

Review Paper




Effects of Hypertonic Sodium Lactate on Intracranial Pressure in Patients With Traumatic Brain Injury: A Systematic Review and Meta-analysis on Clinical Trial Studies

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ABSTRACT

Introduction: Intracranial pressure (ICP) elevation leading to cerebral edema is a critical condition that should be identified and treated immediately. In this study, we systematically reviewed the articles investigating the role of hypertonic sodium lactate (HSL) in patients with traumatic brain injury (TBI).

Methods: PubMed, Scopus, Embase, and Web of Science were searched to find published articles on the effects of HSL on ICP in patients with a TBI until December 2020. Animal studies, case reports, and studies, including patients with liver and renal failure, cardiac dysfunction, or hypovolemic shock, were excluded. The Newcastle-Ottawa scale checklist was used to assess the methodological quality of eligible articles. Information obtained was classified based on the following criteria: demographic data, methods, intervention, and outcomes.

Results: Our initial search with the predefined search strategy proceeded with 113 studies. Finally, 7 studies were eligible for systematic review, and 3 of them were eligible for meta-analysis. A random meta-analysis of 3 articles comparing ICP before and after the infusion of HSL showed a reduced ICP following the use of HSL in traumatic brain injuries (P=0.015).

Conclusion: Our study demonstrated the undeniable role of HSL in managing increased ICP in patients with brain injury. Nevertheless, conducting more clinical studies to assess the possible side effects of HSL seems crucial.

Keywords:
 Sodium lactate, Intracranial pressure (ICP), Brain injury

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Highlights

- Reduction of intracranial pressure (ICP) was seen after infusion of hypertonic sodium lactate (HSL) in traumatic brain injuries.
- HSL probably had a role in managing increased ICP by increasing serum osmolarity.
- HSL seems to be a reasonable substitute for fluid resuscitation after brain injury.

Plain Language Summary

ICP elevation leading to cerebral edema is a critical condition that should be identified and treated immediately. In this study, we systematically reviewed the articles investigating the role of HSL in patients with traumatic brain injury (TBI). A random meta-analysis of 3 articles showed that ICP was reduced after infusion of HSL in traumatic brain injuries. It also had a role in managing increased ICP by increasing serum osmolarity. It seems that HSL is a reasonable substitute for fluid resuscitation after brain injury.

1. Introduction

Traumatic brain injury (TBI) is one of the most important causes of cerebral dysfunction, and it is the reason for more than 30% of post-injury mortalities (Cassidy et al., 2004; Herbert et al., 2017). Increased intracranial pressure (ICP) following TBI is the main predisposing factor for death in the patients. Hyperosmolar therapy could ameliorate this condition (Fenn III & Sierra, 2019; Gerber et al., 2013). However, osmotherapy has been debated as the treatment of choice for these patients, considering the complex and nonselective nature of osmotic mediators' effects (Bergersen, 2015). The mechanism attributed to hyperosmolar agents is that they increase the oncotic movement of water into the intravascular space and decrease the blood viscosity. As a result, hyperosmolar agents reduce the cerebral intracellular fluid and increase the cerebral blood flow (CBF) (Berthet et al., 2012).

Mannitol and hypertonic saline (HTS) solutions have been used as hyperosmolar therapy in patients with elevated ICP (Francony et al., 2008). Traditionally, mannitol has been recommended as the first choice of osmotherapy in TBI (Maas et al., 1997). However, hypotension, especially in the hypovolemic state, and rebound rise in ICP are the main drawbacks of mannitol (Anonymus, 2000; White et al., 2006). In refractory cases of increased ICP following mannitol administration, HTS increases brain oxygenation and reduces ICP (Ogden et al., 2005). Moreover, HTS has a more pronounced and longer-lasting effect than mannitol on elevated ICP and causes no rebound increase in ICP (Kerwin et al., 2009).

Hence, some recent studies report HTS as the superior hyperosmolar agent (Mangat et al., 2020). No clear recommendation was made in a recently published meta-analysis regarding the choice of hypertonic saline or mannitol in treating patients with TBI-induced elevated ICP (Fatima et al., 2019). However, some concerns exist about nephrotoxic effects and metabolic acidosis following high chloride-containing solutions. Chloride as a nonorganic anion in sodium solution has no role in osmotic therapy, and previous studies have suggested replacing chloride with other organic anions.

