

Original

TURP Syndrome and Changes in Body Fluid Distribution

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To investigate changes in body fluid distribution during transurethral prostatectomy (TURP) using 3 % sorbitol irrigant and to assess the causal factors of TURP Syndrome. A total of 61 patients were enrolled in the study. Irrigant absorbed (V-abs), blood loss (B-loss) and Δ ICF and Δ ECF (volume increased from initial intra- and extra-cellular fluid) were computed using laboratory data. We classified patients into either a TURP syndrome group (TURS) or an asymptomatic group (ASTM). Although B-loss was larger in TURS (mean 860 ml) than in ASTM (170 ml, $p < 0.01$), there was no significant difference in V-abs (1740 vs. 1680 ml), Δ ECF (760 vs. 1170 ml), and Δ ICF (130 vs. 340 ml). The Δ ECF in TURS was not sufficiently large to compensate for B-loss, whereas the Δ ECF in ASTM was. We conclude that TURP syndrome is likely not caused by dilutional hyponatremia, but rather by bleeding and the resultant hypovolemia without appropriate extracellular fluid replenishment when 3% sorbitol is used as the irrigant.

Keywords: Prostatectomy-adverse-effects, Water-Electrolyte-Imbalance-etiology, Body-Fluid-Compartments-drug-effects, Hyponatremia-etiology, Osmolality

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Introduction

Irrigating fluids used during transurethral prostatectomy (TURP) do not contain electrolytes, and thus do not facilitate dispersion of high-frequency electric currents from the resectoscope. In place of electrolytes, carbohydrates such as glucose, sorbitol, mannitol, or glycine are added to control the osmolality of the fluid. Dilutional hyponatremia occurs when a large volume of the irrigating fluid is absorbed through destructed vessels into the vascular space. Dilutional hyponatremia has been considered to be a major cause of TURP syndrome¹⁾. However, we encountered three patients whose plasma sodium concentrations were below 100 mmol L⁻¹ during TURP, and yet these patients exhibited only mild hypotension and mild CNS disturbance²⁾. None of the patients manifested severe CNS symptoms such as convulsion, blindness, or loss of consciousness, as described in the literature^{1, 3-6)}. We suspected that other pathophysiological factors must be involved in TURP syndrome. Thus, we planned the present study.

Irrigating fluids commonly used in Japan are prepared below normal plasma osmolality to provide a good

view of the operative field through a resectoscope without causing hemolysis due to low osmolality. This fluid reduces plasma osmolality when it is absorbed into vessels, and consequently causes a movement of water into the extracellular and intracellular spaces. The purpose of this study was to investigate changes in body fluid distribution and to identify the causal factors involved in TURP syndrome.

Methods

A total 61 patients with benign prostate hypertrophy (American Society of Anesthesiologists Physical Status Classification I or II) scheduled to undergo TURP were enrolled in the study. Institutional approval was granted and informed consent obtained from all patients. The patients were premedicated with meperidine 1 mg kg⁻¹ and atropine 0.5 mg given 1 hour preoperatively. Anesthesia was induced by spinal block through intervertebral space (L 3-4 or L 4-5) with 0.3% hyperbaric dibucaine. All patients whose level of analgesia was higher than Th-4 were excluded from the study. No supplemental drugs such as narcotics or benzodiazepines were given during surgery. Normal saline was administered to correct for any preoperative

