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Review Article

Updates on Irrigation Fluids in Endourology and TUR Syndrome - A Systematic Review

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Abstract: Endourological procedures are considered to be the minimally invasive procedure among all urological strategy and cause dreadful complication even in experienced hands. Endourological procedure requires irrigating fluid to dilate mucosal space, to remove the blood clots, fragments, resected tissue from the surgical field and enhance the vision properly. Various irrigating fluids are available in the market, but few plays an important role based on price, properties, and availability. A detailed review of the various irrigating fluids used in Endourological procedures that have lesser adverse effects, different modalities of treatment and the current state of TUR syndrome was performed. A detailed review was performed of medical literature to identify the articles relevant to irrigation fluids and TUR syndrome in Endourology. Preferred Reporting Items for Systematic reviews and Meta-Analysis guidelines were followed while conducting this study. Two authors reviewed all the articles confirming to search criteria. All non-English, conference poster presentations, letters to editor, and case reports were excluded. Articles remaining after exclusion were analyzed under one of these heads: Properties of irrigation fluids, Patho –physiology of TUR syndrome, management of TUR syndrome. This article reviews the various irrigant solutions used in endourology in the present day practice, and their advantages and limitations.

Keywords: Irrigation Fluids, TUR Syndrome, Endourology

1. Introduction

Transurethral resection of the prostate syndrome is first reported by Creevy in 1947. It is defined as a clinical condition characterized by cardiovascular and neurological changes subsequent to acute changes in intravascular volume and plasma solute concentrations consequent to excess absorption of irrigating fluid [1]. Distilled water was used as an irrigating fluid during early periods of endourological procedures. However due to adverse effects with distilled water causes severe morbidity like hemolysis and alarming mortality [2]. Glycine is a non-essential amino acid is metabolized in the liver into ammonia. It is iso-osmotic (2.2%) solution, easily available in the market, reasonably cheap causes less adverse effect compare to distilled water. In 1948, Nesbit used 1.1% glycine in 213 cases, has no hemolysis but more cardiovascular and neurological complications. During his earlier period, he has more hemolysis with distilled water as an irrigating fluid [2]. Few years later, the modern non-electrolyte solutions containing glycine, mannitol or sorbitol were introduced to prevent haemolysis, without dispersing the electric current used for cutting with the resectoscope. Minimal amount of irrigating fluid (1-2 liters) gets absorbed in 7-11% of patients undergoing transurethral resection of Prostate (TURP) and engender in transurethral resection (TUR) syndrome [2].

During prostate resection, exposure of the venous sinuses and damage to the prostatic capsule leads to systemic absorption of large volumes of irrigation fluids. Absorption of these hyposomolar irrigation fluids can result in pulmonary edema, congestive heart failure, and dilutional hyponatremia, which can manifest as neurologic symptoms such as severe headache, seizures and coma [3, 4]. The degree of absorption depends on the duration of the procedure (lasting more than 60 minutes) and the hydrostatic pressure of the irrigation fluid (the height of the irrigating fluid above the patient). On

average, 10-30 ml of irrigating fluid is absorbed per minute, which may increase to 200ml /min [5].

TURP Syndrome is combination of electrolyte disturbances occur due to absorption of the irrigation fluid used during TUR procedure. To prevent this, ideal irrigating fluids and newer Endo urological techniques are important. TUR syndrome is also seen in other endoscopic procedures like Ureterorenoscopy, Percutaneous nephrolithotomy, and Transcervical resection of endometrium. Hence usage of bipolar TURP with normal saline has the same efficacy of monopolar TURP with any other fluid [1, 6].

2. Methodology

2.1. Study Design

A detailed review of medical literature was performed to identify the articles relevant to irrigation fluids and TUR syndrome in Endourology. Preferred Reporting Items for Systematic reviews and Meta-Analysis guidelines were followed while conducting this study.

