SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY

TRIVANDRUM - 11

LIST OF PROCEDURES DONE

PROJECT REPORT

NAME : SUNIL PANDIT

PROGRAMME : M.Ch. (Neurosurgery)

MONTH AND YEAR OF SUBMISSION : November, 1992

LIST OF PROCEDURES DONE
PROJECT REPORT

TITLE OF THE PROJECT: **EFFECTS OF INTRAVENOUS GLYCEROL IN AN EXPERIMENTAL CANINE MODEL OF RAISED ICP AND ITS COMPARISON WITH MANNITOL**

NAME ..... SUNIL PANDIT

PROGRAMME : M.Ch. (Neurosurgery)

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CERTIFICATE

I, Dr. SUNIL PANDIT. hereby declare that I have actually performed all the procedures listed / carried out the project under report.

Signature.....

Place : TRIVANDRUM

Name in SUNIL PANDIT

Date : 21/11/92 capital letters

Forwarded. He has carried out the minimum requirement of procedures / etc.

Signature 21/11/92

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Name	
Page	of
Date	

CONTENTS

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Sunil Pandit

INTRODUCTION

The medical treatment of raised intracranial pressure (ICP) remains a challenging problem despite an intensive search for a safe and effective agent. In 1956, Javid and Settlage[18] opened a new era when they introduced the use of hypertonic urea in the treatment of cerebral edema and increaced ICP. Since then many other drugs have been tried and found useful. Among these are osmotic and nonosmotic diuretics and corticosteroids. Urea, glycerol and mannitol are examples of osmotic diuretics. Of these the most commonly used agent is mannitol.[30,19].

Lately there has been a resurgence of interest in the ICP reducing effects of glycerol (Garcia-Sola[10]; Node[28]). The advantages attributed to glycerol over mannitol include prolonged reduction of intracranial pressure, no rebound phenomenon, minimal fluid and electrolyte disturbances and significant nutritive value. However, a major problem has been the high incidence of intravascular haemolysis, haemoglobinuria and renal failure, especially with higher concentrations (Hagnevik[16]) It was felt that a less concentrated solution would obviate this side-effect without compromising the therapeutic benefits.

It is difficult to find experimental studies comparing the effects of these hyperosmotic agents (Garcia-Sola et al[10]; Gaab et al[13]; Guisado et al[14]; Ohta et al[29]). These studies primarily focused on cerebral edema either by producing a cold injury (Gaab et al[13]; Garcia-Sola et al[10]) or by ligating an artery (Guisado et al[14]; Ohta et al[29]).

There is no study comparing the effects of mannitol and glycerol on an experimental model of raised ICP. Hence the present study was undertaken to observe the short term effects of mannitol and glycerol in an experimental situation of raised intracranial pressure produced by venous hypertension.

AIMS & OBJECTIVES

1. To develop an experimental model of raised intracranial pressure.

2. To study the effects of 10% glycerol on raised intracranial pressure.

3. To compare its effects with 20% Mannitol.

4. To document the advantages and disadvantages of each therapy.

REVIEW OF LITERATURE

Glycerol was introduced as an agent to reduce intracranial pressure in 1961 (Bovet et al[3]). Since then numerous experimental and clinical studies have been carried out to evaluate the effect of this drug. Glycerol given intravenously has been recommended at widely divergent doses. While some studies have used glycerol infusion over a short time (0.5 gm/kg body wt in 10 minutes), others have recommended prolonged infusion therapies (500 ml infused over 4-6 hrs or even longer).

Glycerol causes a rapid increase in plasma osmolality primarily due to an increase in blood glycerol concentration (McCurdy et al)[24]. Osmolar equilibrium occurs largely as a result of dehydration of brain. In an experiment conducted by Guisado et al[14], glycerol was infused intravenously into anaesthetised dogs. Continuous infusion was manitained for 12 hours and plasma levels were maintained at 12mM (low infusion rate) and 34mM (high infusion rate). After 6 hours of infusion they noted that both CSF and plasma osmolality had increased by 14 mosm. above control values. Most of the observed increase in CSF osmolality was a result of dehydration.

In 1977, Gaab and Pflughaupt[13] reported on an experiment comparing glycerol (10%) with dexamethasone and a combination of mannitol and sorbitol, on a rat model. A cold injury was produced using a $16mm^2$ probe at -75^oC. They concluded that glycerol significantly reduces the increased water and sodium content of the brain as compared to dexamethasone or a combination of mannitol and sorbitol. No rebound effect was noted with glycerol. Plasma electrolyte, haemoglobin, haematocrit, leucocyte and thrombocyte values showed temporary reduction which quickly returned to normal after infusion.

In 1991 Garcia-Sola[10] reported a comparative experimental study on the short and long term effects of mannitol and glycerol in goat. Intracranial pressure was raised by cryogenic injury produced by a 4mm canula which was placed over the dura mater for 10 minutes. The temperature of the canula was - 160^oC. The intracranial pressure, cerebral blood flow and blood pressure were monitored for 3 days. Mannitol 20% was given in the dose of 1 gm/kg body wt in 10 minutes and glycerol in the dose of 0.5 gm/kg body wt. in 10 minutes twice daily. Immediately after infusion mannitol caused a sudden momentary increase in the cerebral blood flow coinciding with a rise of blood pressure which was explained by a sudden expansion of blood volume. In contrast BP did not vary with glycerol and there was only a mild

increase of CBF. An early decrease in intracranial pressure was observed in both groups. The rebound phenomenon occured with mannitol which was absent in glycerol treated animals. Comparing the long term effects, in the mannitol treated animals, not only did the ICP not decrease but showed a tendency to be higher than control values. This long term rebound effect was thought to be due to the passage of mannitol into the brain and its accumulation there. In contrast, after repeated glycerol infusions, there was no sign of the long term rebound effect. Thus they concluded that glycerol had a clear advantage over mannitol in the control of intracranial hypertension secondary to vasogenic cerebral edema.

Ohta et al[29] in 1991 reported a study on the effect of glycerol on the haemodynamics of acutely induced ischaemic area in the cerebral cortex of cats. The ischaemic zone was created by clipping the middle cerebral artery at its origin. Intravenous 10% glycerol was administered at a rate of 5ml/kg/hr beginning 1 and 2 hours after clipping of the MCA. Their results showed that glycerol infusion improved the CBF to some extent in ischaemic areas with high CBF if the infusion was started 1 hour after clipping. The beneficial effect was doubtful when CBF was low or glycerol was started 2 hours after producing ischaemia.

Kashiwagi et al[20] in 1992 reported on the effect of timing and dose of glycerol on experimental ischaemic brain edema model. They carried out bilateral ligation of the common carotid artery. 10% glycerol was administered at 20mg/kg for 3 hours starting immediately or 3 hrs after ligation. They found no significant difference in survival rates. Brain water changes were not significantly different.