fluid deficit and to maintain normal blood pressure. Five or ten mg of ephedrine was given whenever the systolic blood pressure dropped below 80 mmHg. The irrigating fluid used in the study contained 3% sorbitol (Uromatic S, Baxter Travenol, Inc.) with an osmolality of 170 mOsm kgH₂O⁻¹. Blood was sampled before administration of iv fluids and after surgery to obtain pre- and postoperative-values. In cases where transfusion was necessary, the blood sample immediately before the transfusion was treated as the postoperative one. In cases where the patient manifested CNS symptoms or cardiac symptoms, the blood sample was taken and was treated as the postoperative one. Plasma osmolality (Posm), blood urea nitrogen (BUN), blood sugar (BS), plasma sodium concentration (Na), and hematocrit (Ht) were measured using the Osmo-Stat OM-6020 (Kyoto Daiichi Kagaku, Kyoto), Hitachi 7250 (Hitachi, Tokyo), GA1140 (Kyoto Daiichi Kagaku, Kyoto), Sinchron (Beckman, USA), and Sysmex SE9000 (Toa Medical Electronics, Tokyo), respectively. We also recorded the amount of irrigating fluid used, weight of the resected prostate, duration of surgery, and amount of normal saline administered.

According to symptoms during surgery, we classified the patients into two groups. If a patient manifested CNS symptoms (restlessness, headache, nausea, irritability, confusion, blindness, seizure, or coma) or cardiac symptoms such as arrhythmia and hypotension (systolic blood pressure < 80 mmHg) in the absence of acute circulatory consequences attributable to spinal anesthetic, he was classified into the TURP syndrome group (TURS), with all others being classified into the asymptomatic group (ASTM). According to the laboratory data obtained, we classified the patients into two groups. If the post-Na was below 130 mmol L⁻¹, the patient was classified into the hypo-natremia group (Hypo-Na), with all others being classified into the normal-natremia group (Norm-Na). Thus, some patients were in both the TURS group and in the Hypo-Na group.

In Hypo-Na, calculated Posm ($c\text{-Posm} = 2\text{Na} + \text{BS}/18 + \text{BUN}/2.8$)⁷⁾ and measured Posm ($m\text{-Posm}$) were compared before and after surgery.

To ensure that ΔPosm ($\text{pre-Posm} - \text{post-Posm}$) can be used as an indicator of irrigating fluid absorption, the correlation coefficient between $V\text{-abs}$ and ΔPosm and that between $V\text{-abs}$ and ΔNa ($\text{pre Na} - \text{post Na}$) were calculated. We then performed a linear regression analysis (corrected with y intercept = 0).

By putting the obtained values into a modified version of the equation of Guyton AC⁸⁾, irrigating fluid

absorbed ($V\text{-abs}$), blood loss ($B\text{-loss}$), increased volume of intracellular fluid (ΔICF), and increased volume of extracellular fluid (ΔECF) could be determined (see the Appendix for details). Instead of measured Posm, we adopted effective Posm ($\text{measured Posm} - \text{BUN}/2.8$) to calculate these variables, since urea can penetrate the cell membrane and is considered to be an ineffective osmol⁷⁾. Body weight (bw) $\times 0.4$, $bw \times 0.2$, and $bw \times 0.07$ were adopted as the initial ICF, ECF, and blood volume values, respectively. As they could not be measured directly, the osmolality and hematocrit levels of the lost blood were assumed to be the average of the pre- and post-values.

Values were expressed as mean \pm standard error (SE). Statistical analysis was performed using chi-square test and Student's paired or unpaired t-test, and $p < 0.05$ was considered to be significant (indicated by "*" in the tables and figures).

Results

Of 61 patients, 16(26%) were diagnosed as having TURP syndrome and 18 as being hyponatremic. Table 1 presents the numbers of cases with TURS, ASTM, Hypo-Na, and Norm-Na. The chi-square test revealed a significant correlation between TURP syndrome and hyponatremia (chi-square = 4.38, $p = 0.036$). Table 2 presents the patients' backgrounds and surgical procedures. A statistical comparison (Student's unpaired t-test) was made between TURS and ASTM. The amount of irrigating fluid used, weight of the resected prostate, and amount of normal saline administered in TURS were larger than those in the ASTM group ($p < 0.05$). Table 3 presents the measured and calculated data. The ΔNa and ΔHt were smaller in TURS than in ASTM. Of the calculated data, $V\text{-abs}$, ΔECF , and ΔICF did not differ significantly between TURS and ASTM, whereas $B\text{-loss}$ was larger in TURS than in ASTM ($p < 0.01$).

