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Glycine 1.5% for Irrigation Should Be Abandoned

Key Words

Glycine · Irrigation · Complications · Physiology ·
Prostatectomy

Abstract

Background: Glycine 1.5% has long maintained a dominating role as an irrigating solution for monopolar transurethral resection of the prostate (TURP), as well as for certain other transurethral procedures. **Materials and Methods:** This review summarizes the findings of systematic experimental and clinical studies in which glycine 1.5% for irrigation was infused/absorbed and the outcome compared to at least one other irrigating fluid, including the isotonic saline used for bipolar TURP. **Results:** There were 11 studies in animals, 3 in volunteers and 6 in patients undergoing TURP. With only one exception, which is probably due to low power, these studies either show a poorer outcome after administration or absorption of glycine solution or else that glycine 2.2% is more toxic than glycine 1.5%. The poorer outcomes consisted of more tissue damage or higher mortality (animals) or more symptoms (volunteers and patients). **Conclusion:** The safety of monopolar TURP would be improved by replacing glycine 1.5% with some other electrolyte-free fluid. The author argues that glycine 1.5% should be abandoned completely.

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History

Glycine in sterile water was introduced for bladder irrigation in 1948 [1] and has since then been used for irrigation during millions of operations. Benefits include good visibility with a low degree of stickiness. Production is inexpensive, and there is no risk of allergy, as glycine is an endogenous amino acid. Some skepticism arose when it was found that glycine absorption might cause visual disturbances [2] and hyperammonaemic encephalopathy [3], but glycine still maintained a good reputation for as long as 40 years after the classical description of the 'transurethral resection (TUR) syndrome' in 1956 [4].

Fluid absorption was difficult to measure in the old days, which ruled out the possibility of performing randomized trials to discover which fluid was associated with the mildest adverse effects. The fluids were simply trusted. Systematic comparative studies of the biological and haemodynamic effects of irrigating fluids did not begin until the late 1980s. Many of them were initiated by the author who, when summarizing the results, is surprised that glycine solution is still being used.

Survival

Early studies show that 2–5 g/kg of concentrated glycine is fatal in a dog [5, 6]. Correction for the interspecies difference in metabolic rate suggests that the lethal dose in a human weighing 70 kg corresponds to between 2.5 and 5.5 litres of glycine 1.5% [7].

Three later studies in mice, including a total of 340 animals, confirmed that the glycine dose is a statistically significant and independent risk factor for death when irrigating fluid is infused intravenously [8–10]. Injecting glycine intraperitoneally in 150 mice yielded the same result [11]. The lethal dose for 50% of the test population in the mouse appears to be 3 g/kg [8].

Large amounts of glycine apparently pose a greater threat to life than other irrigating fluids [8, 9]. In one of the mice studies, mortality was 80% after glycine 1.5%, 68% after sorbitol 2%-mannitol 1% and 40% after mannitol 5% [9]. Another example is that 3 out of 7 rabbits died shortly after infusion of 100 ml/kg glycine 1.5% with ethanol 1%, which did not occur with any of 3 glycine-free fluids [12].

Pathology

Glycine 1.5%, but not Ringer's acetate or water, given retroperitoneally to rats caused degenerative changes in the liver and toxic cellular changes in the kidneys [13].

In the rabbit study mentioned above, glycine solution, but not mannitol 3%-ethanol 1%, caused oedema of the liver cells and (in particular) of the collecting tubules of the kidney. Myocardial hypoxia and inflammation was found only after infusion of glycine. Four pathologists scored the cytological changes in various organs and reported them to average 1.9 for glycine 1.5%, 2.9 for glycine 1% (both with ethanol 1% added), 1.6 for sorbitol 2%-mannitol 1%, 0.6 for isotonic saline and 0.3 for mannitol 3%-ethanol 1% [12].

Several other studies have focused on the effects of glycine on the heart. In a model used to assess cardiotoxicity, living cardiomyocytes were mixed with various irrigating fluids and examined by light microscopy. Glycine 1.5% with and without ethanol 1% caused more cell death than sorbitol 2%-mannitol 1%, whereas mannitol 3%-ethanol 1% was in an intermediate position [14].

Mice showed myocardial hypoxia and inflammation even when sacrificed between 2 and 7 weeks after having received glycine solution. These signs were more common in the order glycine 2.2% > 1.5% > 1.0% but were

mild or absent in controls and in 5 animals given mannitol 5% [15]. In another study, the hypo-osmotic properties of glycine 1.5% contributed to rupturing of the histoskeleton, the incidence of which was only half as high for isotonic saline both with and without glycine 1.5% [16].