Another hyperosmolar solution studied in patients with elevated ICP is hypertonic sodium lactate (HSL) (Ichai et al., 2013). Lactate, as an organic anion, is a suitable energy source for brain cells, and sodium lactate might work not only as a hypertonic agent but also as a metabolic fuel for the brain (Ichai et al., 2009; Leverage & Mustafa, 2002; Rice et al., 2002). HSL could decrease ICP through the osmotic effect of hypertonic sodium and the cerebral vasodilator effect of lactate (Gordon et al., 2008). Ichai et al. mentioned that HSL's effect was even more potent than mannitol in reducing ICP in some trials (Ichai et al., 2009). Notably, in a recent study on patients with TBI-induced elevated ICP, Arifianto et al. (2018) introduced HSL as a choice for fluid therapy. Considering HSL's beneficial roles in TBI, in this study, we systematically reviewed the articles investigating HSL's therapeutic role in patients with TBI.

2. Materials and Methods

Data sources and search strategy

We performed our search in electronic databases, including PubMed, Embase, Scopus, and Web of Science, for studies investigating the effect of hyperosmolar agents on increased ICP in patients with TBI. Two independent investigators (Arash Akhavan Rezayat, and Behnaz Rohani) searched the relevant published articles from January 2000 to December 2020. We searched the literature applying a different combination of our keywords, including TBI, hypertonic agents, and their related terms. PubMed search strategy that consisted of various concepts of our keywords was as follows:

(“Brain injury”) OR (“brain injuries”) OR (“brain injuries, traumatic”) OR (“brain injuries, diffuse”) OR (“brain concussion”) OR (“head injury”) OR (“head injuries”) OR (“head injuries, penetrating”) OR (“cerebrovascular trauma”) OR (“craniocerebral trauma injuries”) OR (“cerebral hemorrhage, traumatic”) OR (“TBI”) AND (“hypertonic saline”) OR (“saline solution, hypertonic”) OR (“hypertonic sodium”) OR (“sodium chloride”) OR (“lactate”) OR (“sodium lactate”) OR (“hypertonic sodium lactate”) OR (“hyperosmolar sodium lactate”) OR (“mannitol”) OR (“osmotic diuretic”) OR (“osmotic diuretics”) OR (“diuretics, osmotic”).

We also searched for grey literature using Open Grey, ProQuest Dissertations, and theses full texts.

Inclusion and exclusion criteria

All published randomized control trials in English literature involving our keywords were included for further evaluation. Our inclusion criteria were as follows: All patients were older than 16, suffered from TBI, and had ICP above 20 mm Hg. Animal studies, case reports, and studies on patients with liver and renal failure, cardiac dysfunction, or hypovolemic shock were excluded. We also excluded studies that did not directly compare the effects of hypertonic saline or mannitol on elevated ICP or did not provide sufficient primary data.

Study selection

After checking for duplications, two investigators independently reviewed all studies' titles and abstracts to meet our inclusion and exclusion criteria. Any disagreement was discussed with the third reviewer. The flow diagram of the selection process of the studies is presented in Figure 1.

Data extraction

We extracted the information on the first author, publication time, country, study design, patient number, mean age, gender ratio, and interventions. The other reviewer resolved any disagreements on the selected studies.

Demographic data, methods, interventions, and outcomes were extracted from the included manuscripts and documented.

Data analysis

Data from included studies were pooled using a random-effect model. All continuous data were summarized as the standard difference in Means \pm SE and analyzed using comprehensive meta-analysis. The inconsistency index (I^2) was used to measure heterogeneity, with $I^2 > 50\%$ indicating substantial heterogeneity. $P < 0.05$ was considered statistically significant.

