A comparison of the effect of 1.5% glycine and 5% glucose irrigants on plasma serum physiology and the incidence of transurethral resection syndrome during prostate resection

JUSTIN W. COLLINS, SEAMUS MacDERMOTT*, RICHARD A. BRADBROOK*, FRANCIS X. KEELEY Jr and ANTHONY G. TIMONEY
*Bristol Urological Institute, Southmead Hospital, Bristol, *Torbay Hospital, Torquay, UK*

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OBJECTIVE

To examine changes in the pathophysiology and frequency of the transurethral resection (TUR) syndrome with two irrigation fluids, as variable amounts of irrigation fluid are absorbed during TUR of the prostate (TURP), and although polar solutes are required to prevent an effect on diathermy, the solutes may have effects when absorbed.

PATIENTS AND METHODS

Between December 2001 and March 2003, 250 patients were included in a prospective randomized trial comparing glycine 1.5% with 5% glucose irrigation fluids. We measured blood loss, fluid absorption, temperature change, biochemistry including a glycine assay, and peri-operative symptoms. Blood samples were taken immediately before and immediately, 5 and 24 h after TURP. Irrigating fluid absorption during TURP was measured with 1% ethanol as a marker and breath ethanol measurements. Operative details were recorded, including the type of anaesthesia (with or with no sedation), resection time and weight of resected tissue. Peri-operative symptoms were documented prospectively. TUR syndrome was defined as a serum sodium level of ≤125 mmol/L with two or more associated symptoms or signs of TUR syndrome.

RESULTS

Five (2%) patients had TUR syndrome; all five were irrigated with glycine, although this difference was not statistically significant ($P = 0.06$). Of the five men, three had hypotension, four were tired, one was nauseous, two had parasthesia, two had 'uneasiness', one had blurred vision and two were confused; none had chest pain. There was a large variation between the groups in the level of glycine assayed immediately after TURP; a high glycine level was associated with the TUR syndrome ($P = 0.01$). There was no difference between the groups in levels of sodium, potassium, urea, creatinine, osmolality, calcium, haematocrit, albumin serum levels or peri-operative blood loss (defined as a change from before to after TURP in haemoglobin level, accounting for transfusions).

CONCLUSIONS

An increase in serum glycine was associated with TUR syndrome; there were large variations in the amounts of glycine absorbed, reaching levels many times the upper limit of normal. In other studies, glycine was reportedly toxic, and that the levels recorded were many times the upper limit of normal may have both immediate and long-term effects.

KEYWORDS

glycine toxicity, osmolar concentration, TURP, irrigation fluid, TUR syndrome, adverse events

INTRODUCTION

Since the introduction of TURP by McCarthy in 1926, the problem of which irrigation fluid to use during the procedure has caused wide-ranging debate, up to and including the present. For standard TURP the criteria for an ideal irrigant are: it must irrigate the surgical field; not be an electrical conductor and not affect diathermy; have good visual acuity and be 'user-friendly'; have similar osmolality to serum; minimal side-effects when absorbed; and can be detectable by the surgeon when excess volume is absorbed.

Glycine solution is the most commonly used irrigant and has been used in TURP for >50 years. In 1948, Nesbitt and Glickman [1] used glycine at 1.1% and 2.1% to prevent the haemolysis that occurred when sterile water was used as an irrigant. TURP has several recognized complications; one of the more serious and potentially fatal is the TUR syndrome.

Estimates of the incidence of TUR syndrome range from 0% [2], 1% [3], 2% [4], 7% [5] to 10% [6–8], but it is currently poorly defined and many mild cases can be falsely attributed to old age, anaesthetic complications and excessive blood loss. The symptoms arising might also differ depending on the choice of irrigating fluid [9].

For over 20 years, urologists in one district general hospital used only 5% glucose as their irrigant of choice, and their clinical experience lead them to think that 5% glucose solution is not toxic and is entirely satisfactory as an irrigating fluid for use during endoscopic surgery [10]. These urologists have apparently not been aware of problems with stickiness of the instruments or caramelization of the cutting loop diathermy during surgery, and consider 5% glucose to appear optically identical to 1.5% glycine.

PATIENTS AND METHODS

Between December 2001 and March 2003, 250 patients undergoing TURP in two hospitals (Southmead and Torbay) were recruited to a prospective randomized trial,

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FIG. 1. A plot of the sodium level the day after TURP against that before TURP in 244 patients, for 120 patients irrigated with glucose (1) or 124 with glycine (2), with regression lines shown for both plots.

