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A COMPARATIVE STUDY OF TOLVAPTAN (15 MG AND 30 MG) TO PREVENT HYPONATREMIA IN TRANSURETHRAL RESECTION OF PROSTATE SURGERY-A RANDOMIZED DOUBLE BLIND STUDY

Anaesthesiology

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ABSTRACT

Purpose: The aim of our study is to compare two doses 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 tolvaptan 30 mg 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 –A (tolvaptan 15mg grp). The mean level of sodium significantly increased post-operatively in group –B (tolvaptan 30mg grp).
Conclusion: We conclude single dose of tolvaptan 30 mg found to effective in prevention of hyponatremia in patients undergoing TURP.

KEYWORDS

Tolvaptan, Hyponatremia, Benign prostatic hyperplasia

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a non-cancerous enlargement of the prostate. The prostate gland presses against and compresses the urethra as it grows larger with age. Bladder wall becomes thicker. Bladder weakens and loses its ability to totally empty, leaving some urine after micturation.[1]

The narrowing of the prostatic urethra and urine retention caused by an inability to effectively empty the bladder cause a number of issues in benign prostatic hyperplasia.

Treatment option:
Medical - Alpha blockers combined with 5 alpha reductase inhibitors are used to treat mild to moderate BPH, which reduces urinary symptoms but does not reduce prostate gland size.

Surgical – Transurethral resection of prostate (TURP) surgery is regarded the gold standard for treating urethral blockage caused by benign prostatic hyperplasia, transurethral resection of prostate.

After cataract extraction, TURP is the second most common surgical treatment performed on people over the age of 65 yrs.[2]

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

Fluid is continuously irrigated into the bladder to allow direct vision and wash away blood and debris.

Several types of fluid are available for use during a TURP procedure, but the ideal irrigant should be:
- Iso-osmolar and nonhemolytic
- Non-electrolytic
- Non-toxic
- Transparent
- Non-metabolizable
- rapidly excretable
- inexpensive and sterile

Irrigating solutions available are:
- saline and lactated ringer's solution
- water
- glucose 5.4 %
- urea 1.8%
- sorbitol 3.3%
- mannitol 3%
- crystal
- glycine 1.5 % (currently most common)

TURP is performed done in the lithotomy position, with slight head-down tilt. The most widely used irrigation fluid in our institution is glycine 1.5 percent, which has an osmolality of 220 mosmol kg-1 and is hypotonic when compared to plasma (280-300 mosmol kg-1). [4]

The complications of TURP surgery are bleeding, TURP syndrome, sepsis, incontinence, urine retention etc.

The irrigating fluid is absorbed by the prostatic venous plexus during prostate resection, resulting in dilutional hyponatremia, bradycardia, hypotension/hypertension, nausea, vomiting, mental disorientation, and visual problems associated with hyponatremia.[5]

The anaethesia technique of choice of TURP is spinal block One of the primary concerns in TURP surgery is electrolyte imbalance.

OVERHYDRATION SYNDROME (TURP SYNDROME) - Bradycardia, hypertension and cerebral sign form a triad.

TURP syndrome is caused by the absorption of irrigating fluid through the prostatic venous plexus, which is exposed after surgery due to breaches in the prostatic capsule. During TURP surgery, the irrigating fluid is generally absorbed at a rate of 20 ml/min. For the average case, there is a total of 1 -1.5 litres.

Until recently, salt supplementation and water restriction were the mainstays of hyponatremia treatment. Because dysregulation of arginine vasopressin (AVP) is involved in the majority of hyponatremia events, an AVP receptor antagonist has been a target of pharmacological development for the past 30 years. To start the development of an antagonist, a peptide analogue of AVP was chosen. Despite initial promising results, human testing revealed that these compounds were partial AVP receptor agonists, and further study was halted. Use of nonpeptide, small-molecule AVP receptor antagonists (Tolvaptan) for prevention and treatment of hyponatremic episodes is recently approved.

With this aim a comparison is done to see the efficacy of two different doses of tolvaptan to prevent hyponatremia in patients undergoing TURP surgery.

MATERIAL AND METHODS

This is randomized double-blind study conducted on 60 adults ASA grade status1 and 2 of age group between 45-80 yrs scheduled for elective TURP under spinal anaesthesia from January 2020 to June 2021 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 tolvaptan 30mg 2 hrs before surgery after doing electrolytes of the patients in the morning.

All patients were subjected to preanesthetic 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 disesase, cerebrovascular disease and malignancy were excluded from the study. Metastasis in the lumber 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 spo_2 were attached sub arachanoid 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 27.0; 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 postoperatively and statistical analysis was done.