3. Results

Selection process results

Our initial search with the predefined search strategy proceeded in 34 studies from the Scopus database and 32 publications from the PubMed database. Furthermore, 32 additional publications were included by searching the Web of Science. Also, reviewing Embase added 15 articles to the studies above. Removing duplicates resulted in 70 studies. The title and abstract screening excluded 40 studies. Subsequently, 30 remaining full texts were assessed; 7 studies did not provide enough information, 10 articles were irrelevant, and 6 were animal studies. Finally, 7 studies (Fenn III & Sierra, 2019; Gerber et al., 2013; Halestrap & Price, 1999; Herbert et al., 2017; Holloway et al., 2007; Ichai et al., 2009; Ichai et al., 2013) were eligible for this systematic review, of which 3 studies (Gerber et al., 2013; Halestrap & Price, 1999; Ichai et al., 2009), comprising ICP between before and after injection of HSL, were eligible for a meta-analysis. The selection process is detailed in Figure 1 PRISMA (the preferred reporting items for systematic reviews and meta-analyses) flow chart.

Characteristics of the included studies

Of 138 initially reviewed papers, 131 were removed, and 7 articles were assessed for eligibility using the Newcastle-OTTAWA scale. Studies from France, Switzerland, and Indonesia were evenly distributed, with two articles from each country. One study was conducted in

Table 1. Characteristics of the included studies

Study	Country	Design	Number of Patients	Group	Sex (M/F)	Mean±SD/No. (%)		Drug Administration	Formulation	Dose
						Age (y)				
						HSL	Control Group			
Bisri et al., 2016	Indonesia	RCT	60	HSL/HSS	47/13	30.23±14.89	28.43±15.53	Bolus	Na 504.15 mmol/L, K 4.02 mmol/L, Ca 1.36 mmol/L, Cl 6.74 mmol/L, Lactate 504.15 mmol/L	290.18±1.3 mOsm/kg
Carteron et al., 2018	Switzerland	Before-and-after trials	23	HSL	12/11	59	-----	Continuous	hypertonic lactate (HSL) 1,000 mmol/L; Concentration: 30 µmol/kg/min)	303±6 mOsm/L
Ichai et al., 2013	France	RCT	60	HSL/control group	54/6	40±18	33±15	Continuous	Na 504 mmol/L, K 4 mmol/L, Ca 1.36 mmol/L, Cl 6.74 mmol/L, L-lactate 504.1 mmol/L	301±10 mOsm/kg
Ahmad et al., 2014	Indonesia	RCT	42	HSL/manitol	35/7	37.19±16.62	35.04±12.90	Bolus	504 mmol/L Na ⁺ (equivalent with Na ⁺ in 3% NaCl), 4 mmol/L K ⁺ , 1.35 mmol/L Ca ²⁺ , 6.74 mmol/L Cl ⁻ , 504.1 mmol/L lactate	1100 mosm/L
Aramendi et al., 2020	Uruguay	Before-and-after trials	41	HSL	17/24	50.9±3.2	-----	Bolus	Sodium mmol/l 504 Lactate mmol/l 504 Chloride mmol/l 6.72 Calcium mmol/l 1.36 Potassium mmol/l 4 Osmolarity mOsm/l 1.02	302.6±12 mOsm/kg
Ichai et al., 2009	France	Before-and-after trials	34	HSL/manitol	24/10	37.6(4)	33.8(3.2)	Bolus	Na 504 mmol/L, K 4 mmol/L, Ca 1.36 mmol/L, Cl 6.74 mmol/L, lactate 504.1 mmol/L	298.6 (7.3) mOsm/kg
Bouzat et al., 2014	Switzerland	Before-and-after trials	15	HSL	12/13	40±15	-----	Continuous	Na 1,000 mmol/L, lactate 1,000 mmol/L	320 mosm/L

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Uruguay. Four studies (Fenn III & Sierra, 2019; Gerber et al., 2013; Herbert et al., 2017; Ichai et al., 2013) (were randomized trials, of which 3 (Aramendi et al., 2020; Holloway et al., 2007; Ichai et al., 2009) were before-and-after trials. The total number of patients from the initial 7 articles was 275, and 98 were included in the final 3 analyzed studies. Two included studies (Halestrap & Price, 1999; Ichai et al., 2009) (were prospective inter-

ventional, and 1 (Gerber et al., 2013) was a prospective open randomized study.

