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COMPARISION OF EFFECTIVENESS OF IRRIGATION FLUID MANNITOL 5% WITH THAT OF GLYCINE 1.5% IN PREVENTING POST TURP HYPONATREMIA

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ABSTRACT

INTRODUCTION: *Transurethral resection of the prostate (TURP) requires the use of an irrigating fluid to remove blood and debris to visualize the operating area. Glycine solution is the most commonly used irrigant & has been used in TURP for > 50years. There is now increasing evidence, highlighting the toxicity of glycine 1.5% solution when absorbed during TURP causing TUR syndrome.*
On the other hand the severity of the syndrome can probably be modified by using mannitol 5% instead of the most widely used glycine 1.5% as an irrigating fluid.
MATERIALS AND METHODS:
STUDY DESIGN: *Quasi-experimental study*
PLACE OF STUDY: *Urology department at Liaquat National Hospital, Karachi.*
DURATION OF STUDY: *Six months from 11.05.2006 to 10.11.2006.*
SAMPLE SIZE: *50 patients in each group.*
SAMPLING TECHNIQUE: *Non-probability, purposive*
SAMPLE SELECTION:
Inclusion Criteria: All patients undergoing transurethral resection of prostate.
Exclusion Criteria:
1. Patients with cardiac failure. 2.Patients with COPD & pulmonary edema.
3. Patients with hypoprotienemia 4. Patients with chronic renal failure.
5. Patients with hematological disorders including bleeding diathesis. 6.Patients with hyponatremia. 7. Patients with severe lower urinary tract infection.
RESULTS: *The study was carried out in 100 patients divided into two groups, both groups underwent TURP. Group-A included 50 patients in which mannitol 5% used as an irrigant. Group-B also included 50 patients treated with Glycine 1.5%. No significant change noted regarding post operative serum sodium level. Only three patients out of fifty in group "B" developed visual disturbances. One patient developed tachycardia in group "A" while two patients developed tachycardia in group "B" & three patients needed ICU monitoring in group "B".*
CONCLUSION: *In conclusion Mannitol 5% proved better irrigation solution as compared to Glycine 1.5% for Trans urethral resection of Prostate in prevention of post TUR syndrome due to causes other than serum sodium level.*

KEY WORDS: Mannitol 5 % Solutions, Post turp Hyponatremia, Glycine 1.5%

INTRODUCTION:

The prostate is an organ linked with the endocrine system. It has been stated that the prostate gland is the male organ most commonly associated with either benign or malignant neoplasms [1].

Benign prostatic hyperplasia (BPH) is the most frequent problem in ageing men, commonly resulting in bothersome lower urinary tract symptoms (LUTS).[2]

The initial changes of BPH begin at about 35 years. The average adult prostatic weight is about 18 mls, with increasing age there is increase in the weight of prostate. The decision for treating a patient with enlarged prostate is not yet codified and it is configured according to the size of prostate, presentation of symptoms, availability of equipments, expertise and need of the patient.[3]

It is estimated that in men 80 years old or older, 90% show histological evidence of

the condition, 81% have BPH related symptoms and 10% suffer urinary retention.[4] Approximately 25% of all men would eventually require some type of treatment for clinical BPH. [5]

There are various medical & surgical therapies are available for the treatment of BPH but transurethral resection of the prostate (TURP) is still the gold standard for the surgical treatment of symptomatic benign prostatic hyperplasia. [6]

The use of TURP is justified as it is 90% effective in removing infravesical obstruction & symptoms due to BPH.[7]

Newer therapies are constantly being introduced that hope to match the long-term symptom relief success of TURP.[8] Currently, these techniques include transurethral electro vaporization and vaporizing resection, laser ablation, interstitial laser coagulation, laser resection, transurethral microwave thermotherapy, bipolar TURP, high-intensity focused ultrasound, and expandable braided wire-mesh urethral stents. So far, none has proven to be superior to TURP on a long-term basis.[9]

Transurethral resection of the prostate (TURP) requires the use of an irrigating fluid to remove blood and debris to visualize the operating area. Despite modern technique, unpredictable amount of irrigating fluid, which usually consists of glycine 1.5% in sterile water, mannitol in 3 or 5%, sorbitol, 5% dextrose water, plain water, normal saline etc enters the circulation during nearly every routine TURP. This may give rise to clinical symptoms involving the cardiovascular and central nervous system usually referred to as the trans urethral resection syndrome(TUR syndrome).[10]

TUR syndrome is defined as serum sodium level ?125m.mol/L associated with mental confusion, bradycardia, hypotension/ hypertension, nausea, vomiting and visual disturbances, in severe cases may lead to a significant morbidity or even to a preventable mortality.[11]

Symptoms range from nausea and malaise, with mild reduction in the serum sodium, to lethargy, decreased level of consciousness, headache, and if severe, seizures and coma. Neurologic symptoms most often are due to very low serum sodium levels (usually <115 mEq/L), resulting in intracerebral osmotic fluid shifts and brain edema. This neurologic symptom complex can lead to tentorial herniation with subsequent brain stem compression and respiratory arrest, resulting in death in the most severe cases. [12]

Sodium is the dominant extra cellular cation and cannot freely cross the cell membrane. Its homeostasis is vital to the normal physiologic function of cells. The normal serum sodium level is 135-145 mEq/L.