Numerous clinical trials have reported the effects of glycerol on raised ICP and cerebral edemo following infarction. The results of the trials are given below:

Authors	No. Patient/ Control	Design	Type	Dosage	End point	Conclusion
Mathew[23]	25/29	R,DB*	Infarct + ICH	500ml	Outcome	Beneficial
Gelmer[11]	50/50	R	Infarct	?	28 d	No Impr.
Frithz[9]	50/50	?**	Infarct	?	24 m	Probably effective
Gilanz[12]	30/31	R,DB	Infarct + ICH	500ml 6 d	14 d	Beneficial
Larsson[21]	12/15	R,DB	Infarct	500ml 6h-6d	14 m	No impr.
Freidli[8]	32/24	R,DB	Infarct		6 m	Probably effective
Frei[7]	18/23/ 20	R,DB	Infarct	500ml 4h-7d	6 m	Not effective
Bayer[1]	85/88	R,DB	infarct	500ml	1 yr	Beneficial
Gaab[38]	12	-	ICP	0.5gm/ kg body wt.	Con- trol of ICP	Beneficial

* = Random, Double Blind
** = Not specified

MATERIAL AND METHODS

A total of 10 dogs were taken for the experiment. Each dog was premedicated with atropine and phenargan. For aggressive dogs diazepam was also given. General anaesthesia was induced using thiopentone, and the dogs were intubated with a cuffed endotracheal tube. Nitrous oxide and oxygen mixture was used for maintenance of anaesthesia.

The femoral artery was cannulated to monitor the blood pressure. A central venous line was placed to monitor the central venous pressure. The dog was catheterised to monitor the urine output and to collect urine samples. Through a parietal burrhole, a catheter was introduced into the subarachnoid space and connected to a pressure transducer. The dural opening was sealed watertight around the catheter with a pursestring suture and muscle packing. Through a transverse incision in the neck the internal and external jugular veins and the caudal thyroid vein were ligated. The intracranial pressure, blood pressure central venous pressure and urine output were monitored continuously.

The dogs were divided into 3 groups. In the control group (2 dogs) after inducing a state raised ICP, no further intervention was done. In the mannitol treated animals, 1

gm/kg body wt was infused rapidly (over 10 mins.) and the response noted. In the glycerol treated group, 0.5 gm/kg body wt was infused rapidly (over 10 mins.) and the response was observed. Urine samples were taken periodically to check for evidence of hemoglobinuria. The results obtained in 3 animals treated with mannitol and 5 animals treated with glycerol were analysed. The intracranial pressures and blood pressure were measured every 15 minutes for 1 hour and thereafter every 30 minutes for 4 hours. In addition, central venous pressure and urine output were monitored so as to maintain adequate hydration.

RESULTS

In the mannitol treated group, the intracranial pressures were recorded as follows:

TABLE-1A (values in mmHg)

No.	Base line	After ligation	5m	15m	30m	45m	1h	1.30h	2h	2.30h	3h	3.30	4h
1.	2	30	36	45	20	12	17	16	17	19	20	23	26
2.	3	30	32	36	13	14	13	14	16	13	15	16	20
3.	3	28	30	35	13	13	15	17	16	18	20	21	21

In the glycerol treated group, the following values were recorded.

TABLE-1B (values in mmHg)

No.	Base line	After ligation	5m	15m	30m	45m	1h	1.30h	2h	2.30h	3h	3.30	4h
1.	2	27	24	18	12	11	11	11	12	11	13	14	13
2.	3	28	26	23	21	20	7	8	7	10	11	10	10
3.	1	30	28	25	23	21	21	23	21	22	23	23	24
4.	3	31	28	24	16	16	16	18	16	18	20	20	20
5.	2	30	24	20	16	16	10	10	12	10	13	15	14

Simultaneous recording of blood pressure was done in each animal (Values are mean arterial pressure in mm Hg.)

Mannitol group:

TABLE-2A

No.	Base line	After ligation	5m	15m	30m	45m	1h	1.30h	2h	2.30h	3h	3.30	4h
1.	93	92	113	116	89	90	92	92	90	91	97	96	96
2.	100	101	103	113	111	105	102	103	103	103	103	102	103
3.	96	97	103	103	98	96	95	97	96	97	99	99	99

Glycerol group:

TABLE-2B

No.	Base line	After ligation	5m	15m	30m	45m	1h	1.30h	2h	2.30h	3h	3.30	4h
1.	97	97	96	97	96	97	98	98	93	92	95	95	95
2.	102	107	103	103	101	106	110	110	103	105	105	102	103
3.	100	102	100	100	102	103	100	100	101	92	96	97	100
4.	96	96	97	98	99	100	103	103	107	101	102	104	103
5.	90	92	93	94	92	96	97	97	95	94	93	93	93

The cerebral perfusion pressure was calculated for each animal form the above data:

Mannitol group:

TABLE-3A (values in mmHg)

No.	After ligation	5m	15m	30m	45m	1h	1.30h	2h	2.30h	3h	3.30	4h
1.	62	77	71	69	78	75	76	73	72	77	73	70
2.	71	71	77	98	91	89	89	87	90	88	86	83
3.	69	73	68	85	83	80	80	80	79	79	78	78

Clycerol group:

TABLE-3B (values in mmHg)

No.	After ligation	5m	15m	30m	45m	1h	1.30h	2h	2.30h	3h	3.30	4h
1.	70	72	79	84	86	87	87	81	81	82	81	82
2.	79	77	80	80	86	103	102	96	93	94	92	93
3.	72	72	75	79	82	79	77	80	70	73	74	76
4.	65	69	74	83	84	87	85	91	83	82	84	83
5.	62	69	74	76	80	87	87	83	84	80	78	79

