Title: Effects of Hypertonic Sodium Lactate on Intracranial Pressure in Patients with Traumatic Brain Injury: A Systematic Review and Metanalysis on Clinical Trial Studies

Running Title: Sodium Lactate and Intracranial Pressure

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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.

Method: PubMed, Scopus, EMBASE, and Web of Science were searched to find published articles on the effects of HSL on ICP in patients with a traumatic brain injury until December 2020. Animal studies, case reports, and studies, including liver and renal failure patients, cardiac dysfunction, or hypovolemic shock, were excluded. The Newcastle–Ottawa Scale checklist was used to assess the methodological quality of eligible articles. Information was gathered based on the following: Demographic data, methods, intervention, and outcomes.

Results: Our initial search with the predefined search strategy proceeded 113 studies. Finally, seven studies were eligible for systematic review, which three of them were eligible for meta-analysis. A random meta-analysis of three 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 hypertonic sodium lactate's undeniable role in managing increased ICP in patients with brain injury. Nevertheless, conducting more clinical studies for assessing the possible side effects of HSL seems crucial.

Keywords: Sodium lactate; Intracranial pressure; 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, which could be ameliorated by hyperosmolar therapy (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 [5]. 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 [6].

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 intracranial pressure are the main drawbacks of mannitol (Anonymous, 2000; White et al., 2006). In refractory cases of increased intracranial pressure 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 does not cause a rebound increase in ICP (Kerwin et al., 2009). Hence, some newer studies reported HTS as the superior hyperosmolar agent (Mangat et al., 2020). No clear recommendation was made in recently published meta-analysis regarding the choice of

hypertonic saline or mannitol, in the treatment of patients with TBI-induced elevated ICP (Fatima et al., 2019). However, there are some concerns 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; Leverve & Mustafa, 2002; Rice et al., 2002). HSL could decrease intracranial pressure, thorough osmotic effect of hypertonic sodium and cerebral vasodilator effect of lactate (Gordon et al., 2008). Ichai et al. mentioned that HSL's effect was even more potent than mannitol's effect on reducing ICP in some trials (Ichai et al., 2009). It is noteworthy that a recent study on patients with TBI-induced elevated ICP, Arifianto et al. introduced HSL as a choice for fluid therapy (Arifianto et al., 2018). Considering HSL's beneficial roles in TBI, in this study, we systematically reviewed the articles investigating HSL's therapeutic role in patients with traumatic brain injury.

2. Material and Methods

2.1. Data sources and search strategy

We performed our search using 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 (A.A.R. and B.R.) conducted the search from January 2000 to December, 2020. We searched the literature applying a different combination of our keywords, including traumatic brain injury, 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.

2.2. 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 intracranial pressure (ICP) above 20 mmHg. Animal studies, case reports, studies with liver and renal failure patients, 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.

2.3. Study selection

After checking for duplications, two investigators independently reviewed all studies' title and abstract 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.

2.4. 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, intervention, and outcomes were extracted from the included manuscripts and documented.

2.5. Data analysis

Data from included studies were pooled using a random-effect model. All continuous data were summarized as the standard difference in means and standard error and analyzed using comprehensive meta-analysis. The inconsistency index (I2) was used to measure heterogeneity with I2 >50% indicating substantial heterogeneity. P-value<0.05 was considered statistically significant.

3. Result

3.1. Selection process results

Our initial search with the predefined search strategy proceeded in 34 studies from Scopus database and 32 publications from PubMed database; furthermore, 32 additional publications were included through searching 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, seven studies did not provide enough information, ten articles were not entirely relevant, and six were animal studies. Finally, seven [15, 18, 21-25] studies were eligible for this systematic review of which three studies [18, 21, 24], comprising intracranial pressure between before and after of injection of HSL, were eligible for a meta-analysis. The selection process is detailed in Figure 1 PRISMA flow chart.

3.2. Characteristics of the included studies

Out of 138 papers that were initially reviewed 131 papers were removed and a total of seven articles were assessed for eligibility using Newcastle-OTTAWA scale. Included studies from France, Switzerland and Indonesia were evenly distributed as they had two articles each. One study was conducted in Uruguay. Four [15, 18, 22, 25] of seven studies were randomized trials, of which three [21, 23, 24] were before-and-after trials. Total number of patients from the initial seven articles was 275, and 98 patients were included in the final three analyzed studies. Two of the included studies [21, 24] were prospective interventional, and one [18] of them was a prospective open randomized study.

