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## Mini Review

# Safety a Major Concern with Neurotherapeutic in Traumatic Brain Injury -

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## INTRODUCTION

Neurotol, a R&D product from Venus Medicine Research Centre in glass bottle for IV infusion in case of trauma, brain injury, neurological surgeries and in management of ICP. One of the major challenge associated with these indications is neurotoxic side effects resulting in sequelae which turn out to be more or equally serious complications even after the trauma is cured. Neurotol offers enhanced safety and efficacy over market competitor products in case of glycerol based neurotherapeutics in a clinical set up. The formulation of Neurotol contains mainly 3 ingredients viz. Mannitol, glycerol and a chemical vector RD011.

Glycerol is one of the most widely used active ingredient for parenteral (IV) administration for treatment of brain oedema of ischemic, toxic, metabolic and inflammatory origin. Glycerine alone as infusion has been used in many countries and in India Glycerol (10%) with Mannitol (10%) is approved for IV infusion by DCGI for Cerebral oedema management in Cerebral Infarction, Intracerebral Hemorrhage, Head Injury, Subdural hematoma, Brain tumor, Encephalitis, Meningitis. The same composition is being sold by Venus under brand name Neurotol. Glycerol when used in 1.2 g/kg body weight reduces cerebral oedema. Glycerol and Mannitol alone or in combination can be used for ICP management. Mannitol and glycerol, two sugars with good osmotic diuretic properties are used to maintain the osmotic pressure in the cranium. Mannitol when used in dose of 1.5-2 g/kg body weight, reduces raised Intra Cranial Pressure (ICP) within 30 - 60 minutes and is used to treat cerebral oedema [1]. However, the addition of glycerol to mannitol avoids rebound oedema likely to be observed with plain mannitol when administered. This provides a strong rationale for the combination of mannitol with glycerol for the management of increased intracranial pressure and cerebral oedema [1]. We confirm that Glycerol infusion is readily used product in various countries and contains glycerol as an active ingredient with therapeutic category “osmotic diuretic” and thereby reduces intra cranial pressure and also prevents rebound hypertension as occurs with mannitol alone.

Cerebral Edema (CE) is a dangerous life-threatening condition where the brain's water content rises and lead to increased intracranial pressure. CE may develop as a result of an inflammatory reaction and is a prominent feature of cerebral trauma, massive cerebral infarction, hemorrhages, abscess, tumor, allergy, sepsis and hypoxia [2,3]. The treatment of CE is complex and currently there is no effective clinical treatment for this medical emergency. Brain is protected by a hard and inflexible skull so has very little space to expand. Hence CE may lead to reduced oxygen supply to brain cells and can even lead to death. Brain edema is an important feature of brain tumors and often contributes to neurologic dysfunction and impaired quality of life [4,5].

Morbidity and mortality have remained high despite improvements in our understanding of pathophysiological mechanisms associated with CE and more effective treatment is required. An “ideal” agent for the treatment of CE would be one that would selectively mobilize and /or stop the formation of edema fluid with a fast onset and prolonged duration of action, and with minimal side effects.

Mannitol is the most widely researched and commonly used osmotic agent for CE. However the exact mechanisms of action remains undefined. Osmotic and hemodynamic effects are the main proposed mechanisms for the Mannitol in this intricacy [6,7].

However, use of Mannitol in reducing Intracranial Pressure (ICP) is not risk free. Previous reports suggests possibility of aggravated edema after prolonged administration of Mannitol. Glycerol, another osmotic agent provides a therapeutic alternative and has been found to exert beneficial effects in controlling ICP in edema and other pathological conditions. Previous studies suggest that “rebound phenomenon” after administration of glycerol solution may be less prominent, because it is metabolized intra cellular. Further, Glycerol may improve ischemic brain energy metabolism as evident from available literature [8,9].

A combination product of Mannitol and Glycerol has been developed with the primary objective of avoiding “rebound edema” associated with monotherapy of Mannitol. Combination product also enhances the diffusion of water from cerebrospinal fluid back into systemic circulation by elevating the osmolality of the plasma. Main mechanisms that may be responsible for this protective effect include redistribution of cerebral and regional cerebral blood volume and reduction in focal cerebral edema. Apart from this Glycerol (10%) also provides an alternative source of energy either by directly metabolized by the brain or indirectly via enhancing lipogenesis, if glucose is lacking [10,11].