Fig. 1 presents the calculated and measured Posm values before and after surgery in the Hypo-Na group. Calculated Posm did not differ significantly from measured Posm preoperatively, whereas the former value was smaller than the latter postoperatively ($p < 0.01$).

Plotting $V\text{-abs}$ against ΔPosm and ΔNa (Fig. 2) revealed that $V\text{-abs}$ correlated strongly to ΔPosm rather than to ΔNa . The correlation coefficients of $V\text{-abs}$ vs ΔPosm and $V\text{-abs}$ vs ΔNa were 0.98 and 0.60, respectively. The linear regression equation of $V\text{-abs}$ against ΔPosm was as follows: $V\text{-abs(L)} = 0.356 \times \Delta\text{Posm}$ (mOsm kgH₂O⁻¹)

Table 1. Chi-square test for independence between TURS and Hypo-Na

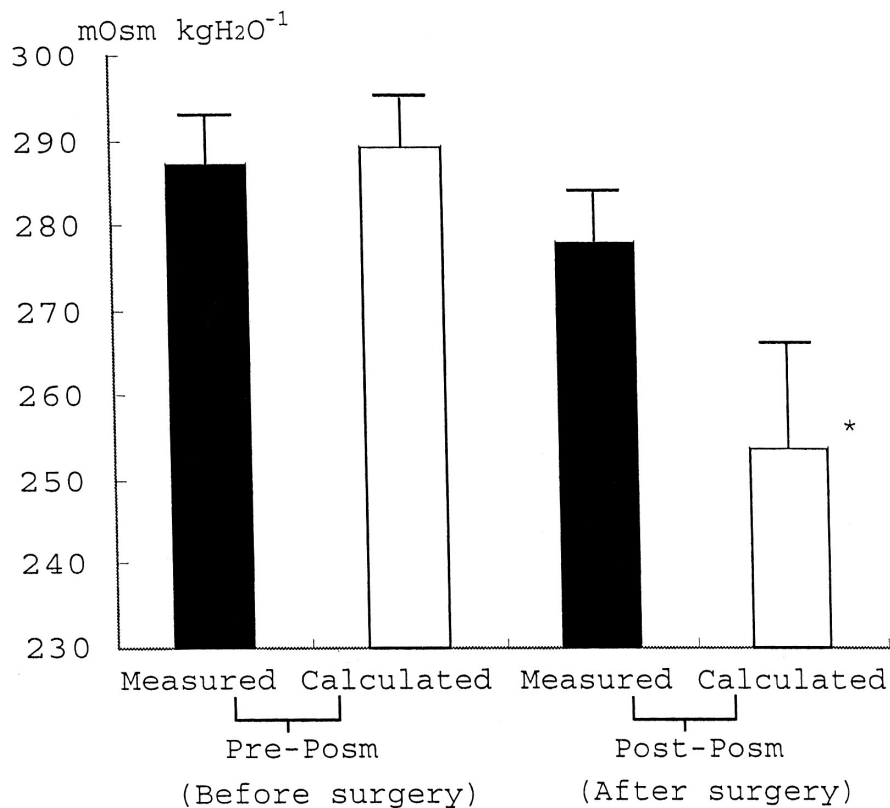
	Hypo-Na(+)	Hypo-Na(-) (Norm-Na)	Total
TURS (+)	8	8	16
TURS (-) (ASTM)	10	35	45
Total	18	43	61

Table 2. Patient and surgical background

	Total (n = 61)	TURS (n = 16)	ASTM (n = 45)
Age (yr)	72.4 ± 1.1	75.9 ± 2.4	71.1 ± 1.2
Body weight (kg)	59.5 ± 1.2	57.7 ± 2.1	60.1 ± 1.4
Irrigant used (L)	23.2 ± 1.0	26.8 ± 2.0*	22.0 ± 1.1
Resection period (min.)	59.4 ± 2.3	65.6 ± 4.6	57.2 ± 2.7
Weight of resected prostate (g)	24.1 ± 1.9	36.9 ± 4.1*	19.5 ± 1.7
Normal saline given (ml)	894 ± 42	1084 ± 87*	827 ± 44

