DOI: 10.1590/0004-282X20150039

ARTICLE

Effect of volume replacement during combined experimental hemorrhagic shock and traumatic brain injury in prostanoids, brain pathology and pupil status

Efeito da reposição volêmica durante o choque hemorrágico combinado com traumatismo cranioencefálico sobre prostanóides, patologia cerebral e *status* pupilar

Fernando Campos Gomes Pinto[1], *Matheus Fernandes de Oliveira*[2], *Ricardo Prist*[3], *Maurício Rocha e Silva*[4], *Luiz Fernando Ferraz da Silva*[5,6], *Antonio Capone Neto*[7]

ABSTRACT

Traumatic brain injury (TBI) is the main cause of trauma-related deaths. Systemic hypotension and intracranial hypertension causes cerebral ischemia by altering metabolism of prostanoids. We describe prostanoid, pupilar and pathological response during resuscitation with hypertonic saline solution (HSS) in TBI. **Method:** Fifteen dogs were randomized in three groups according to resuscitation after TBI (control group; lactated Ringer's (LR) group and HSS group), with measurement of thromboxane, prostaglandin, macroscopic and microscopic pathological evaluation and pupil evaluation. **Result:** Concentration of prostaglandin is greater in the cerebral venous blood than in plasma and the opposite happens with concentration of thromboxane. Pathology revealed edema in groups with the exception of group treated with HSS. **Discussion and conclusion:** There is a balance between the concentrations of prostaglandin and thromboxane. HSS prevented the formation of cerebral edema macroscopically detectable. Pupillary reversal occurred earlier in HSS group than in LR group.

Keywords: traumatic brain injury, volemic resuscitation, pathology, inflammation.

RESUMO

O traumatismo cranioencefálico (TCE) é a principal causa de morte relacionada ao trauma. O choque hemorrágico e hipertensão intracraniana causam isquemia cerebral alterando o metabolismo de prostanóides. Neste estudo, relatamos o comportamento dos prostanóides, resposta pupilar e patologia durante a reposição volêmica com solução salina hipertônica (SSH) no TCE. **Método:** Quinze cachorros foram randomizados em três grupos (controle, grupo de Ringer lactato e grupo de SSH) e foram avaliados tromboxane, prostaglandina, avaliação patológica macroscópica e microscópica e *status* pupilar. **Resultado:** A concentração de prostaglandina é maior no sangue cerebral em comparação ao plasma, e o inverso ocorre com o tromboxane. A patologia revelou edema em todos os grupos, com exceção do grupo tratado com SSH. **Discussão e conclusão:** Existe um equilíbrio entre concentrações cerebrais e plasmáticas de prostaglandina e tromboxane. A SSH protegeu o cérebro da formação de edema pós traumático.

Palavras-chave: traumatismo cranioencefálico, reposição volêmica, patologia, inflamação.

Head injury is the main cause of trauma-related deaths in over 60% of cases[1,2,3,4,5]. Hemorrhage and shock are observed in up to 20% of patients with head injuries[6,7,8,9,10,11,12]. Hypotension, even for very brief periods, is a well-established cause of secondary brain injury, and contributes to worse outcomes[13,14,15].

[1]Universidade de São Paulo, Hospital das Clínicas, Instituto de Psiquiatria, Divisão de Neurocirurgia Funcional, Sao Paulo SP, Brazil;
[2]Hospital do Servidor Público Estadual de São Paulo, IAMSPE, Departamento de Neurocirurgia, Sao Paulo SP, Brasil;
[3]Universidade de São Paulo, Faculdade de Medicina, Divisão de Pesquisa, Sao Paulo SP, Brazil;
[4]Universidade de São Paulo, Departamento de Fisiologia, Sao Paulo SP, Brazil;
[5]Universidade de São Paulo, Departamento de Patologia, Sao Paulo SP, Brazil;
[6]Hospital Israelita Albert Einstein, Sao Paulo SP, Brazil;
[7]Hospital Israelita Albert Einstein, Unidade de Terapia Intensiva, Sao Paulo SP, Brazil.
Correspondence: Matheus Fernandes de Oliveira; Rua Luís Góis, 1333/apto 23; 04043-150 Sao Paulo SP, Brasil; E-mail: mafernoliv@yahoo.com.br
Conflict of interest: There is no conflict of interest to declare.
Received 10 January 2015; Accepted 03 February 2015.

Several studies have demonstrated that elevated intracranial pressure (ICP) impairs protective mechanisms against blood loss and hypotension, creating a substantial treatment challenge[1,2,3,13,14]. The type of fluid used for volume replacement can have a significant impact on ICP. As hyperosmolar therapy has been used to reduce elevated ICP due to a variety of causes, including traumatic brain injury (TBI), the use of hypertonic saline solution (HSS) for resuscitation of head-injured patients has been considered an appealing strategy[6,7,8,9,10].