The meta-analysis was carried out for ICP reduction according to data reported in 3 articles. Drug administration characteristics in 4 publications (Aramendi et al., 2020; Bisri et al., 2016; Ichai et al., 2009; Muhammad & Hanna, 2014) were bolus, while the other 3 studies

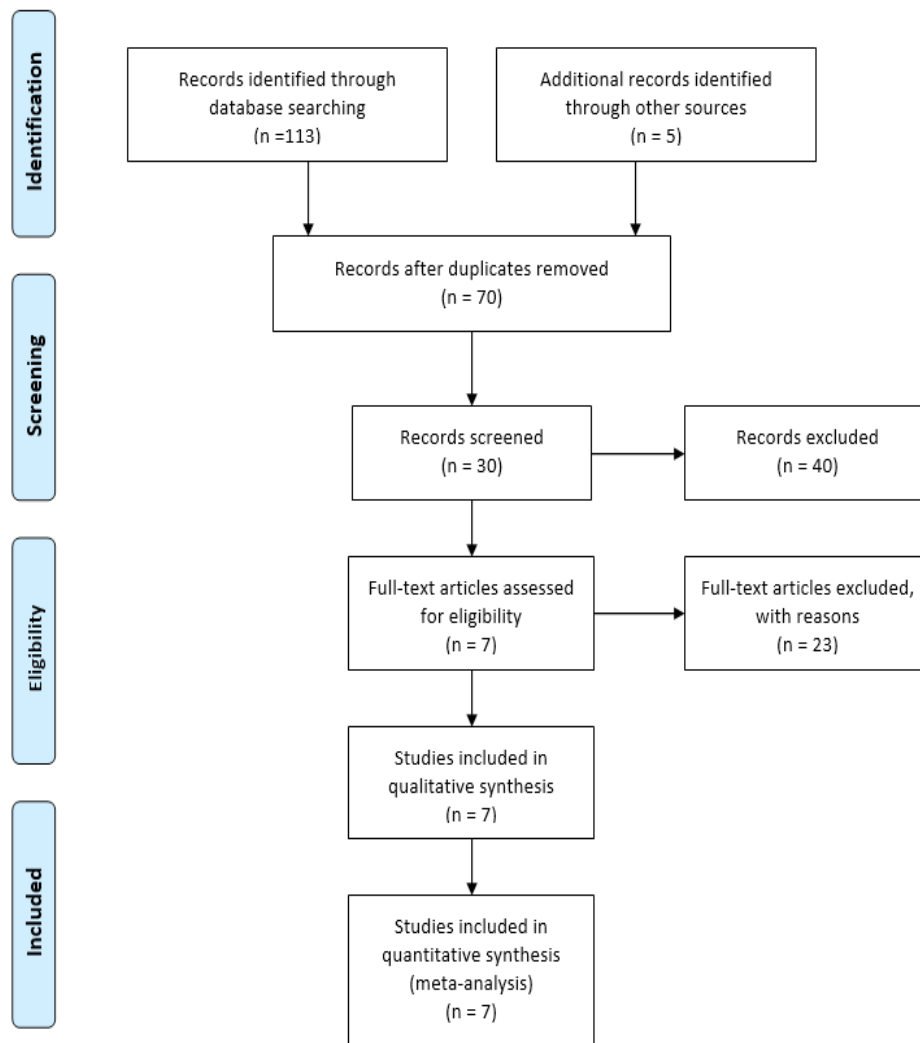


Figure 1. PRISMA

utilized the continuous form. Study characteristics are presented in Table 1.

Critical appraisal

The risk of bias assessment of our final articles is demonstrated in Table 2. Of the 7 included studies, 5 (Aramendi et al., 2020; Bouzat et al., 2014; Carteron et al., 2018; Ichai et al., 2009; Ichai et al., 2013) had an overall moderate risk of bias, and 2 (Bisri et al., 2016; Muhammad & Hanna, 2014) had a high-quality risk of bias.

Study outcomes

The pooled meta-analysis revealed a significant effect on ICP reduction in the use of HSL. Details were reported separately, including ICP, sodium osmolality, and neurological outcomes.