Table 3. Measured and calculated data

	Total(n=61)	TURS(n=16)	ASTM(n=45)
ΔPosm (mOsm kg ⁻¹)	-5.0 ± 0.6	-5.6 ± 1.2	-4.7 ± 0.7
ΔNa (mmol L ⁻¹)	-7.2 ± 1.0	-12.9 ± 2.4*	-5.2 ± 0.9
ΔHt (%)	-6.6 ± 0.6	-10.6 ± 1.2*	-5.1 ± 0.5
V-abs (L)	1.70 ± 0.22	1.74 ± 0.44	1.68 ± 0.25
B-loss (L)	0.35 ± 0.07	0.86 ± 0.15*	0.17 ± 0.06
ΔECF (L)	1.06 ± 0.18	0.76 ± 0.37	1.17 ± 0.20
ΔICF (L)	0.28 ± 0.06	0.13 ± 0.12	0.34 ± 0.07

**Fig. 1.** Mean and SD of pre- and post-Posm (measured and calculated value) in hypo-Na group. "*" represents statistical significance ($p < 0.01$, paired t-test) between measured and calculated value.

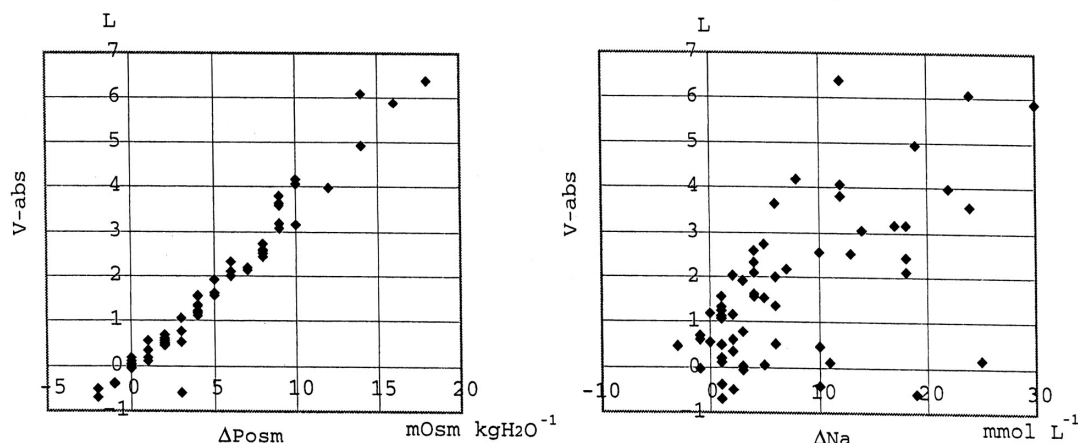


Fig. 2. V-abs data plotted against ΔPosm (left) and ΔNa (right).

Discussion

METHODS :

Clinically, it is very difficult to measure volume changes in body compartments. Hahn R and co-workers reported on a method of calculating ΔICF and ΔECF in an animal study where they adopted a simple model using infused glycine solution⁹. They calculated ΔECF by a dilutional method of plasma sodium concentration and ΔICF by an indirect subtraction method. Since sodium concentrations change if water shifts from one compartment to another, this parameter is not useful for calculating volumes in body compartments. Our previous study also suggested that sodium concentration did not correlate with either V-abs or ΔECF , whereas Posm did¹⁰. Among many laboratory parameters, plasma osmolality is the only one that has the same value in each body compartment (plasma, interstitial and intracellular fluid) where each sodium concentration is different. Osmotic pressure is extremely high (about 5500 mmHg) compared with hydrostatic pressure and colloid oncotic pressure, and thus water immediately moves into a higher osmolar pressure compartment along the pressure gradient⁸. The present study computed volume changes in body compartments using Posm as a force to drive water between ECF and ICF. The formulas we adopted were derived from Guyton's textbook of physiology⁸, and we modified them for the present study. The mean volume of irrigation fluid absorption had been reported to be 1225 g^{3,11} and 1990 g¹² in which body weight was measured before and after surgery. These values are close to our value of 1700 ml. Hahn reported¹³ that the mean blood loss was 689 ml, which was twice that observed in the present study for the total patient population, 350 ml, but close to the data