TABLE 1A

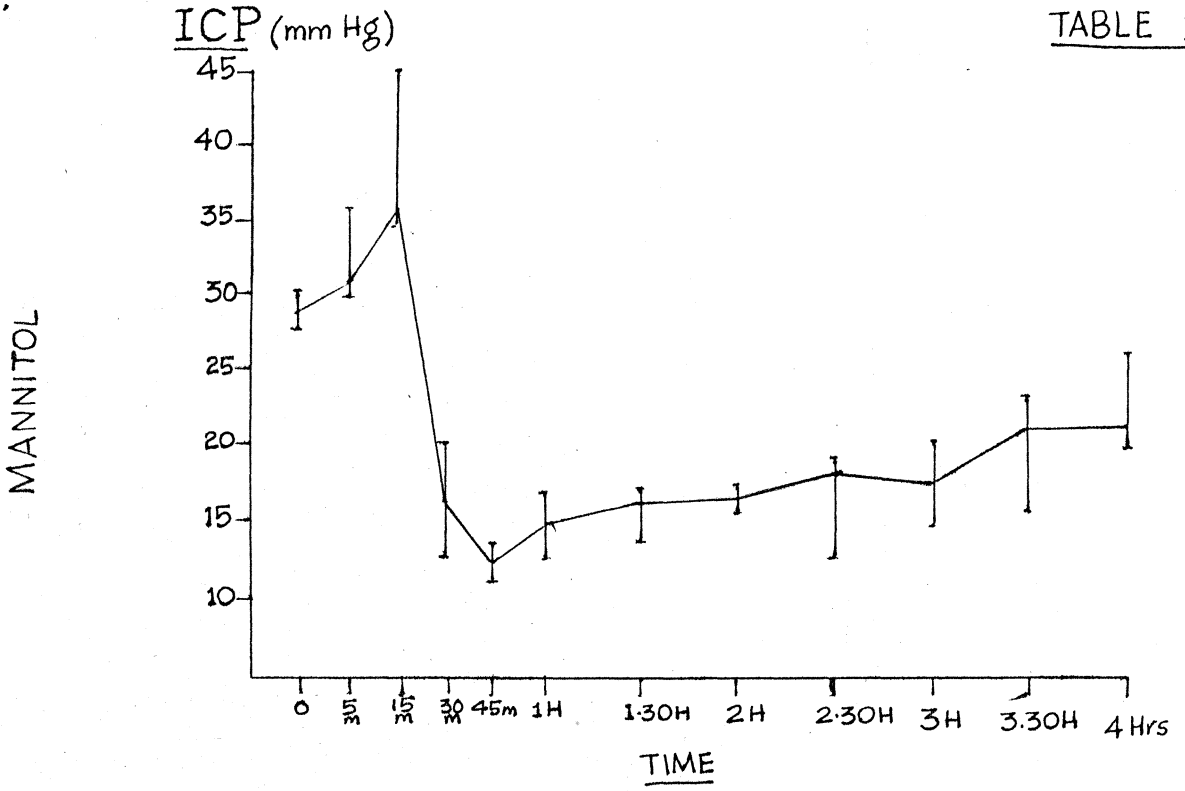
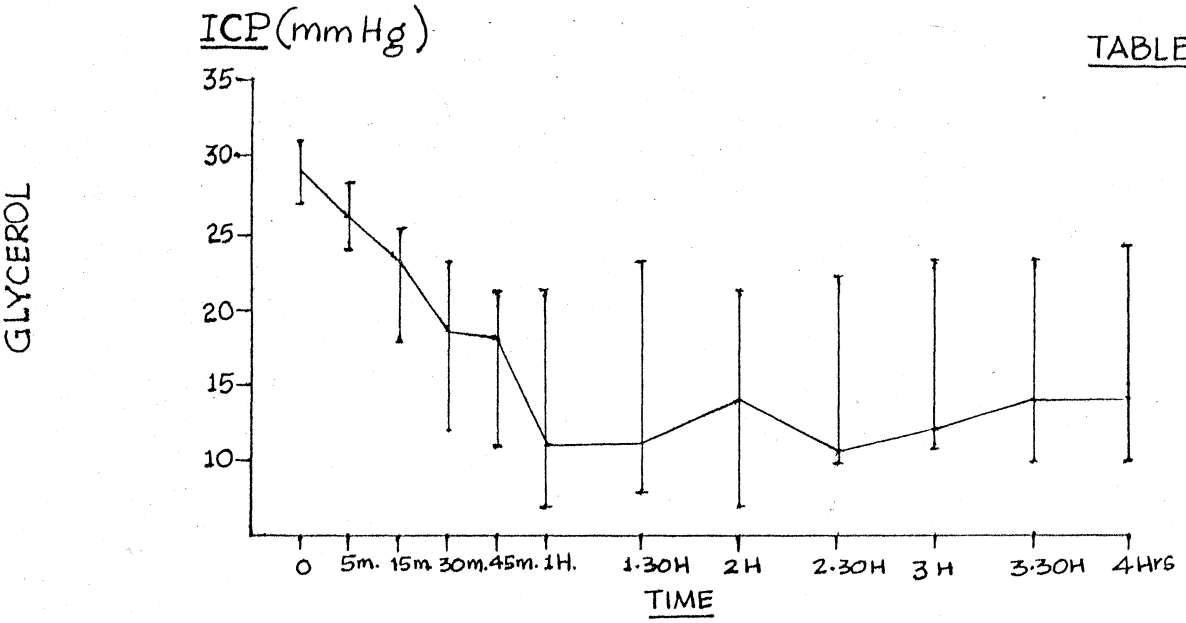


TABLE 1B



EFFECT OF MANNITOL & GLYCEROL ON I.C.P.

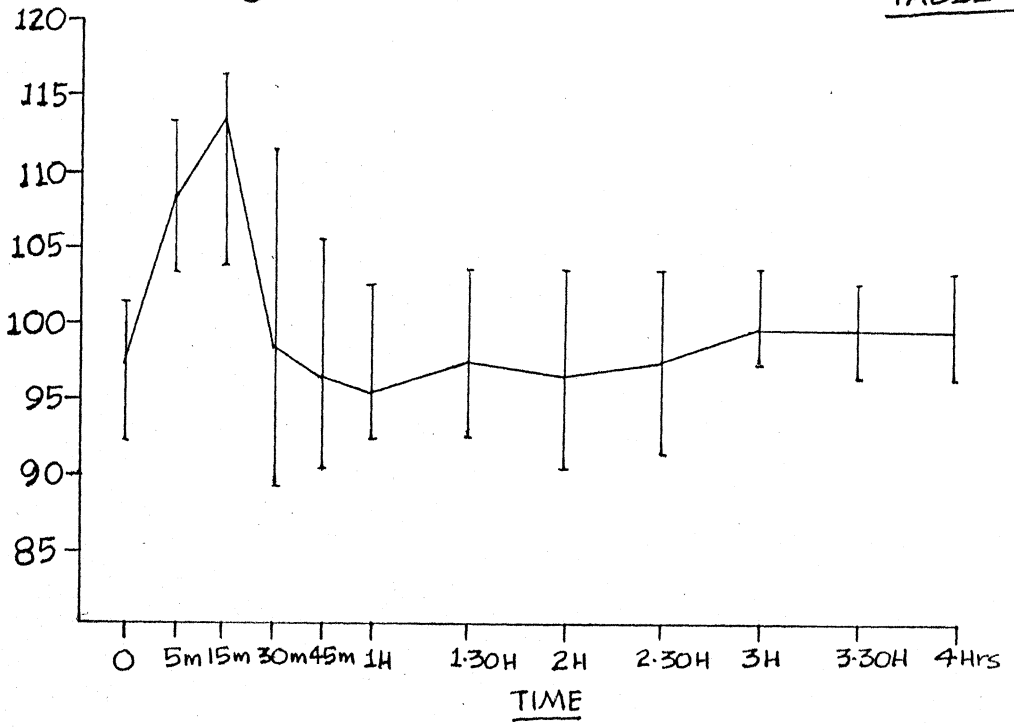
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM 695 011