## RATIONALE FOR PHARMACEUTICAL DEVELOPMENT

Glycerol based parenterals are one of the most widely used in clinical practice for the treatment of brain oedema of ischemic, toxic, metabolic and inflammatory origin. Mannitol and glycerol, two sugars with good osmotic diuretic properties are used to maintain the osmotic pressure in the cranium. Mannitol when used in dose of 1.5 -2 g/kg body weight, reduces raised Intra Cranial Pressure (ICP) within 30-60 minutes and is used to treat cerebral oedema [1]. Glycerol when used in 1.2 g/kg body weight reduces cerebral oedema. Either Glycerol or mannitol can be administered individually by parenteral route. Individual formulations are readily available in the market. However the addition of glycerol to mannitol avoids rebound oedema likely to be observed with plain mannitol when administered. This provides a strong rationale for the combination of mannitol with glycerol for the management of increased intracranial pressure and cerebral oedema [1].

RD 011, an excipient with proven reduction of vascular instability, lessening hypoxic damage, and protection against cytokine or excitatory amino acid damage, has been used to develop this formulation. The excipient has membrane stabilizing properties which is of utmost importance in case of neuroprotection. The pathophysiology of ischemic brain injury and Traumatic Brain Injury (TBI) involves a number of mechanisms (Figure 1) leading to neuronal injury, including excitotoxicity, free radical damage, inflammation, necrosis, and apoptosis. Brain injury also triggers auto-protective mechanisms, including the up-regulation of anti-inflammatory cytokines and endogenous antioxidants. Secondary brain damage following severe head injury is considered to be a major cause for poor outcome. Hence, there is a great need for neuroprotective therapies.

Categories of drugs tested for Neuroprotective effect for traumatic brain injury (4):

1. Anti-inflammatory agents
2. Anti-oxidants



3. Apoptosis inhibitor
4. Bradykinin antagonist
5. Ion-channel blockers (calcium)
6. Necrosis inhibitor
7. Neurotrophic factor- For example nerve growth factor, brain derived neurotrophic factor
8. NMDA receptor antagonist and others

Understanding the current research, an agent with multiple effect is more likely to provide effective neuroprotection and repair than one operating primarily on a single, or a small number of, injury mechanisms.

To address the current unmet need, VMRC has come out with a magnesium based chemical vector RD011. It acts by several mechanism that covers most of the ideal mechanism by which neuroprotection is proved to be achieved by preclinical and clinical studies.

**Ideal Properties of Chemical Vector**

- Increase regional cerebral blood flow to ischemic brain areas and prevents secondary ischemic attack [5-8].
- Non-specific antagonism of all sub-types of voltage sensitive calcium channel. Block N-Type and L-Type calcium channels, prevents cellular calcium entry through N-Methyl-D-aspartate receptor channels, reduces calcium induced mitochondrial dysfunction [6-12].