Additionally, hemorrhagic hypotension associated with intracranial hypertension causes decreased cerebral blood flow and cerebral ischemia by altering the synthesis, activation, and release of potent vasoactive substances-vasoactive prostanoids, such as prostacyclin (PGI2) and thromboxane (TXA2)—and may interfere with cerebrovascular reactivity[16,17,18,19,20,21].

A previous report by our group evaluated the systemic and cerebral, hemodynamic, and oxygenation responses to different solutions used for volume replacement during the early phases of hemorrhagic shock (HS) associated with TBI[1]. We now report the results of further evaluations, including assessment of prostanoid, pupillary, and pathological response, during fluid replacement with HSS in experimental TBI.

METHODS

This study was conducted at the Experimental Division of the Heart Institute (InCor), Hospital das Clinicas, Faculty of Medicine, University of São Paulo (HC-FMUSP), in accordance with international standards for the use of experimental animals[22], after being approved by the Scientific Committee of the Heart Institute and the FMUSP Research Ethics Committee.

Experiments were performed on 15 mongrel dogs (weight 16.3 ± 1.9 kg), which were fasted overnight with free access to water. Anesthesia was provided with ketamine (10 mg/kg) and halothane (1.5% during preparation and insult, 0.5% during treatment). After orotracheal intubation, mechanical ventilation was initiated (Harvard Apparatus 708, South Natick, MA) to keep end-tidal CO_2 (ETCO2) between 32 and 37 mmHg (Dixtal DX 1265 capnometer, Manaus, AM, Brazil).

The femoral artery and vein were cannulated with P240 catheters. A pulmonary artery catheter (93A-131H-7F, Baxter Healthcare Corporation, CA) was inserted through the right jugular vein and connected to a cardiac output monitor (model 9520A, American Edwards Lab, CA). Cardiac output parameters were acquired by averaging two measures. The hemodynamic catheters were connected through pressure transducers (P23XL Viggo-Spectramed, Statham, CA) to a multichannel acquisition system (MP100, Biopac System, CA). Measured variables were recorded and analyzed on a personal computer using Acknowledge 3.0 for Windows software.

The left transverse sinus was cannulated through a 2-mm burr hole to obtain cerebral venous blood samples. An intraparenchymal fiberoptic ICP sensor (model 110-4B, Camino NeuroCare Inc., San Diego, CA) was placed in the right parietal lobe through an 2-mm burr hole drilled in the parietal bone and connected to a ICP monitor (V420-7, Camino Laboratories, San Diego, CA). A 1-cm diameter hole was drilled into the left parietal bone for delivery of fluid percussion by a specific device (Fluid Percussion Machine, Bioengineering Division, InCor/HC-FMUSP, São Paulo, Brazil); a deflated epidural balloon (#5 Foley catheter) was also placed in the epidural space through this hole. Core temperature was kept in the 36ºC-38ºC range with heated blankets.

Insult

HS was induced by withdrawal of blood through an aortic catheter over 5 to 10 minutes to a mean arterial pressure (MAP) of 40 mmHg. The shed blood was heparinized and stored. TBI was induced by fluid percussion (4 atm). After fluid percussion, the epidural balloon was inflated with approximately 5 mL to a target ICP of 20 to 25mmHg. The experimental design simulated the clinical scenario of prehospital and early hospital resuscitation phases, including intracranial hematoma drainage (Figure 1).

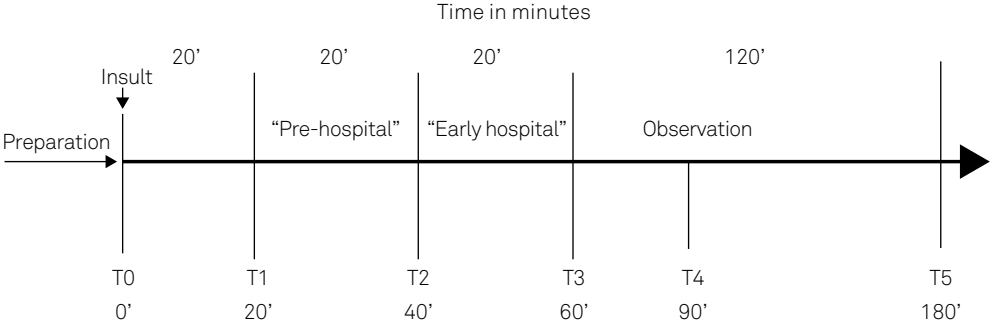


Figure 1. Experimental design: T0-T1: insult period: HS and TBI; T1-T2: prehospital treatment period; T2-T3: early hospital treatment: the same solution used during pre-hospital period for MAP = 70mmHg. Blood for Ht = 30% was started at this phase. At 60' (T3), the epidural balloon was emptied; T3 –T5: observation period (Ht aimed at 30% and MAP at 70mmHg); T5: sacrifice; Blood samples were collected at T0, T1, T2, T3, T4 and T5.

Groups

Fifteen mongrel male dogs, weight 13 to 20 kg, were randomized to one of three groups: HS + TBI + HSS (n = 5), simulating prehospital treatment with 3% saline solution (HSS), 8 mL/kg over 10 minutes; HS+TBI+LR (n = 5), simulating prehospital treatment with lactated Ringer's (LR) solution, 16 mL/kg over 10 minutes; and HS+TBI (n =), a control group in which no fluids were provided.

