Clinical Efficacy of Mannitol (10%) with Glycerine (10%) Versus Mannitol (20%) in Cerebral Oedema

Dr. Avinash Shankar¹*, Dr Shubham², Dr Amresh Shankar³, Dr. Anuradha Shankar⁴

¹MD(internal Medicine),DNB(E&M);PhD Postgraduate in Endocrinology & Metabolism (AIIMS-Delhi) Chairman ,National Institute of Health & Research Institute of Applied Endocrinology Warisaliganj (Nawada) Bihar 805130, India.

² MD (Paediatrics) Consultant Paediatrician Delhi, India.

³ BAMS (BRABU) MHA, Hon Director AarogyamPunarjeevan Ram Bhawan, Ara Garden Road, Jagdeo path,Baily Road PATNA 14,800014, India.

⁴ BAMS (BRABU) Senior Research Fellow Regional Institute of Ayurveda ,Itanagar (Arunachal Pradesh), India.

*Corresponding Author: Dr. Avinash Shankar, MD(internal Medicine),DNB(E&M);PhD Postgraduate in Endocrinology & Metabolism (AIIMS-Delhi) Chairman, National Institute of Health & Research Institute of Applied Endocrinology Warisaliganj (Nawada) Bihar 805130, India.

Abstract: Cerebral oedema is a common cause of unconsciousness and various manifestation in Cerebrovascular accident, head injury, convulsive disorder and encephalitis either due to infection or toxin due to failure of energy dependant Sodium Potassium ATPase pump resulting accumulation of sodium and water in addition release of free radicals and proteases due to activation of microglial cells disrupts cell membrane and capillaries.

Objective of Study: Comparative assessment of clinical efficacy of Mannitol 10% with Glycerol 10% versus Mannitol 20% in cerebral oedema of varied origin

Materials & Methods: In this study 1171 patients of cerebral oedema of various aetiology attending Medical Emergency of RA Hospital & Research Centre, Warisaliganj (Nawada) Bihar been selected for comparative evaluation of Mannitol (10%) with Glycerol (10%) versus Mannitol (20%) intravenously to adjudge the clinical efficacy and safety profile.

Result: Patients of Group A taking Mannitol (10%) with Glycerol (10%) had grade I clinical response in 99.6% % (584/586) without any adversity, residual neurological deficit Or mortality and morbidity while patients of Group B on Mannitol (20%) only 18.4% (108/585 ) with 15.7% ( 92) mortality and morbidity in 47.6% (279 )cases.

Keywords: Cerebral oedema, Cerebrovascular accident, Sodium potassium ATPase pump, free radicals, Protease, mortality, morbidity.

1. INTRODUCTION

Cerebral oedema is a common sequel of cerebro vascular accident (CVA). Head injury, convulsive disorder and infective or toxic involvement of brain. Cerebral oedema pathogenesis at cellular level is complex as - damaged cells swell, injured blood vessels leak and blocked absorption pathways force fluid to enter brain tissues. Cellular and blood vessel damage activate an injury cascade i.e.-release of glutamate into the extracellular space opens Calcium and sodium entry channels on cell membranes. Membrane ATPase pumps releases one calcium ion in exchange for 3 sodium ions which create an osmotic gradient promoting increase water entry to cells and causes dysfunction but not necessarily permanent damage. Ultimately hypoxias deplete the cells’ energy stores and disable the sodium – potassium ATPase reducing calcium exchange (1, 2, 3)

Failure of the energy-dependent sodium pump in the cellular membrane causes accumulation of Sodium and water to the intracellular space to maintain osmotic gradient while accumulation of Calcium inside the cell activate intracellular cytotoxic processes. Formation of genes like c-foc and e-jun and cytokines and other intermediary substances initiate inflammatory response. Activation of...
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Microglia cells releases free radicals and proteases attacks on cell membranes and capillaries which results in the cells recovery impossible(4,5,6,7).

In addition negligent and lack of proper restriction, investigation and health care counselling and education, people suffer with dreaded sequel of hypertension i.e. Cerebrovascular accident results in unconscious, convulsion, paralysis and coma which modify the outcome of the disease and increases the mortality.

To overcome the brain oedema, the commonly prescribed urgent measure remains intravenous mannitol and oxygen inhalation. Usually Oral glycerol remains the choice to relieve brain oedema.

Considering the clinical effect of oral glycerol and availability of Mannitol 10% with Glycerol 10%, a clinical study was conducted to evaluate the clinical effect and safety profile of 10% glycerol with 10% mannitol versus Mannitol 20% in management of cerebral oedema of either origin.