ICP

Five trials (Aramendi et al., 2020; Bouzat et al., 2014; Carteron et al., 2018; Ichai et al., 2009; Ichai et al., 2013) reported information on ICP. A study by Ichai et al. (2009) that compared ICP reduction using mannitol and sodium lactate showed a significantly lower ICP with sodium lactate infusion (group effect $P=0.0161$). Other before-and-after trials also reported positive effects on ICP. Carteron et al. (2018) reported ICP reduction after three hours in comparison with baseline (8 ± 6 vs 10 ± 5 mm Hg), $P<0.01$. Aramendi et al. (2020) showed a significant decrease in ICP after 30 and 60 minutes compared to the preinfusion state ($P=0.0001$). Another study by Bouzat et al. (2014) assessed the cerebral metabolic effects of HSL. In this study, HL therapy positively affected both ICP reduction and brain glutamate during three hours of infusion. Another study by Ichai et al. (2013) showed a reduction in raised ICP episodes in comparison

Table 2. Quality assessment of included studies

Ref.	Selection	Comparability	Exposure	Total Score
Bisri et al., 2016	3	2	3	8
Carteron et al., 2018	2	0	2	4
Ichai et al., 2013	2	0	2	4
Ahmad et al., 2014	3	2	3	8
Aramendi et al., 2020	2	0	2	4
Ichai et al., 2009	3	0	3	6
Bouzat et al., 2014	2	0	2	4

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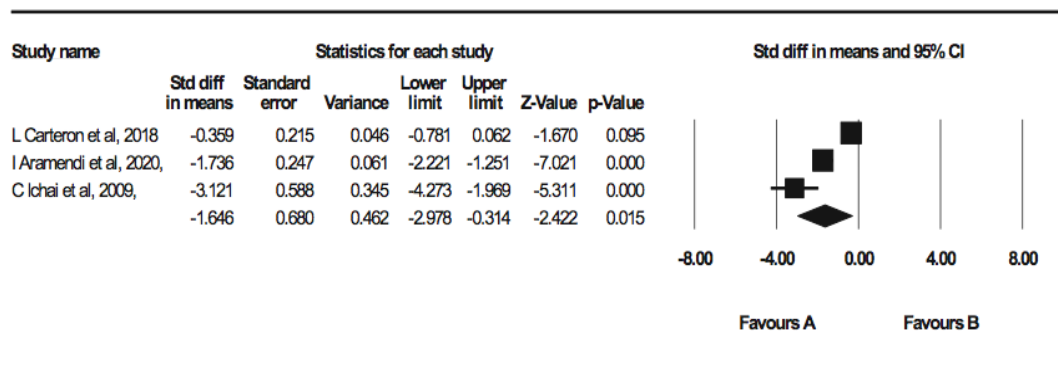
with the control group during the 48-h study: 23 vs 53 episodes ($P < 0.05$).

Serum sodium and serum osmolality

In two studies (Carteron et al., 2018; Ichai et al., 2013), sodium osmolality was increased between the two groups. In one study by Ichai et al. (2013), there was a significantly higher cumulative sodium intake and output between two groups of case and control (0.9% saline solution) in 48 h ($P < 0.01$). Also, Carteron et al. (2018) reported a significant increase in sodium and osmolality in a 3-h HS infusion (146 ± 3 vs 152 ± 3 mmol/L; $P < 0.001$ and 303 ± 6 vs 314 ± 7 mOsmol/L; $P < 0.001$). In another study by Ichai et al. (2009), there was no significant difference between mannitol and lactate therapy. In another trial by Bisri et al. (2016), serum sodium and osmolality levels were increased within 15 minutes in the HSS group compared to the HSL group, which remained unchanged ($P < 0.001$).

Neurological outcomes

In 4 studies, the Glasgow outcome scale (GOS) was used for neurologic function assessment (Bouzat et al., 2014; Carteron et al., 2018; Ichai et al., 2009; Ichai et al., 2013). Ichai et al. (2013) assessed GOS for HSL and the control group after 6 months. Although survivors had poorer neurological outcomes among the control group (9 versus 4), there was no significant difference between the two groups ($P = 0.14$). Carteron et al. (2018), with the use of a 3-h HSL solution, reported ten patients with good neurological recovery (GOS 4 or 5) at 6 months (out of 20 survivors and 3 deaths). Another study by Ichai et al. (2009) reported better outcomes using HSL compared with mannitol. Bouzat et al. (2014) reported 15 patients receiving a 3-h of HSL infusion, of which 9 had good recovery of neurologic function (GOS 4 or 5), 6 patients with GOS 3 did not have a good outcome (including 2 with severe disability), and 1 patient with GOS 2 and 3 with GOS 1 had died.