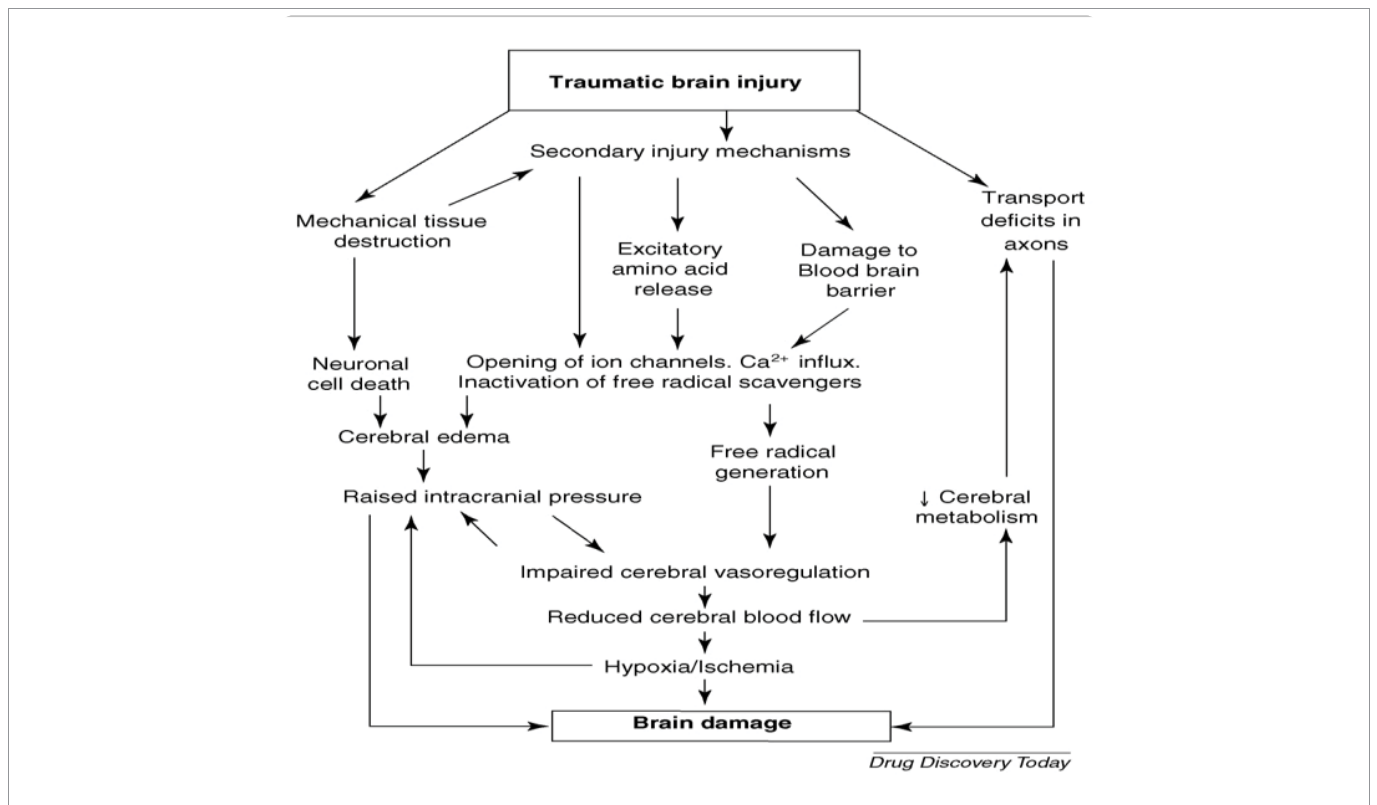
- Non-competitive blockade of the NMDA subclass of glutamate receptor [13].
- Glutamate release inhibition [14].
- Enhanced recovery of cellular energy metabolism after ischemia [2].
- Has potent anticonstrictor effects against relevant mediators including endothelin-1, angiotensin-II, [15] prostaglandin F2 alpha, Serotonin, [16] and excitatory amino acids [17].
- Stimulates neurogenesis [18].
- Anti- apoptotic, anti-oxidant [19] (superoxide dismutase and glutathione peroxidase) [20]
- Up regulation of Brain-Derived Neurotrophic Factor (BDNF) [20,21]

As per our in-house data:

- Chemical vector has Increased malondialdehyde, MMP-9 (Matrix metallo-protenase), and GSH (glutathione) levels.
- Decrease in Xanthine oxidase, adenylate kinase and MDA (malondialdehyde)
- Decreased brain water level
- 28 days sub- acute toxicity data

**Neuroprotective Effect**

Neurotol provides a better neuroprotective effect in comparison to other marketed products. A number of neuropathological processes are linked with glutamate excitotoxicity and oxidative stress that lead



*Drug Discovery Today*

**Figure 1:** Sequence of events following traumatic brain injury as this segment has great unmet need, leading pharm companies are actively involved and has their pipeline in this segment. Pipeline drugs for Neuroprotective agents (3): As TBI injury involves different mechanism, different categories of drugs has been tested for neuroprotective effect.

Competitive environment

Drugs or approaches	Company group	Development stage (trial name)	Mechanism of action
Nimodipine	Bayer	HIT 4	Calcium channel blocker
SNX-111	Neurox/Parke Davis	I/II (terminated due to high mortality)	N-type calcium channel blocker
Corticosteroids	Pharmacia/Upjohn, Pfizer	CRASH	Anti oxidative effect
Darbeopetin alfa	Amgen	II	Erythropoiesis and neuroprotection
Dexanabol	Pharmos	II	NMDA receptor antagonist
Recombinant factor VIIa	NovoSeven	I	Haemostatic effect
Methylphenidate (Ritalin)	Novartis	IV	Dopamine antagonist
Amantadine	Banner Pharmacaps	II	Dopaminergic agonist
Anatibant	Solvay	II	Bradykinin B2 antagonist
Progesterone	Emory University Investigational Drug Service	II (ProTECT)	Multiple effects (anti-inflammatory, anti-oxidative, anti-apoptotic)
Rosuvastatin (Crestor)	AstraZeneca	I	$\beta$ -hydroxy- $\beta$ -methylglutaryl coenzyme A reductase inhibitor
EPO	Amgen	III	Erythropoiesis and neuroprotection