In 15 pigs, glycine 1.5% had higher overall scores for myocardial tissue changes (myocardial hypoxia, interstitial dilatation, focal necrosis and rupture of the histoskeleton) compared to animals randomized to receive mannitol 5% [17].

Volunteers

Intravenous infusion studies of irrigating solutions have been performed in humans and allow a comparison of adverse effects. Hahn et al. [18] infused 1 litre over 20 min on 4 different occasions. All 10 volunteers who received glycine 2.2% reported symptoms like prickling sensations in the skin, flushing, blurred vision, discomfort, slight nausea and, later, exhaustion. Some participants had problems performing complex tasks for the rest of the day. The severity of the symptoms correlated with the blood ammonia level, which rose to a maximum of 354 $\mu\text{mol/l}$ (normal range 11–35). Glycine 1.5%-ethanol 1% was followed by prickling sensations in the skin but not with the marked symptoms reported for glycine 2.2%. The increase in blood ammonia was modest. Two different mannitol solutions were not followed by any symptoms.

Prickling sensations, tiredness and occasionally visual disturbances were a routine observation in 3 subsequent infusion studies involving glycine [19–21]. One of them, which allowed a comparison with mannitol 3%, showed that glycine 1.5% was followed by a significantly higher incidence of symptoms [21].

Clinical Studies

Numerous 'transurethral resection syndromes' with haemodynamic shock and depressed consciousness have been described with the use of glycine 1.5% [22–25], but symptoms were often attributed to the accompanying hyponatraemia. However, the introduction of ethanol-containing irrigating fluids, with which fluid absorption can be measured by expired-breath tests [26, 27], opened up the possibility of a statistical approach to the symptomatology when progressively more glycine 1.5% is absorbed [28].

By recording the symptoms using a prospective scale, the adverse effects profiles for different irrigating fluids could also be compared in the clinic. The dimension of such patient series is then an issue, as fluid absorption of clinical significance (>1 litre) occurs in only 1–8% of patients [27–30]. In general, a population of fewer than 300 patients carries an incidence of fluid absorption too low to allow a meaningful comparison between patterns of adverse effects between 2 irrigating fluids.

In 1997, no difference in the number and severity of symptoms following absorption of glycine 1.0 or 1.5% was found when studied in a double-blind fashion in 423 patients with transurethral resection of the prostate (TURP), of whom 77 absorbed irrigating fluid [29].

In the following year, glycine 1.5% was compared with mannitol 3% in 394 patients, of whom 52 absorbed irrigating fluid [30]. Here, a statistically significant difference in the number of symptoms was found, in favour of mannitol 3%. The same number of circulatory symptoms for increasing absorption volumes occurred with both fluids, but neurological symptoms (including nausea, headache and visual loss, among others) increased only for glycine 1.5%. Absorption of glycine instead of mannitol caused an almost fivefold increase in the risk of neurological symptoms.

A study by Coppinger's group [31] in the UK randomized 205 TURP patients to receive either glycine 1.5% or sorbitol 2.7%–sorbitol 0.5% for bladder irrigation. Fluid absorption was measured by gravimetric weighing (not ethanol). No difference in the incidence of symptoms was found. A difference from previous studies is that half of the patients underwent the TURP under general anaesthesia.

Collins et al. [32] randomized 250 TURP patients to glycine 1.5% or glucose 5%. Five patients developed TUR syndrome, all of whom had received glycine.

Yousef et al. [33] compared symptoms in 360 patients following irrigation with glycine 1.5%, glucose 5% and isotonic saline. The resection weights were unusually large (average 90 g). TUR syndrome occurred in 14% of patients in the glycine group but in none in the other two groups.

Akan et al. [34] found hypervolaemia from absorption of mannitol 5% and a rise in blood ammonia from glycine 1.5%, which is consistent with findings by others [18]. No TUR syndrome was found, but no prospective registration of symptoms seems to have been made. The inclusion of only 60 patients offers low power for group comparisons.

Table 1 shows a summary of the findings of studies comparing adverse effects of irrigating fluids in animals and humans.

Special Problems with Glycine

Vision

Glycine is an inhibitory neurotransmitter, and a surplus might impair vision for 4–8 h [35–38]. Slow infusion of 1 litre of glycine solution in volunteers deteriorated visual acuity in half of them. Measurement of visual evoked potentials showed that the nerve signal transmission between the eye and the occipital cortex slowed down [39]. Visual acuity might be slightly impaired by combined sorbitol-mannitol solutions as well, probably as a result of occipital oedema, but the condition does not proceed to blindness [19, 31].

