Oral glycerol for the treatment of traumatic intracranial hypertension

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Hyperosmolar agents are a primary therapeutic modality employed in the treatment of traumatic intracranial hypertension. Profound hyperosmolarity accompanied by systemic dehydration is a potentially serious problem when these drugs are used repeatedly for control of intracranial pressure. Because glycerol, a water-soluble alcohol, is metabolized in the liver, its dehydrating capacity may be reduced in comparison to other agents. A series of 15 patients were treated with oral glycerol (0.5 to 1.0 gm/kg) with only minor changes in serum electrolytes, glucose, and urea nitrogen. Serum osmolarity rose from a baseline of 305 mOsm/liter to 355 mOsm/liter after 10 days of therapy. Glycerol was found to be effective and safe when employed in this protocol and proved to be a valuable adjunct to the standard methods available for control of intracranial hypertension.

KEY WORDS • glycerol • hyperosmolarity • intracranial hypertension • rebound • intracranial pressure

Intracranial hypertension is a potentially fatal complication of many conditions of the central nervous system. Beneficial effects on both morbidity and mortality have been reported in several clinical studies with aggressive management of cerebral edema. The introduction of intracranial pressure (ICP) monitoring devices has promoted intensive study of various drugs and drug regimens for the treatment of intracranial hypertension, and has allowed for a rational approach to many pharmacological decisions.

Management of traumatic intracranial hypertension requires a multimodality treatment plan. Hyperosmolar compounds have served as the primary therapeutic agent in many treatment protocols, while controlled hyperventilation, corticosteroids, and venting of cerebrospinal fluid (CSF) are widely used adjuncts. Despite these methods, successful long-term reduction of ICP due to traumatic cerebral edema has never been accomplished by a single application or use of any drug or mode of therapy. Prolonged, repeated therapeutic trials have been the rule. Mannitol, the most commonly employed hyperosmolar agent, may cause profound hyperosmolarity, systemic dehydration, and rebound of ICP with chronic use. Complications of prolonged intravenous therapy have stimulated interest and study of alternative drugs.

This clinical investigation examines the effectiveness of oral glycerol administration in reducing elevated ICP, principally in cases of craniocerebral trauma. Glycerol is a water-soluble trivalent alcohol normally present in human tissues as an integral part of both fats and triglycerides. Since it is readily metabolized, primarily in the liver, systemic hyperosmolarity may be reduced and dehydration limited. An evaluation of the effectiveness, time course, dosage, and complications associated with prolonged oral glycerol administration is presented.

Clinical Material and Methods

Study Population

Twelve patients were studied following severe craniocerebral trauma. Three patients with intracerebral or intraventricular hemorrhages were also monitored and admitted for study (Table 1). There were nine males and six females in the group, with ages ranging from 3 to 34 years (average 21.3 years). The average Glasgow Coma Scale score of 5.7 (range 3 to 10) attests to the severity of injury.

Management

All patients were seen by a neurosurgeon in the emergency unit. Endotracheal intubation either was
instituted at that time or had been performed at the scene of the accident. Controlled hyperventilation was begun to maintain arterial PCO2 between 25 and 35 mm Hg and to ensure adequate oxygenation. Arterial blood gases were frequently evaluated so as to maintain these parameters. Computerized tomography (CT) was performed on admission in all patients. Patients with hematomas were excluded if the lesion was surgically removed. In most cases, diffuse cerebral lesions were demonstrated with punctate hemorrhages and reduced ventricular volume. Repeat scans were performed at intervals to exclude a late lesion that was surgically correctable.

An epidural fiberoptic ICP transducer* was chosen for monitoring the ICP. The sensor was implanted through a right frontal burr hole immediately after completion of the CT scan. Sensor function was calibrated using a water column of known height before and after removal from the patient. Accurate ICP recording revealed insignificant drift from the baseline when compared with concomitant lumbar puncture pressures. There were no infections or hematomas with the use of this system.

