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Original article

Irrigation with water during transurethral resection of the prostate (TURP) induces intravascular hemolysis

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Background: The transurethral resection syndrome TUR syndrome is the most serious complication following transurethral resection of prostate (TURP).

Objective: We compared 5% dextrose in water with sterile water as an irrigating solution and evaluated postoperative intravascular hemolysis.

Methods: A prospective, randomized, controlled trial of 41 benign prostatic hypertrophy (BPH) patients who underwent TURP. The differences between preoperative and postoperative free plasma hemoglobin were measured by using a spectrophotometric method to determine the degree of intravascular hemolysis. Serum glucose and electrolytes were measured preoperatively and postoperatively. Signs and symptoms of TUR syndrome were recorded. Prostatic tissues were weighed. Volumes of irrigating fluid were recorded.

Results: Free plasma hemoglobin was significantly increased in the sterile water group (n = 21) and higher than in the 5% dextrose in water group (n = 20) ($p < 0.001$). The postoperative plasma glucose was higher in the 5% dextrose in water group ($p = 0.007$). None of patients developed a TUR syndrome. There was no difference in other serum electrolytes between both groups.

Conclusion: Intravascular hemolysis can be prevented by using 5% dextrose in water instead of sterile water. No correlation between hemolysis and TUR syndrome was found in TURP patients with postoperative stable serum sodium.

Keywords: Benign prostatic hypertrophy, intravascular hemolysis, transurethral resection of prostate, transurethral resection syndrome

Benign prostatic hypertrophy (BPH) is the most common benign tumor of ageing men. It is caused by proliferation of epithelial and smooth muscle cells of the prostate. Symptoms of BPH include urinary discomfort, hematuria, bladder stones, recurrent urinary tract infection, bladder outlet obstruction, and sexual dysfunction [1-3], but up to 19% patients are asymptomatic [4]. The incidence of acute urinary retention in BPH patients is about 2% [5]. Several medical treatments and surgical procedures are approved to relieve the BPH symptoms, such as α-adrenoreceptor antagonists, 5α-reductase inhibitors, or combined medications [6-8]. Novel and less invasive surgical techniques, including laser enucleation, transurethral microwave thermotherapy, and transurethral needle ablation are emerging [9-12]. However, 2003 AUA guidelines recommend that transurethral resection of the prostate (TURP) remains the criterion standard surgical intervention. This is especially true for patients who have moderate to severe lower urinary tract symptoms, experience acute urinary retention, or other BPH-related complications and medical treatment failure. [4, 9, 11]. The TURP operation is safe, requires short-stay hospitalization and a short period of catheterization to eradicate urinary symptoms and BPH complications. The recurrence rate of BPH that needs additional operations is as low as 5% over 5 years [13].

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Postoperative complications include severe perioperative bleeding, which requires blood transfusion, intraoperative infection, urinary incontinence, retrograde ejaculation, sexual dysfunction, and fluid overload. These complications can be expected in less than 20% of cases [14-16]. Fluid overload is the most common complication and is caused by significant intraoperative fluid being absorbed into the systemic circulation. In an uncomplicated procedure, approximately 5%–10% of the fluid used for irrigation during the operation (approximately 1–2 liters) would be absorbed into the circulation. However, in rare circumstances, the amount of absorbed fluid is much greater. Sudden fluid overload can cause postoperative renal damage, brain edema, and hyponatremia [15]. Other risk factors for TUR syndrome include prolonged operating time and surgical complications. Other adverse consequences, such as bleeding, infection, stricture, sexual dysfunction, urinary incontinence, and urinary retention are infrequent [16, 17].