During a simulated early in-hospital treatment phase, the two treatment groups received shed whole blood transfusion targeted to a hematocrit of 30% and HSS or LR, according to the specific group, to maintain mean arterial pressure (MAP) greater than 70 mmHg. After 60 minutes, the epidural balloon was deflated in the treatment-group animals, simulating intracranial hematoma drainage. The balloon was kept inflated throughout the experiment in control animals.

MAP (mmHg) and ICP (mmHg) were measured or calculated using standard formulas. Biochemical and blood gas analyses were performed using a STAT Profile Ultra analyzer (Nova Biomedical, Waltham, MA).

Statistical analysis

Results were expressed as mean plus standard deviation. Analysis of variance (ANOVA) was used for between-group comparisons. Differences were evaluated by Student's *t*-test and accepted as statistically significant when p-values were < 0.05.

Measurement of thromboxane B2 and 6-keto prostaglandin F1 alpha

At three distinct time points—T0' (baseline), T40' (40 minutes, end of prehospital treatment), and T90' (30 minutes after the end of the hospital treatment period), brain venous blood and central arterial blood samples were collected for immunoassay measurement of the stable metabolites of TXA2 and PGI2: thromboxane B2 (TXB2) and 6-keto prostaglandin F1 alpha respectively.

Samples (10 mL blood each) were collected into dry tubes and centrifuged at 3000 rpm for 15 minutes. Serum aliquots (2 mL) were then pipetted into microcentrifuge tubes (Eppendorf®) and stored at -70°C.

In due course, the samples were thawed and subjected to chemical extraction in specific columns of commercially available kits (Thromboxane B2 Enzymeimmunoassay Biotrak System - code RPN221, and 6-Keto_Prostaglandin F1 Alpha Enzymeimmunoassay Biotrak System - code RPN220; Amersham Biosciences UK Limited). After elution with ethyl acetate, the samples were dried by centrifugation (Speed-Vac, model SC 210a, Manufacturer Institute Inc. Savant, Holbrook, New York, USA) in a vacuum system for 60 minutes. The absorbance data obtained from the assays were applied to a specific formula and the concentration in pg/mL was determined after plotting a standard curve.

Pathology

Gross examination

After euthanasia (T180'), through an extended calvarectomy, the dura was carefully opened and the supratentorial portion of the brain removed en bloc to the level of the midbrain; the cerebellum was not removed. A biparietal coronal section at the level of the lateral ventricles was performed to evaluate the cerebral cortex, white matter, and the interior of the ventricles. Brains were identified and kept in closed containers with 10% formalin for at least 1 month before microscopic evaluation. We considered macroscopic cerebral edema the nacreous and swollen aspect of the brain parenchyma.

Microscopic examination

After removal, brains were fixed in 10% formalin for 20 days. To identify brain structures, several sequential coronal sections were made across the brain. The following segments were evaluated: right and left frontal cortex, right and left parietal cortex, right and left temporal cortex, right and left occipital cortex, right and left basal ganglia (putamen, caudate, and thalamus), and right and left hippocampus. These sections were cut into 4-µm slices and stained with hematoxylin and eosin.

To evaluate ischemic injury in each region, a semiquantitative analysis was performed by two blinded pathologists. The degree of ischemic injury was graded on a scale of 0 to 4, based on the presence of neuronal shrinkage, presence of red neurons, and neuropil atrophy. The score ranged from zero to four, as more ischemic features were detected. Differences between means in the study groups were analyzed using ANOVA.

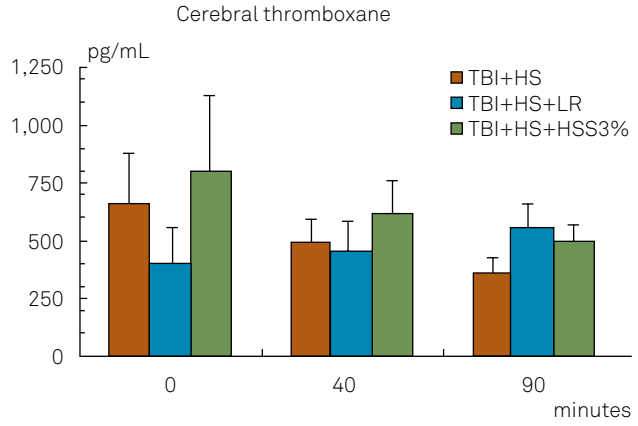
Pupillary examination

Before starting the experiment, all dogs were evaluated and found to exhibit equal pupils and symmetrical pupillary light reflex. During the experiment, pupils were assessed every 10 minutes. The presence of anisocoria or mydriasis and the progression of pupillary changes during the experiment – with respect to reversal of pupillary change to the normal pattern – were considered significant.