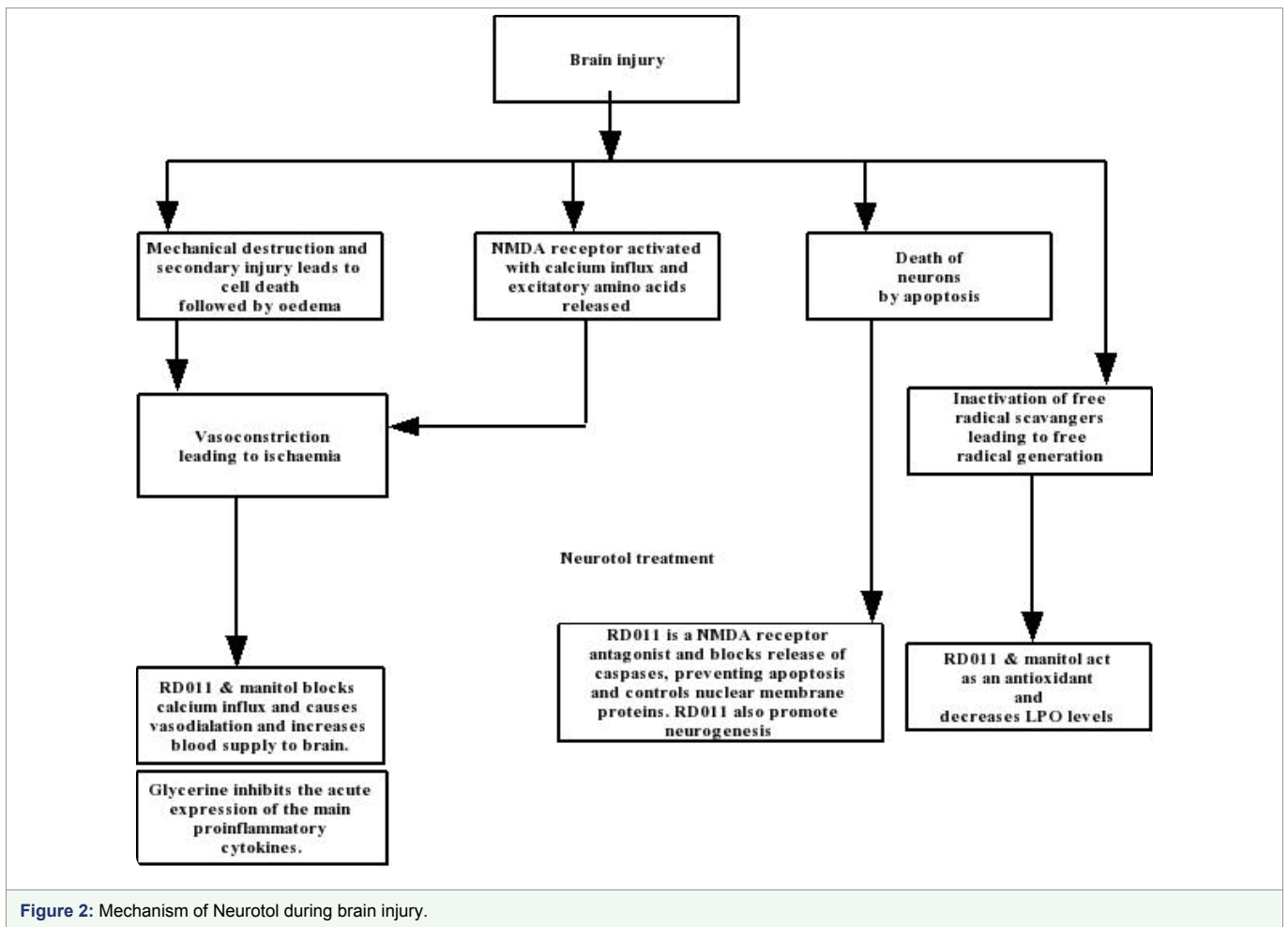


Figure 2: Mechanism of Neurotol during brain injury.

