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Assessment of Three Acute Responses to Traumatic Brain Injury

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Abstract
Traumatic brain injury has a devastating effect on millions worldwide each year. As yet, there are no methods which have been proven to improve recovery from the trauma. Current treatment protocols revolve around reducing secondary insult, such as hypoxia, hypotension, and cerebral edema, which raises intracranial pressure. The purpose of this study is to assess the efficacy of three responses to traumatic brain injury. Two of them, the administration of hypertonic saline and the administration of progesterone, are pharmacologic, while the third, the performance of a decompressive craniectomy, is surgically invasive. A number of original studies have been analyzed to develop an understanding of the topic. It was concluded that hypertonic saline should only be given to patients in whom surgery is indicated, while progesterone should be a widespread acute response. For relatively young patients suffering from uncontrollable intracranial pressure, decompressive craniectomy should be considered as an immediate response as well.

**Progesterone**

Progesterone is administered in a similar fashion to hypertonic saline. The concept of using progesterone to alleviate problems caused by traumatic brain injury was discovered when researchers noticed a significant sex difference in trauma outcome in correlation to hormonal cycling. Female rats with elevated levels of progesterone showed reduced tissue damage and improved behavioral recovery (Shear, et al. 2002). As progesterone has been used safely on humans for years, it was hoped that it would have a positive effect on people with traumatic brain injury (Wright, et al. 2007). While the mechanism is unknown as of yet, progesterone has been shown to reduce cerebral edema, prevent neuronal loss, improve functional outcome, and inhibit oxidative damage in the central nervous system. It might also promote peripheral remyelination of axons following injury. Progesterone is lipid soluble, so it rapidly crosses the blood-brain barrier to reach equilibrium within an hour of administration (Shear, et al. 2002; Wright, et al. 2007; Xiao, et al. 2008).

**Decompressive Craniectomy**

Decompressive craniectomy is a surgical measure which is taken when patients present with dangerously high intracranial pressure. Part of the skull is removed to allow room for the brain to swell. Proponents of decompressive craniectomy state that it can relieve uncontrollable intracranial pressure by increasing the volumetric capacity of the intracranial cavity. Cranietomies have been performed since the early nineteenth century, with varying degrees of success (Akyuz, et al. 2010; Morgalla, et al. 2008).

**Methods**

This study was performed through analysis of published original studies on the effects of hypertonic saline, progesterone, and decompressive craniectomy on traumatic brain injury. Sources include TouroLib databases, PubMed databases, and the archives of Lancet.

**Discussion**

Hypertonic saline was found in all cases to be safe for use. Shackford, et al. (1998) do caution that solutions that are too hypertonic are liable to reversibly open the blood-brain barrier, cause cerebral edema, and increase intracranial pressure. However, great care is taken to assure that proper proportions are used. Solutions that are 7.5% hypertonic saline have been shown to be both safe and effective (Bulger, et al. 2010; Cooper, et al. 2004; Mattox, et al. 1991). Administration of hypertonic saline causes a slight increase in intracranial compliance, as shown by a decrease in mean intracranial pressure in patients receiving hypertonic saline, as compared to a positive trend in the intracranial pressure of patients receiving Lactated Ringer’s solution. This data was observed on the second day following trauma (Shackford, et al. 1998).

When administering hypertonic saline, fluid input must be increased, as the saline decreases the fluid balance. No cases of renal failure or neurological complications due to hypernatremia or hyperosmolarity have been found, but precautions should be taken all the same (Shackford, et al. 1998).

Patients receiving hypertonic saline showed a higher rate of nosocomial infection due to the increased rate of the bloodstream. The increased amount of fluid output also led to a higher incidence of urinary tract infections. In addition, administration of hypertonic saline might cause regulation of the A3 receptor on neutrophils, which would cause an increase in susceptibility to infection (Bulger, et al. 2010). Patients receiving hypertonic saline required a greater number of interventions to lower intracranial pressure over the course of their hospitalization, but the difference was not significant (Shackford, et al. 1998).