Hyponatremia is an important and common electrolyte abnormality that can be seen in isolation or, as a complication of other surgical procedures. It is defined as a serum level of less than 135 mEq/L and is considered severe when the serum level is below 125 mEq/L. [13]

Hypo-osmolality (serum osmolality <260 mOsm/kg) always indicates excess total body water relative to body solutes or excess water relative to solute in the extracellular fluid (ECF), as water moves freely between the intracellular compartment and the extracellular compartment. This imbalance can be due to solute depletion, solute dilution, or a combination of both. [14]

For standard TURP the criteria for an ideal irrigant are:

1 It must irrigate the surgical field.
2 Not to be an electrical conductor.
3 Does not affect the diathermy.
4 Have good visual acuity & be "user friendly".
5 Produce minimal side effects when absorbed. [15]

Glycine solution is the most commonly used irrigant & has been used in TURP for > 50years. There is now increasing evidence highlighting the toxicity of glycine 1.5% solution when absorbed during TURP. Research has shown that it has direct & indirect cardio toxic effects in animals. It also increases the release of atrial natriuretic peptide (ANP) there by enhancing sodium loss & contributing to TUR syndrome. Metabolism of glycine give rises to glycolic acid & ammonia; high levels of blood ammonia have also been suggested as a possible cause of post TUR syndrome. Previous studies showed a correlation b/w symptom of TUR syndrome & hyper ammonemia after using 2.2% glycine & TURP.[16]

Another potentially safer alternative to glycine irrigation in TURP is normal saline with bipolar diathermy. [17] Use of isotonic saline as an irrigant instead of glycine with the new bipolar resectoscope for TURP in high-risk patients (with large prostates that require lengthy resection) could avoid this complication, making this disorder a diagnosis of the past.[18]

The risk of neurological symptoms after TURP is 4.8 times higher for glycine 1.5% than for mannitol 3%. An increase of 1000 ml in the volume of fluid absorbed increased the risk of circulatory and neurological symptoms by a factor of 4.4 and 3.4, respectively.The severity of the syndrome can probably be modified by using mannitol 5% instead of the most widely used glycine 1.5% as an irrigating fluid.[19]

MATERIALS AND METHODS

Study Design: Quasi-experimental study
Place of study: Urology department at Liaquat National Hospital, Karachi.
Duration of study: Six months after the approval of synopsis.
Sample size: 50 patients in each group.
Sampling technique: Non-probability, purposive

SAMPLE SELECTION:

Inclusion Criteria:

All patients undergoing transurethral resection of prostate.

Exclusion Criteria:

1 Patients with cardiac failure.
2 Patients with COPD & pulmonary edema.
3 Patients with hypoprotienemia.
4 Patients with chronic renal failure.
5 Patients with hematological disorders including bleeding diathesis.
6 Patients with hyponatremia.
7 Patients with severe lower urinary tract infection.

DATA COLLECTION PROCEDURE:

Pre-operative assessment:

1. Patients will be included from urology ward, out patient and emergency department of Liaquat National Hospital.
2. Detailed history will be taken in accordance with the inclusion and exclusion criteria.
3. General physical condition will be assessed.

PATIENT PREPARATION:

1. Informed & written consent will be taken from the patients.
2. Patient will undergo investigations i.e. Complete Blood Count, RBS, urine detail report & serum chemistry as a preparation for general / spinal anesthesia.
3. X-ray chest & ECG will be done as a pre-requisite for cardiac & anesthesia fitness.

Per Operative assessment:

1. Vitals will be monitored continuously through out procedure.
2. Time of resection and height of irrigation source will be noted.
3. Amount of irrigation fluid will be recorded.
4. Intravenous fluid during resection of prostate will be same in both group patients.

Randomization:

1. All patients will be randomly divided into two groups A & B by simple random sampling i.e. these 100 patients will be selected by using random number tables.

2. Group "A" mannitol 5% will be used as an irrigation fluid.
3. Group "B" Glycine 1.5% will be used as an irrigation fluid.

Surgery:
1. Operation will be performed under spinal / general anesthesia.
2. Surgical procedure performed will be transurethral resection of prostate.