to neuronal damage and death. Glutamate is believed to be a major excitatory neurotransmitter involved in various functions including learning, memory and motor function of brain. Additionally, it is involved in neuronal tissue damage during cerebral ischemic hypoxia caused by accumulation of excess glutamate in the central nervous system [20-22]. Till date, two pathways for glutamate toxicity have been described: first is receptor mediated which involves activation of glutamatergic receptors and second is oxidative pathway, which includes disturbances of redox homeostasis of the cell [23]. The excess glutamate leads to excessive activation of glutamate receptors and is believed to play a role in the pathophysiology of many diseases [24].

Excess levels of glutamate allow the Ca<sup>2+</sup> influx into the cytosol. Excess calcium in the cytosol of the cell triggers the activation of glutamate receptors through ionotropic N-Methyl- D- Aspartate (NMDA) receptors as well as kinases including Ca<sup>2+</sup>/calmodulin-dependent kinases (CaMK), Mitogen Activated Protein Kinases (MAP), which causes changes in neuronal structure and function [25,26]. Glutamate receptor activation also stimulates an increase in mitochondrial respiration (electron transport) to generate the ATP necessary to drive the activity of ion-motive ATPase's that restore ion gradients across cellular membranes [24]. Mitochondrial Ca<sup>2+</sup> uptake and increased mitochondrial respiration can result in



production of damaging free radical superoxide anion [25]. These free radicals interact with the neuron's membrane structures, including nuclear, mitochondrial and cellular membranes that trigger neuronal cell death, a process called excitotoxicity [26]. An increasing number of reports have shown that reactive oxygen species (ROS) provoked by glutamate-linked oxidative stress are involved in brain injury [24]. ROS leads to oxidative stress which is involved in numerous neuropathological disorders such as ischemic stroke, Traumatic Brain Injury (TBI), depression, Alzheimer's disease, Parkinson's disease [27-29]. Neuronal injury is also associated with a decline in both total and free brain magnesium concentrations that could persist over several days. The neuroprotective efficacy of magnesium has been attributed to a variety of the effects of this molecule on patho-physiological mechanisms during and after cerebral ischemia, vasodilatation, inhibition of the NMDA Enhanced receptor and anti-convulsant properties [30].

Over 30 years, mannitol has been used clinically as an osmotherapeutic drug on brain injury which protects the brain by reducing blood viscosity [31,32]. Despite its neuroprotective action, it is associated with the "rebound phenomenon" [33]. Glycerol is another agent that has been used in the treatment of brain oedema caused by ischaemia or trauma [34]. Apart from its hypertonic nature it also act as a free radical scavenger, antioxidant and activator of plasma prostaglandin resulting in vasodilation [31,32,35].

Magnesium salt based RD011 typically provides its neuroprotective activity by four different mechanisms viz.

1. Hemodynamic stability.
2. Prevention of excitement injuries and neuronal stabilization (membrane stabilization properties).
3. Antioxidant properties.
4. Anti-inflammatory properties.

Thus, the use of RD011 has a definitive edge in terms of better safety and efficacy with added neuroprotection. Hippocampus, a major component of human brain plays an important role in learning and memory [36]. It has been reported that hippocampus is the most sensitive to various neurological insults such as hypoxia-ischemia, seizure and prolonged stress [37]. Despite the clinical importance of neuronal injury, currently there are no effective medicines to combat diseases caused by glutamate excitotoxic cascade.

Therefore, RD 011 is added to provide a neuroprotective effect to neurotol which clearly provides an edge over the competitors [38].

In another study [39], glycerol based parenteral neurotherapeutics in glass and plastic containers were tested for leachables and extractable. Leachables and extractables are one of the most common sources of contamination in injectables. The amount of these contaminants may increase to toxic levels in case of glycerol based parenteral dosage forms used in neurotherapeutics. Glycerol, a plasticizer, softens the core plastic material and thus the number and amount of leachables increase. Three different glycerol based marketed injectable formulations, two available in plastic [Polypropylene (PP)/ Low Density Poly Ethylene (LDPE)] and the other in glass container, were kept under stress and accelerated stability testing and subjected to various tests including Gas Chromatography-Mass Spectroscopy (GC-MS) to study the type and amount of leachable. Several new leached out toxic components were identified in case of plastic (PP and LDPE) container and none in case of glass container. Presence

of Bisphenol A at a concentration more than 12 times higher/bottle compared to the recommended Maximum Allowable Dose Level (MADL) and di butyl phthalate another highly toxic compound at a concentration 2.7 times higher/bottle than tolerable daily intake decided by National Toxicology Programmed are alarming findings. In vivo animal studies confirmed the neuro and endocrine disruptive potential of these impurities as well as hepatotoxicity due to oxidative stress. Thus it is concluded that Neurotol in glass container is a much safer option than those that are packed in plastic container.

