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Surgical brain injury: prevention is better than cure

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1. ABSTRACT

Neurosurgical procedures can cause inevitable brain damage resulting from the procedure itself. Unavoidable cortical and parenchymal incisions, intraoperative hemorrhage, brain lobe retraction and thermal injuries from electrocautery can cause brain injuries attributable exclusively to the neurosurgical operations and collectively referred to as surgical brain injury (SBI). This particular brain damage cannot be demarcated from the underlying brain pathology and has not been studied previously. Recently, we developed rat and mouse models to study SBI and the underlying cellular mechanisms. The animal modeling mimics a neurosurgical operation and causes commonly encountered postoperative complications such as brain edema following blood brain barrier (BBB) disruption, and neuronal cell death. Furthermore, the SBI animal model allows screening of known experimental neuroprotective agents and therapeutic agents being tried in clinical trials as possible pretreatments before neurosurgical procedures. In the present review, we elaborate on SBI and its clinical impact, the SBI animal models and their clinical relevance, and the importance of blanket neuroprotection before neurosurgical procedures.

2. SURGICAL BRAIN INJURY

2.1. Surgical brain injury

Neurosurgical procedures are invasive regardless whether they are performed in elective or emergency settings. Due to the unique nature of the nervous system, there is an element of inevitable brain damage due to the neurosurgical procedure itself. Infact, some neurosurgical operations for brain stem, spinal cord and in posterior cranial vault have been acknowledged to be intrinsically linked to postoperative neurological deficits regardless of how careful the operation has been performed (1).

This particular brain injury attributable exclusively to the neurosurgical procedure affects the functional and normal brain tissue such as the periphery of tumor resection site and is referred to as the surgical brain injury (SBI). The causes for SBI are manifold and include predetermined cortical incisions to access any deeper pathological tissue (2;3), retraction of brain lobes or hemispheres (4), intraoperative bleeding (5), and thermal injury due to electrocoagulation. Endoscopic surgeries and stereotaxic guided procedures are designed to minimize the

invasiveness of neurosurgical procedures. Nevertheless, these procedures also lead to inevitable brain injuries and complications (5-8). The SBI cannot be easily demarcated from the underlying brain pathology and hence has not been studied as an independent outcome variable but nevertheless is acknowledged (1). Our group introduced novel animal models (described in appropriate section below) using rats and mice last year to study brain damage exclusively due to SBI (9-12).

2.2. Impact of surgical brain injury

There are over 800,000 cranial and spinal neurosurgical operations performed in the United States alone (www.neurosurgerytoday.org). Postoperative complications after neurosurgical procedures and the resulting mortality and morbidity are important issues in medical management of these patients. Even if there are no life threatening and serious complications in most cases, neurosurgical patients usually have to be monitored closely especially in the intensive care unit translating into longer hospital stay and increased cost of patient care. Additionally, there is an important issue of neurological and neurobehavioral functional deficits which have long-term implications due to added expenditure for physiotherapy and rehabilitation.

Medicolegal impact of SBI may be a bigger issue than the actual clinical management of patients. Recently, American Medical Association has reported that 75% of neurosurgeons do not operate on children and 79% of all physicians practice defensive medicine due to liability crisis and fear of lawsuits (AMA, March 2006, FK11:06-0207:1200:3/06). This resulting practice of defensive medicine results in excessive expenditure of $70-$126 billion ("Addressing the New Health Care Crisis," U.S. Department of Health and Human Services, March 2003). Neurosurgeons are thus likely to exercise caution instead of trying to enforce more curative options which may need a more aggressive approach. Thus, a blanket neuroprotection pretreatment is the need of the hour in clinical medical practice.

2.3. Blanket neuroprotection

Osmotic agents, steroids and diuretics are routinely used to reduce the postoperative complications after neurosurgical operations. Steroids are helpful in ameliorating brain tumorogenic edema, however, have not shown a definite therapeutic effect in clinical trials for ischemic stroke, intracerebral hemorrhage, aneurysmal subarachnoid hemorrhage, and traumatic brain injury (TBI) (13). Infact, the CRASH trials have demonstrated that steroids are harmful after TBI (14). Some anesthetic agents (15;16) and other therapeutic modalities such as intraoperative hypothermia (17;18) may provide cerebral neuroprotection. Intraoperative hypothermia, however, has its own drawbacks and is not widely practiced (17-19). Thus, inspite of adjunct treatments, neurosurgical procedures are associated with critical postoperative complications such as brain edema and ischemia (20-22) with delayed healing.