Postoperative Assessment:
1. Post TURP in recovery, blood sample will be taken to measure sodium, for comparison with pre-operative serum sodium levels.
2. Number of patients who would develop confusion, nausea vomiting, visual disturbance, Dyspnoea, hypertension, tachycardia, shock or coma after TURP will also be recorded.
3. Duration of hospital stay in both groups of patients will be recorded.
4. All information will be recorded on proforma.

DATA ANALYSIS PROCEDURE:
The data was entered and analyze into Statistical packages for social science (SPSS version 10.0). Frequency and percentage were computed for categorical variable like age, quantity of fluid, time of resection, visual disturbance, heart rate, blood pressure, need of ICU care, hospital stay for both groups. Mean and standard deviation were computed for quantitative variables like hemoglobin, urea, and serum sodium level for both groups.
Independent sample t-test was applied to compare mean difference between groups for the variables hemoglobin, urea, and serum sodium level.
Paired t-test was applied to compare mean difference within subject effect for hemoglobin, urea, and serum sodium level. Chi-Square test was also applied to check proportion difference between groups for age groups, quantity of fluid, time of resection, visual disturbance, heart rate, blood pressure, need of ICU care, hospital stay. $P < 0.05$ was considered level of significant.

RESULTS
The study was carried out in 100 patients divided into two groups, both groups underwent TURP. Group-A included 50 patients in which mannitol 5% used as an irrigant. Group-B also included 50 patients treated with Glycine 1.5%.
Comparison of age between groups is presented in table 1. The most of the patients were belonged 60-69 years age in both groups. The patient age was not significantly different in the glycine and mannitol groups.
The resection rate was 58% gm. per minute in group A and 40% in group B. The resection rate was not significantly different in the glycine and mannitol groups ($p=0.29$) as shown in table 3.
The mean hemoglobin difference was not statistical significant between groups while pre and post operative treatment shown mean hemoglobin significantly ($p< 0.01$) change in both groups as shown in table 4. Comparisons of mean of urea between groups were also presented in table 4. The mean difference was not statistical significant between the groups and pre and post operative treatment.
The mean serum sodium level difference was not statistical significant between the groups but it was statistical significant within (pre and post operative treatment) the subject at $P < 0.01$.
Comparison of visual disturbance, heart rate and bold pressure also showed no significant difference in the two groups.
The length of hospital stay in group-I, and in group-II, are presented in table 9. The proportion difference was not statistical significant among the groups at $P= 0.274$.

DISCUSSION
An important issue in the safety of TURP procedures is the type of irrigation fluid used. Before isotonic solutions were available, water was used as an irrigant; however, this was associated with significant morbidity because of water intoxication and intravascular hemolysis. Currently, the most commonly used fluids for irrigation are glycine 1.5% which is slightly hypotonic & is the most commonly used irrigant during urological procedures like cystoscopy or transurethral resection of prostate (TURP). Hyponatraemia has been well reported as a complication of using hypotonic glycine as the irrigant. One should be aware of the various pathophysiological mechanisms of the development of hyponatremia in these patients so as to effectively treat them.
These solutions are continuously absorbed during the resection through prostatic bed but also a small amount of fluid can be absorbed through the venules along the bladder wall. In addition, a ruptured prostatic capsule or lacerated urinary bladder can promote increased glycine absorption. Absorbed glycine initially remains in the extracellular compartment but being an osmotically active agent glycine attracts water from the intracellular space and produces a dilutional hyponatremia and a raised osmolar gap. Thus, during the initial phase, when large part of glycine remains in the extracellular compartment, the amount of solution absorbed during the irrigation determines the severity of hyponatraemia. With greater absorption volumes (greater than 3 litres) hypervolumic hyponatraemia or water intoxication occurs. A small to moderate amount of absorbed glycine extracts more intracellular water increasing the osmolar gap and causing dilutional hyponatraemia or glycine toxicity. Later, glycine is eventually transported into the intracellular space and undergoes breakdown into its various metabolites like creatinine, carbon dioxide, water, ammonia, serine, glucose, hippurate, glyoxylate, formate, and oxalate. Renal excretion of glycine, glycine metabolites, and excess extracellular free water subsequently adjusts electrolytes and serum osmolarity back toward baseline values. During this corrective or late phase glycine metabolites, particularly ammonia, may cause ammonia toxicity.[20]
Clinical manifestations during the initial phase of glycine toxicity causing hypervolumic hyponatraemia or water intoxication include headache, visual disturbances, restlessness, initial hypertension followed by hypotension, bradycardia, agitation, confusion, coma, and death.[5] Osmotic haemolysis can lead to anaemia and thrombocytopenia. Severe metabolic acidosis due to glycine metabolites like hippurate, glyoxalate, and formate can also occur. Hypocalcaemia, which may be severe, can result from the formation of complexes of calcium and oxalic acid. Transient visual disturbances is not a uncommon symptom and may be due to direct neurotoxicity of glycine. Patients with smaller amounts of irrigant absorbed are usually asymptomatic. An important guide to treat patients is to classify them on the basis of their electrolyte and osmolar status. The most important laboratory abnormality is hyponatraemia with or without a raised osmolar gap. Metabolic encephalopathy may be related to hyponatraemia, hypo-osmolarity, or hyperammonaemia. Asymptomatic patients with serum sodium concentrations >120 mmol/l usually respond to simple discontinuation of glycine infusions. If serum sodium concentrations are <120 mmol/l or symptoms of glycine toxicity are present, the serum osmolar gap should guide therapy. In patients with a normal serum osmolar gap, hyponatraemia occurs as a result of excess extracellular free water. Correction of hyponatraemia in this setting may require hypertonic saline. Serum sodium should not be corrected faster than 1.5 to 2.0 mmol/ hour over 3–4 hours or >10 mmol/l in the first 24 hours and <18 mmol/l in the first 48 hours so as to avoid central pontine myelinolysis. In acute symptomatic