RESULTS

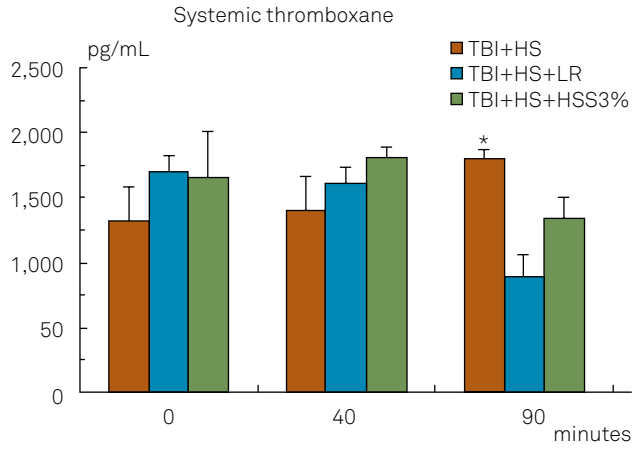
Systemic inflammatory response and brain release of thromboxane B2 and 6-keto prostaglandin F1 alpha

There were no statistically significant differences in baseline values between the groups. Prostaglandin concentrations were higher in cerebral venous blood than in plasma, and thromboxane concentrations were higher in plasma than in the central venous circulation (Figures 2, 3, 4 and 5).



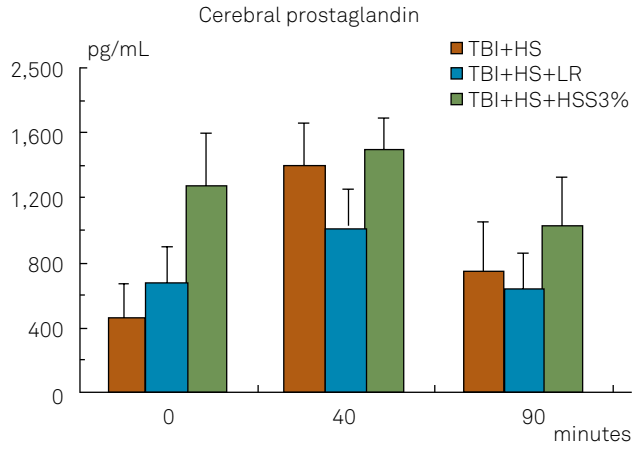
TBI: traumatic brain injury; HS: hemorrhagic shock; LR: lactated Ringer's; HSS: hypertonic saline solution.

Figure 2. Cerebral thromboxane.



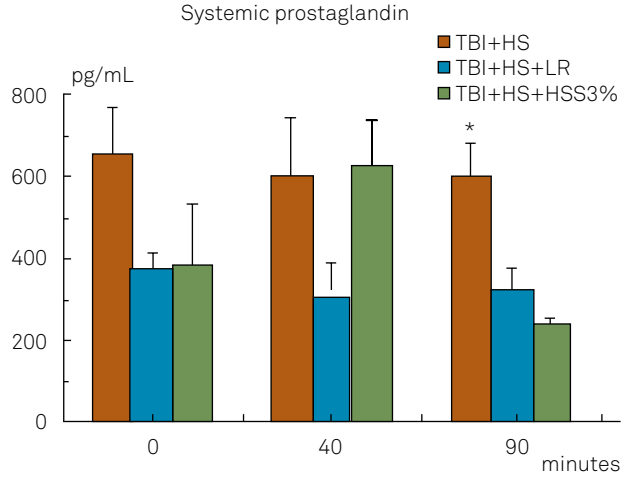
TBI: traumatic brain injury; HS: hemorrhagic shock; LR: lactated Ringer's; HSS: hypertonic saline solution.

Figure 3. Systemic thromboxane (* = significative statistical difference).



TBI: traumatic brain injury; HS: hemorrhagic shock; LR: lactated Ringer's; HSS: hypertonic saline solution.

Figure 4. Cerebral prostaglandin.



TBI: traumatic brain injury; HS: hemorrhagic shock; LR: lactated Ringer's; HSS: hypertonic saline solution.

Figure 5. Systemic prostaglandin.

Control group

In this group, systemic thromboxane levels increased progressively, showing a statistically significant difference at T90, with the highest value (1,800 pg/mL) compared to the treatment groups. Systemic prostaglandin levels remained stable throughout the experiment (statistically significant at T90), with the highest value (600 pg/mL) compared to the treatment groups.

Cerebral thromboxane levels decreased progressively, but with no significant difference as compared with the other groups. Cerebral prostaglandin levels increased up to T40 and declined thereafter until T90, without significant differences in relation to the other groups.