Hyperammonaemia

Mental tests disclose slight confusion after glycine absorption [40], and confusion is statistically more common when 0.3–1 litre is absorbed compared to minimal absorption [28]. A complicating fact is that 10% of the patients who absorb glycine [3, 41] also show a marked increase in blood ammonia, which adds to the symptomatology [18, 42, 43]. Others may have a high serum glycine concentration but only a negligible rise in blood ammonia.

Vasopressin

Glycine produces inappropriate secretion of vasopressin, which worsens hyponatraemia by causing water retention. In sheep [44, 45] and humans [35, 46, 47], the amount required to increase plasma vasopressin seems to be between 1.5 and 2 litres of glycine 1.5%. Smaller amounts do not have this effect [19, 20].

Cell Oedema

Even iso-osmotic (5%) mannitol solution causes some degree of cell oedema due to the natriuresis caused by administration of electrolyte-free fluid [17]. The oedema becomes more severe after glycine absorption [17, 20], as this amino acid is apparently pumped into the cells. A marked (tenfold) dependency of the plasma half-life on the dose suggests that glycine slowly re-enters the plasma [48]. In one study of large-scale absorption, two thirds of the plasma glycine was metabolised after 4 h, while the content in skeletal muscle remained high [49].

Heart Function

In animals, glycine solution causes myocardial swelling [7, 9], which is coupled with bradycardia and prolongation of the QRS duration on the electrocardiogram (ECG) [9, 16, 17]. No gross ECG aberrations occurred for 24 h

Table 1. Studies that include a comparison between adverse effects of irrigating fluids

Population	Outcome measure	Irrigating fluid	Route	Ref.
Mouse	death	glycine 2.2% > glycine 1.1% > glycine 1.5%	i.v.	8
Mouse	death	glycine 1.5% > sorbitol-mannitol > mannitol 5%	i.v.	9
Mouse	death	glycine 1.5% with and without isotonic saline > isotonic saline	i.v.	10
Mouse	death	glycine 2.2% < glycine 1.5% < glycine 1.1%	i.p.	11
Rabbit	death; tissue pathology	3/7 rabbits died from glycine 1.5% but none from sorbitol-mannitol, isotonic saline or mannitol 3%; pathologists scored cell damage: glycine 1.1% > glycine 1.5% > sorbitol-mannitol > isotonic saline > mannitol 3%	i.v.	12
Rat	tissue pathology	glycine 1.5% > Ringer's acetate and sterile water	r.p.	13
Myocytes	cell death	glycine 1.5% > mannitol 3% > sorbitol-mannitol	mixing	14
Mouse	myocardial hypoxia and inflammation	glycine 2.2% > 1.5% > 1.0%	i.v.	15
Mouse	rupture of heart histoskeleton	glycine 1.5% > isotonic saline with and without glycine 1.5%	i.v.	16
Pig	myocardial damage	glycine 1.5% > mannitol 5% > mannitol 3%	i.v.	17
Sheep	death	1/7 died after glycine 1.5% versus 0/7 after isotonic saline	i.v.	44
Volunteers	symptoms	glycine 2.2% > glycine 1.5% > mannitol 3 and 5%	i.v.	18
Volunteers	symptoms; cardiac output	mild symptoms from glycine 1.0% and 1.5% but not from mannitol 3% or sorbitol-mannitol; decrease in cardiac output only from the glycine solutions	i.v.	19
Volunteers	symptoms	more symptoms after glycine 1.5% compared to mannitol 3%	i.v.	21
TURP patients	symptoms	no difference between glycine 1.0 and 1.5%	fluid absorption	29
TURP patients	symptoms	glycine 1.5% > mannitol 3%	fluid absorption	30
TURP patients	symptoms	glycine 1.5% = sorbitol-mannitol	fluid absorption	31
TURP patients	symptoms	glycine 1.5% > glucose 5%	fluid absorption	32
TURP patients	symptoms	glycine 1.5% > glucose 5% and isotonic saline	fluid absorption	33
TURP patients	blood ammonia	glycine 1.5% > mannitol 5%	fluid absorption	34

Some of the examined irrigating fluids also contained ethanol 1% as an indicator of fluid absorption. i.v. = Intravenous; i.p. = intraperitoneal; r.p. = retroperitoneal.

when young volunteers received 1.2 litres of glycine 1.5% [21], but release of cardiac enzymes and subacute flattening of the T wave was common in prostate patients who absorbed 1–3.5 litres of the fluid [50]. Glycine has repeatedly been shown to raise the diastolic arterial pressure in young men [15, 16, 18], which is sometimes [4, 51] but not always [20, 28] observed in older prostate patients.