All patients were treated in a semi-erect position, elevated 30° at the waist. Intubated patients underwent tracheostomy between the 5th and 7th day unless extubation was anticipated by the 10th day. The decision to employ dexamethasone was left to the individual physician. Eleven patients received a load ing dose of 10 mg followed by 4 mg every 6 hours. Two patients received 20 mg every 6 hours, and two patients did not receive steroid. No specific acute effect on ICP was noted with steroid administration.

Glycerol was used as the primary agent for control of ICP in all patients. Criteria for administration of the drug consisted of sustained pressures of 300 mm H2O or higher, pressure waves, or rapid wide fluctuations of pressure. The treatment protocol specified a dosage of 0.5 to 1.0 gm/kg every 3 to 4 hours, as indicated by the ICP and duration of action of the drug. Specific individual dosages ranged from 4 to 70 gm (average 54 gm). A 50% solution was given by mixing a 100% glycerol solution with an equal volume of either 5% dextrose in water or 5% dextrose in 0.4% normal saline, depending upon the systemic electrolyte status. This solution was then administered through a nasogastric tube, the initial placement of which had been confirmed by x-ray film, and from which normal gastric secretions could be aspirated. The nasogastric tube was then clamped for the next 2 to 3 hours, after which aspiration confirmed movement of the solution through the pylorus. If no change in ICP was achieved or a significant volume of solution was aspirated, intravenous mannitol was administered and another trial of the drug was initiated 4 to 24 hours later. The absence of bowel sounds was not an absolute contraindication to the use of the drug. Patients having undergone exploratory laparotomy requiring bowel anastomosis or closure of fistulas were excluded, although a negative abdominal exploration did not preclude treatment with glycerol. Urinary water and electrolyte losses were not actively replaced. Intravenous fluid intake was held constant, although alterations in the type of fluid administered were allowed.

Intracranial pressure recordings were analyzed by determining the pressure at 30-minute intervals from the time the drug was administered until the next dose was given. Recordings of ICP were judged acceptable for evaluation in 396 of the 558 trials (71%); 162 treatment periods (29%) were incomplete or otherwise unacceptable for analysis. The 84 incomplete recordings were due to interruption of the record for diagnostic procedures, such as CT scanning, or prolonged therapeutic modalities, such as cast changes or chest physiotherapy. Malfunction of the sensor accounted for 19 incomplete records while 59 trials were unacceptable because of lack of essential information. The unused records were randomly distributed in time.

Laboratory Method

Glycerol blood and urine levels were determined in eight patients. Blood specimens were obtained every 30 or 60 minutes from a different venous source and immediately centrifuged, decanted, and refrigerated until all samples had been collected. Urine samples were obtained from a Foley catheter.

Glycerol was extracted from the samples with isopropanol after dilution with 0.9% NaCl. The glycerol content of the extracts was then measured on the triglyceride channel of a Technicon auto-analyzer II†

* Epidural fiberoptic intracranial pressure transducer manufactured by Ladd Research Industries, Burlington, Vermont.

† Auto-analyzer II manufactured by Technicon Instruments, Tarrytown, New York.
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using the Hantsch reaction, in which glycerol is oxidized to formaldehyde and condensed with diacetyl-acetone and ammonia to produce 3,5-diacyl-1, 4-dihydrobutidine, a fluorescent product. Serum electrolytes were obtained at the start of each glycerol study and at random points during the next 3 hours. Serum osmolarities were determined by a standard freezing-point method.

Results

Intracranial Pressure

Figure 1 represents the maximum percentage reduction of ICP for the 396 trials as a function of the initial ICP (ICPi), calculated as:

\[
\text{ICPi} - \text{ICPm} \times 100
\]

The ICP decreased by 50% or more in 282 trials (71%), by 60% or more in 176 (44%), by 80% or more in 110 (28%), and by 90% or more in 45 (11%). Eleven trials (3%) resulted in sustained elevation of ICP. The percentage of reduction did not correlate directly with the initial pressure. That is, patients with higher pressures at the time of glycerol administration did not necessarily have greater percentage reductions than did those with lower initial pressures. Mean ICP at various times after oral glycerol intake is shown in Fig. 2 for adults and children.