2.2. Selection Criteria

The inclusion criteria was randomized controlled trials, Systematic reviews and Meta-Analysis, ongoing trials, retrospective and prospective cohort studies, and single arm studies related to the above terms. A full text review of all the selected articles was performed. Two authors reviewed all the articles confirming to search criteria. All non-English, conference poster presentations, letters to editor, and case reports were excluded. Articles remaining after exclusion were analyzed under one of these heads: Properties of irrigation fluids, Patho –physiology of TUR syndrome, management of TUR syndrome.

3. Results and Discussion

3.1. Properties of an Ideal Irrigation Fluid Are [Table 2]

1) Electrically non- conductive (to allow diathermy to work);
2) Transparent (allows visualization);
3) Isotonic;
4) Non-hemolytic;
5) Not metabolized;
6) Non- toxic;
7) Inexpensive;
8) Sterile.

No such irrigation fluid currently exists.

3.2. Uses of Irrigation Fluids

1. Distend the bladder and prostatic urethra;
2. Flush out the blood and tissue fragments;
3. Improves visibility.

3.3. Irrigation Fluids in Endo Urology

1.5% glycine, sterile water, Normal saline and glucose water are the most widely used irrigating fluids in urological endoscopic procedures in India.

3.3.1. Sterile Water

Though sterile water has many qualities of an ideal irrigating fluid, it has several disadvantages too.

Disadvantages:

1. Hypotonicity, causing hemolysis,
2. Dilutional hyponatremia,
3. Shock,
4. Acute renal failure.

The availability of newer cheaper alternatives has put it out of use now.

3.3.2. Normal Saline

Normal saline cannot be used as an irrigating fluid during standard prostatic resection, because its ionic content dissipates the current preventing both cutting and coagulation. Normal saline is used for irrigation with bipolar resection because it is the nearly iso-osmolar irrigate used and it eliminates the possibility of TUR syndrome [2, 7]. Saline conducts electric current, so it is used for bipolar TURP and the current passes through the saline medium between the lobes before returning to the generator. Results demonstrate bipolar TUR in saline caused less drop in hemoglobin and sodium levels and less fluid overload than the conventional monopolar TURP, but it can cause hyperchloremic acidosis because of excess chloride content [2, 6].

3.3.3. Bipolar Saline TURP

Bipolar saline TURP is safe and eliminates the risk of TURP syndrome in high-risk patients with large prostates that require lengthy resection. Issa et al. in a case study concluded that bipolar saline is a safe and eliminates the risk of TUR syndrome in high-risk patients with large prostates [8]. Michielsen et al concluded in his study that a bipolar transurethral resection in saline system is as efficacious as monopolar transurethral prostate resection but it is safer than the latter because of the lesser changes in post-operative sodium, and the smaller risk of transurethral resection syndrome [7].

Bipolar diathermy is precise and safe as the path of current flows only through the volume of tissue between the poles of each electrode [7]. The risk of electrode burns, alternative current pathway burns and interference with pace makers or other electrical implants is therefore eliminated. It also reduces the risk of obturator nerve excitation and “Obturator Kick” [7, 8] [Table 1].

3.3.4. 5% Glucose in Sterile Water

Glucose in sterile water was used till mid 80’s due do easy availability and easy sterilization [9]. This is not a widely used irrigating fluid since glucose produces tissue charring at the site of resection and associated hyperglycemia produced when glucose is absorbed into the circulation. 5% glucose solution is physiologically safer than glycine because it is readily metabolized throughout the body when absorbed

intravenously; thus, the incidence of complications is lower [3]. Hyperglycemia is a potential problem and appears to be proportional to the duration of surgery Hence in diabetes patient serum blood sugar monitoring is not accurate. It also causes stickiness of surgeons' gloves and instruments. 5% glucose during TURP produced immediate postoperative hyperglycemia; and it was not associated with ECG changes in a study performed by Collins et al [3, 5].

3.3.5. Glycine

Glycine, an endogenous amino acid can be suitable for irrigating fluid. Glycine is isotonic with plasma only at a concentration of 2.2%, but the side effects of glycine at this concentration are more. The osmolality of 1.5% glycine is 230 mosm/l compared to serum osmolality of 290 mosm/l and hence cardiovascular and renal toxicities can occur at this concentration. Further lowering of the concentration of glycine can lead to more complications due to hypo tonicity and hence less glycine concentration cannot be used for irrigation purposes during resection [10].