Many therapeutic agents such as growth factors: erythropoietin and granulocyte colony stimulating factor (G-CSF), statins, and anti-oxidants such as NXY-059 are already shown to be neuroprotective in experimental studies and are being tried out in clinical trials in cerebrovascular disorders (23-25). However, many neuroprotective agents developed for TBI and acute stroke have failed to improve clinical outcomes due to one overwhelming and critical factor i.e. a narrow therapeutic window for brain protection. Many neuroprotective agents will work when administered as pretreatment or just immediately after the brain injury; however, they will be ineffective when administered outside the therapeutic window which is usually when majority of the patients will arrive at the hospital. However, the concept of protecting against SBI and providing blanket neuroprotection before neurosurgical procedures makes pretreatment with known neuroprotective agents clinically relevant.

Presently there are no standard routinely used treatment regimens with neuroprotective agents used either pre-, during, or post-surgically to prevent the inevitable brain injuries associated with routine neurosurgical procedures. A therapeutic regimen to provide blanket neuroprotection can be designed using the known neuroprotective agents. No studies have been done to test this particular concept. Recently, we created novel animal models in rodents and mice to address the issue of brain injury caused exclusively by neurosurgical procedures (9-12).

2.4. Animal models

The rationale for developing the rat and mouse models was to mimic a neurosurgical operation and produce commonly seen postoperative complications such as blood brain barrier disruption, brain edema and neuronal cell death. Furthermore these models allow us to study basic mechanisms and pathophysiology of SBI, and to evaluate specific treatment strategies against it. The mouse SBI model has a further advantage in using transgenic animals.

In brief the animal modeling is as follows. The rat and mouse modeling is similar; only difference is related to surgical co-ordinates. The animals are anesthetized and placed prone in a stereotaxic frame with the head fixed. They do not need to be intubated. Skin and connective tissue are cut by a midline incision and the underlying periosteum is reflected to expose the right frontal skull. The sagittal and coronal sutures and bregma are identified. An operating square area (3.5 mm edge in mouse model and 6 mm edge in rat model) is marked such that the left lower corner of the square is at the bregma (Figure 1A). A micro-drill is used to thin out the margins of this square to translucency without penetrating the skull. The bone piece between the margins is then gently lifted to expose a cranial window displaying the underlying right frontal lobe of the brain covered by dura (Figure 1A). The dura is carefully incised and reflected avoiding the subdural vessels to expose the underlying right frontal lobe.

In our previous studies, the frontal lobe was partially resected by a clean cut using flat blade. The amount of resected brain tissue did not vary significantly

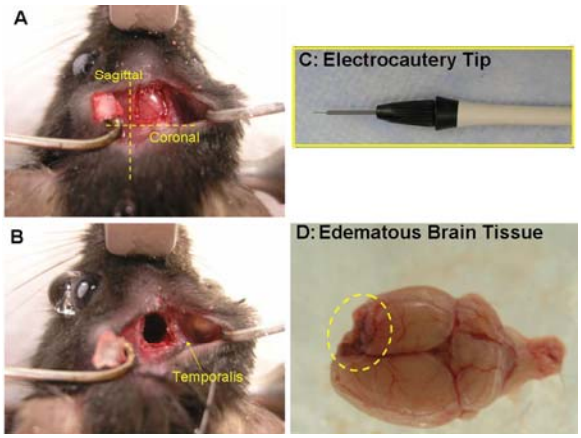

Figure 1. Animal Modeling for SBI. The figures 1 A and 1B show the animal modeling using mice. Figure 1A shows the intact dura covering the exposed brain in the cranial window fashioned by drilling out the skull. Co-ordinates: 3.5mm edge square cranial window with left lower corner at bregma. Figure 1B shows the cavity after resection and achievement of hemostasis. Temporalis muscle can be identified in the picture. Figure 1C shows the tip of the monopolar electrocautery used for excising the brain (partial frontal lobe resection) in a piecemeal manner. Figure 1D shows the edematous brain tissue surrounding the site of resection.

between animal groups. After recent modifications, a monopolar electrocautery (Figure 1C) is used to incise and sever a part of the frontal brain 1.5 mm lateral of sagittal and 1 mm proximal of coronal sutures (similar to earlier studies). The incisions are made progressively from top (cortex) to the base of the skull. The brain is excised in a piecemeal manner alternating with hemostasis measures using packing and saline irrigation. The excised cavity is further monitored for bleeding and after confirmation of hemostasis the wound is closed (Figure 1B). The dura, skull piece and overlying connective tissue are placed in original position and skin sutured with 3-0 silk (Ethicon) on a reverse cutting needle. Sham surgery includes only craniotomy without any dural incisions. Vital signs and core body temperature are monitored throughout the procedure. The procedure takes approximately 45 minutes with experience.