Name	Sunil Pandit
Page	of
Date	21/11/1992

MAP (mm Hg)

TABLE 2A

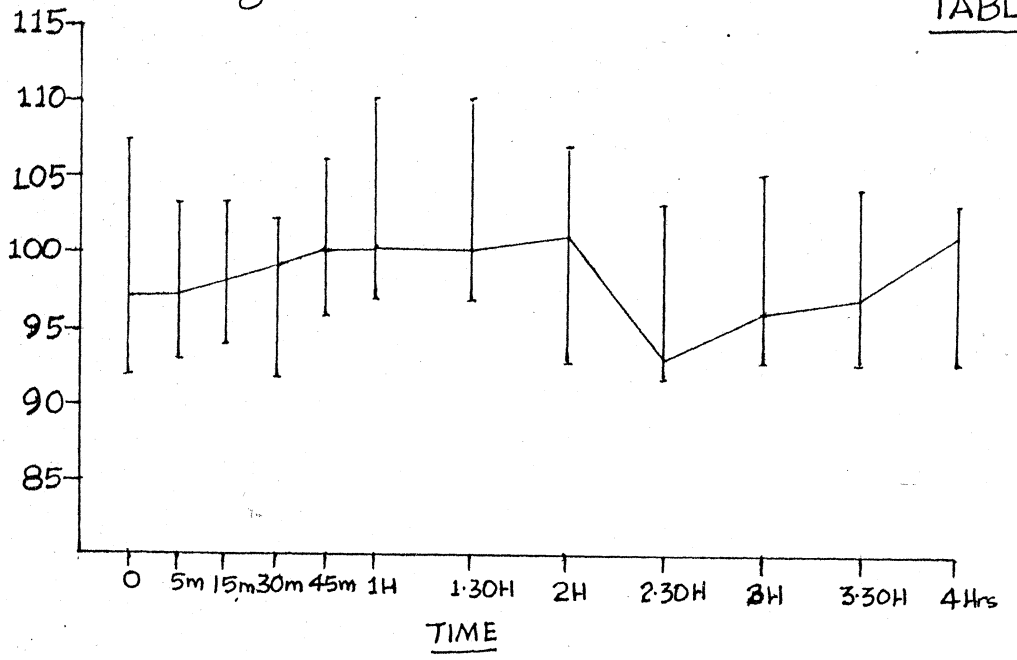
MANNITOL



MAP (mm Hg)

TABLE 2B

GLYCEROL



EFFECT ON MEAN ARTERIAL PRESSURE

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM 695 011

Name	Sunil Pandit
Page	of
Date	21/11/1992

TABLE 3A

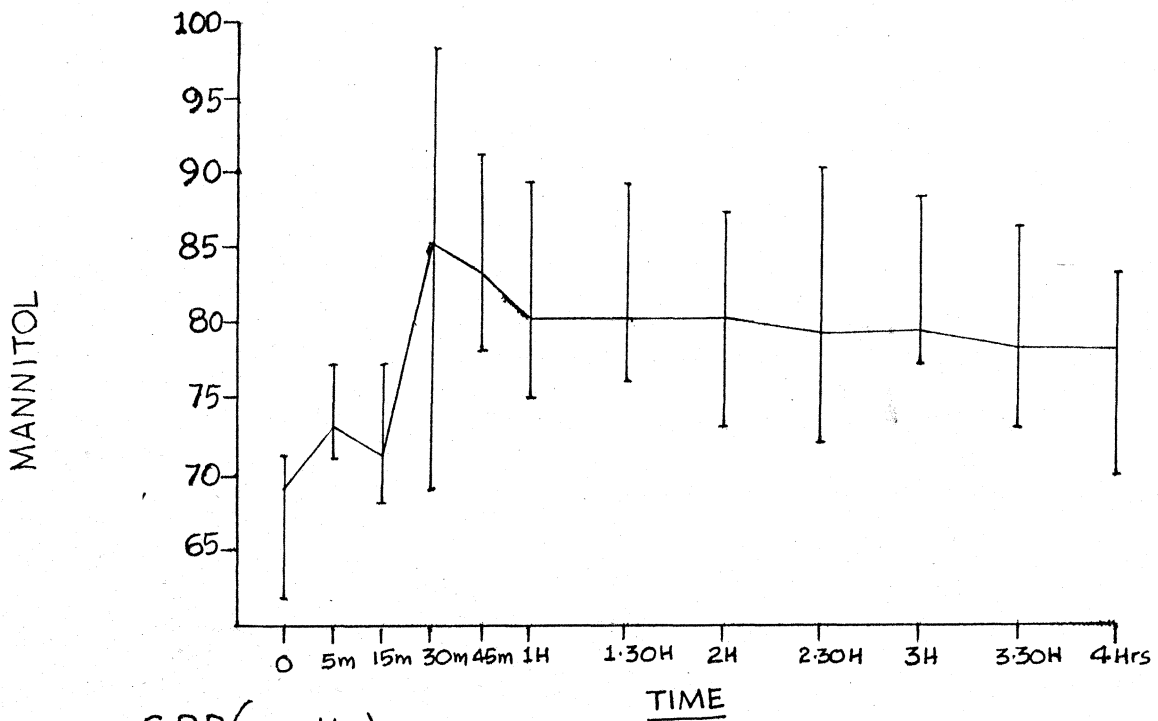
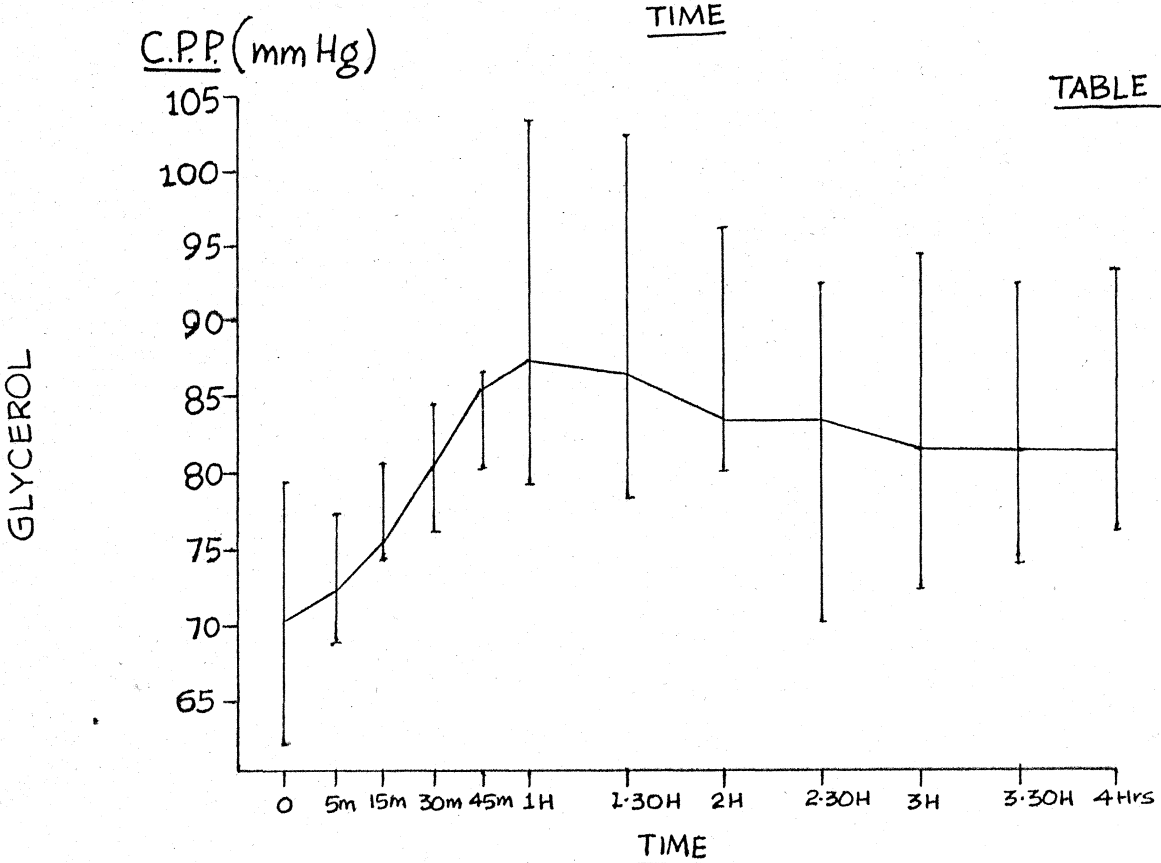