Effects of lactated Ringer's solution

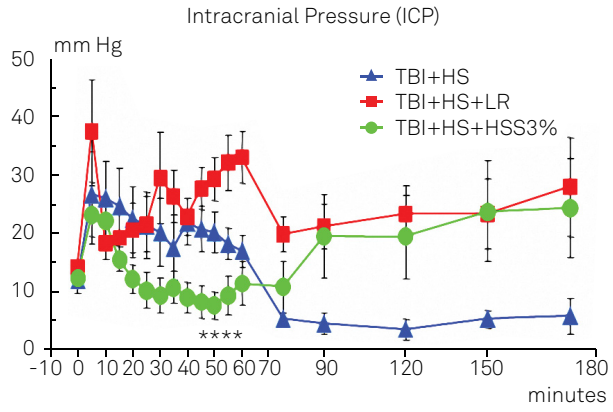
During early in-hospital treatment phase (40'-60'), infused blood volume was 12.9 ± 4.8 ml/kg. In hospitalar phase, LR volume infused was 5.9 ± 9.6 ml/kg.

ICP presented with progressive increasing and was higher than in control group and HSS 3% group. When epidural balloon was deflated, ICP decreased and became stable at around 20 mmHg (Figures 6 and 7).

In the LR-treated group, systemic levels of thromboxane and prostaglandin decreased progressively. In the brain, thromboxane levels increased while prostaglandin levels decreased, although the differences were not statistically significant.

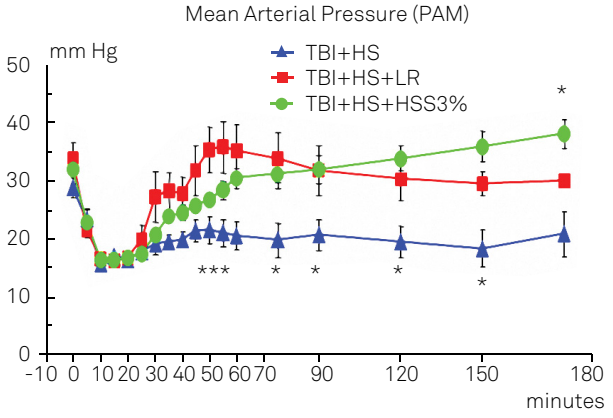
Effects of hypertonic saline solution

During early in-hospital treatment phase (40'-60'), infused blood volume was 11.3 ± 4.0 ml/kg. In hospitalar phase, HSS 3% volume infused was 3.8 ± 4.3 ml/kg. Differences in infused blood and cristaloid volumes between groups were not statistically significant.



TBI: traumatic brain injury; HS: hemorrhagic shock; LR: lactated Ringer's; HSS: hypertonic saline solution.

Figure 6. Intracranial pressure (ICP) for each group in treatment protocol.



TBI: traumatic brain injury; HS: hemorrhagic shock; LR: lactated Ringer's; HSS: hypertonic saline solution.

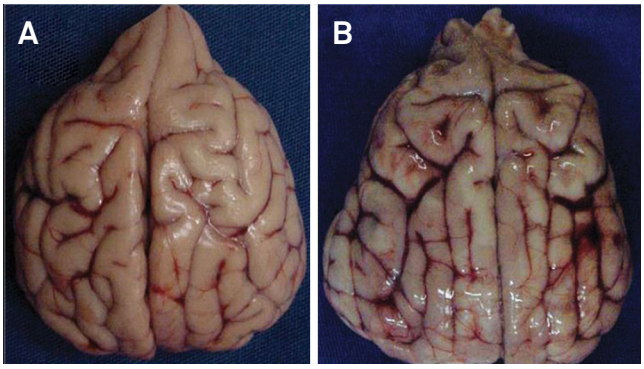
Figure 7. Mean arterial pressure (MAP) for each group in treatment protocol.

ICP after HSS 3% was the lowest in 60 initial minutes. When epidural balloon was deflated, ICP decreased and became stable at around 20 mmHg (Figures 6 and 7).

In the HSS-treated group, systemic thromboxane levels increased slightly up to T40 and declined thereafter; systemic prostaglandin levels behaved similar, but both the increase and the subsequent decline were more pronounced. Cerebral thromboxane levels decreased progressively while cerebral prostaglandin levels increased slightly up to T40 and then decreased, although with no statistically significant differences.

Gross examination of cerebral tissue

The most striking result was the identification of edema in the brains of all control (untreated) animals and in the LR group; in the HSS-treated group, no edema was identified. The other gross findings were similar across the three groups: traumatic subarachnoid hemorrhage (TSAH), two cases of acute subdural hematoma (ASDH), three left frontotemporal contusions, and two cases of intraventricular hemorrhage (Figure 8).



TBI: traumatic brain injury; HS: hemorrhagic shock; LR: lactated Ringer's.

Figure 8. Superior view of two experimental brains. A is an example of normal brain and B is an example of bihemispheric edema, with diffuse hemorrhage (dog number 14, HS + TBI + LR group).

Microscopic examination of cerebral tissue

Microscopic examination of the brain (frontal, temporal, parietal, occipital, and hippocampal regions) showed significant differences across groups, particularly in the presence of ischemic lesions in the right and left hippocampi when comparing the HSS-treated group versus the untreated control group; such injuries were most evident in the untreated group (Figures 9 and 10).

Pupillary examination

The majority of the dogs showed pupillary changes (11 of 15 dogs). Findings were anisocoria, with the left pupil being larger than the right (7 of 11 dogs), or bilateral mydriasis (4 of 11 dogs). Most pupillary changes were manifested within 20 minutes, immediately before the start of the prehospital treatment phase.