### Clinical Efficacy Data

A retrospective study was carried out in a tertiary care hospital in India on 108 patients between January 2013 to November 2014. The patients were administered with either fixed dose combination of Mannitol 10% + Glycerol 10% or Mannitol (20%). Among these, 54 clinically cured patients, 30 were considered in the study, while the rest were excluded from the study. Demographic characters like gender, age, weight and height patients were recorded. The vital signs like pulse, temperature and BP were also recorded

A total 30 subjects included were divided in 2 treatment arms of 15 patients each. Each treatment arm received either Neurotol FDC of Mannitol 10% + Glycerol 10% or Mannitol (20%) (50-200 g, 250 - 1000 ml) by intravenous (i.v) route. Treatment therapy was decided according to disease therapy by the concerned physician.

Patients in the age group of 18-70 years were included in the study. Patients were selected, on the basis of sustained elevated intracranial pressure of more than 20 mmHg for more than 10 min. Patients who had preexisting renal abnormalities or serum creatinine levels greater than or equal to 2.0 mg/dl were excluded. Patients were also excluded if they had leakage or drainage of cerebral fluid, unstable respiratory and haemodynamic conditions.

Data collected and evaluated included patient initials, age, weight, height, gender, pulse rate, respiratory rate, blood pressure, body temperature. The efficacy of treatments was assessed by measured GCS (Glasgow Coma Scale) score and intracranial pressure changes. GCS provides a reliable, objective way of recording the conscious state of a person. The scale evaluates 3 (eye, verbal and motor) responses. In this study sum of values were considered. The lowest possible GCS (the sum) is 3 represents deep coma or death, while the highest is 15 (fully awake person). ICP is the pressure inside the skull and thus in the brain tissue and Cerebrospinal Fluid (CSF). In this study 20 mm Hg was considered the upper limit of normal ICP. Adverse events that occurred during the observational period were collected regardless of causality to the drug. The presence/absence of ADR onset after the start of treatment, name of the ADR, date of onset, seriousness, progress, medication taken for the ADR, outcome, and date of outcome, drug-event relationship, and suspected concomitant medication were evaluated for all ADRs.

Table 1 represents demographic parameters of the study. A total of 30 patients were enrolled in the retrospective study. 15 patients were in each treatment arm. Mean age of patients was 59.71 + 8.957 and 54.11 ± 10.555 in Neurotol FDC of Mannitol + Glycerol and Mannitol treatment arms respectively. All other baseline characteristics (gender, height, weight, pulse rate, respiratory rate and blood pressure) are summarized in table 1. Subjects were similar across both groups with respect to these characteristics.

### DISCUSSION



A combination product of Mannitol and Glycerol was developed indigenously for the treatment of CE. Mannitol is in use for CE since long time back. Clinical data demonstrates that Mannitol an osmotic agent reduces ICP and helps in clearing extra fluid from brain back to systemic circulation [40]. However, chances of ‘rebound edema’ limits its therapeutic utility [33]. Further prolonged administration of Mannitol may results in electrolyte imbalance and requires close supervision for the development of cardiopulmonary complications in addition to neurological assessment [41]. Present study compares the safety, tolerability and efficacy of this new Neurotol (Mannitol + Glycerol + RD 011) with Mannitol in CE patients. The most important finding of this study was that Neurotol displayed better safety and efficacy profile than Mannitol alone therapy.

Efficacy evaluation was carried out by the determination of GCS score and ICP measurement. GCS is a reliable and objective way of recording the conscious state of a person. GCS provides a score in the range of 3-15 and patients with scores of 3-8 are considered to be in the state of coma [42]. In our study treatment with Neurotol FDC (Mannitol + Glycerol) increased GCS score significantly ( $p < 0.001$ ) from  $10.07 \pm 1.223$  to  $14.67 \pm 0.488$  indicating a favorable clinical outcome with the treatment. Treatment with Mannitol increased GCS score but it was not significant ( $p > 0.05$ ) from baseline values. Cruz et al [43]. Reported that high dose of Mannitol improves GCS score.