TABLE 3B



EFFECT ON CEREBRAL PERFUSION PRESSURE

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM 695 011

Name	Sunil Pandit
Page	of
Date	21/11/1992

Both hyperosmotic agents produced a decrease in intracranial pressure. The decrease was greatest 30 to 45 minutes after infusion. This reduction of intracranial pressure was equally intense for both groups. The lowest levels obtained were 44.8% of basal value.

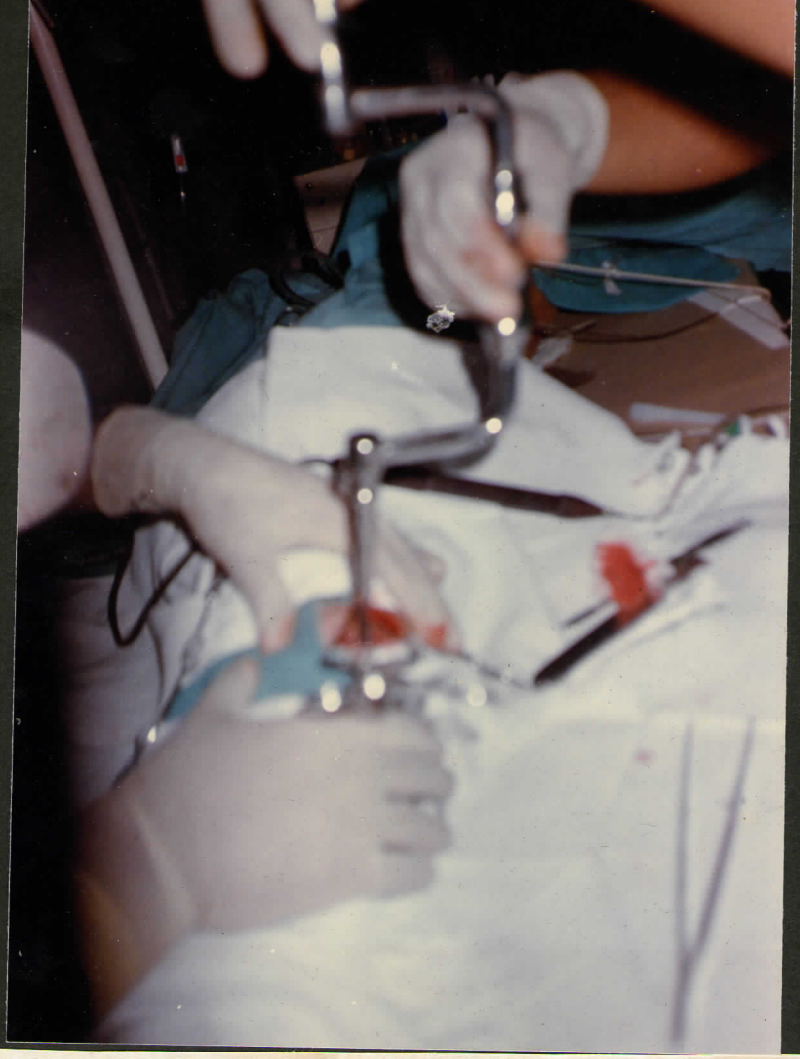
Following the infusion of mannitol there was a sudden momentary rise in blood pressure which coincided with a rise in ICP. However, this settled down quickly aand by 30 min post infusion, the ICP had reduced significantly. No such rise of ICP and BP were seen in glycerol group and visible reudction ICP had occured by 15 min. The rise in blood pressure in the mannitol treated group was 12.6% with a corresponding rise in ICP of 25.6%.

In the mannitol group, 4 hours after infusion, the intracranial pressure was 75.6% of the baseline, whereas in the glycerol group the ICP was still 44.8% of baseline. In neither case did it surpass the basal value.