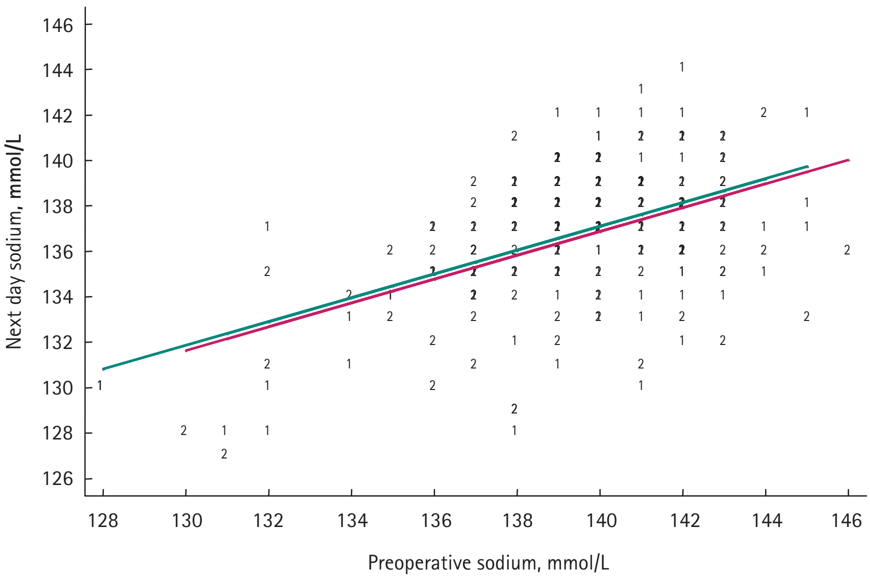

TABLE 1 TUR syndrome by treatment group and the glycine level after TURP

	TUR syndrome?		
Treatment	No	Yes	Total
Glucose	115	0	115
Glycine	113	5	118
Total	228	5	233
Glycine after TURP, µmol/L			
<400	138	0	138
≥400	88	5	93
Total	226	5	231

and randomly allocated to either irrigation during TURP with glycine 1.5% or 5% glucose. All patients gave fully informed consent and were assessed with immediate preoperative blood analysis and electrocardiograms [11].

Only patients with spinal anaesthesia were included in the analysis and their operative details recorded. The protocol requested that sedation was not used, but if sedation was required then lethargy was not included as a symptom of TUR syndrome. The irrigant selected was unknown to both the surgeon and anaesthetist, as the irrigants were put into unmarked bags. The amount of irrigant absorbed was measured by breath ethanol levels on an alcolmeter, using a nomogram [12]; the total irrigation fluid absorbed by each patient was recorded. The duration of TURP, weight of resected tissue, volume of irrigant used and evidence of prostatic capsule perforation were recorded. Blood transfusions were recorded and a standard protocol was for two 8-hourly bags of normal saline to be prescribed; no patient received i.v. dextrose or dextrose saline after undergoing TURP.

After TURP, in recovery, blood samples were taken to measure haemoglobin, haematocrit, sodium, potassium, urea, creatinine, glucose, osmolality, calcium and glycine. Glycine was analysed using anion-exchange chromatography with ninhydrin detection on an amino-acid analyser. Blood samples were rechecked at 5 and 24 h after TURP, and all results compared with values before TURP.

The TUR syndrome was defined as a sodium level after TURP of ≤125 mmol/L [4], with two or more symptoms or signs of TUR syndrome. Symptoms or signs attributed to TUR syndrome were nausea, vomiting, bradycardia, hypotension, hypertension, chest pain, mental confusion, anxiety, parasthesia, and visual disturbances. Any symptoms or signs of TUR syndrome noted during TURP were also recorded.

Analysis of covariance was used to test for differences between the blood values the day after TURP for the two treatment groups, adjusting for baseline (before TURP) values. Interactions between treatment group and baseline values were examined and retained if significant at the 5% level. If the baseline values did not influence the next-day values, either a two-sample *t*-test or a Wilcoxon test was used to assess the next-day values as appropriate. Model assumptions were also assessed graphically.

RESULTS

In all, 124 patients were randomized to receive 5% glucose and 126 to receive 1.5% glycine; the mean (SD, range) age of the patients was 74.3 (8.9, 48–96) years. There was no significant difference between the groups in sodium levels (Fig. 1) or for the changes in potassium, urea, creatinine, osmolality, calcium, haemoglobin or haematocrit.

Five of the 233 patients for whom the TUR syndrome status could be determined had TUR syndrome (2.1%, 95% CI 0.7–5.0; Table 1). Of the five patients who had TUR syndrome, one had bradycardia, three had hypotension, four were drowsy, one was nauseous, two had prickling, two experienced uneasiness, one had blurred vision and two were confused; none had chest pain. Although all five patients with TUR syndrome were in the glycine group and none of the patients in the glucose group developed TUR syndrome, this difference did not reach statistical significance (Fisher's exact test, $P = 0.06$, $n = 233$).