As the rapidity of ICP reduction is of clinical importance, the percentage of reduction during the first half-hour after ingestion of the drug was studied (Fig. 3). The ICP was reduced by 50% or more during the first half-hour in 145 trials (37%), but continued to rise during this time in 31 trials (8%) before a reduction in pressure was seen.

The time from ingestion of glycerol to the lowest recorded pressure (ICPm) was variable but often char-

![Fig. 1. Percent reduction of intracranial pressure (ICP) in 396 trials calculated as \(\frac{\text{ICPi} - \text{ICPm}}{\text{ICPi}} \times 100\), where ICPi = initial ICP pressure, and ICPm = minimum pressure at any time after glycerol ingestion.](image)

![Fig. 2. Mean intracranial pressure (ICP) values in 260 trials in 12 adults (left) and 135 trials in three children (right). Vertical lines represent standard deviation. I = ICP at time of glycerol ingestion.](image)
characteristic for a given patient. Figure 4 demonstrates that the ICPm occurred at 1 hour after glycerol administration in 41% of trials and at 1½ hours in 30%. In 16% of trials the ICPm was reached 30 minutes after ingestion.

Electrolytes

Serum sodium rose during the first 4 days of treatment but then demonstrated a plateau for the next 4 days at a concentration less than 150 mg/100 ml (Fig. 5A). Potassium (Fig. 5B) and glucose concentration (Fig. 5D) demonstrated no specific trend. Blood urea nitrogen (BUN) levels (Fig. 5C) rose during the first

![Fig. 3. Percentage reduction of intracranial pressure (ICP) during the initial 30 minutes after glycerol ingestion.](image1)

![Fig. 4. Time after glycerol ingestion of maximum intracranial pressure reduction (ICPm) for all patients. The total number of trials was 391.](image2)

![Fig. 5. Results during the first 10 days of treatment. Standard deviation is represented by vertical lines. A: Sodium concentration. B: Potassium concentration. C: Blood urea nitrogen concentration. D: Glucose concentration. E: Serum osmolarity.](image3)
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7 days of therapy as expected for patients placed on a moderate fluid restriction regimen. After 1 week of therapy, BUN concentrations were less than 40 mg/100 ml. Serum osmolarity continually rose during the treatment period (Fig. 5E). Final osmolarity on Day 10 was 50 mOsm greater than the initial average osmolarity. Average 24-hour fluid intake was 3069 cc/day, of which 372 cc was oral glycerol. Mean measurable fluid loss was 2962 cc/day.

**Serum Glycerol Concentrations**

Twelve studies of serum glycerol concentration were completed in eight patients. In nine of these studies, absorption of the drug was recognized by a substantial elevation of the glycerol concentration from the initial baseline concentration. These studies are presented in Fig. 6. The initial glycerol concentrations in successful trials ranged from 6 to 292 mg/100 ml depending upon the day of study and number of previous glycerol trials. Maximum serum levels ranged from 33 to 360 mg/100 ml.

Three trials demonstrated a steady decline in the serum glycerol concentration. Intracranial pressure demonstrated either no change or a gradual elevation during these studies. One patient had received 200 mg of pentobarbital 1 hour prior to glycerol administration. Another patient received the same dosage of glycerol 3 hours after the failed trial and demonstrated a marked reduction in ICP from 700 to 150 mm H₂O in 1 hour. Serum concentration of glycerol rose 46 mg/100 ml during this successful trial. No single factor could be found to account for failure of absorption in these three patients.

The effectiveness of the drug as determined by a reduction of ICP by at least 50% was not dependent upon the absolute initial glycerol concentration. The critical factor in effecting a reduction in ICP was the rate of change from the initial concentration to a maximum level.

Absorption of the drug was not dependent upon serum glycerol concentration. The three patients failing to absorb the drug had concentrations of 2, 71, and 88 mg/100 ml prior to the failed trial. In all patients studied, a rapid elevation of serum glycerol from the initial concentration resulted in a rapid concomitant reduction of ICP. Alterations in serum glycerol concentrations were always accompanied by simultaneous changes in serum osmolarity. No significant changes were found in serum sodium, potassium, BUN, or glucose concentrations during the 3 or 4 hours of the study.