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Figure 2. Comparing ICP before and after infusion of HSL in included studies

Notes: A diamond data marker represents the standard differences in means and 95% confidence interval for the outcome of interest.

Meta-analysis

The forest plot of the random meta-analysis of three articles approved data on reduced ICP in using HSL in traumatic brain injuries ($P=0.015$). Details are presented in [Figure 2](#).

4. Discussion

According to the controversies on the effect of hyperosmolar agents, we reviewed the articles investigating the role of HSL in managing TBI.

The backbones of the therapeutic goal during TBI are maintaining sufficient CBF and energy supply for the injured brain ([Anonymous, 2000](#); [Aramendi et al., 2020](#)). The brain's glucose use may be impaired after acute injury, leading to a poor outcome ([Jalloh et al., 2013](#); [Ichai et al., 2009](#)). One of the suitable alternative substrates investigated in vitro and in vivo for over twenty years is lactate ([Jourdain et al., 2016](#)). To adjust to the shortage of glucose, the primary energy source for the brain, neurons start to increase the lactate's uptake and usage ([Gallagher et al., 2009](#); [Glenn et al., 2015](#); [Jalloh et al., 2013](#)). Then, lactate can replace the missing glucose in different pathways, including protein synthesis and redox protection ([Barros, 2013](#)). Recent animal studies ([Berthet et al., 2012](#); [Jourdain et al., 2016](#); [Roumes et al., 2020](#)) have mentioned the potential role of lactate therapy in brain injury based on its capacity to act as an energy substrate. Astrocytes and oligodendrocytes start to increase lactate production, which could eventually be exported to the neurons when neurons are under stress and energy shortage. Accordingly, lactate's presence seems necessary for the neurons' survival after brain injuries ([Mächler et al., 2016](#); [Magistretti & Allaman, 2018](#)). It has also been reported that the systemic administration of lactate in animal models could enhance cerebral angiogenesis. This relatively long-term effect of the lactate is through the hydroxycarboxylic acid receptor 1 (HCAR1) ([Morland et al., 2017](#)). [Roumes et al. \(2020\)](#) discussed the lactate's ability to reduce brain lesions after hypoxia-ischemia in neonatal rats. He further exhibited that the co-injection of lactate and a lactate dehydrogenase inhibitor completely inhibits the neuroprotective effects.

The energy substrate role of lactate also does such prevention. Lactate can also modulate CBF through different mechanisms connected with CBF and brain energy turnover. Its action regulates the Nicotinamide-adenine dinucleotide (NADH/NAD⁺) redox ratio in the glycolysis cycle and through HCAR1 and cyclic AMP formation (cAMP) ([Bergersen, 2015](#)). Astrocytes and lactate

can act as regulators for vessel diameter. An increase in the extracellular level of lactate causes the accumulation of prostaglandin E₂, eventually leading to vasodilation ([Gordon et al., 2008](#)). Our meta-analysis found that ICP decreases significantly before and after administrating the HSL among patients with TBI. It is well known that elevated ICP and cerebral hypoperfusion after the TBI for even 5 minutes are associated with poorer neurological prognosis ([Brain, 2007](#); [Stein et al., 2011](#)). As mentioned, lactate is responsible for vasodilation and could decrease cerebral vascular resistance. This reduction accordingly might increase CBF, which is related to a better outcome after TBI ([Stein et al., 2011](#)). Despite being less hypertonic than mannitol because of its carriers' nature, HSL could alter the ICP more powerfully than mannitol ([Halestrap & Price, 1999](#); [Ichai et al., 2009](#)). Although lactate gets metabolized quickly, the inorganic ions in the lactate solution are non-metabolizable. Intracellular chloride efflux will compensate for the excessive sodium ions that remain in extracellular space after administrating HSL to sustain the charges' neutrality on both sides of the plasma membrane. Consequently, water will follow the chloride ions to the extracellular space, regulating the cellular volume and preventing cellular swelling ([Ichai et al., 2009](#)). Notably, a clinical trial evaluating the effects of hypertonic lactate on patients with brain injury recorded an increase in systemic sodium levels and osmolarity, all remaining within the normal range ([Ichai et al., 2009](#)).