of TURS, 860 ml. These findings support the use of the present methods.

LIMITATION OF THE METHODS :

1. Urine output and insensible water loss were neglected because they could not be measured clinically. They likely had an effect on the calculated values in the present study.
2. The osmolality and hematocrit levels of the lost blood were assumed to be the average of the pre- and post-values because they could not be measured directly.
3. The premises in Appendix ignored the patient variation, such as $\text{ECF} = \text{body weight} \times 0.2$, etc. (However, these may be permissible because initial ECF is ultimately subtracted to determine ΔECF)

ABOUT THE RESULTS:

The main findings of the present study are as follows.

1. The amount of irrigating fluid used (Table 2)
2. The amount of resected prostate (Table 2)
3. The amount of normal saline administered (Table 2)
4. The sodium concentration (Table 3)
5. The amount of blood loss with low hematocrit (Table 3) showed a correlation with TURP syndrome.
6. Plasma sodium concentrations did not contribute significantly to plasma osmolality (Fig. 1, Table 3)
7. Irrigating fluid absorption was strongly correlated to ΔPosm , but not significantly to ΔNa (Fig. 2).
8. TURP syndrome was related to hyponatremia (Tables 1, 3).

We interpret the present results as followings.

Findings 1, 2, 3. (Amount of irrigating fluid used, amount of resected prostate, and amount of normal saline (Table 2) were related to TURP syndrome.)

Since resection of a large amount of prostate might lead to massive bleeding, the patients developed TURP syndrome despite the administration of saline to maintain

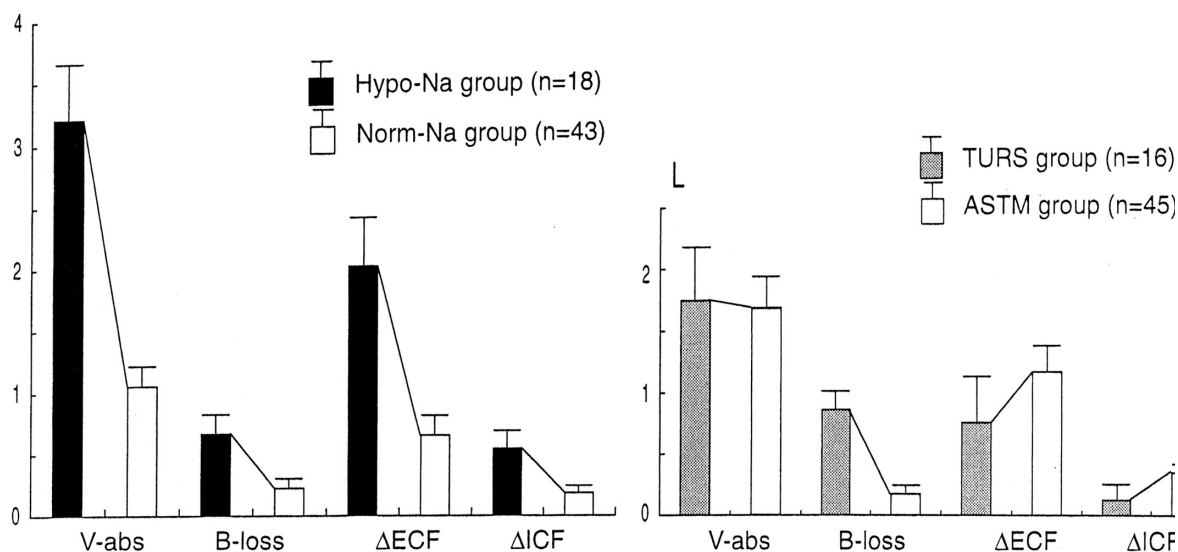


Fig. 3. Mean and SE of V-abs, B-loss, Δ ECF, and Δ ICF in the Hypo-Na vs. Norm-Na Group (left), and in the TURS vs. ASTM group (right).