Glycine is an inhibitory neurotransmitter in the spinal cord, brain stem and retina. Using 1.5% glycine as irrigation causes less features of TURP syndrome like restlessness, headache, and tachypnoea, a burning sensation in the face or limbs and visual impairment. Glycine is metabolized by oxidative deamination, by the liver and kidneys, to glyoxylic acid and NH_3. NH_3 has a cerebral depressant effect which manifests like *headache, restlessness, confusion, seizures, and encephalopathy.* When absorbed in large amounts has a direct effect in heart and retina [1, 2, 9].

Advantage of 1.5% Glycine:

1. Low cost, cheap as sterile water;
2. Less hemolysis;
3. Less incidence of renal failure.

3.3.6. Mannitol

Mannitol, though does not have the toxicities of glycine, it drives water out of cells and may enhance circulatory overloading. The cost of mannitol is also higher compared to glycine. The elimination of mannitol through kidney will be decreased in patients with impaired renal function. Absorption of mannitol solution causes intravascular volume expansion more than 1.5% glycine, while sorbitol–mannitol takes an intermediate position [9].

3.3.7. Cytal

Cytal, a mixture of sorbitol 2.7% and mannitol 0.54% widely used in USA as an irrigating fluid, has not gained popularity in India due to its high cost and non availability. It is non electrolytic, hypo-osmolar with an osmolarity of 178 and is rapidly cleared from the plasma. 2.7% sorbitol-0.54% mannitol solution is as equally hypotonic as 1.5% glycine; the osmotic diuretic property of mannitol may maintain the effective osmolality of plasma, which protects against cerebral edema from excess free water. In the body, sorbitol is metabolized to fructose, which may cause reaction in patient with hypersensitivity to fructose [9].

3.3.8. Urea 1%

Urea produces crystallization on the instruments during resection and hence not preferred. It is not used in borderline renal failure, diabetic patients as it cause acute on chronic renal failure [9].

4. Pathophysiology of TUR Syndrome

4.1. Hyponatraemia

The excessive absorption of irrigating fluid will rapidly dilute the serum sodium concentration results in fall in sodium concentration that will create an osmotic gradient between intracellular fluid and extracellular fluid, leading to net fluid shift away from intra-vascular compartment resulting in cerebral edema and raised intra-cranial pressure. Sodium concentration below 120mMol/L defines severe TURP syndrome [11] [Table 3].

Formulas are useful in determining the rate of correction, the first for estimating total body water and the second for estimating the amount of sodium needed to normalize the low serum sodium levels.

1) Total body water = weight in kg x 0.6.
2) Sodium deficit = (140 – observed plasma Na) x total body water.

Furosemide and bumetanide act within minutes on the ascending loop of Henle where they inhibit chloride uptake, which causes urinary sodium loss and promote salt-wasting after TURP [11]. Mannitol also causes sodium loss during the first 12 hours after TURP but does not lower serum level during the first three to five postoperative hours [12].

4.2. Fluid Overload

Absorption of irrigating fluid via the prostatic venous plexus will occur in most TURP procedure. The average rate of absorption is 10- 20 ml/min, and therefore length of procedure may have an effect on the total volume absorbed. Fluid absorption leads to rapid volume expansion, which cause hypotension and reflux bradycardia. Patients with left ventricular dysfunction may furthermore develop pulmonary edema as a result of the acute circulatory overload [13].

Factors affecting intravascular absorption:

i. Number and size of the venous sinuous opened.
ii. Size of the gland: more than 50 cc.
iii. Duration of exposure: Less chance of TUR syndrome if the operative procedure is less than an hour.
iv. Hydrostatic pressure of the irrigation fluids.
v. Increase venous pressure: Irrigation fluid bottles should be at the height of 60 cm from the pubic symphysis.
vi. Integrity of the prostatic capsule.
vii. Vascularity of the diseased gland.

