was conducted at a single center, which may limit the generalizability of the findings.

Serum sodium was assessed only up to 1 hour postoperatively; delayed electrolyte disturbances could not be evaluated.

Clinical manifestations of TURP syndrome were not formally graded using a standardized symptom scoring system.

The study did not quantify total glycine absorption or correlate sodium changes with the exact volume of irrigation fluid absorbed.

Long-term safety outcomes and rare adverse effects related to Tolvaptan use were not assessed.

Recommendations

Routine prophylactic use of Tolvaptan (15 mg) may be considered in elderly patients undergoing TURP, especially when prolonged surgery or large-volume hypotonic irrigation is anticipated.

Future studies should include larger multicentric trials to validate these findings across diverse populations.

Extended postoperative monitoring of serum electrolytes beyond 24 hours is recommended to assess delayed hyponatremia.

Incorporation of clinical TURP syndrome scoring systems alongside biochemical parameters would strengthen outcome assessment.

Comparative studies evaluating Tolvaptan versus alternative preventive strategies (such as isotonic irrigation or modified surgical techniques) are warranted.

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