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Viewpoint

Individualizing hyperosmolar therapy for management of intracranial hypertension

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Abstract

Intracranial hypertension is a major cause of morbidity and mortality in patients with brain injury. If not appropriately treated, it can precipitate brain ischemia, brain herniation and death. Hyperosmolar therapy remains the main armamentarium for management of raised intracranial pressure, especially in patients with diffuse lesions and where surgical options are not applicable. Substantial amount of studies have tried to explore the superiority of hypertonic saline or mannitol over the other. Due to significant heterogeneity in the pathophysiology of patients, variation in treatment threshold, method of drug administration and drug concentration, substantial evidence is lacking to support one agent over other. Hypertonic saline may be more effective than mannitol for lowering raised intracranial pressure. Well designed novel trials need to try to find the answer. Clinical, pathophysiological and biochemical data should be incorporated at bedside while individualizing selection of hyperosmolar therapy, with the aim to improve outcome and minimize harm.

Keywords: hyperosmolar therapy, hypertonic saline, individualized therapy, intracranial hypertension, mannitol.

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Hyperosmolar agents remain the mainstay of therapy for management of intracranial hypertension.[1] Use of mannitol or hypertonic saline is recommended in the early steps or early tiers while managing raise intracranial pressure (ICP).[2,3] Mannitol is a sugar alcohol available as a 20% solution. It causes tissue dehydration, including the brain and causes osmotic diuresis. It can be administered through both the peripheral or central venous access, but required in-line filter and may require warming to dissolve crystals before administration. Measurement of trough osmolar gap is helpful to monitor drug elimination. Careful monitoring for possible dehydration, hypotension and electrolyte imbalance due to diuresis is necessary. Administration of large dose of mannitol can induce renal injury and acute kidney injury. Hypertonic saline (HS) is available in concentration ranging from three to 23.4%. HS causes intravascular volume expansion that may precipitate pulmonary

edema and heart failure in susceptible patients with low cardiac reserves. Administration in patients with chronic hyponatremia can potentially precipitate osmotic demyelination syndrome. However, the higher reflection coefficient of 1.0 as compared to 0.9 with mannitol, would reduce the risk of rebound cerebral edema. There are risks for acute kidney injury, coagulopathy, thrombophlebitis and hypernatremia, with administration of HS. Central venous access is necessary for administration of HS with concentration of 7.5% or higher.[1,2,4] It is obvious that neither of these two agents are ideal for all the patients.

Recent practice guidelines fail to provide specific recommendations in favor of one agent over another. It is due to low level of precision and insufficient quality of evidence from the existing studies and trials.[5] Meta-analysis of randomized trials involving six studies and 171 patients comparing mannitol and HS for management of raised ICP in patients with traumatic brain injury (TBI) suggest a trend favoring the use of HTS over mannitol. However, multiple methodological limitations exist in the meta-analysis like different formulations and dose of HTS used in studies, heterogeneous patient population and varying threshold of ICP used for treatment.[6] At equimolar dose, HTS may be more effective than mannitol in patients with TBI and may confer longer duration of ICP reduction. At 30 minutes after administration, there was no difference in ICP reduction between HTS and mannitol, but the ICP reduction was more significant at 60 and 120 minutes.[7] However, uncertainty persists about the preferred agent in patients with raised ICP due to different pathological conditions. The optimal means (bolus or continuous infusion), dose and concentration of administration are yet to be determined. The effect of hyperosmolar agents on neurological and long term outcomes need to be explored.[5,7]

Patients with brain injury and intracranial hypertension are heterogeneous. There is considerable difference in pathophysiology underlying intracranial hypertension between the patients. Moreover, different mechanisms for raised ICP may be present in a same individual at different point of time. Recently, management of these brain injured patients purely based on ICP threshold has been questioned. The main principle of care for management of brain injury is to avoid secondary brain damage. Several pathophysiological mechanisms may be responsible for nutrient supply-demand imbalance, besides raised ICP or decreased cerebral perfusion pressure. Seizure, inadequate sedation, increased cerebral metabolic rate, abnormality in oxygen diffusion and mitochondrial dysfunction, all may impair aerobic cellular metabolism in injured brain. That may be the reason why ICP threshold guided use of hyperosmolar agents have not translated to improved neurological outcomes. Besides clinical examination with Glasgow Coma Scale or FOUR score in addition to ICP monitoring, incorporation of multimodality neuromonitoring at bedside can unravel the significant heterogeneity of these brain injured patients. Brain tissue oxygenation monitoring, electroencephalography, cerebral microdialysis and ICP wavefrom analysis can be helpful. Bedside determination of state of cerebral autoregulation using pressure reactivity index (PRx) may help to manage patients within their individual range of autoregulation, which may improve neurological outcome.[8,9]

Current understanding from the studies and guidelines are unable to recommend one agent over the other, except for the trend in favor of HTS over mannitol.[5-7] Precision oriented future randomized controlled trial can be challenged by the significant heterogeneity of patient population, resulting in smaller homogenous groups and a longer time frame required for recruitment of patients. Registry based randomized controlled trial involving large collaborative multicentric data registry can retain the benefit of randomization and at the same time facilitate rapid recruitment of samples with cost effectiveness. As the patient outcome is dependent on multiple interventions occurring simultaneously, effectiveness of individual treatment can be tested using platform trials. Though it sound intriguing and promising, the path for finding precision in managing intracranial hypertension is challenging, more so in places with resource limitations.[10] Till we have better answers and convincing directions based on research and guidelines, the reasonable approach for choosing hyperosmolar agents should be based on multiple factors. Choice should be based on availability of the agent, underlying pathophysiology of the patient, serum sodium level, haemodynamic status of the patient, intravascular volume status and state of renal function. HTS may not be universally available, especially in places with resource limitation. Moreover, administration of 7.5% or higher concentration of HTS requires central venous access.

Rapid administration of HTS in patients with chronic hyponatremia may precipitate osmotic demyelination syndrome, although the data is very sparse. HTS may be beneficial in patients with trauma and hypovolemia. In these patients, mannitol may induce dieresis and further hemodynamic instability. On the other side, administration of HTS in patients with diminished cardiovascular reserve may cause volume overload and cardiovascular decompensation. Both the agents my cause renal injury, with possibly mannitol causing more harm when administered in high dose. Patients with subarachnoid hemorrhage may benefit from HTS when compared to mannitol, considering the need to maintain euvolemia. Based on the available evidence, when both the agents are equally applicable, HTS may be preferred to mannitol.[4-7] It would be prudent to incorporate the available clinical and biochemical data to individualize hyperosmolar therapy in patients with intracranial hypertension, in an attempt to improve patient outcome and to avoid harm.

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