4.3. Hyperammonemia

The primary pathway used by the liver and kidneys is oxidative deamination which leads to the formation of two potentially toxic metabolites: glyoxylic acid and ammonia. The brain also contains a glycine cleavage enzyme system that

splits glycine into carbon dioxide, a one-carbon fragment, and ammonia. An increase of serum ammonia during TURP is the result of glycine absorption because patients undergoing retro pubic resections without glycine do not develop hyperammonemia [1, 2, 13].

4.4. Hyperglycemia

Signs of glycine toxicity include nausea, vomiting, headache, malaise, and weakness. Glycine may also exert toxic effects on the kidney. Hyperoxaluria from metabolism into oxalate and glycolate has also been proposed as a route where by glycine could cause renal failure. Cerebral edema results from a decrease in serum sodium concentration caused by dilution and by urinary loss of sodium ions associated with osmotic diuresis. Visual disturbances in TURP syndrome vary in severity from blurred vision to complete blindness [2, 13]. Patients with cortical blindness lose all visual sensation (light perception and the blink reflex) but retain the pupillary responses to light and accommodation. Glycine is now gaining acceptance as the most likely cause of visual aberrations during the TURP syndrome. Vision returns to normal within 24 hours as glycine approaches normal [8, 2, 1].

4.5. Septicemia

One third of the patients have infected urinary system, during resection of prostatic tissues prostatic venous sinuses are opened, irrigation under high pressure with infected urine enters blood stream results in septicemia. Patient presented with fever, chills and rigor, bradycardia, hypotension and acute kidney injury [2, 14].

4.6. Disseminated Intravascular Coagulation (DIC)

The release of Endotoxins in Gram negative organism is the mechanism which provokes DIC. Process of coagulation and fibrinolysis are dysregulated, resultant in bleeding. Calcium is an important coagulation cofactor involved in the intrinsic and extrinsic pathways, as well as the conversion of fibrinogen to fibrin in the coagulation cascade. Serum ionized calcium decreased significantly after TURP in DIC patients, which could result from the dilution caused by irrigating fluid absorption. Tissue factor, a transmembrane glycoprotein present in the surface of endothelial cells is released in response to exposure to cytokines and Endotoxins plays a major role in the development of DIC [14, 15].

Table 1. *Advantages of Bi-polar TURP using Normal saline.*

1.	Less TURP syndrome
2.	Resection time need not be limited to one hour
3.	Improved training opportunity
4.	No Diathermy pad required
5.	No Obturator jerk
6.	Decreased bleeding and clot retention
7.	Decreased chance of blood transfusion
8.	Improved visibility
9.	Very large prostates (> than 100 gm) can be resected quite safely
10.	No Cardiac device stimulation
11.	Less hospitalization
12.	Less catheterization time

*TURP- Transurethral resection of prostate.

Table 2. *Properties of various irrigation fluids in TURP.*

SOLUTION	OSMOLALITY (mOsm/kg)	ADVANTAGES	DISADVANTAGES
DISTILLED WATER	0 (hypo)	Electrically inert Improved visibility Inexpensive	Hemolysis Hemoglobinuria Hemoglobinemia Hyponatremia
GLYCINE (1.5%) GLYCINE (1.2%)	220 (iso) 175 (hypo)	Less likelihood of TURP syndrome	Dilutional hyponatremia, visual impairments, Hyperammonemia, Hyperoxaluria
NORMAL SALINE (0.9%)	308 (iso)	Less incidence of TURP syndrome	Ionized, cannot be used with unipolar-diathermy.
RINGER LACTATE	273 (iso)	Less incidence of TURP syndrome	Ionized, cannot be used with unipolar-diathermy
MANNITOL	275 (iso)	Isomolar solution Not metabolized	Osmotic diuresis, Acute intravascular expansion
SORBITOL (3.5%)	165 (hypo)	Same as glycine	Hyperglycemia, Lactic acidosis Osmotic diuresis
CYTAL (Sorbitol 2.7% + mannitol 0.54%)	178 (iso)		Expensive, non availability

Table 3. *Manifestation of Hyponatremia.*

Serum Sodium (mEq/ l)	CNS* changes	CVS* changes	ECG* changes
115- 120	Confusion Restlessness	Hypotension Bradycardia	Wide QRS Complex
111-114	Somnolence Nausea	Cardiac depression	Bradycardia Wide QRS complex
< 110	Seizures coma	CHF	Ventricular tachycardia or fibrillation

*CNS- Central Nervous System, CVS- Cardio Vascular System, ECG- Electrocardiogram.