adequate blood pressure. Large prostates might necessitate long operating durations and consequently a large amount of irrigating fluid.

Findings 4, 5. (Sodium concentration and amount of blood loss with low hematocrit (Table 3) were related to TURP syndrome.)

The bag of irrigating fluid was positioned 60–80 cm above the patients. The hydrostatic pressure of the irrigant at the operative field was approximately 60 to 80 cm H₂O. This pressure does not overcome the arterial pressure, but the irrigating fluid may enter into venous sinus. If massive bleeding occurs, the patient may manifest TURP syndrome. If massive irrigant absorption occurs, dilutional hyponatremia may develop. Fig. 3 shows the calculated findings for Hypo-Na, Norm-Na, TURS, and ASTM. Although we excluded Fig. 3 from the results to ensure statistical accuracy (the same sample cannot be used to perform statistical analyses twice), the figure suggests that a large amount of V-abs and a consequent large Δ ECF may be the causes of hyponatremia. In TURS, however, a small Δ ECF does not compensate for an equivalent amount of B-loss. Δ ECF in ASTM are sufficiently large to compensate for a small amount of B-loss about one seventh of Δ ECF. These findings suggest that TURP syndrome is likely not caused by dilutional hyponatremia, but rather by bleeding and consequent hypovolemia without appropriate extracellular and/or intravascular fluid replenishment.

Finding 6. (Plasma sodium concentration did not contribute significantly to plasma osmolality (Fig. 1, Table 3))

As shown in Fig. 1, a significant difference was observed

between measured and calculated Posm postoperatively. Δ Posm in Table 3 is also too small to be expected from Δ Na. Δ Posm must be roughly twice as much as Δ Na⁷. These findings indicate that hyponatremia does not result in a hypo-osmolar state. Given that sorbitol is not normally present in plasma, it follows that the standard equation used in this study ($\text{Posm} = 2\text{Na} + \text{BS}/18 + \text{BUN}/2.8$) does not contain a value for sorbitol contribution.

Thus, the discrepancy between measured and calculated Posm is likely attributable to some amount of sorbitol derived from the irrigating fluid postoperatively⁶. In other words, measured Posm is not as reduced as expected from the plasma sodium concentration. This in turn suggests that any intracellular fluid shift (e.g., brain edema) is less than that expected from the plasma sodium concentration. This may be one of the two reasons why the CNS symptoms are not so severe in spite of extreme hyponatremia, which we mentioned previously. (Another reason will be discussed later in this section.) CNS excitability is driven by a hypo-osmolar state, not by hyponatremia itself¹⁴. The slight decrease in measured Posm after surgery was probably caused by absorption of hypo-osmolar irrigating fluid. If we had used an isosmotic irrigant, (e.g., 5% sorbitol solution instead of 3% (170 mOsm kgH₂O⁻¹)), the measured Posm would not have changed postoperatively. If we had used distilled water as an irrigating fluid, hyponatremia would have resulted in a hypo-osmolar state, exactly as expected from the sodium concentration.

Finding 7. (Irrigating fluid absorption was strongly correlated to Δ Posm, but not significantly to Δ Na (Fig. 2).)

The correlation coefficient between V-abs and ΔPosm was 0.98, and that between V-abs and ΔNa was 0.6. Posm, therefore, may be a better parameter than Na as a monitor of fluid absorption.