The risk of excessive fluid absorption during TURP depends on skill of the urologists, the operating time, and type of fluid used for irrigation. Sterile water, glycine solution, normal saline, and 5% dextrose in water are common irrigating solutions used. Sterile water was observed to be associated with higher chances of intravascular hemolysis and acute renal failure compared with other irrigating fluids [18]. Nesbitt and Glickman reported that 1.1% and 2.1% glycine induced a significantly lowered the degree of hemolysis compared with sterile water, and lowered the incidence of the TUR syndrome [19]. TUR syndrome is uncommon, but it can cause serious surgical complications caused by severe hyponatremia because of massive absorption of low sodium irrigating fluid. However, recent studies reported that glycine irrigation is associated with a higher prevalence of the TUR syndrome than normal saline, 5% dextrose in water or sterile water. Collins reported that no patient developed TUR syndrome post-TURP when using 5% dextrose in water, but it occurred in the 1.5% glycine group. This finding is supported by findings from numerous investigators including those from a previous study [20]. Collins also revealed that TUR syndrome-free patients seemed to have insignificant changes in pre- and postoperative levels of sodium, potassium, urea, creatinine, osmolarity, calcium, hematocrit, and albumin serum level (defined as a change from before to after TURP in hemoglobin level, accounting for transfusion) [21], while many evidences indicated that hyponatremia and hyperkalemia are common in postoperative TURP patients using 1.5% glycine irrigation [22].

It is unfortunate that urologists in most of the hospitals in Thailand and some other countries use sterile water as an irrigating fluid during TURP. This inevitably increases the risk of fluid absorption, intravascular hemolysis, and TUR syndrome. Intravascular hemolysis is a result of abruptly decreased plasma osmolarity, and can be found in massive hypo-osmolar fluid-absorbing patients. It was believed that 1 liter of sterile water, absorbed within an hour, can reduce plasma sodium level by 8 mEq/L, and abruptly decreased serum osmolarity and could aggravate intravascular hemolysis and TUR syndrome-like symptoms. Some urologists prefer to use 5% dextrose in water or normal saline, which are isotonic, as an irrigating fluid to prevent massive hemolysis postoperatively. This study aimed to investigate the association between intravascular hemolysis and the type of irrigating fluid used intraoperatively, and the risk for TUR syndrome development postoperatively.

Patients and methods

Subject and specimen collection

Forty-one patients who underwent TURP at King Chulalongkorn Memorial Hospital were enrolled in this prospective, randomized, controlled trial and randomly allocated to either irrigation during TURP with sterile water or 5% dextrose in water. The sample size of this study was calculated by using a pilot study of differences between free plasma hemoglobin pre- and post-TURP in both sterile water and 5% dextrose in water groups. The mean and standard variation of free plasma hemoglobin in the sterile water group were 59.01 and 42.84 mg/dL, and in the 5% dextrose in water group were 12.95 and 34.02 mg/dL, respectively. Patients who had diabetes mellitus, chronic hemolysis, rhabdomyolysis, or had received blood transfusions within 3 months before or during TURP were excluded. Informed consent was given in writing by all participants. The research protocol was approved by the Ethics Committee, Faculty of Medicine, Chulalongkorn University.

Preoperative blood samples were collected individually in the morning before TURP. Complete blood count, fasting plasma glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, and free plasma hemoglobin were measured.

Immediately after TURP, a second blood sample was collected. Prostatic tissues were weighted. Volumes of input and output irrigating fluids were recorded.

A third blood sample was taken in the late postoperative TURP period, which is about 24 hours after TURP was performed.

Symptoms and signs of TUR syndrome were observed. Postoperative hyponatremia is defined by a sodium level after TURP of <125 mEq/L. Fully developed TUR syndrome included hyponatremia with two or more symptoms or signs of the TUR syndrome such as nausea, vomiting, bradycardia, hypotension, hypertension, chest pain, mental confusion, anxiety, paresthesia, or visual disturbances.

Free plasma hemoglobin measurement

Free plasma hemoglobin was calculated by spectrophotometry. Blood samples were collected in an EDTA container and sent to the laboratory within 1 hour for immediate centrifugation and plasma separation. Plasma was treated with $Na_2(CO_3)$ and measurement of absorbance (OD) at the wavelength of 415, 450, and 700 nm calculated by the equation:

Free plasma Hb (mg/dL) = $154.7\ A_{415} - 130.7\ A_{450} - 123.9\ A_{700}$ (Carl A.B., Tiezt Textbook of Clinical Chemistry 2nd edition (1994), WB Saunders Company).