All five patients with TUR syndrome (Table 1) had glycine levels above the normal range (150–399 µmol/L), at a mean (range) of 28 915 (16 686–36 800) µmol/L, a fluid absorption of 3.6 (2.6–4.1) L, and a resection time of 47.6 (35–58) min; four had prostate capsule perforation noted during TURP. In the glycine group overall, there was significant variation in the glycine assay results, with some values many times the upper limit of normal.

There was evidence of an association between TUR syndrome and raised glycine levels at the end of TURP (Fisher's exact test, $P = 0.01$, 231 men). Patients with TUR syndrome were more likely to have a glycine level outside the normal range than those who did not have TUR syndrome; the median level of

glycine in the glucose, glycine, TUR syndrome group and non-TUR syndrome group groups was (μmol/L) 241, 791, 29 665 and 317, respectively.

In the glycine group there was no evidence to suggest an association between glycine levels and osmolarity at the end of TURP (Spearman's rank correlation coefficient, 0.05, 119 men), but the sodium levels tended to decrease with increasing glycine levels (Spearman's rank correlation coefficient –0.57).

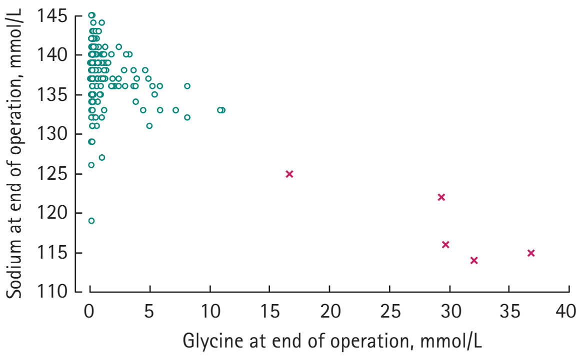

FIG. 2.
A plot of the sodium and glycine levels at the end of TURP for 231 patients; values from those men with TUR syndrome are shown as crosses.

There were 124 patients in the glucose group, of whom 13 were diabetic; they were managed peri-operatively with a standard protocol for diabetic patients, receiving i.v. insulin infusion. Immediately after TURP in these 13 patients the median (interquartile range, range) glucose level was 8.1 (5.6–10.3, 5.6–23.9) mmol/L, but by the second blood sample at 5 h after TURP all patients were within the normal range.

None of the patients in the glucose group developed TUR syndrome, although one had a serum sodium value of <125 mmol/L after TURP (Fig. 2) but did not fulfil the criteria for TUR syndrome, as he had no symptoms or signs of TUR syndrome. This patient, according to the breath ethanol nomogram [7], had absorbed just under 3 L of 5% glucose irrigation, and the glucose and sodium levels immediately after TURP were 40 and 119 mmol/L, respectively; 5 h later the respective levels had returned to normal, at 5.9 and 135 mmol/L; Table 2 gives values for all patients in the glucose group.

TABLE 2 Serum glucose values after TURP in the glucose group (124 patients)

Glucose, mmol/L	Median (interquartile range, range) [number]
Immediately after TURP	6.1 (5.2–9.9, 4.2–40) [121]
5 h after TURP	6.5 (5.7–7.9, 3.8–15.8 [113]

DISCUSSION

Endoscopic surgery of the genitourinary tract requires the use of an irrigating fluid. The absorption of some irrigant occurs during almost every TURP [12]. Volumes of irrigation fluid absorbed can be difficult to predict, although the volume tends to be greater in extended and bloody operations [13]. In the 1950s, several studies were undertaken to determine the amount of fluid absorbed during TURP. Hagstrom (1955) weighed patients before and after TURP, and calculated that ≈20 mL/min of fluid was absorbed by the patient. However, there appeared to be a wide variation among patients; Oester and Madsen, using a double-isotope technique, showed in 1969 that the mean was ≈1 L, and that a third of the fluid was absorbed intravenously, when the venous sinuses were opened, meaning that most of the fluid was in the periprostatic area. Currently surgeons are more aware of the dangers of irrigant absorption and most would attempt to limit the duration of TURP; however TUR syndrome still occurs.

Several irrigant solutions are available, including sorbitol-mannitol and glycine; the former is used in Europe but glycine is most common in the UK and North America. There is now increasing evidence highlighting the toxicity of 1.5% glycine solution when absorbed during TURP [14]. Glycine is an amino acid present in humans at <400 μmol/L; at higher concentrations research has shown it has direct and indirect cardiotoxic effects in animal studies [15,16], and pathophysiological action in stimulating, amongst other things, the release of atrial natriuretic peptide, thereby enhancing sodium loss and contributing to hyponatraemia, which is part of the TUR syndrome [17]. The amount of glycine absorbed seems to have an independent contribution to cerebral effects in volunteers [18] and to mortality in mice [19].