Maximum glycerol concentration was achieved between 60 and 90 minutes in a majority of the studies. Although data were collected at 30-minute intervals only, this parallels the findings of maximal ICP reduction demonstrated in Fig. 4.

Serum glycerol concentration at the end of 3 hours was lower than the initial level of glycerol in three of nine studies. In four studies, final concentrations were greater than the initial concentration by 17 mg/100 ml or less. The final concentrations of glycerol in the two remaining studies were 32 and 54 mg/100 ml greater than the initial concentration.

All patients experiencing a significant elevation in serum glycerol concentration demonstrated a brisk diuresis. In most cases, the period of maximum diuresis accompanied the period of maximum elevation of serum glycerol concentration. Absolute changes in urinary flow rates could not be obtained, as baseline values were not available.

Random urine samples were obtained on 17 occasions in seven patients. A stepwise increase in glycerol excretion during the 3 hours of the study was not seen. In 11 of the 17 samples the concentration of urinary glycerol was between 2.04 and 2.58 gm/100 ml. In the remaining studies it was found that samples had been obtained early in the course of therapy, or poor absorption of the drug had occurred.

**Fig. 6.** Serum glycerol concentration in six patients in nine trials at different times after ingestion.
Glycerol is a trivalent alcohol with a molecular weight of 92 gm. It is water-soluble and will form esters with both organic and inorganic acids. After entry into the metabolic cycle by conversion to glycerol-3-phosphate, an enzyme-mediated step, it may be converted to glyceride lipids, or carry reducing equivalents to mitochondria for oxidative phosphorylation and cellular respiration.

Previous studies employing glycerol as a major therapeutic modality have primarily focused on the treatment of cerebral infarction, experimental ischemia, or edema. Other patients with pseudotumor cerebri, Reyes syndrome, and viral meningoencephalitis have been treated.

Reduction of ICP by glycerol is generally attributed to the establishment of an osmotic gradient between blood, CSF, and brain. Our study adds further support to this hypothesis. Serum osmolalities and glycerol concentrations paralleled each other in their elevation and were concomitant with a rapid reduction of ICP. Previous authors have suggested that an acute increase in plasma osmolality of 30 to 35 mOsm is required before a net movement of water out of brain tissue can occur. In this study, much smaller elevations of serum osmolality resulted in significant reduction of ICP. Equivalent glycerol concentrations necessary to raise serum osmolality 30 to 35 mOsm were rarely achieved, although the response of ICP to much smaller glycerol elevations was remarkable.

The metabolic effects and fate of exogenously administered glycerol, and particularly the use of glycerol as an energy substrate by the brain, have been studied by several authors. Sloviter, et al., induced hypoglycemia in rabbits and observed characteristic electroencephalographic (EEG) changes. Intra-arterial infusions of a 10% glycerol solution caused a reversion of the EEG to a normal pattern, implying glycerol utilization by the brain. Goodner, et al., determined the activity of glycerol kinase in the brains of rats. This enzyme is required for entry of glycerol into mammalian metabolic pathways. Although the cerebral concentrations were small in comparison to those in liver and kidney, definite activity was present in the hypothalamus, anterior pituitary, and cerebral cortex. Further in vitro studies demonstrated oxidation and conversion of glycerol to lipids by incubated brain tissue slices. Many reports are accumulating to demonstrate utilization of glycerol as a metabolic substrate by the brain.

Glycerol administration may offer several additional metabolic benefits. In this series of 12 adult patients, an average of 55 gm of glycerol was given four to six times a day. If the drug was totally absorbed by the gastrointestinal tract, an average of 1182.5 calories/day were provided. Brennan, et al., have shown a diminution of nitrogen loss in the urine during glycerol infusions of 26 and 80 gm/day, sim-
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ulating the nitrogen- and presumably protein-sparing
effect of intravenous fat emulsions. Glycerol is also highly gluconeogenic^2^ and urico-
suric.6,12 Experimental evidence has suggested that the
gluconeogenic process is a function of the liver,^5^ and
that gluconeogenesis from other precursors is in-
hibited when glycerol is infused in bulk amounts.49