Statistical analysis

SPSS for Windows, version 13 was used to test for differences between the plasma variables in both participating groups. ANCOVA was used to assess the change of free plasma hemoglobin preoperatively and postoperatively. An unpaired *t* test was used to assess other blood values and variables. To verify the correlation between free plasma hemoglobin and serum sodium Pearson's correlation coefficient was examined. Statistical significance was defined as $p < 0.05$.

Results

Of 41 patients, 21 were enrolled into the sterile water and 20 into the 5% dextrose in water group. Average age of all participants was 69.4 ± 9.3 years old (range 49 to 88 years old). There was no significant difference in age, operative time, irrigating fluid volume used during the operation or the weight of prostate tissue resection (**Table 1**). Amongst these patients, 76% underwent TURP (81% in sterile water and 76% in 5% dextrose in water groups), while the rest have simultaneously additional operations. Prostatic cancer was diagnosed in 4 patients (10% in sterile water and 10% in 5% dextrose in water).

Table 1. Baseline characteristics of participants in sterile water and 5% dextrose in water groups

	Sterile water	5%DW
Number	21	20
Age (year)	67.43±9.90	71.45±8.33
Operation time (minute)	57.14±26.81	51.75±22.32
Volume of irrigating fluid (liter)	15.66±8.72	13.86±7.77
Weight of prostatic tissue (gram)	24.71±16.64	16.30±11.60
Type of operation (person)		
- TURP	17	14
- TURP with cystolitholapaxy	1	2
- TURP with cystolitholapaxy and herniorrhaphy	0	1
- TURP with TRUS-biopsy	1	1
- TURP with transperineal prostatic biopsy	1	0
- TUR with TUI-BN	1	0
- TUR with TUI-BN with visual urethrotomy	0	1
- TURP with bilateral orchidectomy	0	1
Pathological report		
- Benign prostatic hypertrophy	19 (91%)	18 (90%)
- Prostatic cancer	2 (10%)	2 (10%)

5%DW = 5% dextrose in water, TURP = transurethral resection of prostate, TRUS = transrectal ultrasound, TUI-BN = transurethral incision of bladder neck

Preoperative, immediate postoperative and late postoperative total hemoglobin, BUN, creatinine and electrolyte were not significantly changed (**Table 2**), although hyperglycemia was observed in immediate postoperative patients who underwent TURP with 5% dextrose in water irrigating fluid. Immediate postoperative plasma glucose level was 105.1 ± 32.3 and 169.2 ± 91.3 mg/dL in the water and 5% dextrose in water groups, respectively, $p = 0.007$.

Regarding intravascular hemolysis and TUR syndrome, we found a markedly increased free plasma hemoglobin level in the sterile water group (280% of baseline level) as shown in **Table 3** and **Figure 1**. Conversely, plasma free hemoglobin concentration in the 5% dextrose in water group was slightly decreased (–20.7% of baseline level). Changes in free hemoglobin level between both groups were significant ($p < 0.001$) whereas none of participants in either group developed any symptoms or signs of TUR syndrome. This finding suggested that, although sterile water irrigation potentially aggravates intravascular hemolysis in postoperative TURP patients, the subsequent TUR syndrome should be rare, or irrelevant. We also found that the increased level of plasma free hemoglobin in the sterile group was neither associated with the operative time nor irrigating fluid volume (data not shown).

Regarding the hyponatremia, none of these participants had serum sodium lower than 125 mEq/L. However, five patients in the sterile water group and three in the 5% dextrose in water group had mild symptoms of nausea or vomiting, and only a single patient in the sterile water group experienced self-limiting elevated blood pressure within 24 hours after TURP. Because of this, we concluded that none of these subjects had fulfilled the criteria for diagnosis of TUR syndrome. We analyzed the correlation between free plasma hemoglobin and serum sodium measured immediately postoperatively and late postoperatively, but no significant correlation was found (data not shown).