Tauzin and Sanz recommended central venous pressure (CVP) to monitor fluid absorption⁴⁾. Given that the irrigating fluid used is a hypo-osmolar crystalloid, most of the fluid shifted into interstitial and intracellular space. In addition, since CVP is a monitor of intravascular volume and of cardiac function, it cannot be used as a quantitative monitor of fluid absorption. Measured body weight can be an exact quantitative monitor^{3, 11-12)}, however, this method is not feasible during surgery. Ethanol, when added to the irrigating fluid can be used to monitor fluid absorption by measuring its concentration in a patient's expirate¹⁵⁻¹⁸⁾. Although this is a very effective method by which to instantly diagnose fluid absorption, it requires tracheal intubation and a special measuring device. The present study findings indicate that measuring plasma osmolality during TURP is a simple and accurate monitor of irrigating fluid absorption.

The slope of the linear regression equations of V-abs against ΔPosm was 0.356, which indicated that one $\text{mOsm kgH}_2\text{O}^{-1}$ reduction of plasma osmolality is a results from irrigant absorption at 356 ml. It should be noted, however, that this was from the use of 3% sorbitol as an irrigating fluid. The results will be different if other irrigating fluids are used.

Finding 8. (TURP syndrome was related to hyponatremia (Tables 1, 3).)

The incidence of serum sodium concentration less than 125 mmol L^{-1} after TURP has been reported to be 15%¹⁹⁾ with a mortality rate of 40% when hyponatremia was symptomatic (headache, nausea, vomiting)²⁰⁾. Although

there were 12 patients (20%) in the present study whose plasma sodium concentrations were below 125 mmol L^{-1} , with half being symptomatic, none of the patients developed severe or lethal conditions. What accounts for this difference between findings reported in the literature, the present results, and the patients we mentioned in the introduction? We suspect that severe CNS symptoms such as convulsion, blindness, confusion, and loss of consciousness result from glycine toxicity^{5, 11, 21-25)}. Glycine is a common solute used in North America and Europe that has never been used in Japan clinically. Glycine is an inhibitory CNS transmitter and its metabolites, glyoxylic acid and glycolic acid, have neurotoxic properties^{6, 26-27)}. The non-use of glycine solution as an irrigant in Japan may be the second reason mentioned previously. Therefore, we interpret finding 8 (TURP syndrome was related to hyponatremia.) to indicate that hyponatremia is not a cause of TRUP syndrome, but a result of dilution of irrigating fluid.

Although the present method has some limitations, we believe that the present findings demonstrate the blind spot in the clinical assessment of dilutional hyponatremia and TURP syndrome in TURP surgery.

Conclusion

1. TURP syndrome may not be caused by hyponatremia but rather by hypovolemia resulting from bleeding in cases where the irrigating fluid used is 3% sorbitol.
2. Hyponatremia during TURP surgery does not always result in a hypo-osmolar state.
3. The amount of irrigating fluid absorption can be predicted by measuring plasma osmolality. One $\text{mOsm kgH}_2\text{O}^{-1}$ reduction in plasma osmolality results from irrigating fluid absorption at 356 ml when the irrigating fluid is 3% sorbitol.

Table 4. The body compartments and their volume and osmolality for calculation

	ECF			ICF			TOTAL		
	Volume (L)	osmolality	Total mOsm	Volume (L)	osmolality	Total mOsm	Volume (L)	osmolality	Total mOsm
Initial	$\text{bw} \times 0.2$	preOsm	$0.2\text{bw} \times \text{preOsm}$	$\text{bw} \times 0.4$	preOsm	$0.4\text{bw} \times \text{preOsm}$	$\text{bw} \times 0.6$	preOsm	$0.6\text{bw} \times \text{preOsm}$
V-abs	X	170	170X	0	0	0	X	170	170X
Normal saline	k	288	288k	0	0	0	k	288	288k
B-loss	$-\text{Y}(1-\text{m})$	h	$-\text{Y}(1-\text{m})\text{h}$	$-\text{Ym}$	h	$-\text{Ymh}$	$-\text{Y}$	h	$-\text{Yh}$
Post equi-bration	Z	PostOsm	$\text{Z} \times \text{PostOsm}$	W	PostOsm	$\text{W} \times \text{PostOsm}$	$0.6\text{bw} + \text{X} + \text{k} - \text{Y}$	PostOsm	$(0.6\text{bw} + \text{X} + \text{k} - \text{Y}) \times \text{postOsm}$

The small letter "×" is mathematical symbol.