The maximum reduction of ICP and peak blood
glycerol concentration were obtained 60 to 90 minutes
after oral administration, and confirm other studies. 25,30 Rapid absorption by the stomach and proximal
intestine must occur to elevate plasma concentration.
A maximum absorption capacity has been demon-
strated for isolated rat stomach.20 This capacity to
absorb glycerol is maintained at a constant rate, re-
gardless of the amount or concentration of the drug
present. In many of our trials, a significant reduction
of ICP was seen within the first 30 minutes after
administration. Although the rapidity of ICP reduc-
tion by oral glycerol does not equal that of intravenous
mannitol, we believe that it is adequate and does not
represent a significant disadvantage.

In this study, average daily serum sodium, potas-
sium, and glucose concentrations demonstrated minor
elevations from baseline values. Average BUN values
did rise over the course of 10 days, although a plateau
was demonstrated after several days of therapy. This
elevation of BUN concentration could be expected
with any hyperosmolar diuretic agent used on a
chronic basis where fluid loss is not actively replaced.
Over a 10-day period the average serum osmolarity
rose 50 mOsm from the baseline and was directly
attributable to accumulation of glycerol in the serum.
We remain concerned about the absolute osmolarity,
but have not detected any problems with such levels.
Slow gradual elevation of baseline serum osmolarity
may be tolerated, whereas more rapid accumulation
of osmotically active substances can produce serious
cerebral and systemic complications and death. A
maximum serum osmolarity level considered to be
deleterious has never been established, although clin-
cal outcome has been related to maximum osmolarity
levels.43 No comparable study using other hyperos-
molar agents on a chronic basis is available for com-
parison.

Glycerol administration has been complicated by
intravascular hemolysis,18,54 nonketotic hyperosmolar
hyperglycemia,23,47 and oxalic acid poisoning.24 These
problems are most commonly reported in patients
receiving parenteral therapy with high concentrations
and with fast infusion rates. One of our patients did
develop acute renal failure without hemolysis or he-
moglobinuria. Gastric irritation, manifested by emesis
and nausea, is reported with oral use but was not seen
in this group of patients. Routine studies of the clot-
ing system revealed no abnormalities.

Rebound overshoot of ICP is a problem that may
specifically relate to hyperosmolar agents.23,37 Rotten-
berg, et al.,46 concluded that a rebound phenomenon
seen with oral glycerol was a result of glycerol accu-
mulation in the brain and CSF. A reverse osmolar
gradient is established, and results in the diffusion of
water into the brain and CSF. Several authors have
reported CSF and brain glycerol concentrations of a
significant magnitude after constant intravenous in-
fusions.15-17 However, Crone^7^ and Waterhouse and
Coxon^5^ demonstrated that the permeability of normal
brain capillaries to glycerol is small. The chronic
administration of any hyperosmolar agent may result
in leakage of the osmotically active substance into the
brain and CSF, especially if anatomical disruption of
the blood-brain-CSF barrier has occurred. We found
ICP to be above the initial pressure in 32% of 306
separate trials of the drug. This elevation was 20% or
less of the initial pressure in nearly half of those
manifesting rebound. Clinical deterioration or alter-
ation of vital signs was not encountered during the
period of rebound.

Conclusions

The treatment of patients with traumatic intracra-
nial hypertension requires many therapeutic choices.
Hyperosmolar agents have been included in many
protocols, but chronic use often produces severe sys-
temic dehydration, profound hyperosmolality, and
serious disturbances of water and electrolyte balance.

Glycerol does result in minor alterations of serum
electrolytes, osmolality, and fluid balance, which are
compounded as therapy progresses. It is our impres-
sion, however, that these problems are significantly
reduced with this agent as compared to mannitol or
urea. This study demonstrates that glycerol is effective
in reducing intracranial hypertension in the majority
of trials. While the drug will not reduce ICP as fast as
parenteral agents, absorption and subsequent reduc-
tion of pressure occur with some predictability. Glyc-
erol is a safe and effective adjunct to standard thera-
peutic protocols for the treatment of posttraumatic
intracranial hypertension. It appears to offer several
advantages when chronic hyperosmolar agents are
required.

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