Table 2. Plasma biochemical markers in pre- and post-TURP operation periods, divided by sterile water and 5% dextrose in water groups. Plasma glucose was increased significantly in the 5% dextrose in water group in immediate postoperative period compared with the sterile water group ($p = 0.007$).

	Sterile water			5%DW		
	pre-operative	immediate post-operative	late-operative	pre-operative	immediate post-operative	late-operative
Total hemoglobin (g/dL)	14.8±6.8	13.1±1.7	12.3±1.5	13.5±1.8	12.7±1.6	12.0±1.7
Plasma glucose (mg/dL)	94.3±9.2	105.1±32.3	–	95.7±9.3	169.2±91.3*	–
Blood urea nitrogen (mg/dL)	15.0±5.9	14.5±4.4	13.9±4.5	14.0±6.6	13.2±6.1	11.8±5.2
Serum creatinine (mg/dL)	1.1±0.3	1.0±0.2	1.0±0.2	1.1±0.4	0.9±0.2	1.0±0.2
Serum electrolyte						
- Sodium (mEq/dL)	140.5±5.2	138.8±4.5	139.1±5.0	138.9±3.3	136.5±5.6	137.2±5.2
- Potassium (mEq/dL)	4.1±0.5	3.9±0.5	3.9±0.5	4.3±0.5	3.7±0.4	3.9±0.4
- Chloride (mEq/dL)	102.1±3.6	102.9±4.4	103.4±4.5	101.0±3.2	101.9±4.7	102.9±4.1
- Bicarbonate (mEq/dL)	26.7±3.2	24.9±2.8	24.6±3.1	26.2±3.4	2.5±2.1	24.9±2.6

Table 3. Comparison of free plasma hemoglobin and its change between pre- and post-TURP in sterile water and 5% dextrose in water group (*$p < 0.001$)

Intravascular hemolysis and TUR syndrome	Sterile water	5%DW
Free plasma hemoglobin (mg/dL)		
- Before TURP	25.02±32.79	31.07±30.81
- After TURP	95.12±84.05	24.65±33.61
- Change	71.53±73.82 (+280%)	–6.42±33-79* (–20.7%)
TUR syndrome	0	0