**Objective of Study**

To adjudge the clinical efficacy of Mannitol 10% with Glycerol 10% versus Mannitol 20% in

**Design of Study**

Comparative clinical study

2. **MATERIALS & METHODS**

2.1. Material

Patients of cerebral oedema of either origin attending at RA.Hospital & Research Centre Emergency were selected for evaluation of Mannitol (10%) with Glycerol (10%) versus conventional Mannitol 20% therapy.

2.2. Methods

Parent or attendants of the admitted patients were thoroughly interrogated for the presenting feature onset, its duration, treatment taken and their outcome, any history of such attacks in past. All the patients were examined for their blood pressure, temperature, any marks of injury over the head, blood sugar, and sample collected for other vital parameters assessment. Patients were classified in to two groups comprising equal number of patients i.e.

| Clinical status            | Group A | Group B |
|----------------------------|---------|---------|
| Head injury                | 54      | 54      |
| Cerebro vascular accident  | 315     | 315     |
| Toxemia                    | 5       | 5       |
| Febrile convulsion         | 5       | 5       |
| Convulsive disorder        | 181     | 180     |
| Encephilitis               | 26      | 26      |

All the patients irrespective of their cause of unconsciousness or cerebral oedema were advocated –

- Oxygen inhalation
- Specific treatment (Anti hypertensive measure for hypertension, anti diabetic measure for diabetes mellitus.)
- IV nutrition
- IV chemoprophylaxis
- Other desired measures as per need (anti convulsant for convulsion)
- Diazepam administration is duly restricted.

While group A patients were given Mannitol 10% and glycerol 10% (Glycerol is a potent osmotic dehydrating agent with additional effects on brain metabolism. In doses of 0.25- 2.0 g/kg glycerol) Intravenous and group B Mannitol 20%. (Mannitol in a dose of 1.5 g/kg body weight was infused over a period of 15 minutes, followed by 0.5 g/kg body weight every 8 hours until the patient regained consciousness or for a maximum period of 72 hours.)

Patients were assessed as per following index of assessment i.e.-

3. **INDEX OF ASSESSMENT**

Recovery time from unconsciousness

Status of paralysis
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Neural recovery
- Status of alertness
- Status of speech
- Mental capability
- Motor power and tone

Effect on various bio parameters Post therapy sequel:
- Polyuria
- Polydipsia
- Irritability
- Pulmonary congestion,
- fluid and electrolyte imbalance,
- acidosis,
- electrolyte loss,
- dryness of mouth, thirst,
- marked diuresis,
- urinary retention,
- Oedema,
- headache,
- blurred vision,
- convulsions,
- nausea,
- vomiting,
- hypotension,
- tachycardia,

To assess the safety profile of the administered drug the basic bio parameters i.e. - haematological, hepatic and renal profile are repeated

On the basis of clinical achievement clinical response was graded as

Grade I: Complete recovery from unconsciousness within 6 hrs
No convulsion, Recovery from paralysis (motor power and tone) without any adversity and residual neuropsychiatric presentation or change in bio parameters.

Grade II: Complete recovery from unconsciousness within 12 hours
No convulsion, Recovery from paralysis (motor power and tone) without any adversity and residual neuropsychiatric presentation or change in bio parameters.

Grade III: Improvement in unconsciousness, complete recovery in >48 hrs, Occasional convulsion, improvement in power and tone, presence of adversity like polyuria, polydipsia, hypotension, tachycardia, blurred vision, post therapy urinary retention, marked change in bio parameters.

4. Observation
Among the admitted 1171 patients of cerebral oedema 797 (68%) and 374 (32%) respectively were of male and female respectively. Majority patients ( ) were of age >50 years though 14 cases were of age 10-15 years.
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Table 1. Number of patients of cerebral oedema

| Age group (in yrs) | Male | Female | Total |
|--------------------|------|--------|-------|
| 10-15              | 09   | 05     | 14    |
| 15-20              | 11   | 07     | 18    |
| 20-25              | 28   | 13     | 41    |
| 25-30              | 64   | 34     | 98    |
| 30-35              | 58   | 26     | 84    |
| 35-40              | 87   | 29     | 116   |
| 40-45              | 54   | 24     | 78    |
| 45-50              | 58   | 30     | 88    |
| 50-55              | 110  | 54     | 164   |
| 55-60              | 130  | 70     | 200   |
| >60                | 188  | 82     | 270   |
| Total              | 797(68%) | 374(32%) | 1171 |