While many studies have attempted to prove the superiority of hypertonic saline over other standard protocols, such as mannitol and Lactated Ringer’s solution, most have been unsuccessful. Out of five studies analyzed, only one study conclusively stated that hypertonic saline was universally preferable to mannitol. In that study, Battison, et al. (2005) administered four doses each to nine patients. Two doses were of hypertonic saline and two were of mannitol, in no particular order. The minimum intracranial pressure was measured ten minutes before each treatment and was compared with the minimum intracranial pressure an hour after each treatment. While hypertonic saline reduced the intracranial pressure slightly more than mannitol did, there was no significant difference. The duration of the effect, however, was seen to be significantly longer in hypertonic saline. This study cannot be seen as conclusive, though, as it was only done on nine patients. In addition, the patients received both mannitol and hypertonic saline over a set period of time. As such, the effect could be due to the presence of both mannitol and hypertonic saline in their systems, and cannot be attributed solely to the hypertonic saline.

Hypertonic saline has been shown to work slightly faster than controls. Cooper reports that patients receiving hypertonic saline had a faster rate of decrease in intracranial pressure than those in the control group. However, the study also states that standard protocols are equally effective. All studies concur that there is no significant difference in favorable outcomes of patients who receive hypertonic saline and those who are treated with standard measures (Battison, et al. 2005; Bulger, et al. 2010;...
Cooper, et al. 2004; Mattox, et al. 1991; Shackford, et al. 1998). While it may improve physiologic parameters, the long term benefit of administering hypertonic saline is negligible. Patients who received 7.5% hypertonic saline and those who received Lactated Ringer’s solution showed identical neurologic function after six months. The percentage of patients who survived to hospital discharge was similar. Studies found no significant difference in intracranial pressure for the duration of hospital stay, and there was no discernible difference in Glasgow Outcome Scale values. (Bulger, et al. 2010; Cooper, et al. 2004; Mattox, et al. 1991; Shackford, et al. 1998).

Patients who were to undergo surgery showed a far better outcome when given hypertonic saline in dextran (Mattox, et al. 1991). However, at this time, hypertonic saline in dextran is quite expensive, as compared to the cost of standard treatments, such as Lactated Ringer’s solution and mannitol (Battison, et al. 2005). Therefore, rather than staying as a first tier response to traumatic brain injury, perhaps hypertonic saline should be relegated to a measure which is used only when surgery is indicated.

**Progesterone**

Aside from its long history of safe use, progesterone has been proven to be completely safe for use in humans. A study was performed with the express purpose of determining the safety of progesterone as a response to traumatic brain injury (Wright, et al. 2007). It was found that administration of progesterone was in no way harmful to patients, and it was indicated that it might be beneficial to their recovery. Furthermore, endogenously released progesterone causes a 1°F increase in core body temperature. This deviation from standard basal temperature might hinder neurologic outcome in a patient with traumatic brain injury. However, the study found that no such increase in body temperature manifested in relation to administered progesterone.

Multiple studies have found immense short term and long term benefits from the use of progesterone as an acute response to traumatic brain injury. Patients receiving progesterone had significantly fewer deaths due to neurologic causes. At 30 days postinjury, the mortality rate of patients receiving progesterone was less than half of that of the control group (Wright, et al. 2007). A significant difference in neurologic outcome was evident up to six months post-treatment, with the experimental group having a 58% favorable outcome as compared to the control’s 42% (Xiao, et al. 2008). In addition, treated patients showed a decrease in cerebral edema, necrotic cavity formation, and neuronal loss as compared to control groups, which presented with neuronal and glial shrinkage and neutrophil infiltration. For example, necrotic cavity formation decreased by approximately 20% in treated patients. A decrease in apoptosis was noted, as well as an increase in peripheral remyelination of axons, an inhibition of oxidative damage in the central nervous system, and an overall enhanced recovery from cortical, cerebral, and spinal cord injury (Pan, et al. 2007; Shear, et al. 2002; Wright, et al. 2007; Xiao, et al. 2008).