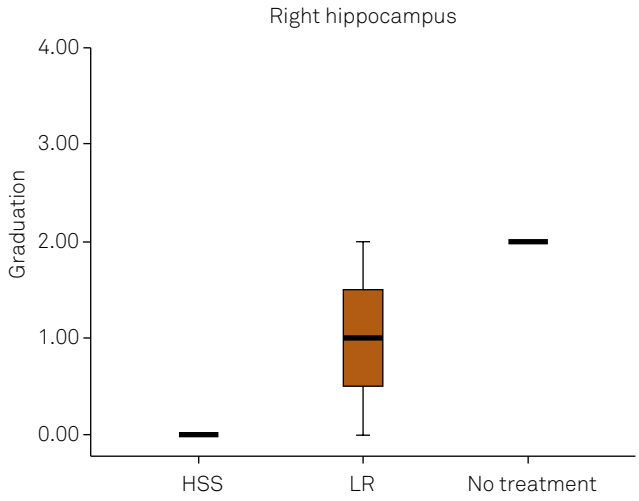
In the HSS group, two of four animals with anisocoria had early reversal to normal pupillary response at T40. Conversely, in the LR-treated group, in the two cases in which there was reversal of mydriasis, this occurred at T90.

Discussion

Systemic inflammatory response and brain release of thromboxane B2 and 6-keto prostaglandin F1 alpha)

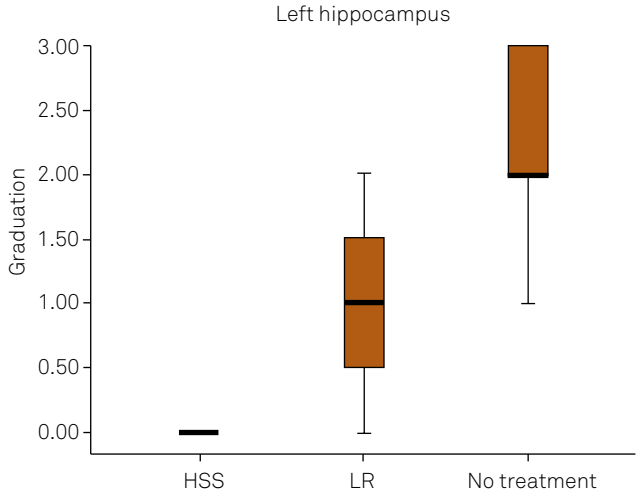
Various mammalian cells and tissues oxidize arachidonic acid from cell membranes into physiologically active components. These components include prostacyclin, thromboxanes, prostaglandins, and leukotrienes. Regardless of its etiology, cerebral ischemia stimulates the synthesis, activation, and release of vasoactive and immunologically active substances[16,17,18,19,23,24,25,26].

The biological effects of prostacyclin are opposite to those of thromboxane A2. Prostacyclin is a vasodilator and potent platelet aggregation inhibitor, whereas thromboxane A2 is a vasoconstrictor and platelet aggregation promoter. The physiological balance between the activities of prostacyclin and



LR: lactated Ringer's; HSS: hypertonic saline solution.

Figure 9. Histological analysis of right hyppocampus. There was significant statistical difference in this topography between HSS 3% group and control.



LR: lactated Ringer's; HSS: hypertonic saline solution.

Figure 10. Histological analysis of left hyppocampus. There was significant statistical difference in this topography between HSS 3% group and control.

thromboxane A2 is probably important for maintaining a healthy vascular bed[23,24,25,26].

Widespread cerebral ischemia causes release of TXB2, the principal metabolite of thromboxane A2 (TXA2), an eicosanoid with potent vasoconstrictive and platelet aggregating properties. This increase in TXB2 in the cerebral venous circulation, which persists for up to 2 hours after reperfusion, is associated with cerebral hypoperfusion[23,24,25,26].

Hemorrhagic shock associated with increased intracranial pressure (20 mmHg) causes decreased cerebral blood flow and a significant increase in the release of TXB2 into the cerebral venous circulation. Isolated HS sufficient to reduce cerebral perfusion pressure to levels found in combined HS and TBI, however, does not increase cerebral venous TXB2. This suggests that both incomplete and complete cerebral ischemia are associated with generation of TXA2 in the brain; however, it does not explain whether the increase in TXA2 is a secondary phenomenon to ischemia or whether TXA2 produces cerebral ischemia through its vasoconstrictor effects[16,17,18,19].

In our experiment, plasma concentrations of thromboxane in central blood samples were always higher than those found in cerebral blood, regardless of the analyzed group. The opposite pattern was observed for prostaglandin concentrations, which were consistently higher in the cerebral venous circulation. This suggests the existence of a balance between prostaglandin and thromboxane concentrations.

