

Role of Hypertonic Sodium Lactate in Traumatic Brain Injury Management

Abstract

Traumatic brain injury (TBI) following increased intracranial pressure (ICP) is a neuroemergency case which should be managed promptly to prevent secondary brain injury. This will lead to a condition called cerebral energy dysfunction which is an important determinant factor toward worse outcome. Lactate, which was historically known as an end waste product, now is considered as an alternative cerebral energetic fuel. Hypertonic sodium lactate (HSL) is a promising hyperosmolar fluid which serves not only to decrease ICP but also to readily supply exogenous lactate to fulfill increased cerebral energy demand. Pioneer studies have shown the harmlessness and usefulness of HSL in treating pathological condition including TBI.

Keywords: Hypertonic sodium lactate, intracranial pressure, traumatic brain injury

Introduction

Cerebral energy dysfunction in traumatic brain injury (TBI) is one of the most important determinant factors that should be recognized in the early management of TBI. This condition becomes one of the strong predictors toward worse clinical and neurological outcome if it is not managed promptly.^[1] In the early phase of TBI, brain develops hypermetabolism to adapt from injury which affects glucose usage in the blood.^[2] Glucose requirement increases, and if it is not equaled by the glucose adequate supply, it will result in brain starvation and cerebral energy dysfunction which lead to the worse prognosis.^[3,4] The main objective treatment of TBI patients is to prevent or minimize the secondary brain injury by maintaining adequate blood flow to increase oxygen and glucose supply.^[6] In the past, glucose is considered as the one and only substance which can be metabolized by the brain to gain energy; however, the latest researches showed that lactate can be utilized as emergency or primary addition for cerebral energetic substrates.^[5-7] It was first introduced by Pellerin and Magistretti in 1994 as astrocyte-neuron lactate shuttle hypothesis (ANLS).^[8] Hypertonic sodium lactate (HSL) is the only fluid which not only has the effects as a lactate supplementation but also functions as the hyperosmolar therapy for the TBI patients with increased intracranial pressure (ICP).

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In this article, we will discuss the effectiveness of HSL as the lactate supplementation without ignoring the main effect as the hyperosmolar therapy based on the latest clinical evidence.

Cerebral Metabolism: What Have We Learned?

Pertinent studies from the last decades have changed the concept of cerebral metabolism in normal and abnormal conditions of brain. Basically, in normal conditions, human brain mainly utilized glucose as the main energy source for maintaining normal functions. The energy was generated from aerobic metabolisms which require adequate oxygen supply, through the glycolysis process and tricarboxylic acid cycle (TCA) of the pyruvate.^[9] This process is highly effective energy production, which can generate 36 adenosine triphosphate (ATP) molecules per molecules of glucose. Besides its main function as energy fuel, glucose also acts as neurotransmitter and the regulator of cell redox state through pentose phosphate pathway.^[1] The illustration of normal cerebral metabolic pathway is described in Figure 1a.

Following TBI, human body will be put in a great stress which results in hypermetabolism state as compensatory method. More energies are required to maintain the normal function of brain such as maintaining Na⁺/K⁺-ATPase pump activity.^[1] When the energy requirement of

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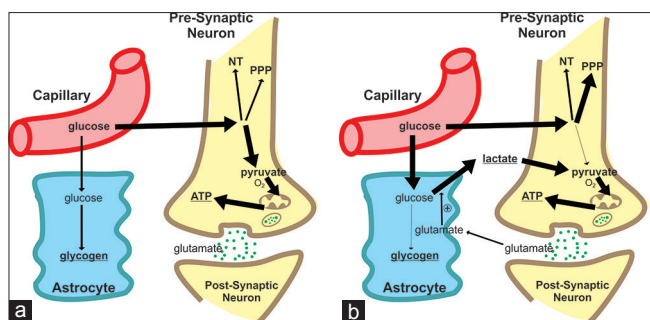