RESULT AND ANALYSIS

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-

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

The mean preoperative sodium of group-A was 135.24±3.51 (meq / L) and group B was 136.86±3.19 (meq / L).

The mean postoperative sodium of group-A was 134.10±3.16 (meq / L) and group- B was 138.66±3.31 (meq / L) as shown in table 2.

There was a significant difference in postoperative sodium 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 postoperative sodium level between the two groups (A and B). the mean level of sodium significantly reduce postoperatively in group- A (tolvaptan 15 mg).

The mean level of sodium significantly increased postoperatively in group-A.

Table 1: Demographic and surgical details data

Variable	Group A (n=30) Mean±SD	Group B (n=30) Mean±SD	p- value
Age (years)	67.50±9.25	69.53±9.63	0.4080
Weight (kg)	70.20±7.08	68.83±8.88	0.0934
ASA Grade 1 Grade 2	23 7	21 9	0.5593
Volume of irrigating fluid (lt)	20.23±7.47	19.25±6.84	0.5971
Volume of Prostate resected (gm)	23.35±7.76	25.22±8.40	0.3762
Duration of Surgery (min)	56.90±18.29	60.84±20.10	0.0716

***SD = standard deviation**

Table-2: Sodium changes pre and post operatively

	Group A(n=30) Means±SD	Group B (n=30) Mean±SD	Inter group comparisonp value
Pre op Na+	135.24±3.51	136.86±3.19	0.0567
Post op Na+	134.10±3.16	138.66±3.31	<0.0001
p value	0.0601	<0.0001	

Pre op Na+

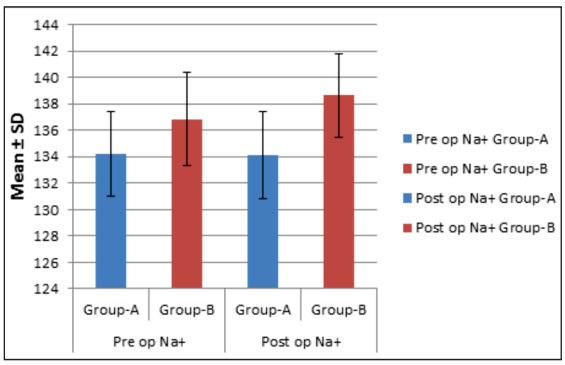
In Group-A, the mean Pre op Na+ of patients was 135.24 ± 3.51.
In Group-B, the mean Pre op Na+ of patients was 136.86 ±3.19.
Distribution of mean Pre op Na+ among the Groups was not statistically significant (p=0.0567).

Post op Na+

In Group-A, the mean Post operative sodium of patients was 134.10 ± 3.16.

In Group-B, the mean Post operative sodium of patients was 138.66 ±3.31.

Distribution of mean Post operative sodium with Group was statistically significant (p<0.0001).



DISCUSSION

BPH (benign prostatic hyperplasia) is a nonmalignant enlargement of prostate gland causing compression of the urethral canal and disruption of the normal flow of urine.

Transurethral resection of prostate (TURP) surgery for BPH is considered the gold standard for treating blockage of the urethra .

TURP syndrome may occur due to excessive absorption of the irrigation fliud during TURP surgery. It 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.[6]

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.

Intravascular volume expansion, intravascular volume loss, hyponatremia, hypoosmolarity, hypoammonemia and hypergly cinemiaare 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 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 sodium chloride. 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 patient operated under regional anaesthesia benefited in the early diagnosis and treatment of TURP syndrome.So regional anaesthesia should be preferred choice in TURPsurgery.

Tolvaptan is an aquaretic drug that work as 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 tubles, 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.

In our study Tab Tolvaptan 15mg(group A) and Tab Tolvaptan 30mg(group B) was given orally 2 hrs before surgery randomly.

We found that postoperatively sodium level was better with 30mg tolvaptan in comparasion with 15mg tolvaptan.

Sunil rajan et al (2018)[7] found Conviptan was safe and effective in correcting hyponatremia in TURP patient.

In similar to our study Dinesh et al (2020) [8] found that Tab Tolvaptan 15mg is effective in prevention of hyponatremia during TURP surgery but they have not compare the different doses of Tolvaptan.

From our study, we conclude that single dose of 30mg Tolvaptan is better than 15mg Tolvaptan in prevention and correction of hyponatremia in TURP surgery.

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 -30 mg was found to be better and more effective in preventing a marked decrease in the serum sodium levels in patients undergoing TURP especially when there is an increase chance of hyponatremia which is noted during prolonged TURP surgery.

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