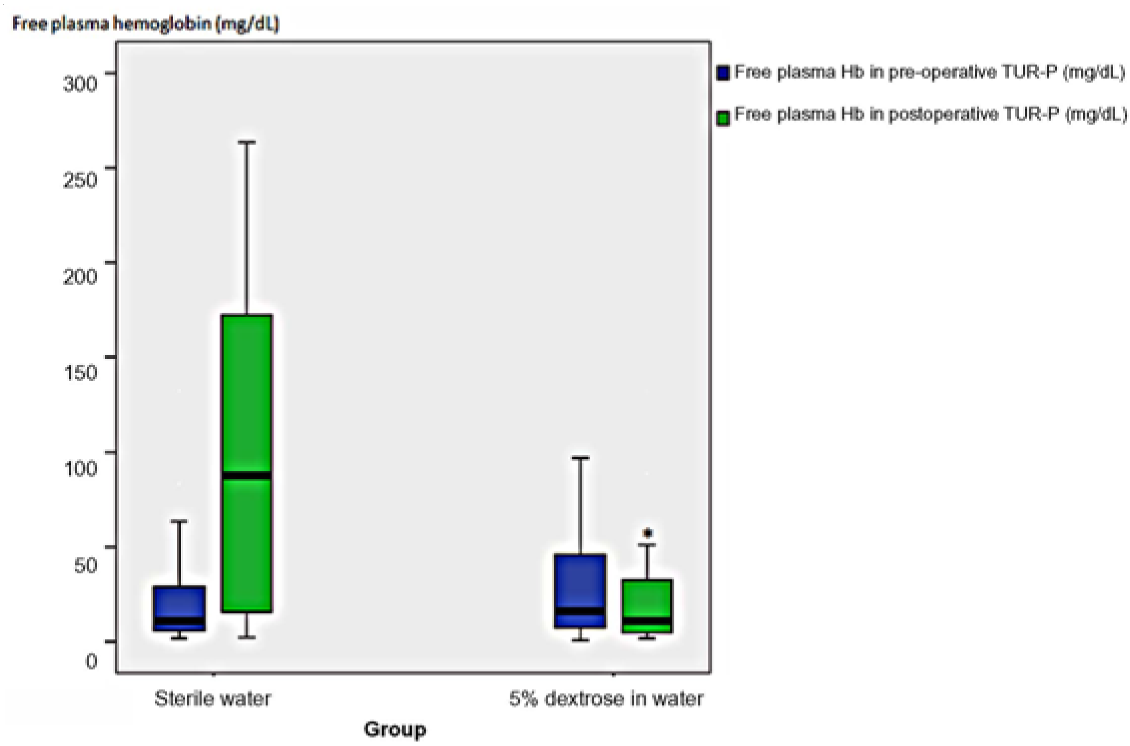

Figure 1. Comparison of free plasma hemoglobin preoperatively and immediately postoperative TURP using sterile water and 5% dextrose in water. Immediate postoperative free hemoglobin level is higher in sterile water group than in 5% dextrose in water group. *$p < 0.001$ compared with sterile water

Discussion

Fluid irrigation is a necessary procedure in any endoscopic surgery of the genitourinary tract. This may result in undesirable, but unavoidable, fluid absorption [23]. It is very difficult to estimate the absorbed fluid volume, even though many techniques for volume evaluation have been introduced, such as the use of serum acid phosphatase level testing [24], load cell transducer [25], the absorption of ethanol [26, 27], the dilution of plasma fluorescein [28], or even plasma electrolyte and glucose changes [22, 29]. All these techniques have limited accuracy in predicting the degree of intravascular hemolysis, subsequent hyponatremia or TUR syndrome.

Intraoperative fluid is absorbed intravenously when venous sinuses are torn; meaning that most of the fluid is in the periprostatic space. Surgeons are concerned of the dangers of irrigant absorption, and attempt to limit the duration of TURP, although the TUR syndrome still occurs. To minimize the risk, several types of irrigating solutions are recommended: including sorbitol-mannitol and glycine. The former is preferred in Europe, but glycine is most commonly used in the UK and North America. There is now increasing evidence highlighting the toxicity of both sorbitol-mannitol and glycine solutions when absorbed during TURP [15, 30, 31].

In Thailand, sterile water is used because it is widely accessible and of low viscosity. The magnitude risk of TUR syndrome with sterile water is controversial, while many are convinced that TUR syndrome occurs only in patients who receive sterile water as an irrigant more frequently than other solutions [18, 20, 27, 32]. Moharari reported that using sterile water was not associated with significant changes in sodium, creatinine and hematocrit, supporting the safety of sterile water [33].

The mechanism of TUR syndrome is massive absorption of hypo-osmolar irrigating fluid into the circulation, causing plasma osmolarity to decrease and fluid leakage from the brain cells, leading to brain edema [34]. Intravascular hemolysis is another complication observed with abrupt change in serum osmolarity. Our objectives in this study were to measure the risk of intravascular hemolysis in TURP patients using sterile water and compare it with 5% dextrose in water, and to determine if the degree of intravascular hemolysis corresponds with TUR syndrome. We hypothesized that the absorption of hypo-osmolar sterile water irrigant could induce intravascular hemolysis compared with isotonic 5% dextrose in water. However, in the present study, we could not demonstrate the correlation between degree of intravascular hemolysis and TUR syndrome, because none of our participants was diagnosed to have developed TUR.

