Review Article

Role of colloids in traumatic brain injury: Use or not to be used?

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Abstract

Trauma is a leading cause of death worldwide and traumatic brain injury is one of the commonest injuries associated with it. The need for urgent resuscitation is warranted for prevention of secondary insult to brain. However, the choice of fluid in such cases is still a matter of conflict. The literature does not provide enough data pertaining to role of colloids in head injury patients.In this article, we have tried to explore the present role of colloid resuscitation in patient with head injury.

Key words: Colloid, crystalloid, edema, head injury

Introduction

Trauma is the leading cause of death world wide and traumatic brain injury (TBI) is one of the commonest injuries associated with it. Not only the mortality is considerable, but also, the degree of morbidity and the overall social outcome are severely affected.[1,2] The need for urgent resuscitation is warranted for prevention of secondary insult to brain.[3] However, the choice of fluid in such cases is still a matter of debate. The literature does not provide enough evidence pertaining to role of colloids in TBI patients. In addition, the existing information is still scanty regarding the use of colloids in patients with different TBI subgroups including isolated head injury, head injury with extra-cranial bleed and among varying severity of head injury. These areas need extensive research and future trials.

In this article, we have tried to explore the present role of colloid resuscitation in patient with head injury with special reference to underlying pathophysiological processes.

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Is there any Need for Fluid Resuscitation?

Severe TBI is associated with approximately two-third of all the TBI cases associated with polytrauma.[4] The incidence of hypotension in TBI patients is much more common due to extra-cranial injury rather than the isolated head injury.[5] These extra-cranial injuries are mainly associated with bleeding and if not managed appropriately, develop into shock. Hence the role of fluid resuscitation becomes crucial to overcome the hypotensive effects of the extra-cranial injury on the cerebral hemodynamics. Thus the prevention of secondary brain insult is the utmost goal of fluid resuscitation.[6] On the other hand, patients with TBI who had no apparent signs of hypovolemia, revealed inadequate tissue perfusion[6] and responded well to fluids and iontropes. Either of the therapy did not increase the intracranial pressure (ICP).[3,7] Thus patients with isolated TBI (without extra-cranial bleed) still require fluid resuscitation to preserve optimum cerebral perfusion pressure (CPP).[7] In addition, Clifton *et al.*, in their retrospective study revealed that a negative balance of approximately 600 ml or more of the fluid was found to be independent determinant of poor neurological outcome in severe TBI patients.[8] These data further supports the importance of fluid resuscitation in TBI patients. However, the retrospective chart review of 776,734 trauma patients showed that half of the patients who received prehospital fluid resuscitation had increased overall mortality. TBI patients (one of the subgroups) were associated with higher mortality in this study.[9] This study develops new insight in the fluid resuscitation especially in TBI patients and in fact challenges the current practice. However, this observation requires further clinical investigations and future trials. At least for now, the goal of fluid resuscitation in such cases would

include improvement in oxygen delivery, maintaining CPP and stabilization of ICP.[3,10]

Why should the Types of Fluids matter in Head Injury Patients?

The two most important physiological factors that stabilize internal milieu of brain are cerebral auto regulation and blood brain barrier (BBB),[5] both are frequently found to be altered in severe TBI.[11,12] Type of fluid affects these variables and consequently patient's neurological outcome.

It is noteworthy that in post-head injury patients many inflammatory cascades get stimulated which in turn cause many local and systemic changes including exaggeration of cerebral edema, disruption of BBB, secondary brain injury, and finally multiorgan dysfunction.[13] The roles of different fluids on these inflammatory mediators have been investigated and were found to be variable.[14] In general, hypotonic or isotonic crystalloids often aggravate the neuro-inflammatory responses and produce worsening of the cerebral edema and confer no neuroprotection. However, fluids like hypertonic saline-dextran combination have been shown to attenuate the inflammatory cascades.[15] In one study, no penetration of hyrdroxyl ethyl starch (HES) into cerebrospinal fluid was observed despite disrupted BBB; however, this study involved only the small group of patients. Thus this observation needs further validation[16] In animal experiments on TBI as well as hemorrhagic shock models, fresh frozen plasma infusion was found to be superior to both artificial colloid and normal saline solutions in reducing the brain edema and lesion size.[17] Thus the type of fluids (crystalloids versus colloids) would have some differential effects on TBI patients depending upon the variable interactions with various biochemical mediators. Among different subtypes of colloids, the data is still inconclusive and need future trials. However current literature reflects the emerging role of the osmolality of an infusion solution rather than the colloid osmotic pressure *per se* as a key determinant in the pathogenesis of cerebral edema formation.[11]

Effects on Cerebral Physiology

Movement of water across the BBB depends on osmotic gradient and the integrity of this barrier. BBB may be disrupted in some areas of brain while intact in other, depending upon the severity of TBI, hence the osmotic effect would also be variable. Initial animal experiments on TBI models favored the use of colloids. In comparison to colloids, crystalloids were shown to produce more cerebral edema in TBI patients.[18,19] It is likely that in severe head injury patients (with disrupted BBB), edema formation would be even worse with the further use of crystalloids. The high oncotic pressure of colloids decreases the cerebral edema formation and is also associated with improvement in the mean arterial blood pressure (MABP), having low infused volume, and decreased neuronal death.[20] In a multicenter trial, all hyperosmotic solutions including 15% mannitol, 10% sodium chloride (NaCl), and hyper HES (7.2% NaCl combined with hydroxyethyl starch) were found to decrease the intracranial pressure in acute TBI patients. However, among all the solutions, hyper HES had a significantly prolonged effect on reduction in ICP with favorable effects on both cerebral as well as hemodynamic parameters.[21] Thus the majority of beneficial effects of colloid were attributed to its unique oncotic property which reduces the formation of cerebral edema and hemodynamic property which keeps the MABP in optimal range.