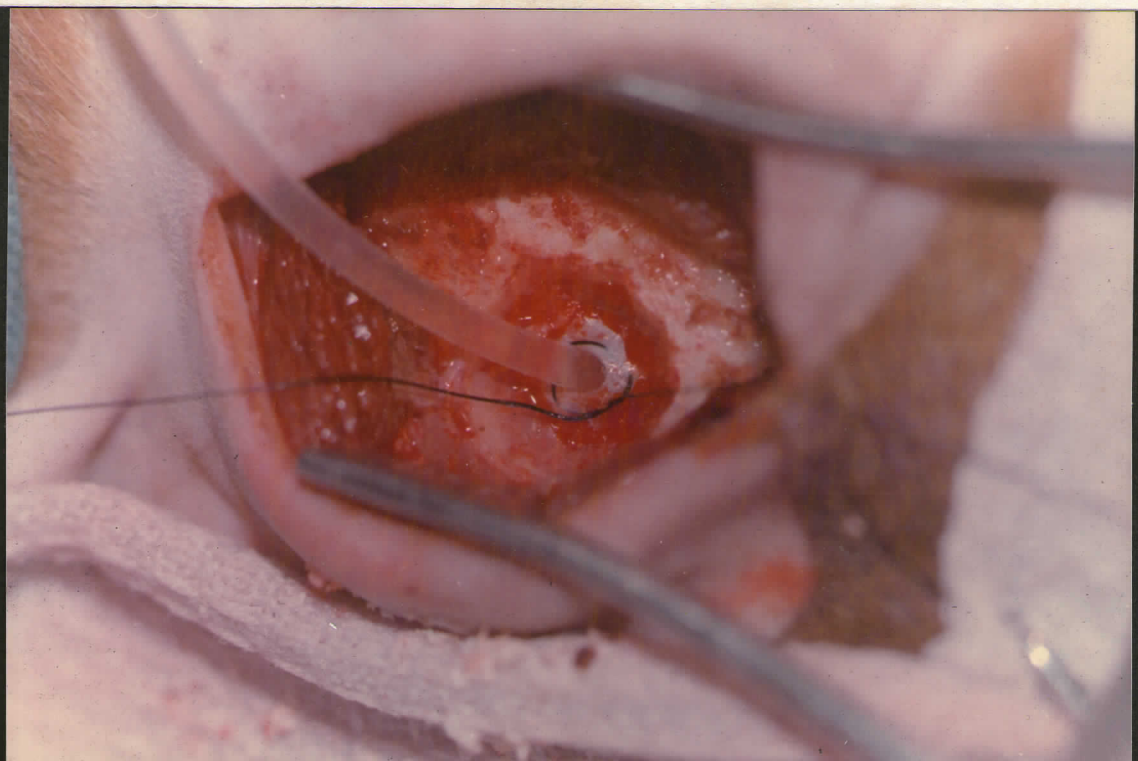
There was no significant difference in the cerebral perfusion pressure in both the groups. The perfusion pressure tended to rise with the reduction of ICP.

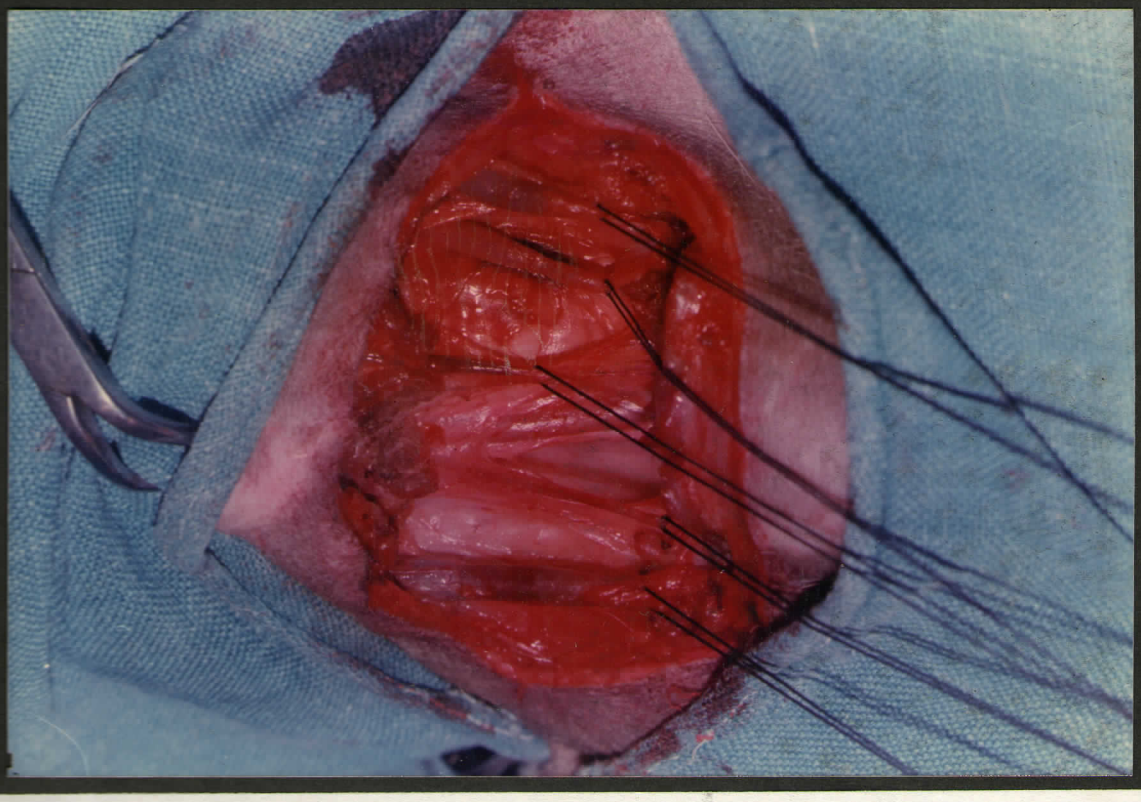
Haemoglobinuria was noted in 3 of 5 animals in the glycerol group. One dog had severe hemoglobinuria with urinary haemoglobin 179 mg/dl at 30 min. post infusion. In

the other two, it was mild with urinary haemoglobin at 6.38 mg/dl and 10.11 mg/dl respectively. No urinary haemoglobin was detected in the other two animals.



After exposing parietal dura through a burr hole (Ph.1), a catheter has been introduced in the subarachnoid space. The purse-string suture is shown (ph.2)





Veins exposed in the neck prior to ligation. Both external jugular veins are laterally placed, internal jugulaars medially situated and caudal thyroid vein is in the midline.

DISCUSSION

Intracranial hypertension is a potentially serious complication of many conditions of the central nervous system. Beneficial effects on both morbidity and mortality have been very well documented with aggressive management of raised ICP. The introduction of ICP monitoring devices has promoted an intensive research of various regimes and has allowed for a rational approach to the problem. Hyperosmolar compounds have served as primary therapeutic agents in many treatment protocols, while controlled hyperventilation, ventricular drainage and corticosteroids are widely used (Leech and Miller[22]). Mannitol is the most commonly employed hyperosmolar agent and it causes a rapid reduction of raised intracranial pressure (Wise and Chater[35]) but its prolonged use is complicated by hyperosmolar states, fluid and electrolyte imbalances and the rebound phenomenon (Node and Nakazawa[28]). In view of these complications there has been a reawakening of interest in glycerol and other pharmacological alternatives.

Glycerol, a trivalent alcohol with a molecular weight of 94 Daltons was introduced as a drug to reduce intracranial pressure in 1961 (Bovet et al[3]). It is water soluble and forms esters with both organic and inorganic acids. It has

the unique advantage that it can be given intravenously as well as orally with an almost similar benefit to the patient (Cantore et al[4]).