There were no statistically significant differences between the treated groups (LR and HSS) regarding cerebral and plasma concentrations of thromboxane and prostaglandin. However, the control group (no treatment) exhibited significantly higher thromboxane and prostaglandin concentrations after 90 minutes. The progressive increase in central arterial plasma concentrations of thromboxane in the control group shows the influence of untreated hemorrhagic shock and pulmonary circulation ischemia on levels of this mediator.

Gross examination of cerebral tissue

The presence of edema in the brains of all control and LR-treated animals and the absence of cerebral edema in all HSS-treated animals suggests that HSS prevented the formation of macroscopically detectable cerebral edema.

Other findings, such as traumatic subarachnoid hemorrhage, acute subdural hematoma, cerebral contusion, intraventricular hematoma, and corpus callosum and subcortical hemorrhages simply confirm that the experimental model of traumatic brain injury used in this study induces both focal and diffuse cerebral lesions.

Microscopic examination of cerebral tissue

Considering the selective vulnerability of some areas of the central nervous system to ischemia, we found that there was a significant difference between the control group and the HSS-treated group regarding presence of ischemia in the right and left hippocampi.

A larger sample would probably have allowed statistical confirmation of a potential difference between LR and HSS in this aspect.

Pupils

It is known that shock itself can lead to pupillary changes, especially bilateral mydriasis, due to a vigorous adrenergic response that culminates in pupillary dilation[1,2,3,4,5]. However, intracranial injuries with mass effect, which cause uncal herniation, can trigger anisocoria with ipsilateral pupillary dilation secondary to compression of parasympathetic fibers in the third cranial nerve against the tentorium cerebelli. Reversal of shock with fluid resuscitation might be able to reverse pupillary changes generated by this adrenergic mechanism[1,2].

We noticed earlier reversal of the pathological pupillary pattern in the HSS-treated group (at 40 minutes) than in the LR-treated group (reversal at 90 minutes). Thus, HSS can provide early benefits secondary to reversal of brain herniation if administered in the prehospital environment.

In conclusion, treated groups (LR or HSS) presented no statistically significant differences between them in cerebral and plasma concentrations of thromboxane and prostaglandin. However, control group (no treatment) showed values of systemic plasma concentration of thromboxane and prostaglandin significantly higher at 90 minutes, suggesting more aggressive inflammatory response after TBI. Then, the group treated with 3% HSS presented no cerebral edema detected macroscopically and did not disclose ischemic hippocampus like control group. Finally, pupillary reversal occurred earlier in HSS group than in LR group. Those findings suggest HSS to be a valuable therapeutic intervention to prevent inflammatory events following TBI.

