



Original Research Article

The role of tolvaptan in prevention of hyponatremia in patients undergoing transurethral resection of prostate surgery- A randomized double blind study

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ABSTRACT

Purpose: The aim of our study to determine the role of tolvaptan in prevention of hyponatremia in transurethral resection of prostate surgery.

Materials and Methods: This is randomized double-blind study conducted in 60 ASA grade status 1 and 2 patients age group between 45-80 yrs undergoing TURP under spinal anaesthesia in urology operation theatre in Mahatma Gandhi hospital Jaipur after receiving permission from hospital ethical committee. A detailed history, complete physical examination and routine investigation were done for all patients followed by informed written consent was obtained. Patients are randomly divided into 2 groups. In group A -30 patients who received orally tab tolvaptan 15 mg and group B-30 patients who received orally tab multivitamin 2 hrs before surgery after doing electrolytes of the patients in the morning. In both groups age (in yrs), wt (in kg), ASA grade, volume of irrigating fluid (in litres), volume of prostate resected (in gm) and duration of surgery (in minutes) all demographic and surgical details data were compared. Electrolytes were compared in both groups pre and post-operatively and statistical analysis was done.

Results: There was significant difference in post-operative sodium level between the two groups (A and B). The mean level of sodium significantly reduced post-operatively in group –B (control grp). The mean level of sodium significantly increased post-operatively in group –A (tolvaptan grp).

Conclusion: We conclude single dose of tolvaptan -15 mg found to effective in prevention of hyponatremia in patients undergoing TURP.

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1. Introduction

Benign prostatic hyperplasia (BPH) is enlargement of prostate in men which is not cancerous. As the prostate enlarges due to ageing, the gland presses against and pinches the urethra. Eventually, the bladder wall becomes thicker. Ultimately, the bladder become weaken and lose the power to empty completely, leaving some urine after micturation.¹

The narrowing of the urethra and urinary retention due to the inability to empty the bladder properly give rise to many complication with benign prostatic hyperplasia. Mild to moderate BPH is treated medically with alpha blockers combined with 5 alpha reductase inhibitors which relieves urinary symptoms in patients but does not decrease prostate

gland size. Transurethral resection of prostate (TURP) surgery for benign prostatic hyperplasia is considered the gold standard for treating blockage of the urethra due to benign prostatic hyperplasia. TURP is the second most common surgical procedure (after cataract extraction) which is performed above the age of 65 yrs.²

The TURP operation is performed using a resectoscope, through which a diathermy loop is passed during the procedure. The prostatic tissues is resected in small strips under direct vision by using the diathermy loop, which has ability both cut and coagulate.³

The bladder is continuously irrigated with fluid to allow direct vision and to wash away blood and debris. It is performed in the lithotomy position, sometimes with head-down tilt. The most common irrigation fluid used in our

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institution is glycine 1.5% which has osmolality of 220 mosmol kg⁻¹, making it hypotonic in comparison to plasma (280-300 mosmol kg⁻¹).³

The sign and symptoms of early manifestation of TURP including bleeding, TURP syndrome, sepsis, incontinence and retention of urine. Electrolyte imbalance is one of the most worrisome complication of TURP especially due to risk of developing overt syndrome.

1.1. Turp syndrome – Syndrome of over hydration

Triad of bradycardia, increased blood pressure and cerebral sign. TURP syndrome manifest due to absorption of irrigating fluid through prostatic veins exposed by breaches in the prostatic capsule during procedure. During a TURP procedure 20ml/min irrigating solution normally absorbed. There is a total of 1 -1.5 litre for average case.

During TURP resection the irrigating fluid is absorbed through prostatic veins and lead to hypovolumic hyponatremia, bradycardia, hypotension/ hypertension, nausea, vomiting, mental confusion and visual disturbances associated with hyponatremia are most commonly observed sign and symptoms. Spinal anaesthesia is best standard technique of choice for TURP. Spinal anaesthesia provide good postoperative analgesia and has advantage to reduce the stress response to surgery. More importantly, spinal anaesthesia allow the anaesthesiologist to monitor the patients level of consciousness due to which its easy to diagnose the early signs and symptoms of TURP syndrome. If patient complains of periumbilical or shoulder pain this is early recognition of capsular tears and bladder perforation. 3% Hypertonic saline along with diuretics used for dilutional hyponatrimia is not very effective is prevention and treatment of TURP syndrome.