Of the various possible mechanisms by which glycerol can lower intracranial pressure, osmolar dehydration of the brain and decreased CSF production have the most experimental support. The effect of changes in serum osmolality on CSF bulk flow (i.e. CSF production) has been studied and it was found that serum osmolality and bulk flow are linearly related and at high serum osmolalities, bulk flow was almost completely inhibited (Di Mattio et al[5]). This is also consistent with the hypothesis that most or all of the ICP lowering effect depends on the establishment of an osmotic gradient between blood and brain. Measured increases in serum Na^+, blood urea nitrogen (BUN) and blood glucose account for less than 10% of the observed increase in serum osmolality (McCudry et al[24]). Hence it is apparent that most of the observed increase in plasma osmolality is due to an increase in the blood glycerol concentration. Osmolar equilibirum between blood and CSF occurs quite rapidly. This is largely due to dehydration of the brain in response to hyperosmolality. It is partially counterbalanced by the passage of glycerol into brain down a concentration gradient. Six hours after infusion of glycerol, measurable quantities

(2.7 and 3.2 m mol/kg) were obtained in white and grey matter respectively (Guisado et al[14]). Glycerol slowly but effectively passes the blood brain barrier. It enters into the metabolic cycle after conversion to glycerol 3-phosphate. It may initiate recoupling of uncoupled oxidative phosphorylation in ischaemic brain tissue (Solviter et al,[32]) It thus acts as a substrate for metabolism in the brain where it may act as a carbon skeleton for gluconeogenesis (Meyer et al[31]). It is also converted to glyceride lipids.

Rebound overshoot of intracranial pressure is a problem related to hyperosmolar agents (Javid et al[17]). Three mechanisms have been postulated for this effect and they may not be mutually exclusive.

- the blood-brain osmotic pressure is compromised by the entry of the hyperosmolar agent into the brain (Guisado et al[14])

- the total osmotic pressure of CSF increases rapidly to that of blood and continues to higher levels before beginning to fall (Bering and Avman[2]).

- the production of 'new' osmoles by the brain in an effort to reduce serum osmolality (primarily th glutamine content of th brain increases (Lockwood[37]).

Since the brain utilises glycerol effectively, there is less accumulation of glycerol on the brain side to exert a reverse osmotic effect and thus the rebound phenomenon is considerably blunted (Guisado et al[14]).

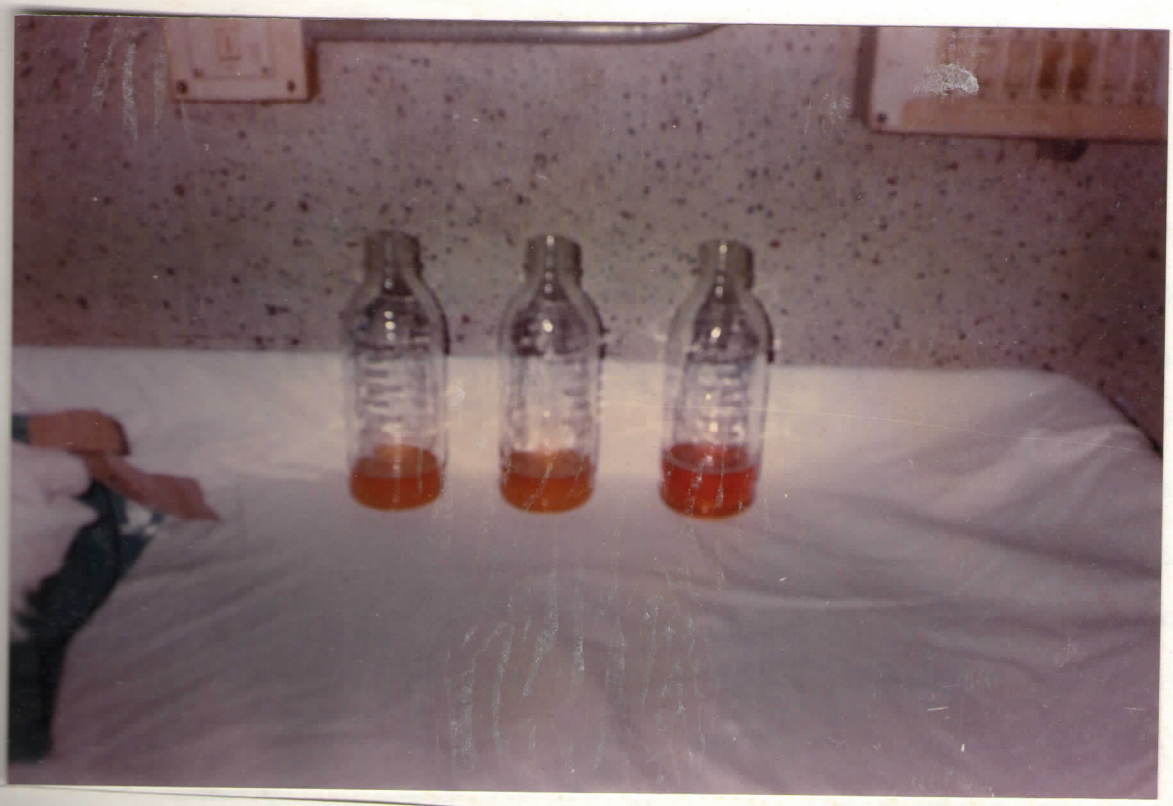
It is evident that glycerol administration is not without risk. The side effects include intravascular hemolysis, hemoglobinuria, renal damage, hyperglycaemia and hyperosmolality (Frank et al[6]). The risk of intravascular hemolysis and hemoglobinuria may in part be due to high concentrations (30% - Cantore[4], 20%-Hagnevik[16] et al). Frei et al[7] in a randomised double blind study documented a 96% incidence of hemoglobinuria in 18 patients treated with 10% glycerol for stroke.

The current study was undertaken because of the lack of experimental studies observing the effects of glycerol on a model of raised ICP. On comparing its effects with mannitol it was found that though ICP fell by an equal amount in both - 55.17%, that decrease in ICP was earlier and more prolonged in the glycerol treated animal as comared to manitol treated animals. The maximum reduction was seen 30 to 45 minutes post infusion in both. In the mannitol group it was preceeded by a raise in ICP coinciding with a rise of BP. This has been explain d by the expansive effect exerted by mannitol on the blood volume. At 4 hours post infusion the rebound effect was seen in the mannitol treated group when