There has been much speculation as to the mechanism behind progesterone. It has been ascertained that it works, but not how it works. Progesterone down-regulates the inflammatory cytokine cascade, which can increase the damage caused by trauma. Trauma causes a release of amino acids, which cause neuronal excitotoxicity. Progesterone might act at the GABA receptor to diminish that excitotoxicity (Shear, et al. 2002). The study by Pan, et al. (2007) posits that progesterone acts as a sigma-1 receptor antagonist, which can initiate the opioid-like capabilities of the receptor. In addition, progesterone inhibits nuclear factor kappa B, which is known to be a pro-inflammatory transcription factor. Nuclear factor kappa B is the activator of numerous inflammatory cytokines, including tumor necrosis factor alpha, interleukin-1 beta, C3, and glial fibrillary acidic protein. Thus, inhibition of nuclear factor kappa B decreases system-wide inflammation (Pan, et al. 2007).

The timing and duration of administration are key to the effectiveness of progesterone. Most studies found a correlation between speedy dispensation of progesterone and favorable outcome. Wright et al. (2007) reports that the greatest benefit is gleaned when progesterone is administered within two hours of injury, but that there is still great advantage when it is given within 24 hours. Pan et al. (2007) and Shear et al. (2002) both started treatment within an hour of injury. It was noted that there is a consistent reduction in formation of cerebral edema when progesterone is given within 24 hours of injury (Shear, et al. 2002). There is a consensus that much of the success of progesterone is dependent upon the timing of its initiation.

The duration of administration is slightly more controversial. One study, citing the contradictory effects of inflammatory cytokines, limited the duration of progesterone to 24 hours. The researchers claimed that while immediately following an injury, inflammatory cytokines are neurotoxic, they are later neuroprotective. Seeking to block the initial harmful effect of inflammatory cytokines yet capitalize on their latent neuroprotective abilities, the study administered progesterone from 30 minutes to 24 hours following injury, at which time they ceased administration of the treatment (Pan, et al. 2007). However, other studies noted that the greatest benefit was attained when progesterone was administered for five days (Shear, et al. 2002; Xiao, et al. 2008). In the experiment carried out by Shear, et al. (2002) on rodents, one group received progesterone for three days, while the other received it for five. It was concluded that five days of progesterone
are necessary to achieve the desired results, namely an alleviation of the neuropathological and behavioral abnormalities which are caused by traumatic brain injury. This finding seems to contradict that of Pan’s. However, as harmful consequences of extending the progesterone treatment have not been found, it might be advantageous to forfeit the possible neuroprotective capabilities of inflammatory cytokines in favor of the documented benefits of an extended progesterone treatment.

**Decompressive Craniectomy**

Craniectomy has long been used as a last resort in the treatment of traumatic brain injury. It is only when indicators of incredibly high intracranial pressure manifest that craniectomy is considered. Such indicators include compression of cortical gyri and basal cisterns, signs of immediate herniation, and cerebral swelling (Morgalla, et al. 2008). In the majority of studies analyzed, craniectomy was only used after standard protocols had failed to lower intracranial pressure sufficiently. As such, it is difficult to assess the efficacy of craniectomy, as it is generally used only on patients with severe injuries who have already undergone other treatments. Usually, by the time a craniectomy is performed, there has been a lapse of time between injury and the surgery (Morgalla, et al. 2008; Olivecrona, et al. 2007), limiting its benefit. Another hindrance to the study of decompressive craniectomy is that due to the surgical nature of the procedure, a blinded study is impossible.

While one study analyzed found decompressive craniectomy to lower intracranial pressure but hinder favorable outcome (Cooper, et al. 2012), four other studies found that long term results justify the surgery (Akyuz, et al. 2010; Morgalla, et al. 2008; Olivecrona, et al. 2007; Qiu, et al. 2009). Cooper, et al’s 2012 study reports that patients who received a craniectomy along with standard treatment showed a less favorable outcome after six months. However, the mortality rate was the same in patients who had undergone the procedure and those who had not. In contrast, Olivecrona, et al. (2007) found a 10% difference in outcome, with those who received a decompressive craniectomy having the more favorable outcomes when compared to patients who received only standard care.