The meta-analysis carried out for ICP reduction according to data reported in three articles. Drug administration characteristics in four (Aramendi et al., 2020; Bisri et al., 2016; Ichai et al., 2009; Muhammad & Hanna, 2014) publications were bolus while the other three studies utilized the continuous form. Study Characteristics are presented in Table 1.

3.3. Critical appraisal

Risk of bias assessment of our final articles is demonstrated in Table 2. Of the seven included studies, five (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, whereas two (Bisri et al., 2016; Muhammad & Hanna, 2014) studies had a high-quality risk of bias.

3.4. Outcomes

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

3.5. Intracranial pressure

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 intracranial pressure. A study by C Ichai et al. (Ichai et al., 2009) that compared ICP reduction using mannitol and sodium lactate showed a significant lower ICP with sodium lactate infusion (group effect P=0.0161). Other before-and-after trials also reported positive effects on ICP. L Carteron et al. (Carteron et al., 2018) reported ICP reduction after three hours in comparison with

baseline (8±6 vs 10±5, P<0.01). I Aramendi et al. (Aramendi et al., 2020) showed a significant decrease of ICP after 30 and 60 minutes compared to preinfusion state (P=0.0001). Another study by P Bouzat et al. (Bouzat et al., 2014) assessed 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 C Ichai et al. (Ichai et al., 2013) showed a reduction in raised ICP episodes in compare with the control group during the 48-h study: 23 versus 53 episodes ($p < 0.05$).

3.6. Serum Sodium and serum osmolality

In two (Carteron et al., 2018; Ichai et al., 2013) studies, there was increased sodium osmolality between two groups. In one study by C Ichai et al. (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, L Carteron et al. (Carteron et al., 2018) reported a significant increase in sodium and osmolarity in 3-h HS infusion (146±3 mmol/L vs 152±3 mmol/L; P<0.001and 303±6 mOsmol/L vs 314±7 mOsmol/L; P<0.001). Whereas in another study by C Ichai et al. (Ichai et al., 2009) between mannitol and lactate therapy, there was no significant difference. In another trial by T Bisri et al. [22], serum sodium and osmolality levels were increased within 15 minutes in the HSS group compared to the HSL group that remained unchanged (P<0.001).

3.7. Neurological outcomes

Glasgow outcome scale (GOS) was used for neurologic function assessment in four (Bouzat et al., 2014; Carteron et al., 2018; Ichai et al., 2009; Ichai et al., 2013) studies. C

Ichai et al. (Ichai et al., 2013) assessed GOS for HSL and control group after six months. Although among the control group survivors had poorer neurological outcomes: nine versus four, there was no significant difference between the two groups (p=0.14). L Carteron et al. (Carteron et al., 2018) with use of 3-h HSL solution reported ten patients with good neurological recovery (GOS 4 or 5) at six months (out of twenty survivors and three deaths). Another study by C Ichai et al. (Ichai et al., 2009) reported better outcomes using HSL compared with mannitol. Bouzat et al. [23] reported 15 patients receiving 3-h of HSL infusion, of which nine had good recovery of neurologic function (GOS 4 or 5), six patients with GOS 3 did not have a good outcome (including two with severe disability), and one patient with GOS 2 and three with GOS 1 had died.

3.8.Meta-analysis

The forest plot of the random meta-analysis of three articles approved data on reduced intracranial pressure in use of 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 hypertonic sodium lactate in the management of traumatic brain injury.

The backbones of the therapeutic goal during TBI are maintaining sufficient cerebral blood flow and energy supply for the injured brain (1, 2). Brain's ability to use glucose may be impaired after acute injury, leading to a poor outcome [26](42). One of the suitable alternative substrates investigated in vitro and in vivo for over twenty years is lactate [27]. 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) .Lactate then can take the place of 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. When neurons are in stress and shortage of energy, astrocytes and oligodendrocytes start to increase the lactate production, which eventually could be exported to the neurons. Accordingly, lactate's presence seems to be necessary for the survival of the neurons after brain injuries (Mächler et al., 2016; Magistretti & Allaman, 2018). It is also reported that 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) receptor (Morland et al., 2017). Roumes H et al. (Roumes et al., 2020) discussed the lactate's ability to reduce the 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.