Fig 1. Pie diagram showing sex wise composition of patients

Out of all majority 630 (53.8%) were of CVA, 361 (30.8%) were of convulsive disorder while 108 (9.2%) were of head injury

Table 2. Shows distribution of patients as per causes of Cerebral Oedema

| Causative factors      | Number of patients |
|------------------------|--------------------|
| Head injury            | 108                |
| Cerebro vascular accident | 630               |
| Toxemia                | 10                 |
| Febrile convulsion     | 10                 |
| Convulsive disorder    | 361                |
| Encephlitis            | 52                 |

Among the selected patients 77.2% were hypertensive out of which 9.3% were with malignant hypertension (average >160)

Table 3. Distribution of patients as per average blood pressure record on admission

| Average blood pressure (in mmHg) | Male | Female | Total |
|---------------------------------|------|--------|-------|
| <120                            | 152  | 115    | 267   |
| 130-135                         | 74   | 46     | 120   |
| 135-140                         | 74   | 39     | 113   |
| 140-145                         | 91   | 38     | 129   |
| 145-150                         | 95   | 40     | 135   |
| 150-155                         | 101  | 57     | 158   |
| 155-160                         | 100  | 40     | 140   |
| >160                            | 80   | 29     | 109   |
| Total                           | 767  | 404    | 1171  |

And 75.5% were diabetic out of which 11.1% were with random blood sugar >400mg%
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**Table 4. Distribution of patients as per random blood sugar status**

| Random blood sugar (in mg %) | Number of patients | Male | Female | Total | Percent |
|-----------------------------|--------------------|------|--------|-------|---------|
| <200                        |                    | 200  | 87     | 287   | 26.8    |
| 200-250                     |                    | 54   | 40     | 94    |         |
| 250-300                     |                    | 166  | 84     | 250   | 22.5    |
| 300-350                     |                    | 89   | 45     | 124   |         |
| 350-400                     |                    | 223  | 68     | 291   |         |
| >400                        |                    | 75   | 50     | 125   | 11.1    |

All admitted cases were unconscious, 36.9% were presenting with convulsion and 53.8% with hemiplegic.

**Table 5. Distribution of patients as per clinical presentation**

| Clinical presentation | Number of patients | Percent |
|-----------------------|--------------------|---------|
| Unconscious           | 1171               | 100%    |
| Hemiplegia            | 630                | 53.8    |
| Right side            | 139                | 22.06   |
| Left side             | 491                | 77.94   |
| Convulsion            | 433                | 36.9    |

67.3% patients been admitted within 24 hrs of incident while rest after 24 hrs

**Fig 2. Bar diagram showing lag period**

Among the patients 704 known hypertensive and 590 known diabetic were not taking any drug while no history has been elucidated in 287 cases.

**Table 6. Distribution of patients as per previous history of illness**

| History of previous illness               | Number of patients |
|-------------------------------------------|--------------------|
| Hypertensive taking AHT                   | 296                |
| Hypertensive never taken any drug         | 701                |
| Known diabetic taking drugs               | 294                |
| Known diabetic not taking any drug        | 590                |
| Unknown                                   | 287                |

Among the selected patients 183 were addict to all types of narcotics while 355 were having no history of any personal habits

**Table 7. Distribution of patients as per their personal habits**

| Personal habits              | Number of patients |
|-------------------------------|--------------------|
| Alcoholic                     | 302                |
| Smoker                        | 254                |
| Tabacco chewer                | 567                |
| Cannabis smoker               | 165                |
| Gutka                         | 214                |
| All types of narcotics        | 183                |
| Non addicts                   | 355                |

865 were pure vegetarian while rest were non vegetarian
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![Fig3. Bar diagram showing dietary status](image)

Patients of group A had complete recovery from unconsciousness by 4 hrs while group B patients taken > 12 hrs and 92 patients fails to revive and succumb.