Figure 1: Cerebral metabolism in (a) normal conditions and (b) following traumatic brain injury.^{1, 9, 10} NT – neurotransmitters; PPP – pentose phosphate pathway; ATP – Adenosine Triphosphate

the brain is not balanced by the glucose supply, brain will utilize lactate as an emergency energy substrate.^[10] This theory is proved by experimental studies using cerebral microdialysis (CMD) in brain glucose-deprived state^[4,11] and studies using jugular bulb venous catheter which have shown increase of cerebral lactate uptake by the brain in TBI setting.^[5] In TBI, there can be disruption in cerebral blood flow which results in brain ischemic or hypoxic condition. In this setting, oxygen supply is not adequate to perform aerobic metabolism; therefore, brain will undergo anaerobic metabolism which is used as compensatory method. Anaerobic metabolisms will produce lactate from cytosolic pyruvate through continuous anaerobic ATP synthesis to generate only 2 ATP molecules. Sustained hypoxic state and anaerobic metabolism will lead to lactate overproduction which shown by increased, elevated lactate-to-pyruvate ratio. This condition will lead to metabolic crisis in which only increase of oxygen supply is the only way to solve the crisis.^[12]

Role of Lactate in Traumatic Brain Injury

Lactate is a waste product of anaerobic metabolism.^[13] This old statement is no longer used. It was Pellerin and Magistretti who introduced ANLS hypothesis. In their study, they described that lactate that was formed within the brain parenchyma through glutamate-activated glycolysis in astrocytes could fulfill energetic needs of neurons during activation.^[8] Since this study have changed the role of lactate in brain energetic fuel, several studies regarding lactate usage are considerably emerged. Animal and human studies showed that elevation of lactate (within a physiological range) can prevent the detrimental neurological effect of hypoglycemia, also substantially diminished catecholamines, growth hormone, cortisol, and symptomatic responses to hypoglycemia.^[14] Experimental data on rat hippocampi with ischemia-reperfusion injury found that lactate can support neuronal survival in conjunction with glucose.^[15] Furthermore, several *in vivo* experimental data support that lactate can decrease lesion volume, reduction of cognitive deficit, increase cerebral blood flow (CBF), and improve EEG function in rats induced by neuronal insult.^[16-22] In 2009, Gallagher *et al.*

demonstrated the first direct human experimental in 14 severe TBI patients using labeled isotopic lactate perfusion through infusion via microdialysis catheters. The result showed that the injured brain utilizes endogenous lactate through the TCA cycle.^[23] Furthermore, in 2015, Glenn *et al.* reconfirmed in their study that lactate production during TBI was increased and was also consumed by injured human brain. They also concluded that exogenous lactate supplementation could help supply neuroenergetic fuel demand during TBI.^[24] This study confirmed the ANLS and supported the concept that lactate could be used as energy substrate. Brain parenchyma might use astrocytic glycolysis to produce lactate as fuel in consequence of the increase of energy needs in TBI. In addition, glutamate, in the setting of nonhypoxic TBI, also stimulates glycogen stored in astrocyte to be metabolized into lactate. This condition is precipitated by the increase of cerebral energy need and only lasting for a short period.^[25] The illustration of lactate's role in neuroenergetics during TBI is shown in Figure 1b.

As the supporting study, Bouzat *et al.* in 2014 conducted prospective study in 15 patients with severe TBI which were monitored with CMD, brain tissue oxygen tension PO_2 ($PbtO_2$), and ICP. Each patient was given with a 3 h intravenous infusion of HSL (aiming to increase systemic lactate to concentration of 5 mmol/L), administered in the early phase following TBI. They concluded that injured human brain can utilize exogenous supplemental lactate aerobically as a preferential energy substrate. HSL therapy also had beneficial cerebral metabolic and hemodynamic effects after TBI by increasing the availability of cerebral extracellular pyruvate and glucose, coupled with a reduction of brain glutamate and ICP.^[26] Quintard *et al.* in their study showed that HSL infusion during TBI significantly increased concentrations of CMD glucose, CMD lactate, and arterial blood lactate. It means that HSL infusion during TBI adds more energy supplies in consequence to increased energy demand by the brain.^[27] This study has convinced us that HSL has many benefits in the setting of TBI management.

The Usage of Hypertonic Sodium Lactate in Traumatic Brain Injury Management

Increased ICP in the TBI patients is a major emergency in the neurosurgery field. If the increased ICP is caused by the space occupying lesions as in the intracranial bleeding, rapid reduction of ICP is indispensable.^[28,29] Decompressive craniectomy becomes the primary choice to control increased ICP if it meets the indication criteria.^[30-32] However, the operative therapy frequently cannot be done due to the condition of TBI patient who does not meet the criteria. At this point, conservative therapy will consider as the primary therapy to reduce increased ICP.^[33] The Brain Trauma Foundation has recommended that ICP-reducing therapy should begin at >20 mmHg