Lactate could also prevent cellular swelling because of its capacity to act as an energy substrate for the brain and its monocarboxylate carriers in the blood-brain barrier ([Holloway et al., 2007](#); [Maran et al., 1994](#); [Pellerin et al., 2005](#); [Rice et al., 2002](#)). During TBI, an increase in lactate levels could appear in two situations, including normal and low oxygen pressure. Such an increase in normal pressure oxygen conditions implicates aerobic glycolysis and lactate oxidation. However, this increase in oxygen-deficient settings suggests anaerobic glycolysis with a poorer prognosis ([Carpenter et al., 2015](#); [Sala et al., 2013](#)). In a recent study, all patients with acute brain injury (ABI) and normal ICP and cerebral perfusion pressure (CPP) showed improved brain perfusion after hypertonic lactate administration ([Bouzat et al., 2014](#)). In another recent animal study, administrating HSL three hours after diffuse TBI seemed beneficial and improved brain metabolism, oxygenation, and perfusion. The group treated with HSL showed fewer mitochondrial changes and reduced lactate levels within their brain cells than the control group ([Millet et al., 2018](#)). Lactate could also have a beneficial role in a variety of non-traumatic lesions like hypoxia-ischemia (HI) and

thrombotic events. In a recent study by Tassinari et al. (2020) on neonatal rats with HI, intraperitoneal administration of high doses of lactate showed positive effects on different functional aspects of the brain. He showed that administering high lactate doses lacks serious complications and could ameliorate neurological reflexes and decrease brain lesions' size. They also reported sensory-motor neuron recovery in the subjected rats. During ischemia lactate levels in the brain are relatively high, and it is to no purpose to add more lactate via systemic administration.

Nonetheless, an animal study by Berthet et al. reported lactate levels within normal ranges of 15 to 60 minutes after transient middle cerebral artery occlusion (Berthet et al., 2012). He stated that both adenosine triphosphate (ATP) shortage and increased energy demand happen during reperfusion after ischemia, emphasizing the pivotal role of the lactate produced during the anaerobic cycle. Such growth in energy demand could justify the depletion of extracellular lactate and the advantages of administrating it (Berthet et al., 2012). Consequently, systemic lactate administration seems to be a favorable option for the TBI management course, whether with or without ischemia. Interestingly, a recent clinical trial assessing HSL's effects on cognitive functions argues that HSL could boost neurologic recovery in patients with mild brain injury (Maas et al., 1997).

Altogether, HSL seems to be a reasonable substitute for fluid resuscitation after brain injury. However, Di-enel et al. (2016) have challenged the effectiveness of lactate and addressed their concerns about its administration complications. They argued that extracellular lactate could decrease the pH of the neurons and astrocytes, consequently increasing NADH production. A rise in NADH levels could interfere with the activity of pH-sensitive enzymes such as phosphofructokinase. Low pH levels inhibit phosphofructokinase activity, which has an important regulatory role during glycolysis and could impede the cycle. Increased levels of NADH could also reduce the accessibility of NAD⁺ during glycolysis. He also argued that this lactate amount could also tamper with the pentose phosphate pathway and oxidative stress management in neurons.

As we previously mentioned, despite the probable side effects of lactate, we cannot disregard its inevitable role in elevated ICP management. Even so, lactate administration should be done with caution and properly evaluated. Considering the lack of sufficient clinical trials, controversial evidence, and the potential capability of lactate therapy in managing patients with TBI, we

strongly encourage fellow researchers to further assess other aspects of lactate therapy in TBI.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Study design: Reza Mosaed, Mojtaba Mojtahedzadeh, Arash Akhavan Rezayat, and Farhad Najmeddin; Methodology: Behnaz Rohani and Aida Ayati Afin; Data collection: Arash Akhavan Rezayat, Behnaz Rohani, and Aida Ayati Afin; Statistical analysis: Arash Akhavan Rezayat; Writing the initial draft: Maryam Taghizadeh-Ghehi, Shahideh Amini, and Mohamad Afshar Ardalan; Final approval; All authors.

Conflict of interest

The authors declared no conflict of interest.

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