2. Materials and Methods

This is randomized double-blind study conducted on 60 adults ASA grade status 1 and 2 of age group between 45-80 yrs scheduled for elective TURP under spinal anaesthesia from January 2019 to June 2020 in urology operation theatre in Mahatma Gandhi hospital Jaipur after receiving permission from hospital ethical committee.

Patients are randomly divided into 2 groups (A & B) n=30 patients for each group using chit box method. In group A -30 patients who received orally tab tolvaptan 15 mg and group B-30 patients who received orally tab multivitamin 2 hrs before surgery after doing electrolytes of the patients in the morning.

All patients were subjected to preanaesthetic check up before TURP surgery followed by informed written consent was obtained. They are assessed with routine investigation for geriatric anaesthesia including haematocrit, E.C.G., Doppler echocardiography. Patients with pre existing renal disease, cerebrovascular disease and malignancy were

excluded from the study. Metastasis in the lumbar spine a contraindication to spinal anaesthesia was also the exclusion criteria.

All patients were given 0.9% NS @3 ml/kg/hr intraoperatively. Standard monitors for heart rate, systemic blood pressure, E.C.G. and spo₂ were attached sub arachnoid block was performed aseptically at L2-L3 OR L3-L4 intervertebral disc space in sitting position and without difficulty producing satisfactory analgesia up to level of T10. Patients were positioned in lithotomy position and TURP surgery procedure was done with warm 1.5% glycine irrigation fluid. The duration of procedure in minutes, the volume of prostate gland resected and the volume of 1.5% glycine used during the procedure were recorded. The serum levels of sodium of all patients were measured 2 hr after surgery.

Statistical analysis was performed with SPSS, version 21 for windows statistical software package (SPSS inc., Chicago, IL, USA). The categorical data was presented as numbers (percent) and were compared among groups using Chi square test. The quantitative data was presented as mean and standard deviation and were compared by student's t-test. Probability was considered to be significant if less than 0.05.

Mean age, weight, and ASA physical status among patients in group A and B were comparable and there was no significant difference between them.

There was no significant difference between the groups as regards the volume of irrigating fluid, the prostate gland resected, and the duration of the TURP surgery (as per tab) Electrolytes were compared in both groups pre and post-operatively and statistical analysis was done.

3. Results

Mean patient age, weight, their ASA grade, volume of irrigating fluid, volume of prostate resected and duration of surgery in both the groups (A and B) are shown in Table 1.

No significant difference was observed among above demographic and surgical detail data.

The mean preoperative sodium of group –A was 137±3.3 (meq/l) and group –B was 138.2±3.06 (meq/l).

The mean postoperative sodium of group –A was 138.3±2.932(meq/l) and group –B was 135.7 ± 2.881(meq/l).

There was a significant difference in post-operative sodium levels between the two groups (A and B).

The mean level of sodium showed statistically reduction (hyponatremia) post-operatively in group–B.

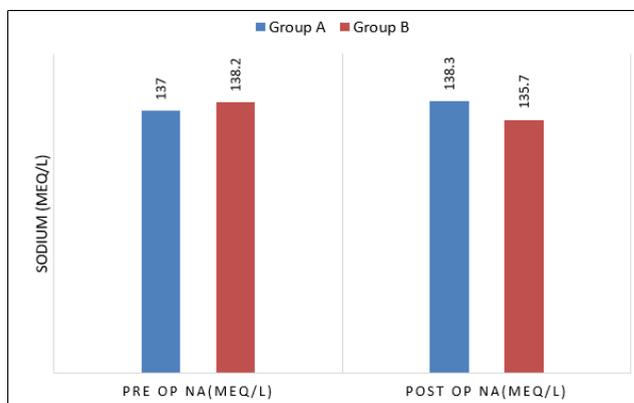
There was significant difference in post-operative sodium level between the two groups (A and B). The mean level of sodium significantly reduced post-operatively in group –B (control grp). The mean level of sodium significantly increased post-operatively in group –A (tolvaptan grp).