References

1. Pinto FC, Capone-Neto A, Prist R, E Silva MR, Poli-de-Figueiredo LF. Volume replacement with lactated Ringer's or 3% hypertonic saline solution during combined experimental hemorrhagic shock and traumatic brain injury. J Trauma. 2006;60(4):758-64. http://dx.doi.org/10.1097/01.ta.0000214581.89316.73
2. Rocha-e-Silva M, Poli de Figueiredo LF. Small volume hypertonic resuscitation of circulatory shock. Clinics (São Paulo). 2005;60(2):159-72. http://dx.doi.org/10.1590/S1807-59322005000200013
3. Balbino M, Capone Neto A, Prist R, Ferreira AT, Poli-de-Figueiredo LF. Fluid resuscitation with isotonic or hypertonic saline solution avoids intraneural calcium influx after traumatic brain injury associated with hemorrhagic shock. J Trauma. 2010;68(4):859-64. http://dx.doi.org/10.1097/TA.0b013e3181af69d3
4. Tan PG, Cincotta M, Clavisi O, Bragge P, Wasiak J, Pattuwage L et al. Prehospital fluid management in traumatic brain injury. Emerg Med Australas. 2011;23(6):665-76. http://dx.doi.org/10.1111/j.1742-6723.2011.01455.x
5. Exo JL, Shellington DK, Bayir H, Vagni VA, Janesco-Feldman K, Ma L et al. . Resuscitation of traumatic brain injury and hemorrhagic shock with polynitroxylated albumin, hextend, hypertonic saline, and lactated Ringer's: effects on acute hemodynamics, survival, and neuronal death in mice. J Neurotrauma. 2009;26(12):2403-8. http://dx.doi.org/10.1089/neu.2009.0980
6. Gantner D, Moore EM, Cooper DJ. Intravenous fluids in traumatic brain injury: what's the solution? Curr Opin Crit Care. 2014;20(4):385-9. http://dx.doi.org/10.1097/MCC.0000000000000114
7. Dekker SE, Sillesen M, Bambakidis T, Jin G, Liu B, Boer C et al. Normal saline influences coagulation and endothelial function after traumatic brain injury and hemorrhagic shock in pigs. Surgery. 2014;156(3):556-63. http://dx.doi.org/10.1016/j.surg.2014.04.016
8. Shein SL, Shellington DK, Exo J, Jackson TC, Wisniewski SR, Jackson EK et al. Hemorrhagic shock shifts the serum cytokine profile from pro- to anti-inflammatory after experimental traumatic brain injury in mice. J Neurotrauma. 2014;31(6):1386-95. http://dx.doi.org/10.1089/neu.2013.2985
9. Wang JW, Li JP, Song YL, Tan K, Wang Y, Li T et al. Hypertonic saline in the traumatic hypovolemic shock: meta-analysis. J Surg Res. 2014;191(2):448-54. http://dx.doi.org/10.1016/j.jss.2014.04.027
10. Van Aken HK, Kampmeier TG, Ertmer C, Westphal M. Fluid resuscitation in patients with traumatic brain injury: what is a SAFE approach?. Curr Opin Anaesthesiol. 2012;25(5):563-5. http://dx.doi.org/10.1097/ACO.0b013e3283572274
11. Phillips CR, Vinecore K, Hagg DS, Sawai RS, Differding JA, Watters JM et al. Resuscitation of haemorrhagic shock with normal saline vs. lactated Ringer's: effects on oxygenation, extravascular lung water and haemodynamics. Crit Care. 2009;13(2):R30. http://dx.doi.org/10.1186/cc7736
12. Schackford SR, Mackersie RC, Holbrook TL, Davis JW, Holingsworth-Fridlund P, Hoyt DB et al. The epidemiology of traumatic death. A population-based analysis. Arch Surg. 1993;128(5):571-5. http://dx.doi.org/10.1001/archsurg.1993.01420170107016
13. Czosnyka M, Smielewski P, Piechnik S, Steiner LA, Pickard JD. Cerebral autoregulation following head injury. J Neurosurg. 2001;95(5):756-63. http://dx.doi.org/10.3171/jns.2001.95.5.0756
14. Anderson JT, Wisner DH, Sullivan PE, Matteucci M, Freschman S, Hildreth J et al. Initial small-volume hypertonic resuscitation of shock and brain injury: short- and long-term effects. J Trauma. 1997;42:592-600. http://dx.doi.org/10.1097/00005373-199704000-00003
15. Doyle JA, Davis DP, Hoyt DB. The use of hypertonic saline in the treatment of traumatic brain injury. J Trauma. 2001;50(2):367-83. http://dx.doi.org/10.1097/00005373-200102000-00030
16. Aibiki M, Maekawa S, Yokono S. Moderate hypothermia improves imbalances of thromboxane A2 and prostaglandin I2 production after traumatic brain injury in humans. Crit Care Med. 2000;28(12):3902-6. http://dx.doi.org/10.1097/00003246-200012000-00029
17. Al-Turki A, Armstead WM. Altered release of prostaglandins by opioids contributes to impaired cerebral hemodynamics following brain injury. Crit Care Med. 1998;26(5):917-25. http://dx.doi.org/10.1097/00003246-199805000-00029
18. Armstead WM, Leffler CW, Busija DW, Beasley DG, Mirro R. Adrenergic and prostanoid mechanisms en control of cerebral blood flow in hypotensive newborn pigs. Am J Physiol. 1988;254(4 Pt 2):H671-7.
19. DeWitt DS, Prough DS. Vasoactive prostanoids and traumatic brain injury. Crit Care Med. 1998;26(5):819-21. http://dx.doi.org/10.1097/00003246-199805000-00008
20. Leffler CW. Prostanoids: intrinsic modulators of cerebral circulation. News Physiol Sci. 1997;12(2):72-7.
21. Grice SC, Chappell ET, Prough DS, Whitey JM, Su M, Watkins WD. Ibuprofen improves cerebral blood flow after global cerebral ischemia in dogs. Stroke. 1987;18(4):787-91. http://dx.doi.org/10.1161/01.STR.18.4.787
22. Eliastam M, Safar P, Shapiro M, Gorovitz S. Ethical aspects of cardiopulmonary-cerebral resuscitation research. Ann Emerg Med. 1984;13(9):874-5. http://dx.doi.org/10.1016/S0196-0644(84)80464-3
23. Holcroft JW, Vassar MJ, Turner JE, Derlet RW, Kramer GC. 3% saline and 7% dextran: 70 in the resuscitation of severely injuried patients. Ann Surg. 1987;206(3):279-85. http://dx.doi.org/10.1097/00000658-198709000-00006
24. Kong DL, Prough DS, Whitley JM, Taylor C, Vines S, Deal DD et al. Hemorrhage and intracranial hypertension in combination increase cerebral production of thromboxane A2. Crit Care Med. 1991;19(4):532-8. http://dx.doi.org/10.1097/00003246-199104000-00013
25. Bulger EM, Cuschieri J, Warner K, Maier RV. Hypertonic resuscitation modulates the inflammatory response in patients with traumatic hemorrhagic shock. Ann Surg. 2007;245(4):635-41. http://dx.doi.org/10.1097/01.sla.0000251367.44890.ae
26. Gong W, Marks JA, Sanati P, Sims C, Sarani B, Smith DH et al. Hypertonic saline resuscitation of hemorrhagic shock does not decrease in vivo neutrophil interactions with endothelium in the blood-brain microcirculation. J Trauma. 2011;71(2):275-82. http://dx.doi.org/10.1097/TA.0b013e318226eb51