One study reported a high incidence of serum troponin elevations (7.5%) after irrigation with either glycine or sorbitol-mannitol [31]. In another study, troponin levels also rose equally in patients who received glycine or glucose, but only serum glycine correlated with ischaemic changes on the ECG [32]. Yousef et al. [33] reported that 6 out of 120 patients developed ischaemic changes on the ECG and that 3 showed elevated serum troponin levels after the surgery; this occurred only with glycine irrigation.

In an epidemiological study, the standardized risk of developing acute myocardial infarction after TURP was 1.46 for patients with glycine absorption >100 ml but only 1.14 for those without absorption (general population

risk = 1.00) [52]. The difference may be due to glycine toxicity. The difference may also reflect the fact that fluid absorption is most common in larger prostates that require lengthy surgery [27]; that also correlates more strongly with the 'metabolic syndrome' [53].

Bipolar Surgery

Bipolar surgery allows perioperative use of electrolyte-containing irrigating solutions, such as isotonic saline and Ringer's lactate. These fluids do not give rise to hyponatraemia, which eliminates this electrolyte disturbance as well as brain oedema as causes of symptoms if volume overload from fluid absorption occurs [44]. Here, measurement of serum sodium can no longer be used to diagnose fluid absorption and identify this complication as the cause of symptoms. In contrast, a rise in serum chloride could possibly be used as an index of saline absorption due to the fact that the chloride concentration in isotonic saline (154

mmol/l) is much higher than in plasma (100 mmol/l). Adding glucose to saline or Ringer's to a concentration of 0.5% is another option and has been suggested as a substitute for assessing fluid absorption by serum sodium [54]. Labelling the fluid with ethanol, just as in monopolar surgery, allows more precise and repeated assessment of the absorption during the surgery to be made [55–59].

Using ethanol, the incidence of fluid absorption seems to be similar for mono- and bipolar electrocautery [55, 56]. Recently, Ran et al. [57] found the absorption to average 900 ml during transurethral enucleation of the prostate as well as during bipolar TURP, while others have found lower mean values [55, 56]. During bipolar vaporization, an operation followed by fewer complications than TURP [58], fluid absorption occurred in 16% of patients, while 5% absorbed >500 ml [59].

No study has prospectively related symptoms to a quantified degree of saline absorption, as has been done for glycine 1.5% [28–30]. Studies of bipolar TURP usually overcome this lack by reporting the number of 'TUR syndromes', which is defined as a combination of poorly specified symptoms that co-exist with hyponatraemia (serum sodium <130 mmol/l) [33, 60] or else as hyponatraemia alone [61–63]. Problems with this approach include the fact that symptoms may be caused by factors other than fluid absorption (such as haemorrhage) and that saline does not decrease serum sodium [28, 44]. The low methodological quality of too many assessments of fluid absorption and its consequences weakens the conclusion that the bipolar technology has eliminated such problems [64, 65].

There are only scarce data comparing the adverse effects of isotonic saline and glycine 1.5%. In mice, an infusion of 200 and 300 ml/kg isotonic saline killed 1/3 of the animals, while 2/3 died from glycine 1.5% [10]. Tissue pathology scoring in rabbits places isotonic saline between mannitol 3% (least damage) and sorbitol-mannitol [12]. Rapid infusion of saline ruptures the myocardial histo-

skeleton of mice, but to a lower degree than glycine 1.5% [16]. The osmotic diuresis and intracellular fluid accumulation are likely to make glycine 1.5% less prone than saline to cause pulmonary oedema. Computer simulations based on kinetic data from volunteers suggest that isotonic saline expands the plasma volume by almost twice as much as the same amount of glycine 1.5% [66, 67].

Although isotonic saline is apparently safer to use than glycine 1.5%, experiences from the use of isotonic saline as an infusion fluid during general surgery identify buffered Ringer's solution as a better choice. Isotonic saline at an amount of 2 litres or more gives rise to hyperchloraemic acidosis [68], which a patient strives to compensate by increased breathing. Remaining non-compensated acidosis stimulates the sympathetic nervous system and, later, weakens the myocardial pumping capacity. Saline reduces the glomerular filtration rate by 10–15% [69] by inducing renal vasoconstriction [70]. Saline also causes abdominal pain and mental dizziness [71]. Such problems do not occur in response to alternative 'balanced' electrolyte infusion fluids, such as Ringer's or a modification of Ringer's acetate called PlasmaLyte. When used during major general surgery, saline-based fluid gives rise to more complications than Ringer-based colloid fluid [71]. In major open abdominal surgery, isotonic saline is associated with more complications and higher mortality than PlasmaLyte [73].

Conclusions

The majority of comparisons made show that glycine solution is the worst choice of irrigating fluid during monopolar TURP. In a minority of studies, glycine has been at best equal, but never superior, to alternative fluids. Glycine apparently has toxic properties that add to the dangers associated with massive fluid absorption.

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