Raised intracranial pressure is the prominent feature of CE [44]. In this study treatment with both Neurotol and Mannitol significantly ( $p < 0.001$  and  $p < 0.05$ ) decreased ICP values. However the reduction effect was more prominent in the Mannitol treated group. The addition of Glycerol to Mannitol provides additional beneficial effects in controlling ICP in edema by providing better osmotic diuretic properties. Previous reports suggests that 10% Glycerol provide an alternative source of energy and may improve ischemic brain energy

**Table 1:** Demographic data (mean  $\pm$  SD) of Neurotol FDC (Mannitol + Glycerol) and Mannitol administered patients

Parameters	Neurotol (N=15)		Mannitol (N=15)	
	Screening	Completion of therapy	Screening	Completion of therapy
Age	59.71 $\pm$ 8.957		54.11 $\pm$ 10.555	
Gender	Male: 8; Female: 7		Male: 10; Female: 5	
Height (cm)	171.64 $\pm$ 8.186		160.67 $\pm$ 10.358	
Weight(kg)	70.36 $\pm$ 17.809	71.90 $\pm$ 15.751	66.11 $\pm$ 9.443	64.83 $\pm$ 9.420
Pulse Rate	63.86 $\pm$ 9.654	61.80 $\pm$ 6.957	67.22 $\pm$ 11.502	63.56 $\pm$ 10.945
Respiratory Rate	21.43 $\pm$ 2.766	23.78 $\pm$ 2.906	21.67 $\pm$ 2.679	20.89 $\pm$ 1.711
Blood pressure				
Systolic Blood pressure (mm/Hg)	157.86 $\pm$ 16.723	154.00 $\pm$ 15.055	158.89 $\pm$ 20.260	155.00 $\pm$ 21.213
Diastolic Blood pressure (mm/Hg)	87.14 $\pm$ 10.690	82.00 $\pm$ 6.325	85.56 $\pm$ 7.838	81.39 $\pm$ 7.823
Body Temperature ( $^{\circ}$ C)	99.01 $\pm$ 0.256	99.00 $\pm$ 0.00	98.67 $\pm$ 1.311	98.64 $\pm$ 1.338

**GCS Score:** The mean baseline GCS score in Neurotol FDC of Mannitol + Glycerol arm was  $10.07 \pm 1.223$  which increased to  $14.67 \pm 0.488$  upon the completion of therapy (Table 2). The increased GCS score was statistically significant ( $p < 0.001$ ) as compared to baseline value. The mean baseline GCS score in Mannitol arm was  $9.40 \pm 1.242$  which raised to  $10.73 \pm 1.624$  upon the completion of therapy however statistical analysis revealed no significant difference.

**Table 2:** GCS score value of Neurotol FDC (Mannitol + Glycerol) and Mannitol during screening and after completion of therapy

	Neurotol		Mannitol	
	Screening	Completion	Screening	Completion
N	15	15	15	15
Mean	10.07	14.67	9.40	10.73
Median	10	15.00	10.00	11
S. Deviation	1.223	0.488	1.242	1.624
Minimum	8	14	7	7
Maximum	12	15	11	13

**Intracranial pressure (ICP) measurement:** In Neurotol FDC (Mannitol + Glycerol) arm the mean baseline value of ICP measurement was found to be  $21.73 \pm 1.831$  which decreased significantly ( $p < 0.001$ ) to  $10.13 \pm 1.06$  upon the completion of therapy (Table 3). However in Mannitol arm the mean baseline value of ICP measurement was  $23.0 \pm 1.773$  which significantly ( $p < 0.05$ ) reduced to  $18.13 \pm 2.10$ .