Appendix

In this study, fractions of body fluids were calculated based on the following two basic principles:⁸⁾

1. The osmolalities of the extracellular and intracellular fluids remain exactly equal to each other except for a few minutes after a change in one of the fluids occurs.
2. The number of osmoles of osmotically active substance in each body compartment, in the extracellular fluid, or in the intracellular fluid, remains constant.

4 variables:

X = irrigating fluid absorbed (L)

Y = blood loss (L)

Z = ECF after equilibration (L)

W = ICF after equilibration (L)

Constants:

bw = body weight (kg)

k = normal saline administered (L)

h (osmolality of lost blood) = $(\text{preOsm} + \text{postOsm})/2$

m (hematocrit of lost blood) = $(\text{preHt} + \text{postHt})/2$

Premises:

ECF = $\text{bw} \times 0.2$

ICF = $\text{bw} \times 0.4$

Blood volume = $\text{bw} \times 0.07$

The fraction of blood volume after equilibration will be one third of Z.

Measured value:

preOsm = effective osmolality* before surgery

postOsm = effective osmolality* after surgery

*effective osmolality = measured osmolality - BUN/2.8

osmolality of irrigating fluid = $170 \text{ mOsm kgH}_2\text{O}^{-1}$

osmolality of normal saline = $288 \text{ mOsm kgH}_2\text{O}^{-1}$

preHt = hematocrit/100 before surgery

postHt = hematocrit/100 after surgery

Equations: (Also see Table 3.)

$$1. Z + W = \text{bw} \times 0.6 + X + k - Y$$

$$2. Z \times \text{postOsm} = \text{bw} \times 0.2 \times \text{preOsm} + 170X + 288k - Y(1-m)h$$

$$3. W \times \text{postOsm} = \text{bw} \times 0.4 \times \text{preOsm} - Ymh$$

$$4. \text{post Ht} = (\text{bw} \times 0.07 \times \text{preHt} - Ym)/(z/3)$$

X, Y, Z, and W can be given by calculating the equations above. X, Y, $(Z - \text{bw} \times 0.2 - k)$, and $(W - \text{bw} \times 0.4)$ represent V-abs, B-loss, ΔECF , and ΔICF in the text, respectively.

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TUR 症候群と体液分布

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前立腺肥大症の経尿道的前立腺切除術では灌流液に3%のソルビトール液を用いるために、破綻した血管から吸収された灌流液により低ナトリウム性のTUR症候群を起こすことが知られている。灌流液の吸収による体液バランスの変化を61名の患者で測定した。吸収灌流液 (V-abs), 出血量 (B-loss), 細胞内液増加量 (Δ ICF), 細胞外液増加量 (Δ ECF) を検査データから計算により求めた。TUR症候群を来した患者群 (TURS) と無症状患者群 (ASTM) に分けた。出血量はTURS (平均 860 ml) が ASTM (平均 170 ml,

$p < 0.01$) より有意に多かったが、V-abs (1740 対 1680 ml), Δ ECF (760 対 1170 ml), Δ ICF (130 対 340 ml) には有為な差が認められなかった。無症状群では Δ ECF (1170 ml) が出血量 (170 ml) を代償できたが、TURSの Δ ECF (760 ml) は出血量 (860 ml) を代償できなかったために、症状が現れたと考えられる。結論として、TUR症候群中の精神症状や循環系の変動は、灌流液による希釈性の低ナトリウム血症というより、出血による血管内容量の低下を吸収灌流液が代償できないことが主因と考えられた。

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