pressures.^[34] One of the main conservative therapies to reduce ICP for TBI patients is hyperosmolar therapy.^[35] Currently, only 2 agents are used for this purpose: Mannitol and hypertonic saline (HTS). Both the fluids have no superiority among them, even though latest studies showed that HTS had more benefits than mannitol in reducing ICP.^[34,36] There is another hyperosmolar fluid which can be used as an alternative to reduce ICP, which is HSL fluid. The reduction of ICP mechanism using HSL is similar with HTS; HSL lowers ICP by increasing intravascular osmotic pressure that will drain extracellular fluid into intravascular compartment. Initially, HSL lowers blood viscosity through increased plasma volume, which results in an increased microvascular flow and tissue oxygenation. Increased tissue perfusion leads to the vasoconstriction reflex that limits blood supply to the brain tissue and, hence, decreases ICP. Meanwhile, because of its hypertonicity, HSL causes increasing of intravascular osmotic pressure and widening of the osmotic gradient between intravascular and extravascular compartments. Eventually, the edematous fluid will be drawn into the blood vessel and greatly contribute to lowering ICP.^[37,38]

HSL 0.5 M is a fluid which can be similarly considered with the HTS 3% because of the same osmolarity (1027 mOsmol/kg vs. 1020.42 mOsmol/kg, respectively). Even though it has the same osmolarity, both of the fluids have different ion composition. HSL contains inorganic cation (Na^+ , K^+ , and Ca^{2+}) and organic anion of lactate, while HTS 3% has inorganic cation and anion of sodium and chloride.^[37] Several researches have been proven that HSL significantly reduces ICP and maintain mean arterial pressure (MAP) remained in the figures recommended by the Brain Trauma Foundation.^[38] In addition, HSL also has the additional effect in the improvement of cognitive function after TBI.^[37] Compared with the other hyperosmolar fluids, it may be caused by the lactate inside the fluid which has effect as fuel additional energy when the brain undergoes anaerobic metabolism and hypermetabolism.

Efficacy Comparison of Hypertonic Sodium Lactate and Other Hyperosmolar Fluids in Traumatic Brain Injury Management

Several pioneer studies have shown the harmlessness and usefulness of HSL in treating pathological condition aside of TBI.^[39] For example, HSL has been shown (i) to restore hemodynamic status in dengue shock syndrome with minimal fluid accumulation,^[40] (ii) to decrease fluid accumulation during burn shock resuscitation,^[41] and (iii) to improve cardiac performance in patients undergoing elective cardiac surgery^[39] and during acute heart failure.^[42] Several studies have been emerged in TBI management using HSL. Starting as the first study, in 2009, Ichai *et al.* conducted a prospective, open randomized study to compare sodium lactate and mannitol in the treatment of episode

intracranial hypertension in severe TBI patients. Thirty-four patients with isolated severe TBI (Glasgow coma scale ≤ 8) and intracranial hypertension were divided into two groups, both received equally hyperosmolar and isovolume therapy, consisting of either mannitol or sodium lactate (1100 mosm/L for LAC and 1160 mosm/L for MAN). Efficacy in lowering ICP after 4 h was the primary endpoint and the percentage of successfully treated episodes of intracranial hypertension as the secondary endpoint. The result showed that the effect of the lactate solution on ICP was significantly more pronounced (7 vs. 4 mmHg, $P = 0.016$), more prolonged (4th-h-ICP decrease: -5.9 ± 1 vs. -3.2 ± 0.9 mmHg, $P = 0.009$), and more frequently successful (90.4 vs. 70.4%, $P = 0.053$) compared to mannitol.^[38]

As the second study, in 2013, Ichai *et al.* conducted a double-blind, randomized, controlled trial including 60 patients with severe TBI requiring ICP monitoring. Patients were randomly assigned in a 1:1 ratio to receive a 48-h continuous infusion at 0.5 ml/kg/h of either SL (SL group) or isotonic saline solution (control group) within the first 12 h posttrauma. The primary outcome was the number of increased ICP (≥ 20 mmHg) requiring a specific treatment. The results showed that SL group decreased the occurrence of increased ICP episodes as compared to control group within 48-h study period (23 vs. 53 episodes, respectively [$P < 0.05$]). These findings suggest that SL solution could be considered as an alternative treatment to prevent increased ICP following severe TBI.^[43]