hyponatraemia, hypertonic saline (3% sodium chloride) is usually given over 3–4 hours and further management is guided by the therapeutic response. The following formulas will help one to determine the amount of hypertonic saline needed to replenish in acute situations:

Na^+ (mmol given as 3%) = ([Na^+ (desired) - Na^+ (measured)]) x estimated TBW

TBW (total body water) in a woman can be calculated as 0.5 x body weight in kilograms (kg) and in men as 0.6 x body weight in kg.

In patients with raised osmolar gaps, hyponatraemia is secondary to glycine itself. Such patients should be considered for haemodialysis to augment renal excretion of glycine and prevent the formation of toxic metabolites. In patients with renal failure, haemodialysis is necessary because they are unable to excrete glycine or free water. When hyperammonaemia with associated symtomatology is found, L-arginine infusion, which inhibits the conversion of glycine to ammonia, should be considered. The severity of glycine toxicity is directly related to the amount of glycine absorbed into the systemic circulation. Patients with severe glycine toxicity, therefore, should be evaluated for an underlying bladder rupture or urethral tear that might otherwise be clinically occult.

Keeping in view of toxicity in using glycine 1.5%, efforts were taken to minimize the risks of post TURP complications like hyponatremia & others to prevent the Post TUR syndrome.

A comparative study done by Collins JW & Macdermott S, published in BJU Int 2005 has shown that glycine1.5% has direct & indirect cardio toxic effects in animals. It also increases the release of atrial natriuretic peptide (ANP) there by enhancing sodium loss & contributing to TUR syndrome. Previous studies showed a correlation b/w symptom of TUR syndrome & hyper ammonemia after using 2.2% glycine & TURP. [11]

In our study we found mannitol safe as compared to glycine because no patient developed serious complication in mannitol arm except two patients developed tachycardia & hypotension. They were treated in ward. While in glycine arm three patients developed tachycardia with low blood pressure, one developed moderately increased in blood pressure & three complained of transient blindness.

Department of Anaesthesia, Karolinska Institute, South Hospital, Stockholm, Sweden conducted a study on fluid absorption in endoscopic surgery published in Br J Anaesth 2006. They concluded that irrigation with glycine solution should be avoided. Preventive measures, such as low-pressure irrigation, might reduce the extent of fluid absorption but does not eliminate the complication. However, the anaesthetist not the surgeon must be aware of the symptoms and be able to diagnose this complication. Treatment should be based on administration of hypertonic saline rather than on diuretics.

Different types of irrigant fluid were tried. Mannitol has been used in different concentrations.

Dr Hahn and his associates performed a double-blind, randomized study of the symptoms associated with absorption of either glycine 1.5% or mannitol 3% during standard TURP in patients from a single hospital who received spinal anesthesia published in J Urol 1998. The irrigating fluid bags contained one of the two solutions. Although there was no difference between groups with respect to circulatory symptoms, neurologic symptoms were more common in the group receiving glycine 1.5%. It is noteworthy that the incidence of neurologic symptoms/nausea was not affected by increasing amounts of absorbed irrigant from 500 to 1000 mL to more than 1500 mL using mannitol 3%, while the same symptoms increased significantly with the use of glycine 1.5%.

In our study 3 patients developed visual disturbance during the procedure of TURP while using glycine 1.5% as an irrigation fluid without any post operative gross change in the serum sodium level.

Over all in our study no gross change noted in post operative serum sodium as compared to pre operative serum sodium in both grougs.

CONCLUSION:

In conclusion Mannitol 5% proved better irrigation solution as compared to Glycine 1.5% for Trans urethral resection of Prostate in prevention of post TUR syndrome due to causes other than serum sodium level.

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