5. Irrigation Fluids on Urothelium Bacterial Adherence

The irrigation solutions like glycine 1.5%, glycerol 3%, mannose 6%, sorbitol 2.7% and mannitol 0.54% all inhibited bacterial growth compared with normal saline. In guinea pigs, the influence on bacterial adherence of irrigation solutions (glycine 1.5%, mannose 6%, and povidone-iodine) was investigated using two different strains of E. coli [1, 2]. After cauterizing one side of the bladder and inoculation with 2.7 x 10 (8) colony forming units under high or low pressure, the bladder were irrigated with the irrigation solutions [12, 16]. There was a stronger adherence of *E. coli* O6 (with type I pili) than of E. coli ATCC 25922 (without type I pili) to bladder urothelium, particularly to the injured side. There was no significant difference between the high- and low-pressure groups. The irrigation solution has some antibacterial activity; it may reduce urinary tract infection [16].

6. Irrigation Fluid in Cardiac Patient

Transurethral prostate resection has an effect on the myocardium perioperatively. Glycine absorption causes echocardiogram changes and it is associated with increased troponin I [13]. Increasing patient age and blood loss is associated with myocardial insult. The risk of increased blood loss was accumulative with each unit lost. Glycine absorption may explain the increase in morbidity and mortality [4]. Laser TURP and saline Bipolar TURP can help to minimize fluid absorption and its complications especially in cardiac and critically ill patients [14].

7. Irrigation Fluid Absorption During Transurethral Resection of the Prostate

The absorption of irrigation fluid during TURP is determined primarily by hydrostatic pressure in the bladder and prostatic venous pressure. In comparison to spontaneously breathing patients, patients undergoing mechanical ventilation with positive pressure have a raised central venous pressure and a reduced venous return, both of which can influence intravascular absorption [5]. The absorption of irrigation fluid during the TURP is significantly more marked amongst spontaneously breathing patients with regional anesthesia in comparison to patients undergoing general anesthesia with positive pressure ventilation [12]. Lower central venous pressure before the start of irrigation should be considered as a possible cause of this effect. Newer techniques, such as bipolar resectoscopes and vaporizing the tissue instead of resecting tissue, would reduce the fluid absorption and its consequences [18]. Reuter et al. demonstrated in 1978 that low pressure irrigation during TURP would limit the risk of intravascular absorption [5].

8. Electrolyte Changes During TURP

Dilutional hyponatremia is the primary cause of TURP syndrome. Irrigating fluid is directly absorbed into the vascular system when prostatic tissue has been cut along with vein by electrocautery [9]. The amount of fluid absorbed via the prostatic veins is 20 mL/min, and can reach up to several liters. Symptoms of hyponatremia usually do not develop until the serum sodium concentration decreases below 120 mEq/L [15]. The osmolality of 1.5% glycine is 230 mOsm/L (hypotonic) as compared to serum osmolality of 290 mOsm/L. Clinical manifestations and ECG changes (peaked T waves, prolongation of QRS complex and PR interval and ventricular fibrillation) of hyperkalemia occur when the plasma level of potassium rise above 6 mEq/L. Hyperkalemia is cardiac toxicity increased in hyponatremia and metabolic acidosis [9]. Less commonly used solutions include sorbitol 3.3%, mannitol 3%, dextrose 2.5-4%, and urea 1%. All these fluids are hypotonic so significant water absorption can occur. TURP lasting for more than 60 min and volume of prostate gland more than 80 mL could be associated with Dilutional hyponateremia. Glycine 1.5%, although slightly hypotonic, is widely used for irrigation as it has good optical properties, is non electrolytic and prevents dissipation of diathermy current during resection. Hypertensive patients were found to be at higher risk of developing postoperative electrolyte derangement. Some antihypertensive, for example, angiotensin converting enzyme inhibitors, are known to inhibit normal regulation of fluid balance and may even cause hyponatremia [11, 15].