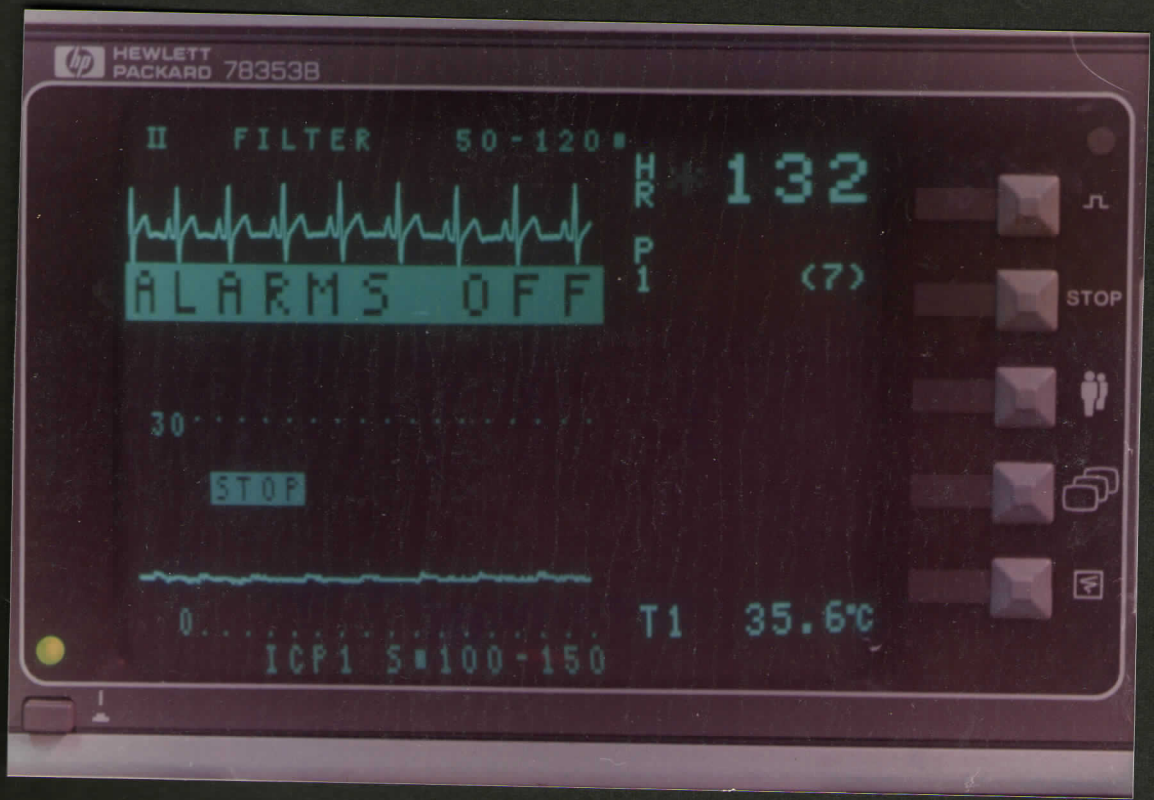
the ICP tended to come upto the baseline level, however it did not cross the baseline. No such rebound effect was seen in the glycerol treated group, where the ICP tended to remain low. A major complication seen in the glycerol treated group as the development of haemoglobinuria in 3 of the 5 animals.

Our findings suggest that intravenous glycerol (10%) gives a good control of intracranial hypertension. Moreover, the effect is not as predictable as mannitol. A major advantage of glycerol over mannitol in the absence of immediate post infusion rise in intracranial presence. In a clinical setting of acute rise in intracranial pressure with impending herniation, the momentary rise in ICP with mannitol infusion may tip the scales towards an unfavourable outcome. In contrast, the increased cerebral blood flow with mannitol may be beneficial in states of ischamia. The lack of rebound phenomena seen with repeated glycerol infusions makes it more effective in the long term management of raised intracranial pressure.

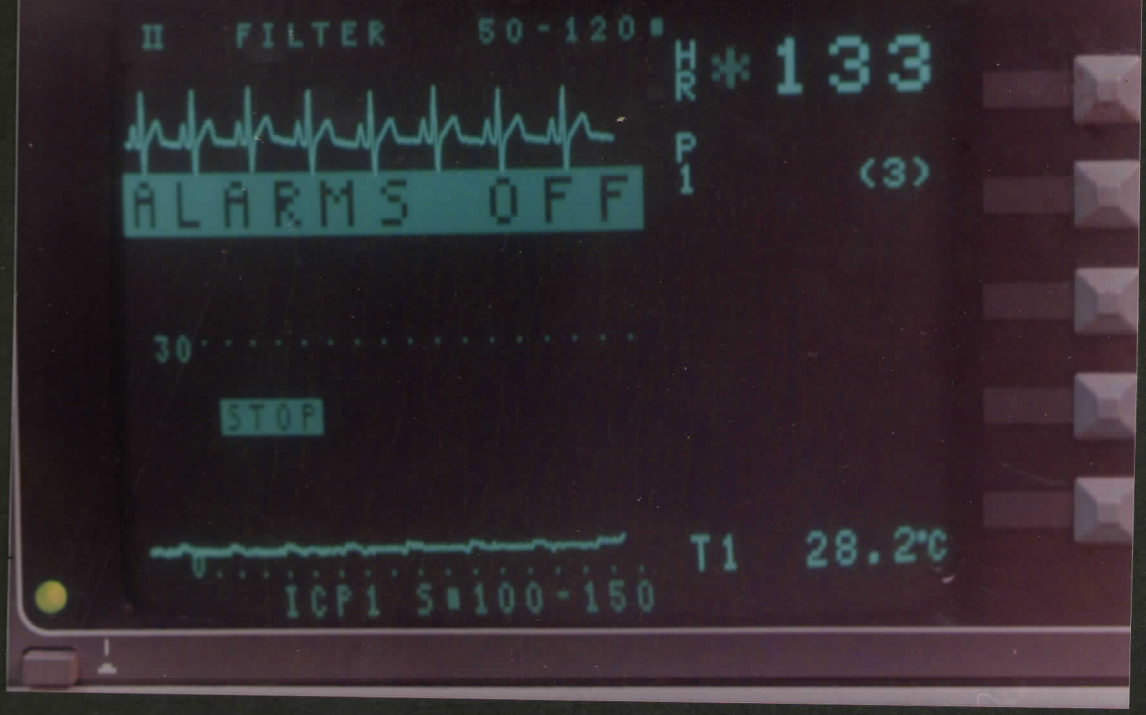
The major problem with glycerol infusion is the risk of hemoglobinuria even with a 10% solution. This may be unacceptable in patients with any degree of renal compromise. Further studies will be necessary to determine ways of surmounting this problem. Studies evaluating the effect of oral glycerol and different concentrations of glycerol are proposed as future studies.



3 consecutive urine samples showing progressively increasing haemoglobinuria



Maximal effect on ICP following infusion of glycerol



ICP recorded at the start of experiment

CONCLUSIONS

1. An experimental canine model of raised intracranial pressure could be effectively and reliably developed by ligation of neck veins.

2. Both mannitol and intravenous glycerol were equally effective in lowering the raised intracranial pressure.

3. Reduction in intracranial pressure was earlier and more prolonged in the glycerol treated group as compared to the mannitol treated group.

4. After the infusion of intravenous mannitol, a transient but significant rise in itracranial pressure was noted.

5. A major complication with glycerol infusion was the high incidence of haemoglobinuria.

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