Table 1: Demographic and surgical details data

Variable	Group A (n=30) Mean±SD	Group B (n=30) Mean±SD	p- value
Age (years)	65.03±9.48	66.77±9.83	0.490
Weight (kg)	63.9±13.41	62.6±11.65	0.690
ASA Grade 1 Grade 2	16 14	22 8	0.180
Volume of irrigating fluid (l)	18.5±9.87	23±11.68	0.112
Volume of prostate resected (gm)	25.54±11.25	36.25±27.79	0.055
Duration of surgery (min)	59.5±21.2	59.27±23.07	0.968

Table 2:

	Group A (n=30) Mean±SD	Group B (n=30) Means±SD	Inter group comparison p value
Pre operative Na (meq/l)	137±3.3	138.2±3.06	0.121
Post operative Na (meq/l)	138.3±2.932	135.7±2.881	<0.001*
Intra group comparison p value	<0.001*	<0.001*	

**Fig. 1:** Comparison of sodium level

4. Discussion

1. BPH (benign prostatic hyperplasia) is a nonmalignant enlargement of prostate caused by growth of both the glandular and stromal elements of the gland. Symptoms occurs as a result of compression of the urethral canal and disruption of the normal flow of urine. Benign prostate hypertrophy responsible for symptomatic obstruction of the cervix vesicae in men who are older than 60 years of age.
2. Its incidence is about 0–1.1%. Excessive absorption of the irrigation solutions used during TURP, which are highly hypotonic in nature can cause dilutional hyponatremia and hypo-osmolality give rise to severe neurological symptoms.

The symptoms of TURP are generally caused by an excessive fluid overload in circulation. Different symptoms may occur depending on the solute which are used in the irrigation fluid.⁴ TURP syndrome may occur due to absorption of the irrigation fluid (2000 ml or more). TURP syndrome which causes headaches, anxiety, confusion,

dyspnoea, arrhythmia, hypotension and seizures and this can be fatal if untreated.

Transurethral resection of the prostate (TURP) is the most common surgical procedure which is performed on male patients over 65 years of age. Irrigation of closed body spaces may lead to perioperative fluid and electrolyte shifts.⁵

During TURP, the wide plexus of venous sinuses often opened and the absorption of the irrigation fluid through these channels causes a group of symptoms and findings that is called TURP syndrome.⁶ Hyponatremia symptoms do not generally apparent up to serum sodium concentrations below 120 mmol/l. But if the plasma is severely hypotonic (Na+ <100 mmol/l), acute intravascular haemolysis may precipitated.⁷

Tolvaptan is an aquaretic drug that work as a selective, competitive vasopressin receptor 2 (V2) antagonist, mainly used for treatment of hyponatremia associated with congestive heart failure, cirrhosis, and syndrome of inappropriate antidiuretic hormone (SIADH). Tolvaptan causes antagonism at V2 receptor which causes a decrease in number of aquaporin -2 channels in renal collecting tubules, resulting in decreased water reabsorption by the kidney.

Thus resulting in a net increase in free water excretion (aquaresis) in the urine there by decreasing water retention and reducing plasma volume which enables serum sodium concentration to rise towards normal. During TURP, an irrigation solution (glycine, sorbitol, mannitol) is used to facilitate surgical visualization and remove blood and resected tissue. The procedure is accompanied by absorption of this irrigation fluid directly through the prostatic venous plexus or more slowly through the retroperitoneal and perivesical spaces.

TURP syndrome is characterised by intravascular fluid volume shifts and the effects of plasma solute absorption. Solute changes such as hyponatremia may alter neurologic

function independent of volume related effects. Although monitoring of serum sodium concentrations during TURP is effective for assessing intravascular fluid absorption, there may be benefit in monitoring serum osmolarity as well.

Hypoosmolarity appears to be the principal factor contributing to the neurologic and hypovolumic changes considered to reflect TURP syndrome supportive care remains the most important therapeutic approach for managing cardiovascular, CNS and renal complication of TURP syndrome. Neuroaxial anesthesia has conventionally been the anesthetic technique of choice for TURP because it allows for monitoring of TURP syndrome symptoms during the procedure.

Intravascular volume expansion, intravascular volume loss, hyponatremia, hypoosmolarity, hypoammonemia and hyperglycinemia are various consequences of TURP syndrome.

TURP syndrome can cause a wide variety of symptoms that include asymptomatic hyponatremia, ECG changes, fatigue, vomiting, confusion, visual loss, coma and death.

The major risk factors for TURP syndrome include the size of the opened venous sinuses, the amount of the irrigation fluid used, using excess amounts of hypotonic intravenous fluids and most importantly, the duration of the resection.