9. Newer Technology of Prostatic Resection

There are newer techniques of prostatic resection like heat therapy, laser prostatectomy, and ultrasound or microwave therapy to vaporize prostatic tissue and coagulate surrounding blood vessels. These techniques are reported to cause less hemorrhage and TURP syndrome than conventional TURP, but specimens for histology cannot be obtained. Since diathermy is not used, normal saline may be used as the

irrigating solution, minimizing the risk of the TURP syndrome [17]. Both Holmium and Thulium fiber laser are compatible with saline and 1.5% Glycine irrigation as irrigation fluids. In laser resection of prostate 1.5% Glycine is preferred as it increases the transparency compared to sterile water or saline owing to the clumping of RBCs and increases vision during resection of prostate [17].

10. Management of TUR Syndrome

Mild adverse effect of irrigation solution needs supportive care only.

A. Adequate Nasal oxygen, B. Intravenous antibiotics (3rd generation Cephalosporin), C. Antiemetic if nausea or vomiting persists. Minimize the fluid absorption by adjusting reservoir height or deploying a suprapubic catheter to reduce the Vesical pressure. Terminate the procedure as soon as possible after adequate hemostasis. Visual impairment should be observed, it will resolve spontaneously within 48 -72 Hrs. Mannitol is useful in promoting diuretic effects and eliminating intravascular volume overload. Absorption of the Irrigation fluids > 2.5 L should be treated in ICU care. Positive pressure ventilation may be necessary where pulmonary edema has developed. Inotropes may be given to support blood pressure. Plasma expansion may be necessary if hypotension and low cardiac output develop. 3% hypertonic saline may be given intravenously for correction of dilutionalhyponateremia, however this must be done carefully as a rapid increase in serum sodium concentration may lead to *Central pontine myelinosis*. Raising the sodium at a rate of 1 mmol/L/hour is considered safe. Desmopressin binds to V2 receptors of the renal collecting duct, which translocates aquaporin channels to the apical lumen of the collecting duct and increases water reabsorption. It can be given at a dose of 2 to 4 mcg intravenously or subcutaneously [11]. Seizures and convulsions may be managed with benzodiazepines. DIC must be managed by transfusion of packed red cells, fresh frozen plasma, fibrinogen and platelet in intensive care unit [15]. Fibrinogen 3-4 gms should be given parentally followed by heparin infusion 2000 units bolus followed by 500 units per hour [18, 19]. In case of retroperitoneal /perivesical fluid collection following TUR procedure needs urgent percutaneous drainage under USG guidance /open drainage to reduce morbidity and mortality [13]. Such drainage procedures will eliminate extra cellular electrolytes that have moved into the fluid pool [19]. Metabolic acidosis should be compensated by parental infusion of buffers. Clouding of consciousness is managed with maintence of free airway and positive pressure ventilation. Parental infusion of calcium may be used to treat acute cardiac disturbance during TUR procedure [20, 21].

11. Conclusion

The introduction of newer medication and surgical techniques for benign prostate hypertrophy has minimized the risk of TURP syndrome. Understanding of the pathophysiology of TURP syndrome has dramatically improved in last two decades. Bipolar Trans urethral resection of prostate, Vaporization and enucleation of prostate in normal saline are as efficacious as monopolar Trans urethral resection but it is safer than latter because of lower incidence of hyponateremia and TURP syndrome. Early detection and appropriate treatment of the TUR syndrome are required for successful outcome. Hence the knowledge of both fluids management and the usage of instrument are very important in a successful Endo urological practice.

Abbreviation

TURP - Transurethral Resection of Prostate.

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