Such prevention is also by the energy substrate role of the lactate. Lactate is also able to act as a modulator for cerebral blood flow (CBF) through different mechanisms connected

with both CBF and brain energy turnover. Its action regulates NADH/NAD+ redox ratio in the glycolysis cycle and through HCAR1 and cyclic AMP formation (cAMP) (Bergersen, 2015). Astrocytes and lactate can act as a regulator for vessel diameter. An increase in the extracellular level of lactate causes the accumulation of prostaglandin E2, which eventually leads to vasodilation (Gordon et al., 2008). Our meta-analysis found that intracranial pressure (ICP) decreases significantly before and after administrating the HSL, among patients with traumatic brain injury. It is well known that elevated ICP and cerebral hypoperfusion after the TBI for even five minutes are associated with poorer neurological prognosis (Brain, 2007; Stein et al., 2011). As mentioned before, lactate is responsible for vasodilation and hence could decrease cerebral vascular resistance. This reduction accordingly might increase CBF, which is related to the better outcome after TBI (Stein et al., 2011)(29,30). 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 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). It is noteworthy that 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 [24].

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. In normal pressure oxygen condition, such increase implicates aerobic glycolysis and lactate oxidation. However, this increase in oxygen-deficient setting suggests anaerobic glycolysis with the 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 also showed less mitochondrial changes and reduced lactate levels within their brain cells, compared to the control group (Millet et al., 2018). Lactate could also have a beneficial role in variety of non-traumatic lesions like hypoxia-ischemia (HI) and thrombotic events. In a recent study by Tassinari et al. (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 administrating high doses of lactate doesn't have any serious complication 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 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 in the course of reperfusion after ischemia, emphasizing the pivotal role of the lactate that has been 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 (30).

Altogether, HSL seems to be a reasonable substitute for fluid resuscitation after brain injury. However, Dienel et al. (Dienel et al., 2016) has challenged the effectiveness of lactate and addressed his concerns on its administration complications. He argued that extracellular lactate could decrease the pH of the neurons and astrocytes, consequently increasing NADH production. Raise in NADH levels could interfere with the activity of the pH-sensitive enzymes such as phosphofructokinase. Low pH levels inhibit phosphofructokinase activity which has an important regulatory role during the glycolysis and could impede the glycolysis cycle. Increased levels of NADH could also reduce the accessibility of NAD+ during the 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 probable side effects of lactate, we cannot disregard the inevitable role of lactate in elevated ICP management. Even so, lactate administration should be 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.

5. Conflict of interest

All authors have no conflict of interest.

6. Acknowledgment

No Acknowledgment.

7. Authors' contributions

Reza Mosaed, Mojtaba Mojtahedzadeh, Arash Akhavan Rezayat and Farhad Najmeddin designed the study. Behnaz Rohani and Aida Ayati Afin conducted literature searches and provided a strategy of research. Arash Akhavan Rezayat, Behnaz Rohani and Aida Ayati Afin reviewed articles and extracted data. Arash Akhavan Rezayat conducted the statistical analysis. Maryam Taghizadeh-Ghehi, Shahideh Amini and Mohamad Afshar Ardalan wrote the first draft of the manuscript, and all authors contributed to and have approved the final manuscript.

8. Highlights

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

9. Plain Language Summary

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. A random meta-analysis of three articles showed Intracranial pressure was reduced after infusion of hypertonic sodium lactate in traumatic brain injuries and had a role in managing increased intracranial pressure by increasing serum osmolarity. It seems that hypertonic sodium lactate is a reasonable substitute for fluid resuscitation after brain injury.

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Table 1: Characteristic of included studies