The risk is increased if the duration of the resection is longer than 60 min. Approximately 10–30 ml/min of fluid is absorbed during resection. Thus, 1800 ml of fluid can be absorbed if the resection lasts for 1 h. Mild -to moderate TURP syndrome may occur in 1–8% of patients. The overall mortality is 0.2–0.8%. It may present as early as 15 min after resection starts or as late as 24 h after operation. Severe TURP syndrome is now rare; however, it carries a mortality of up to 25%. The most critical intervention in the treatment of TURP syndrome is early diagnosis.

The treatment must be arranged according to the severity of the symptoms. First, the absorbed water must be eliminated and hypoxaemia and hypoperfusion must be prevented and must be administered fluids which contain NaCl. Loop diuretics can be used to eliminate excess fluid.

If severe symptomatic hyponatremia is present with impaired consciousness and convulsions, hypertonic saline solutions can be administered. The amount and rate of the hypertonic NaCl solution (3% or 5%) must be adjusted according to the serum sodium concentration of the patient for safely correcting hyponatremia.

The rate of the hypertonic saline solution infusion must not be above 100 ml/h to avoid increasing the fluid overload. The hyponatremia must be treated aggressively to avoid intravascular haemolysis, if serum sodium concentration is below 100 mmol/l. Our patient was administered 150 ml of 3% hypertonic NaCl for 2 hr and 150 ml of 3% NaCl was added to the management fluid. With this treatment, the patient recovered. Hypertonic solutions are used when

serum sodium levels are below 120 mmol/l. The major risk factors for TURP syndrome include the size of the opened venous sinuses, the amount of the irrigation fluid used, using excess amounts of hypotonic intravenous fluids and most importantly, the duration of the resection.

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Acute neurological symptoms (such as confusion and coma) must be treated rapidly, especially if the patient has central pontine myelinolysis which is associated with depressed awareness, difficulty speaking and swallowing,

impaired thinking, weakness or paralysis in the arms and legs, stiffness, impaired sensation and difficulty with coordination.

The chances of bladder perforation are 1% and may give rise to vomiting, excessive sweating and retroperic and lower abdominal pain which depends on the level of regional anaesthesia in conscious patients if Perforation is suspected.

During TURP if sudden hypotension or hypertension occurs together with bradycardia. In patients under spinal anaesthesia, neurological symptoms including vomiting, confusion and irritability can easily diagnosed intra and postoperatively.

Use of mannitol as the first drug of choice in patients with fluid overload condition may worsen the clinical state of the patient and furosemide used as better choice in comparison to mannitol. Furosemide was used as a diuretic if TURP syndrome was suspected.

In conclusion, noticing the clinical symptoms of patients with TURP syndrome during the early stages, making the right diagnosis and rapid accurate interventions for the treatment are important in the management of TURP syndrome, if regional anaesthesia administered. The patients operated under regional anaesthesia benefited in the early diagnosis and treatment of TURP syndrome. So regional anaesthesia should be preferred choice in TURP surgery. The duration of surgery was delayed due to endoscopic cystolithotripsy as well as prostate resection, and TURP syndrome was generally notified during the 50 min of prostate resection.

We concluded that factors like that added and prolonged surgery, increased use of irrigation fluid associated with additional surgery responsible for the development of the TURP syndrome, when TURP surgery was combined with another cystoscopic application. So more careful about time in the multiple cystoscopic procedures if done in the same session.

TURP syndrome is as consequence of intravascular volume shifts and osmolarity.

1. Tolvaptan is started as single oral 15 mg tab 2hrs before surgery effective for correction of acute hyponatremia in TURP surgery.
2. The chances of hypervolumic hyponatremia increase in TURP surgeries in patient with prostate size more than >45 gm and with increase in volume of irrigating fluid. In this study sodium level decreased in control group –B but not below 120 meq/l so there was no clinical manifestation.

Dry mouth, increased thirst, nausea and weakness are common side effect of tolvaptan which is not notice after single tab of tolvaptan 15 mg during study.

On the basis of our study we conclude that single dose of tolvaptan can be used for prevention and correction of hyponatremia in TURP patients.

5. Conclusion

TURP syndrome is one of the serious complication that may occur during the surgical procedure of BPH. TURP are often performed in elderly and suffer from cardiac, pulmonary, renal and endocrine disorders sometimes these patients are dehydrated and develop dyselectrolytemia after surgery.

A single dose of tolvaptan 15mg was found to be effective in preventing a marked decrease in the serum sodium levels in patients undergoing TURP especially when there is an increase chances of hyponatremia which is noted during prolong TURP surgery.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare that there is no conflict of interest.

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