The use of Hypertonic Saline in the Treatment of Post-Traumatic Cerebral Edema: A Review

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Abstract
Effective methods for treating cerebral edema have recently become a matter of both extensive research and significant debate within the neurosurgery and trauma surgery communities. The pathophysiologic progression and outcome of different forms of cerebral edema associated with traumatic brain injury have yet to be fully elucidated. There are heterogeneous factors influencing the onset and progress of post-traumatic cerebral edema, including the magnitude and type of head injury, age, co-morbid conditions of the patient, the critical window for therapeutic intervention and the presence of secondary insults including hypoxia, hypotension, hypo/hyperthermia, degree of raised intracranial pressure (ICP), and disruption of blood brain barrier (BBB) integrity. Although numerous studies have been designed to improve our understanding of the etiology of post-traumatic cerebral edema, therapeutic interventions have traditionally been focused on minimizing secondary insults especially raised ICP and improving cerebral perfusion pressure. More recently, fluid resuscitation strategies using hyperosmolar agents such as pentastarch and hypertonic saline (HS) have achieved some success. HS treatment is of particular interest due to its apparent advantageous action over other types of hyper-osmotic solutions in both clinical and laboratory studies. In this review, we provide a summary of recent literature concerning the pathogenesis and mechanisms involved in the various types of cerebral edema, and the possible mechanisms of action of HS for the treatment of cerebral edema.

Key Words
Cerebral edema · Hypertonic saline · Intracranial pressure · Traumatic brain injury

Introduction
The leading cause of death in individuals between the ages of 15 and 44 in Europe is due to trauma and traumatic brain injury (TBI) accounts for the majority of these deaths. The mortality rates for Europe and the US for the TBI population remains 15–20 per 100,000 per year [1]. In the USA, the highest rate of TBI occurs in people aged 15–25 years and TBI is known to be the main cause of death and disability in people under 40 years of age (http://www.cdc.gov). Most studies indicate that men are far more likely to incur a TBI than women, and persons over the age of 75 years are also at higher risk. Approximately 50% of all TBI is related to motor vehicle-related accidents and 25% to falls. An estimated 5.3 million Americans are living today with disabilities related to TBI, with an annual cost to our health care system of over $48 billion dollars (CDC).

Traumatic brain injury is initiated by high-energy acceleration and deceleration of the brain tissue in the cranium [2, 3]. The natural progression of TBI may be divided into four overlapping phases termed (1) primary injury, (2) evolution of the primary injury, (3) secondary injury and (4) the recovery phase [4]. This
primary injury is followed by a series of secondary or delayed pathological alterations in the internal environment of the brain tissue, which exacerbate the neurological damage. These processes that occur from a few minutes to several hours to days-weeks after the primary injury are known to include cerebral edema. From the therapeutic perspective, it is important to realize that TBI is a heterogeneous disorder. Moreover, the pathologic and clinical consequences of TBI are multifaceted and complex and depend, in part, on the injury (type, localization, severity), patient (genotype, age, gender, pre-existing illness and their treatment, substance abuse, etc.), and whether or not there are accompanying injuries such as fractures, significant blood loss, shock etc.

Cerebral edema is defined as abnormal accumulation of fluid associated with volumetric enlargement of the brain [5]. It is well documented that after TBI, swelling leads to elevations in intracranial pressure (ICP), with marked reductions in both CBF and tissue perfusion, which is a frequent cause of death and poor prognosis in survivors [6]. As edema develops, a threshold is reached after which ICP rises exponentially in response to small changes in water content. Of great importance is the fact that the degree of the swelling assessed on the first CT/MRI scan, obtained soon after injury, is highly correlated with outcome, suggesting that therapy must be introduced as soon as possible to avoid further neurological deterioration [7, 8]. The pathophysiology and treatment of cerebral edema remains the subject of recent debate and research. The therapeutic modalities currently used for cerebral edema include hyperventilation, head elevation, CSF drainage, barbiturates, sedation, decompressive craniectomy, osmotic diuresis, and hyperosmolar therapy [3, 9–20]. However, all of these methods have some limitations [10, 21, 22].

Pathophysiology of Cerebral Edema
Cerebral edema is broadly classified into (1) vasogenic or (2) cytotoxic/cellular edema, affecting the white matter and the gray matter, respectively [23–25]. However, both types of edema frequently co-exist and the clinical manifestations of cerebral edema are generally similar regardless of the type of edema. Brain trauma is often associated with massive depolarization of the neuronal cells synchronous with the mechanical impact. The extent of neuronal depolarization is likely related directly to the magnitude of the mechanical impact [26, 27]. This depolarization causes an influx of sodium and an efflux of potassium leading to an increase in the extracellular K⁺, which increases further over time due to the addition large amount of K⁺ released from the intracellular storage released as a result of axonal death. These mechanisms lead to the formation of cellular edema, the predominant type of edema seen in TBI [28, 29]. It frequently co-exists with vasogenic edema. Clinically, cellular edema appears to be the earliest to develop as a direct sequel of the primary brain injury.

The blood brain barrier (BBB) is a semi-permeable dynamic capillary membrane system [30], anatomically consisting of the endothelial cells which contribute to its impermeability through the presence of tight junctions formed at regions called the Zonulae occludens [31–33]. The basal lamina and the astrocyte foot processes envelop the vessel wall to form a physiologic barrier [34] consisting of the Aquaporin (AQP) channel and many other channels necessary for the maintenance of the homeostasis. Cerebral edema therefore represents an abnormality of the balance of fluid in the interstitial space versus fluid in the intravascular space of the brain. In cases of vasogenic edema, water crosses the BBB either from the vessel (due to anatomical disruption of the tight junction) into the cell via the astrocytic end feet, which surrounds the micro-vessels or through the extracellular space and then into the cell. This can also result from sudden increase in vascular pressure beyond autoregulatory limits or a breakdown in the BBB. This resulting fluid extravasation can range from pure water to frank blood, depending on the magnitude and type of injury and the extent of BBB breakdown. The excessive fluid present will accumulate in the white matter owing to its greater compliance. Clinically, vasogenic edema tends to be a delayed process, often peaking within 72 h of the injury. This type of cerebral edema is seen primarily following TBI, stroke and certain brain tumors [25].

As the edema progresses, compensatory mechanisms are activated to reduce volume and maintain ICP in the normal range [2]. With cerebral edema, as the volume of intraparenchymal fluid increases, there is often a compensatory decrease in the production/increase in the absorption of the CSF and arteriolar constriction. During the first stage of compensation, the patient will be in a state of confusion and drowsiness but ICP will be maintained normal. As brain swelling continues and the compensatory mechanisms are unable to maintain a normal ICP, a second stage is reached where blood flow declines to cause hypoxia/ischemia and hypercapnia. Clinically, there is deterioration of the level of consciousness, altered breathing