Out of all 536 patients of group A achieved normal CNS function without any residual paralysis, improved general condition and normal life status grade I response in 534 without any adversity or alteration in bio parameters while in group B only 212 patients regained power and tone, improved general condition in 108, normal life status 112, altered CNS function in 132 with residual paralysis in 147 grade I clinical response in only 108 with altered bio parameters in 24 cases

**Table8. Out com of the study**

| Particulars               | Number of patients |
|---------------------------|--------------------|
|                           | Group A            | Group B            |
| Consciousness recovery time | 4 hrs             | >12 hrs            |
| Regain in power and tone  | all                | 212                |
| Improved general condition | all                | 108                |
| Quality of life           |                    |
| Normal                    | 586                | 112                |
| Mortality                 | none               | 92                 |
| CNS function              |                    |
| Normal                    | 586                | 214                |
| Altered                   | none               | 132                |
| Residual paralysis        | none               | 147                |
| Safety profile            |                    |
| Renal profile             |                    |
| < 26mg                    | 586                | 472                |
| > 26mg                    | -                  | 21                 |
| Serum Creatinin           |                    |
| <1.5mg                    | 586                | 473                |
| > 1.5mg                   | -                  | 20                 |
| Urine albumin             |                    |
| Positive                  | none               | 24                 |
| Urine RBC                 | none               | 20                 |
| Hepatic profile           |                    |
| Serum bilirubin           |                    |
| <1mg                      | 586                | 493                |
| SGOT                      | 586                | 493                |
| <35 IU                    | 586                | 493                |
| SGPT                      | 586                | 493                |
| <35 IU                    |                    |
| Clinical grade            |                    |
| Grade I                   | 584                | 108                |
| Grade II                  | 02                 | 106                |
| Grade III                 | -                  | 279                |
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| ENROLLED | MANNITOL (10%) + GLYCEROL (10%) | MANNITOL (20%) |
|----------|---------------------------------|----------------|
| CVA      | (630)                           | (586)          |
| Head Injury | (108)                            |                |
| Others   | (433)                           |                |

| Survived | Dead   |
|----------|--------|
| CVA      |        |
| Head Injury |      |
| Others   |        |

- **5. RESULT**

99.6% (584/586) Patients of Cerebral edema on Mannitol 10% with Glycerol 10% intravenously had early regain of consciousness and recovery of power, tone, memory and IQ without any adversity or residual neuro deficit than Mannitol 20% which had grade I clinical response in only 18.4% (108/585) morbidity in 47.6% (279/585) and mortality in 15.7% (92/585) with altered neurological function.

- **6. DISCUSSION**

On injury or ischemia of Central nervous system CNS mediators like Glutamate, free fatty acid or high extracellular potassium compounds are released or activated resulting in swelling and damage of nerve cells. In addition substances like histamine, arachidonic acid and free radicals including nitrous oxide are also known mediators causing cerebral oedema. Bradykinin may be involved after cold lesion, concussive brain injury, traumatic spinal cord and ischaemic brain injury. (8, 9)

In stroke cerebral ischaemia causes loss of membrane ionic pumps and cell swelling while irreversible cell membrane damage is caused by generation of free radicals and proteases.

As per Monro-Kelie hypothesis, change in the volume of any of the three content of skull (inside the skull) i.e. brain – 1400 ml, cerebral spinal fluid (CSF) 150 ml and blood 150 ml change the volume of other. Conversely, primary blood flow disturbances also lead to brain oedema. (10, 11, 12)

Significant supremacy of Mannitol 0% with Glycerol 10% as compared to Mannitol 20% can be explained as:

Mannitol is an isomer of sorbitol, administered intravenously confined to the extracellular space, only slightly metabolized and rapidly excreted by the kidney. Approximately 80% of a 100 g dose appears in the urine in 3 hours. The drug is freely filtered by the glomeruli with less than 10% tubular reabsorption; it is not secreted by tubular cells and induces diuresis by elevating the osmolarity of the glomerular filtrate (13, 14, 15)

Mannitol is used to reduce acutely raised intracranial pressure until more definitive treatment can be applied, e.g., after head trauma. (16, 17)

Such solutions are effective not only in lowering the intracranial pressure, but also in improving the cerebral blood flow and metabolism.

Glycerol is a potent osmotic dehydrating agent with additional effects on brain metabolism. In doses of 0.25- 2.0 g/kg glycerol decreases intracranial pressure in various disease state however, intravenous doses of 1–2 g/kg every 2 hr can be administered safely in severe cases of elevated ICP.

Thus combination of Mannitol and Glycerol decreases the dose of mannitol thus its side effects like diuresis and asthenia in addition Glycerol helps in neural recovery and sustained resolution of cerebral oedema thus ensure prompt recovery of CNS function without alteration in mental capability and IQ. Or residual paresis (18, 19, 20, 21, 22).
7. CONCLUSION

Mannitol 10% with Glycerol 10% proves better than Mannitol 20% as it spares dose of mannitol and protect from mannitol overdose adversity with better CNS bioregulation with any residual neurodificit.

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