The metabolism of glycine gives rise to glycolic acid and ammonia, and high levels of blood ammonia have also been suggested as a possible cause of TUR syndrome [12]. Previous studies showed a correlation between symptoms and hyperammonaemia after infusion of glycine 2.2% [18] and TURP [20].

Nausea, vomiting and confusion occur six to nine times more often when 1–2 L of glycine solution is absorbed than when no absorption is detected [21]. Most patients with a transient deterioration in mental status after TURP have absorbed irrigant [22]. Consciousness appears to be lowered when even more glycine is absorbed [22,23], and this has also been associated with hyperammonaemia [12].

Alternatively, a direct toxic effect of glycine may be part of the mechanism of the cerebral side-effects of glycine absorption [24]. Glycine is an inhibitory neurotransmitter, and the visual disturbances in TUR syndrome are not the same as those expected in cortical oedema. The condition can proceed to transient blindness and is sometimes the only sign of fluid absorption [25]. Light perception is usually lost in cortical oedema, but not in TUR syndrome [26]. Fundoscopy is normal [25] and measurement of intraocular pressure is also unchanged in TUR syndrome, which would indicate that visual changes are not due to cerebral oedema secondary to hyponatraemia [27]. However, there is little doubt that the hyponatraemia resulting from a dilutional effect of all irrigating fluids eventually causes neurological symptoms related to cerebral oedema. Istre *et al.* [28] detected cerebral oedema by CT that correlated with nausea after the absorption of as little as 1 L of glycine 1.5% in females undergoing transcervical resection of endometrium. Restlessness and epileptic seizures are signs of massive absorption; they are most likely caused by hyponatraemia, as these symptoms have been associated with various irrigants, e.g. glycine [6], sorbitol 3% [29], sorbitol-mannitol [30] and sterile water [31].

However, the hyponatraemia associated with TUR syndrome is not simple dilutional hyponatraemia; there is a loss of sodium during the osmotic diuresis associated with irrigant absorption, therefore the urinary excretion of sodium represents an absolute loss, as the irrigant contains no electrolytes [9]. Also, large amounts of glycine have been shown to increase the release of atrial natriuretic peptide in excess of that expected from the volume absorbed, which will further promote natriuresis [17]. This supports our findings that an increase in glycine level is not associated with a change in osmolality caused by a simple dilutional effect, but still results in a lower sodium level.

Serum osmolality usually remains normal or decreases by ≤10 mosmol/kg when fluid is absorbed. However, the change in osmolality correctly indicates tissue oedema only when mannitol is absorbed. As glycine and glucose enter the cells they will be accompanied by water through osmosis, even when serum osmolality is normal. Tissue oedema will therefore be greater than indicated by the serum osmolality. Thus, the terminology 'isotonic hyponatraemia' is not useful when glycine or glucose is used. It is particularly irrelevant when ethanol is used to indicate fluid absorption, as this agent increases the osmolality without redistributing water [9].

A solution of 5% glucose is a standard crystalloid; because glucose is metabolized throughout the body it requires 13 L to be given/absorbed intravenously to expand the intravascular compartment by 1 L. Normal serum osmolality is ≈290 mosmol/kg. The osmolality of 5% glucose is 285 mosmol/kg, as opposed to the osmolality of 1.5% glycine, which is 190 mosmol/kg. This higher osmolality provided by 5% glucose solution may be beneficial in reducing the possible side-effects of cerebral oedema, which can occur after inadvertent absorption of irrigating fluids.

In the present study, for glucose control, there seemed to be no adverse effect of absorbing large quantities of glucose. The largest values were immediately after TURP (range 4.2–40 mmol/L), even in the patient whose glucose level was 40 mmol/L after absorbing 2.8 L of irrigant, who had a normal level of 5.9 at 5 h and 6.3 mmol/L at 24 h after TURP.

Another potentially safer alternative to glycine irrigation is normal saline with bipolar diathermy [32–35]. This relatively new development allows TURP using a familiar technique. Like 5% glucose, normal saline is a more physiological solution that can be given intravenously and with minimal known side-effects. However, there are as yet no large scale randomized studies comparing the clinical effectiveness and cost-effectiveness of this technique compared to standard TURP; such studies are urgently needed.

In conclusion, hyponatraemia and the toxicity of glycine and/or its metabolites explain the clinical symptoms of TUR syndrome. Although endoscopic procedures on the genitourinary system are currently limited to using irrigation fluids, the choice of irrigant is not limited. We recommend that surgeons should consider the use of alternative irrigants to glycine or alternative surgical techniques that allow crystalloids such as normal saline to be used as an irrigant.

CONFLICT OF INTEREST

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Correspondence: Justin W. Collins, Bristol Urological Institute, Southmead Hospital, Westbury on Trym, Bristol BS10 5NB.
e-mail: jwcol@yahoo.co.uk