Isotonic 5% dextrose in water is a common crystalloid used in TURP because glucose is metabolized throughout the body. It requires approximately 13 liters to be absorbed intravenously to expand the intravascular compartment by 1 litre. Normal serum osmolarity is about 290 mOsm/kg. The osmolarity of 5% dextrose in water is 285 mOsm/kg, compared with 1.5% glycine and sterile water, which have an osmolarity of about 190 mOsm/kg and 0 mOsm/kg, respectively [21]. This isotonic property contributed by 5% dextrose in water may be beneficial in reducing the possible side effects of cerebral edema that can occur after inadvertent absorption of irrigating fluids [21, 34]. In addition, our study shows that 5% dextrose in water is more beneficial than sterile water in the prevention of intravascular hemolysis.

However, 5% dextrose in water as an irrigant can induce transient hyperglycemia, an undesirable intraoperative condition in a diabetic patient. Some urologists claim that using 5% dextrose in water can make the operation more difficult because of its viscosity and turbidity. Recent studies reported the same beneficial results with normal saline, another isotonic solution, which is comparable to 5% dextrose in water except for a slightly increased serum sodium level postoperatively [20, 35, 36]. In our opinion, using any isotonic solution will minimize fluid absorption, and stabilize fluid and electrolyte levels pre-, during, and post-TURP. Isotonic solutions also reduce intravascular hemolysis and the likelihood of the TUR syndrome, especially in high-risk patients (large prostate volume, advance age, cardiovascular or cerebral comorbidity).

The present study demonstrated the higher degree of intravascular hemolysis in TURP patients using sterile water than when using 5% dextrose in water. Although we could not show a direct correlation between the severity of intravascular hemolysis and TUR syndrome because none of our study subjects fulfilled the TUR syndrome criteria, we could not find any correlation with any other risk factor associated with TUR syndrome, such as the serum sodium level. Our prior hypothesis was that the degree of intravascular hemolysis represented the severity of serum osmolarity changes, which mostly is a function of serum sodium fluctuation and a crucial factor for TUR syndrome development. We could not demonstrate a correlation between free plasma hemoglobin and serum sodium in each and the combined group in the immediate postoperative and late postoperative periods. This could be because of intravascular hemolysis is not usually associated with TUR syndrome, or that the free plasma hemoglobin is not a sensitive index. For this hypothesis, we are aware that free plasma hemoglobin may not precisely reflect the degree of fluid absorption, as massive volume absorption can trigger hemolysis (increased free plasma hemoglobin concentration) and hemodilution (decreased free plasma hemoglobin concentration). Hemodilution was demonstrated in the past literature in patients who had lower free plasma hemoglobin postoperatively [37]. In our study, we assumed that the decreased free plasma hemoglobin in the 5% dextrose in water-treated patients could be a result of hemodilution. According to this, free plasma hemoglobin or the degree of intravascular hemolysis, could be an indicator for the rapid change in serum osmolarity, but not for causing the TUR syndrome.

Our data show that serum sodium was not significantly changed in the immediate postoperative period even in moderately hemolytic patients in the sterile water group. We concluded that in TURP patients, using sterile water as an irrigant, lowers the risk for TUR syndrome if one can preserve the stability of serum sodium. A negative aspect of using sterile water is an increase in intravascular hemolysis. The significance of this needs further study.

A limitation of this study is that none of the participants had fulfilled the criteria of TUR syndrome or developed hyponatremia. This leads to inconclusive results regarding whether sterile water irrigant could induce the TUR syndrome. The prevalence of the TUR syndrome is 0.3%–0.5%, in prospective controlled trials. One would thus have to enroll more than a thousand patients into each future study group. The present study, with only 41 patients recruited, was too small to arrive at a definitive conclusion.

Conclusion

Sterile water irrigating fluid induces intravascular hemolysis post-TURP because of the sudden change in plasma osmolarity from hypotonic fluid reabsorption.

Although we did not observe hyponatremia or TUR syndrome in either the sterile water or 5% dextrose in water groups, surgeons who use sterile water as an irrigating fluid should be cautious and minimize the duration of TURP to reduce the risk of TUR syndrome.

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