On the contrary, few studies report that the oncotic effect generated by colloids do not decrease the cerebral edema formation after TBI. In addition, the colloids were not associated with either increase in the cerebral oxygen delivery nor decrease in the raised ICP.[22] In fact some of the synthetic colloids increase the blood viscosity and cause decrease in systemic rheological property. Thus, indeed the overall cerebral oxygenation is not improved.[3] However investigators of yet another study did not observe any significant improvement in rheological functions in TBI patients with different concentrations of dextran 40. This observation has been attributed to the early metabolic suppression rather the global ischemia which predominates in the early phase of head injury and thus could not be benefitted by the use of dextran solution.[23] Similarly, the normovolemic hemodilution in both adults and pediatric brain injury models, were found to be ineffective as these tend to cause hyperemia and increased transfer of water content across BBB that produced further cell swelling.[24] The popular 'The Saline versus Albumin Fluid Evaluation (SAFE) study' has been shown to cause increase in mortality among TBI patients who were treated with albumin.[25] This study did not explain the cause of increased mortality in this sub group; however, a dilution coagulopathy was proposed as a probable cause by other investigators.[26] Kawamata *et al.*, showed that high colloid osmotic pressure produced by metabolites or idiogenic osmoles can increase the chances of post concussion edema,[27] and possibility led to the higher mortality in albumin group.

Other Systematic Effects

All synthetic colloids including dextran, gelatin, and HES have dose-related side effects like coagulopathy, renal failure, and tissue storage.[28]

There is altered coagulation homeostasis in severe head injury patients[29] and the administration of synthetic colloids especially dextrans, gelatins, and high molecular weight starches have been shown to cause worsening of hemostasis. Many studies revealed that use of these synthetic colloids decreased the levels of coagulation factors (VII, V111, von Willibrand factor and fibrinogen), caused defect in platelet and erythrocyte aggregation.[30,31] On the other hand, natural colloids like albumin, bind to nitric oxide (NO) and forms nitrosothiols. This prevents NO degradation and cause prolongation of antiplatelet effects.[32] Even use of 6% HES was associated with more pronounced von Willibrand factor dysfunctions in patients with blood group 'O'[33] Few studies showed that isovolemic replacement of blood loss with either 6% HES or 5% human albumin did not affect the overall coagulation.[34] However, depending upon the severity of head injury, minimal to severe coagulative dysfunctions may exist[35] as part of the bidirectional interaction between brain and whole organism to which the use of colloids may further add disturbances in overall hemostasis. A large clinical trial would be needed to explore the clinical incidence as well as the relevance of this dysfunction in the coagulation cascade produced by the colloids.

Anaphylactic reactions though rare, were associated with use of colloids. These reactions can manifest as minor (pruritis, fever, rash) to severe life-threatening symptoms (arterial hypotension, broncospasm). A series of 19,593 patients showed that there was a chance of one anaphylactic reaction for every 456 patients. These reactions were found to be serious in up to 20% of the cases. The risk factors highlighted in this study were use of gelatins, dextrans, prior drug allergy, and male gender.[36] Use of colloids would certainly impose added risks of anaphylaxis in this subgroup of patients.

TBI is associated with acute kidney injury in a considerable number of patients (9-23%) and often presents with consecutive higher mortality.[37,38] Colloids are also found to be associated with increased chances of acute kidney injury and increased use of renal replacement therapy in critical ill patients. The overall mortality was found to be higher with colloid use.[39] Thus it is likely that colloids would add more adverse effects on renal functions in patients with TBI and may affect the overall mortality.[35] However, the role of colloids in worsening the pre existing renal dysfunctions or producing newer kidney injury in TBI patients is still to be elucidated and warrants further research.

The recent Cochrane reviews demonstrated that the use of colloid were not superior to crystalloids in respect to overall mortality especially in patients with trauma, burns, and post-surgery. However, the higher cost would remain a limiting factor for their use. Moreover, there was no significant difference in various types of colloids in view of fluid resuscitation choices.[40,41] Thus, the existing data does not favor the use of colloids in certain subgroup of patients.

Conclusions

In present scenario, considering the cerebral and other systemic adverse effects coupled with existing higher mortality data, colloids does not seem to be fluid of choice for resuscitation in patients with TBI.[11,42,43] Further substantial evidence for this requires a better understanding of the cranial and extra cranial effects of TBI. Until that time local regulations being bedded into a TBI concept may be the solution.

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