2.5. Clinical relevance of models

The SBI model incorporates cortical and parenchymal incisions and intraoperative bleeding which is commonly encountered during neurosurgical procedures. Presently an electrocautery instead of scalpel is used to excise the brain in a piecemeal manner akin to neurosurgical operation with continuous hemostasis measures.

Even though the scale of the partial frontal lobe resection may be similar to brain tumor resection or epilepsy surgery (mostly in the temporal lobe) to some degree, this model is not intended to mimic any specific neurosurgery operation. Instead, this model produces certain amount of brain tissue loss and injury that causes neuronal death, blood brain barrier (BBB) dysfunction and brain edema that occurs during routine neurosurgical operations. Previous reports have documented that the SBI animal model has localized brain edema and BBB disruption in the brain tissue surrounding the resection. The brain edema peaks at 24 hours and starts declining 3 days after the surgery mimicking a clinical scenario (9;10;12).

It is known clinically that brain edema contributes to the brain swelling. Clinical studies indicate that brain water content is a good indicator of brain swelling resulting from the edema. A 1% increase in brain water content is equivalent to 4.3% increase in tissue volume which can cause raised ICP (26;27). The mouse and rat SBI models closely mimic these clinical parameters as it causes approximately 3% increase in brain water content leading to substantial localized brain edema (9-11).

These animal models provide excellent opportunity to test neuroprotective agents being tried in clinical trials as well as those proven in experimental studies as pretreatment strategies for neurosurgical procedures.

2.6. Therapeutic targets for SBI

Presently, there are no therapeutic regimens used to prevent SBI during neurosurgical procedures. However, using the animal models, the known neuroprotective agents from clinical trials and experimental studies can be evaluated as pretreatment modalities against SBI. In published reports we have shown that the SBI causes localized brain edema and BBB disruption. This susceptible brain tissue also shows neuronal cell death, apoptotic changes and oxidative stress (9-12). Recent experiments have revealed significant inflammation involved in SBI (unpublished data). Thus, drugs or therapies that can target apoptosis, inflammation, and oxidative stress and attenuate BBB disruption and brain edema hold promise for blanket neuroprotection before neurosurgical operations.

Therapeutic agents being tried in clinical trials for cerebrovascular disorders such as EPO, G-CSF, and statins are good candidates to evaluate for SBI (23-25). Surprisingly, in our previous study, EPO was found to aggravate brain edema possibly via vascular endothelial growth factor (VEGF) mediated mechanisms (12). Present studies are being carried out with statins and anti-inflammatory agents. Src tyrosine kinase (upstream of mitogen activated protein kinases) inhibition with PP1 (9;10;28) and inhibition of MMP-9 and MMP-2 activity using a specific inhibitor (unpublished data) have shown encouraging results in attenuating BBB disruption and brain edema.

2.7. Bench to bedside

The concept of administering therapeutic agents or delivering therapies aimed at protecting the brain against subsequent damage during neurosurgical procedures was first raised by our group recently (10). As is the case with many clinically used drugs, it

requires a bit of serendipity to bolster the journey of drug development from basic science to clinical use. We have created the SBI animal models i.e the ideal platform to effectively screen multiple putative neuroprotective agents as pretreatments to provide blanket neuroprotection for neurosurgical procedures. Combined with molecular techniques the animal models help to throw more light on SBI and its pathophysiology. As basic research yields more information, a little bit of serendipity can help in development of a blanket neuroprotection for neurosurgical operations.

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Abbreviations: BBB: Blood Brain Barrier, SBI: Surgical Brain Injury, GCSF: Granulocyte Colony Stimulating Factor, VEGF: Vascular Endothelial Growth Factor, MAPK:Mitogen Activated Protein Kinases

Key Words: Surgical Brain Injury, Blanket Neuroprotection, Pretreatment, Neurosurgical Procedure, Animal Modeling, Brain Edema, Blood Brain Barrier

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