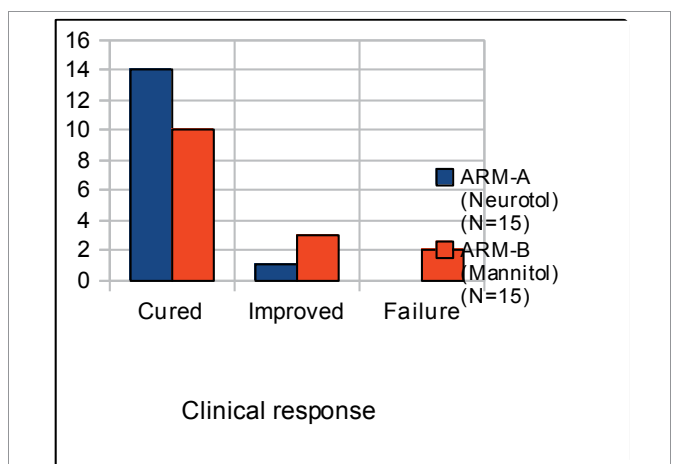
**Table 3:** Intracranial pressure measurement before and after treatment of Neurotol FDC (Mannitol + Glycerol) and Mannitol

	Neurotol		Mannitol	
	Screening	Completion	Screening	Completion
N	15	15	15	15
Mean	21.73	10.13	23	18.13
Median	21.00	10	23	18
S. Deviation	1.831	1.060	1.773	2.1
Minimum	18	8	20	15
Maximum	25	12	26	23

**Clinical Response to the therapy [Neurotol FDC (Mannitol + Glycerol) vs Mannitol]:** In Neurotol FDC (Mannitol + Glycerol) arm, out of 15 subjects enrolled in the study 14 (93%) were clinically cured and 1 subject (7%) was improved on the treatment. While in Mannitol arm, 10 subjects (67%) were clinically cured, 3 subjects (20%) were improved and 2 (13%) subjects were considered as failure to the therapy.

**Table 4:** Clinical response of Neurotol FDC (Mannitol + Glycerol) and Mannitol

Clinical Response	ARM-A (Neurotol) (N=15)	ARM-B (Mannitol) (N=15)
Cured	14 (93 %)	10 (67 %)
Improved	1 (7 %)	3 (20 %)
Failure	0 (0 %)	2 (13 %)



**Graph 1:** Graphical representation of clinical response of Neurotol FDC (Mannitol + Glycerol) and Mannitol in the treatment of cerebral edema



metabolism. In conformance with previous reports our data indicate superior outcome after Neurotol FDC (Mannitol + Glycerol) therapy as compared to Mannitol and inclusion of Glycerol to Mannitol may be responsible for the observed effects.

In this study clinical response to both therapies were evaluated and Neurotol FDC (Mannitol + Glycerol) cured 14 subjects as compared to 10 of Mannitol. Safety profile was assessed by analysis of adverse events based on severity of AEs and on relationship with drugs. Neurotol FDC (Mannitol + Glycerol) treatment displayed lesser AEs [5] as compared to Mannitol [9] and showed safer profile for this therapy. However no severe AE was reported during the course of therapy.

## CONCLUSION

In conclusion, Neurotol FDC (Mannitol + Glycerol) treatment showed better safety, tolerability and efficacy profile than Mannitol treatment. Neurotol FDC (Mannitol + Glycerol) rapidly enters the Cerebrospinal Fluid (C.S.F.) and brain compartments and favorably affects the stroke process. The prime mechanisms may be by promoting redistribution of cerebral blood flow with increase in regional cerebral blood flow and blood volume in ischemic brain and reducing focal cerebral edema [9,35]. Inclusion of Glycerol with Mannitol may be responsible for the observed beneficial effects. However more studies are required to confirm our findings.

Neurotol exerts neuroprotection by combined mechanisms of osmotic activity, free radical scavenging potential and NMDA and calcium channel blockage. It also has hemodynamic stability, membrane stabilization properties as well as anti-inflammatory properties to provide the utmost required neuroprotection during brain injury.

In a 28 days sub-acute toxicity studies, Neurotol was found not to be associated with any serious adverse effects and is safe therapeutic choice for Intra Cranial Pressure (ICP) reduction. In another study, Neurotol was assessed for its activity on xanthine oxidase, adenylate kinase and Malondialdehyde levels in alcohol induced ischemic rat's model. A significant decrease was observed in neurotol treated group suggesting that it has better free radical scavenging activity than competitor products.

In another study the container closure system for neurotol was also found advantageous over its competitors. Neurotol is packed in glass container and it has distinctive advantage over the competitor products that are packed in plastic containers. The plastic containers significantly increase the leachable and extractible profile of the formulations. These leachables and extractibles are harmful to the biological milieu.

Thus, Neurotol has better safety and efficacy and is a drug of choice for physicians requiring glycerol based neurotherapeutics.

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