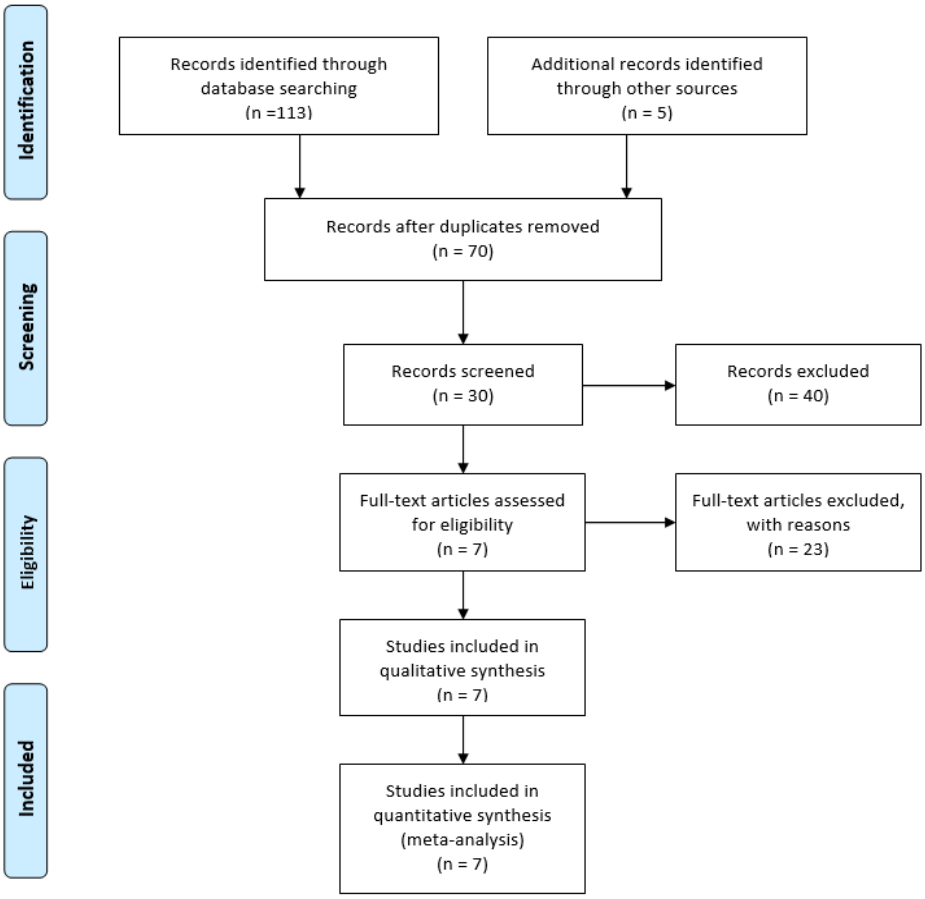
Study	Country	Design	Number of patients	Group	Sex (M/F)	Age (±SD)		Drug Administration	Formulation	Dose
						HSL	Control group			
Bisri et al, 2016	Indonesia	RCT	60	HSL/HSS	47/13	30.23±14.89	28.43±15.53	Bolus	Na 504.15 mmol/L K 4.02 mmol/L Ca 1.36 mmol/L Cl 6.74 mmol/L Lactate 504.15 mmol/L	290.18±1.30 mOsmol/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 mOsmol/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, and L-lactate 504.1 mmol/L	301 ± 10 mOsmol/kg
MR Ahmad et al, 2014	Indonesia	RCT	42	HSL/Mannitol	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 Ca2+, 6.74 mmol/L Cl-, and 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 4.0 Osmolarity mOsm/l 1.020	302.6 ± 12.0 mOsmol/kg
C Ichai et al, 2009	France	before-and -	34	HSL/Mannitol	24/10	37.6 (4.0)	33.8 (3.2)	Bolus	Na 504 mmol/L, K 4 mmol/L, Ca 1.36 mmol/L, Cl 6.74 mmol/L and lactate	298.6 (7.3) mOsmol/kg

		after trials							504.1 mmol/L	
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

Table 2: Quality assessment of included studies

Article	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



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 1: PRISMA flowchart

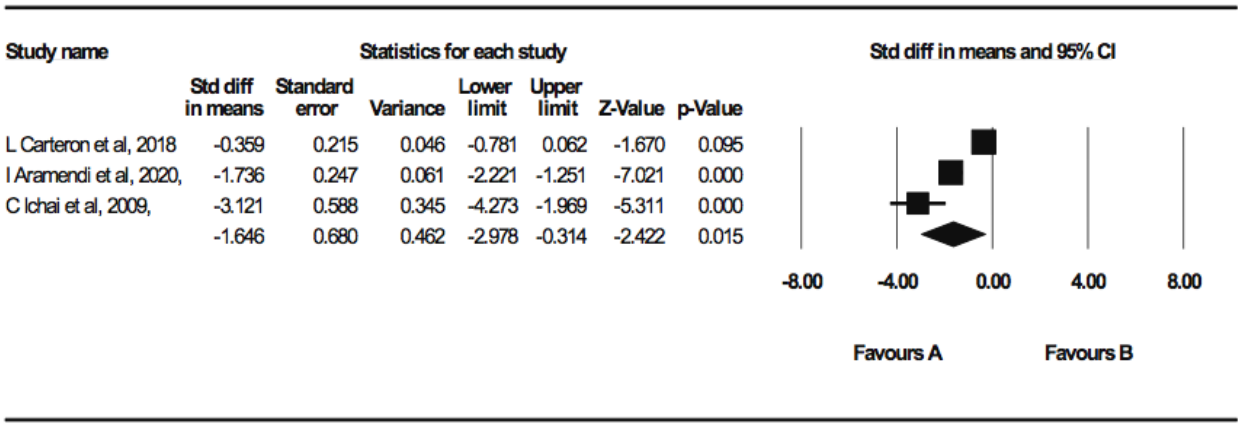


Figure 2: Comparison of intracranial pressure before and after of infusion of hypertonic sodium lactate in included studies; a diamond data marker represents the standard differences in means and 95% confidence interval for the outcome of interest