Review Article

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Controversy in use of mannitol in head injury

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Abstract: The most commonly used drug in the patients of severe head injury is mannitol. The drug is classified pharmacologically as osmotic-diuretic but its mechanism of action in decreasing intracranial pressure is multi-factorial. Despite having dramatic results in the management of head injury patients the drug is still facing many controversies ranging from mechanism of action to the efficacy, especially is the light of evidence based medicine.

Keywords: head injury, mannitol

DISCUSSION

The efficacy of mannitol to decrease intracranial pressure (ICP) lead to its widespread use in neurosurgery since 1960's[1,2,3]. Classically the effect was attributed to the hyper osmotic action of mannitol leading to extraction of water from the edematous brain[4,5], however this mechanism has been questioned on the basis of following observations:

a) ICP falls before any reduction in white matter water content occurs[6].

b) When the ICP is maximally reduced, there is no significant change in the white water content[7].

c) ICP remains high despite a reduction of white matter water by intravenous albumin[8].

Hartwell noted that immediately after transfusing mannitol there was a minor increase in white matter water content followed by a gradual fall with lowest values occurring after 60 minutes and that level was significantly less than before mannitol infusion ($P < 0.025$). Simultaneous ICP recording revealed that ICP had fallen by 84% at 11 minutes (when white matter water content had not decreased). At 19 minutes when ICP was at its lowest, white matter water had fallen by only 33% of its range. ICP than began to rise at 20 minutes while white matter water had been reduced by less than 40%. ICP continued to rise as white matter water continued to fall reaching its minimum at 60 minutes[9].

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Many alterative hypotheses have been put forward to explain the mechanism of lowering of ICP by mannitol. One of them is the change in cerebral hemodynamics induced by mannitol. Mannitol has been proven to increase cerebral perfusion pressure (CPP) and microcirculation perfusion. In a study by Kirkpatrick et al, mannitol was found to increase CPP by 18% and decrease in ICP by 21% without effecting arterial blood pressure. The flow velocity in middle cerebral artery increased by 15.6% and was maximum by the end of infusion and thereafter decayed. Various possibilities have been put forward to explain increase in cerebral blood follow (CBF):

1) Increase is due to increase in CPP; 2) Cerebral vasodilatation; 3) Improved rheology leading to increased flow[10]. Out of these it appears that it is the rheological modification that is having main action because cerebral vascular resistance falls significantly once mannitol is infused so CBF will increase, hence CPP alone can not explain increase in CBF. If cerebral vasodilatation is the main mechanism in increasing CBF, than mannitol should cause rise in ICP that is not seen always[10]. The primary effect of mannitol, therefore, may be reduction in viscosity which results in increase in CBF and cerebral O_2 delivery[11]. Intact auto regulatory mechanisms than result in vasoconstriction which decrease cerebral blood volume and lowers ICP. Rosner et al found that cerebrovascular effects of mannitol are more pronounced at a lower CPP at which the potential vasoconstriction vasoreactivity is the greatest. At lower CPP, there is substantial vasodilatation before mannitol that allowed mannitol administration to be more effective at reducing ICP

through auto regulatory vasoconstriction[12]. With the introduction of concept of evidence based medicine the efficacy of mannitol started to get questioned. Though mannitol is sometimes effective in reversing acute brain swelling but its effectiveness in the management of head injury is not clear[13]. To assess the efficacy of mannitol, an extensive review was done by Wakai A etal. They compared effectiveness of mannitol to other ICP lowering agents[13]. Sayre compared pre-hospital administration of mannitol with placebo. They included patients of head injury with GCS 11 or less and the patients were either administered 20% mannitol 5 ml/Kg over five minutes or placebo (0.9% saline) in equal amounts. In study group RR for death was 1.75% (CI of 95% 0.48 to 6.38) [14]. Schwartz compared mannitol to Phenobarbital in patients of head injury with GCS < 8 and having elevated ICP for longer than 15 minutes. The mannitol group received initial dose of 1gm/Kg of mannitol with additional doses to keep ICP less than 20 torr. The pentobarbital group received pentobarbital as an intravenous dose of up to 10mg/Kg, followed by continuous infusion at 0.5- 3mg/Kg /hr provided that CPP remained above 50 torr. Additional doses were given when ICP was above 20 torr. The mannitol group faired slightly better with RR for death being 0.85, through it was not statistically significant[15].

Fortune JB compared the effects of hyperventilation (HV), mannitol and ventriculostomy drainage. They infused twenty five grams of mannitol over 5 minutes. They found that both ventricular drainage and mannitol infusion were almost equally effective in lowering ICP. Mean oxygen saturation in jugular blood increased by 2.5 ± 0.7% with mannitol while there was almost no change after ventricular drainage and mild decrease with hyperventilation. They concluded that while each of the treatment regimens lowered ICP, but it was only mannitol that significantly increased $SJV0_2$ and presumably global CBF[16].

Berker et al proposed protocols that use HV, VD and osmotherapy. They found that their used reduced mortality by 20%[17]. In study by Cruz J et al it was seen that mannitol could lower the ICP by 33-35% and this lead to increase in cerebral perfusion[18]. Few studies compared efficiency of mannitol and hypertonic saline (HS) to reduce ICP. Many experimental studies found that HS solutions are equivalent to mannitol in reducing ICP[19,20]. Freshman compared 250ml of 7.5% saline with 250ml of 20% mannitol in sheep, both treatments produced same reduction in ICP[19]. Vialet compared 20% mannitol with 7.5% saline in patients of severe head injury. He infused 2ml /kg body weight of either of the two solutions to decrease ICP to < 25mm Hg. They found HS was better than mannitol in reducing mortality[21]. Suarez et al used 30ml of 23.4% saline and found it is effective as 220ml of 20% mannitol. They found 23.4% saline is effective as rescue therapy in patients with refractory intracranial hypertension. They suggested that mannitol may soon lose its reputation to HS as front line osmotherapeutic agent[22].

Paczynski in his review article on osmotherapy described mannitol as being close to an ideal osmotherapeutic agent[23]. Schwartz in his randomized, single blind study compared efficacy of pentobarbital therapy and mannitol. They found that in mannitol group relative risk for death was 0.85 as compared to pentobarbital[15].

CONCLUSION

After surgical evacuation of space occupying lesions the most widely used drug for decreasing intracranial pressure is mannitol. Almost 83% of centres in United States use osmotic diuretics in more than 50% of patients with severe head injury[24]. A study in United Kingdom showed that all the neurosurgical centres use mannitol for raised ICP[25]. A number of studies have failed to document any effectiveness of mannitol in reducing mortality in head injury. However the effectiveness of mannitol for head injury patients in a critical condition is considered to be well established without the need for randomized controlled trials.

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