Patients who had undergone a decompressive craniectomy needed fewer interventions to lower intracranial pressure. They required a shorter period of time on mechanical ventilation, and they spent a shorter amount of time in the intensive care unit (Cooper, et al. 2012). There was a significant reduction in intracranial pressure directly after the surgery, which later stabilized to manageable levels (Olivecrona, et al. 2007). One study found that 40% of patients who were otherwise likely to die had favorable results after undergoing a decompressive craniectomy (Morgalla, et al. 2008).

There are a number of caveats in regard to craniectomies. Firstly, patients who underwent the surgery had a higher incidence of hydrocephalus (Cooper, et al. 2012), which necessitates additional medical or surgical care. Secondly, unilateral craniectomies have been linked to delayed intracranial hematomas and subdural effusion, both of which must be treated through surgical intervention (Qiu, et al. 2009). However, success has been seen in bilateral craniectomies. A problem with all decompressive craniectomies seems to be an increase in transcapillary leakage. The point of a craniectomy is to allow room for swelling. The loss of resistance in the brain leads to transcapillary leakage due to an increase in the transcapillary hydrostatic pressure gradient. In order to counteract this effect of a craniectomy, the transcapillary pressure must be lowered by preventing an increase in arterial pressure and infusing albumin and packed red blood cells (Olivecrona, et al. 2007). These issues are all collateral damage of decompressive craniectomies, but the benefit of the surgery seems to outweigh the detriment.

An important factor to consider is the timing of the procedure. While most craniectomies are performed after standard protocol has been tried and found unsuccessful, thus lengthening the amount of time between the injury and the surgery, this might not be the most advantageous use of craniectomies. Akyuz, et al. (2010) compared the results of craniectomies on patients who received the surgery following standard procedure to those who received the surgery immediately. The first group had their craniectomies around 35.7 hours after trauma, as compared to the second group, who underwent the procedure approximately 4 hours after trauma. It was found that early decompressive craniectomy resulted in a 48% decrease in intracranial pressure. The group which underwent standard protocols before receiving craniectomies yielded a 27.8% favorable outcome as compared to the other group, which had a 50% favorable outcome after 12 months. While the best results were found when the procedure was performed within 4 hours of injury, performing the craniectomy within 48 hours still provides benefit (Qiu, et al. 2009). Using craniectomy as a second tier response hinders the positive effects of the procedure, as an extended amount of time with high intracranial pressure is detrimental to functional outcome.

The size of the decompressive craniectomy is also significant. If the craniectomy is too small, it will not allow the brain enough room to expand. The brain will then swell through the incision, causing external herniation. Bilateral craniectomies have the advantage of providing more space for the brain to expand (Akyuz, et al. 2010).

Age is also an integral consideration when determining the outcome of decompressive craniectomy. In fact, the study done by
Cooper, et al. (2012), which found the least favorable results, was the study which included the oldest patients. It seems that the highest recommended age upon which a craniectomy for traumatic brain injury should be performed is 40, and that it is detrimental to those over 60 (Akyuz, et al. 2010; Morgalla, et al. 2008; Olivecrona, et al. 2007). The greatest benefit is to younger patients. This might be due to a stronger immune system or to an elevated recovery ability in younger patients.

**Conclusion**

These three responses to traumatic brain injury are still being researched. From the studies analyzed, it is apparent that due to the negligible benefit and immense cost of using hypertonic saline, it should be reserved for patients with injuries that indicate surgery. The status of hypertonic saline as a first tier response should be reevaluated. Progesterone, on the other hand, should be initiated into standard protocol. It shows no discernable harm and has been proven to do much good. It is essential that it be included in first tier response, as the immediate administration bears effect on the amount of good it can do for the patient. Decompressive craniectomy should be considered immediately in a case of uncontrollable intracranial pressure in a relatively young patient, so as to capitalize on the efficacy of a rapid craniectomy. In such a case, the gains outweigh potential damage. However, all assessments must be made on an individual basis, as each patient presents a unique set of properties.

**References**