In Indonesia, Bisri *et al.* in 2016 conducted a prospective, single-blind, randomized, controlled study in 60 mild TBI patients who undergo neurosurgery procedure. Patients were randomly grouped into HSL group or hyperosmolar sodium chloride (HSS) group; each group received either intravenous infusion of HSL or NaCl 3% at 1.5 ml/KgBW within 15 min before neurosurgery procedure. The primary goal was cognitive function, as assessed by mini-mental state examination (MMSE) score at 24 h and 30 and 90 days postsurgery and analyzed by the ANOVA with repeated measures test. The results suggested that HSL group had better improvement in MMSE score than HSS group. The authors concluded that HSL infusion during mild TBI improved cognitive function better than 3% sodium chloride.^[37] Furthermore, in 2014, Ahmad and Hanna conducted a randomized, controlled study in 42 moderate TBI patients undergoing craniectomy. The patients were divided into Group M ($n = 21$) received 2.5 mL/kg 20% mannitol and group HSL received 2.5 mL/kg 0.5M HSL. MAP, central venous pressures (CVP), and urine output were measured after induction and at 15, 30, 45, and 60 min after infusion. The results showed that MAP at 60 min was significantly higher in HSL group than M group (81.66 ± 7.85 vs. 74.33 ± 6.18 mmHg; $P = 0.002$). There was no difference in brain relaxation ($P = 0.988$). A significant increase in blood glucose level was observed

Table 1: List of studies regarding efficacy of hypertonic sodium lactate in Traumatic Brain Injury management

| Title | Author | Study design | Sample | Intervention | Observed effect |
|--|--|--|---------------------------------|---|---|
| Sodium lactate versus mannitol in the treatment of intracranial hypertensive episodes in severe traumatic brain-injured patients | Ichai <i>et al.</i> (2009) ^[38] | Prospective open randomized study | 34 Isolated severe TBI patients | Lactate (1,100 mOsm/L, 1.5 ml/kg) vs. mannitol 20% (1,160 mOsm/L, 1.5 ml/kg) to treat elevated ICP, for 15 minutes | HSL was more pronounced, more prolonged and more frequently successful effect on lowering ICP compared to mannitol |
| Half-molar sodium lactate infusion to prevent intracranial hypertensive episodes in severe traumatic brain injured patients: a randomized controlled trial | Ichai <i>et al.</i> (2013) ^[43] | Prospective, double-blind, randomized controlled trial | 60 Severe TBI patients | Patients were randomly allocated to receive a 48-h continuous infusion at 0.5 ml/kg/h of either SL (SL group) or isotonic saline solution (control group) within the first 12 h post-trauma | SL group decreased the occurrence of raised ICP episodes as compared to control group within 48-h study period (23 versus 53 episodes, respectively ($P<0.05$)) |
| Effect of equiosmolar solutions of hypertonic sodium lactate versus mannitol in craniectomy patients with moderate traumatic brain injury | Ahmad <i>et al.</i> (2014) ^[44] | Randomized controlled study | 42 Moderate TBI patients | 2.5 mL/kg 20% mannitol vs. 2.5 mL/kg 0.5M HSL | Half-molar HSL was as effective as 20% mannitol in producing brain relaxation, with better hemodynamic stability and gave significant increase in blood glucose level |
| Exogenous lactate infusion improved neurocognitive function of patients with mild traumatic brain injury | Bisri <i>et al.</i> (2016) ^[37] | Prospective, single blind, randomized controlled study | 60 Mild TBI patients | Patients in each group received either intravenous infusion of HSL or NaCl 3% at 1.5 ml/KgBW within 15 min before neurosurgery. | The MMSE score improvement was significantly better in HSL group than HSS group |

in group HSL (17.95 ± 11.46 mg/dL; $P = 0.001$). The authors concluded that half-molar HSL was as effective as 20% mannitol in producing brain relaxation, with better hemodynamic stability and gave significant increase in blood glucose level.^[44] Studies regarding the efficacy of HSL in TBI management are summarized in Table 1.

Conclusion

Lactate which is historically considered as an end waste product for the last decade emerges as an important fuel and plays an important role in neuroenergetic metabolism. It is clear that now lactate serves as preferential substitute fuel besides glucose in the setting of TBI. In TBI, HSL not only works for reducing ICP but also serves as an exogenous supplementation for increasing supply of neuroenergetic fuel which has quality as neuroprotective fluid. Therefore, HSL may serve as an alternative fluid of choice in managing intracranial hypertension in TBI patients. However, further evidences are warranted to confirm this finding.

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Conflict of interest

There are no conflicts of interest.

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