

NEUROPROTECTION AGAINST SURGICALLY INDUCED BRAIN INJURY

LIGIA TATARANU, MD, PHD, M. R. GORGAN, MD, PHD, B.O. ENE, MD, V. CIUBOTARU, MD, PHD, AURELIA SANDU, MD, ADRIANA DEDIU, MD

Department of Neurosurgery, „Bagdasar-Arseni” Emergency Hospital, Bucharest, Romania

Neurosurgical procedures are carried out routinely in hospitals across the world. Every neurosurgical procedure, regardless the purpose, involves a certain degree of brain injury that results from the procedure itself because of the unique nature of the nervous system. Brain tissue is at risk of injury by various means, including incisions and direct trauma, electrocautery, hemorrhage, and retractor stretch. Fortunately there are various substances with neuroprotective effect on human brain, with different molecular pathways, which can be used, together with surgical protective measures, as therapeutically drugs preventing brain damage during surgery. Among them steroids, some anesthetic agents intraoperative hypothermia are suggested to provide cerebral neuroprotection, but also new established therapeutic agents, such as erythropoietin and statins, Src tyrosine kinase inhibitor, used clinically in patients for different nonneurological disorders, which have also shown promise as neuroprotectants in experimental studies. Any form of pretreatment that proved effective when used before brain injury may have a significant impact on patient recovery and outcome of procedures. This review is intended to raise the question about neuroprotection methods and agents against surgically induced brain injury available today in neuroscience scientific community and stimulate discussions about future approaches and therapies.

Keywords: surgery, brain injury, neuroprotection

INTRODUCTION

Although many innovations in the clinical practice have been implemented, especially with the advent of microscopy and endoscopy, neurosurgical procedures remain invasive regardless of whether they are performed in elective or emergency settings. Some of the neurosurgical interventions such as surgeries for brain stem and spinal cord pathologies are intrinsically linked to postoperative neurological deficits and may lead to serious neurological injuries regardless of how carefully the operation is carried out. A key issue during most neurosurgical procedures is that there is always an element of inevitable injury inflicted on the functional and normal brain while dissecting or eliminating the pathological tissues. This unavoidable injury may exist in many forms, including predetermined cortical incisions to access any deeper pathological tissue [1], retraction of brain lobes or hemispheres [2, 3], intraoperative bleeding [4], and thermal injury due to

electrocoagulation. Endoscopic surgeries and stereotaxic guided procedures are designed to minimize the invasiveness of neurosurgical procedures. However, these procedures are also associated with inevitable brain injuries and complications [4-7].

To reduce the postoperative effects of these brain injuries and decrease the subsequent neurological deficits, osmotic agents, diuretics, and steroids are routinely used [8]. Steroids, although well established in ameliorating brain tumor-associated edema, have not shown a definite therapeutic effect in clinical trials for traumatic brain injury. Some anesthetic agents themselves [9, 10] and therapeutic modalities, such as intraoperative hypothermia [11, 12], are suggested to provide cerebral neuroprotection. Even with adjunct treatments, the standard neurosurgical maneuvers, can cause damage to the surrounding brain tissue and may contribute to or result in critical early postoperative

complications such as brain edema and ischemia or delayed healing [13, 14].

Even if there are no life-threatening or serious complications in most cases, neurosurgical patients have to be monitored closely, especially in the intensive care unit. This translates into longer hospital stay with significant implications for the patient, the healthcare system, and the society. The neurological and neurobehavioral functional deficits can additionally be a source of long-term emotional, social, physical, and financial duress. Moreover, the concerns of causing injury to the surrounding normal and functional brain, especially in vulnerable areas such as brain stem [15], may hamper the approach of the neurosurgeons.

Classically, inevitable brain injury resulting from neurosurgical interventions is not treated separately or prevented by neuroprotective regimen but rather is left to be healed on its own. Presently, new therapeutic agents, such as erythropoietin and statins, used clinically in patients for different cerebrovascular disorders, which have shown neuroprotective effects in experimental studies [16]. We want to take advantage of such therapeutic modalities for use as pretreatment against surgically induced brain injury, as well as any other new procedure.

INCIDENCE OF POSTOPERATIVE COMPLICATIONS IN LITERATURE

In a study of consecutive patients [2] undergoing craniotomy from 1976 to 1984, with CT scans obtained within 7 days of surgery, intracerebral hematomas were detected in 80 of 275 craniotomies for brain tumors (29%) and 15 of 184 craniotomies for intracranial aneurysms (8%). In 31 of the brain tumor procedures (11%) and 7 of the aneurysm procedures (4%), the hematoma measured 3 cm or more in diameter. Only clinically significant hematomas were reported, and routine postoperative scans were not considered. Intracerebral hematomas, most likely to be related to retraction constituted 60% of all hematomas. The highest incidence of hematomas was in surgery for anterior circulation aneurysms (2.1%), where brain retraction is almost certain to have occurred. It is not possible from such studies to separate entirely

retraction-induced injury from bleeding into the tumor resection bed or hemorrhagic infarction secondary to vasospasm.

More recent reports on cranial base surgery report an incidence of approximately 10% of complications that are likely related to brain retraction or maneuvers intended to decrease retraction-induced injury. These complications included intracerebral hematomas, aphasia, hemiparesis, and numbness. In a report on surgery for unruptured aneurysms of the posterior circulation (1971 through 1988), the authors thought that 6 of 167 patients suffered retraction-induced brain injuries (4%). With regard to pineal region tumors, 2 of 12 surgical patients (17%) suffered permanent visual field defects, which the authors attributed to occipital lobe retraction.

Several groups investigating brain retraction pressure have reported on probable retraction-induced injuries during either brain tumor or intracranial aneurysm surgery. Clinically significant postoperative deficits appeared in 3 to 9% of cases. However, one study reported a 22% incidence of CT-evident infarction beneath the tip of the retractor blade; most of the infarctions were not clinically obvious. Infarctions in the region of the retractor blade were particularly common when a relatively high retraction pressure was employed.

It is likely that brain injury secondary to retraction occurs in approximately 10% of major cranial base tumor procedures, and 5% of intracranial aneurysms or cranial tumor (other than the base) procedures. A high-resolution CT or magnetic resonance imaging scan obtained several days postoperatively is necessary to detect lesions not readily apparent at the bedside clinical examination. Undoubtedly, there is considerable variation in the incidence of retraction-induced injury, depending on the difficulty of the procedure, resources available, skill of the operating team, and the criteria used to define brain injury.

RESEARCH OF SURGICALLY INDUCED BRAIN INJURY

Various animal models have been proposed and used for simulating the classical surgical approaches

NEUROPROTECTION AGAINST SURGICALLY INDUCED BRAIN INJURY

and their associated complications. Among them dog, cat, rat or swine models have been chosen and demonstrated the lesional mechanism.

Brain edema

Jadhav and al. [17] created a *in vivo* model to study brain injury caused exclusively by neurosurgical procedures. The frontal lobe surgical injury rat model simulates the surgically induced brain injury by causing cortical and parenchymal damage and the postoperative complications that follow neurosurgical procedures. In addition, it allows the study of molecular mechanisms and signaling pathways involved in surgically induced brain injury and the testing of different pretreatment modalities for neuroprotection.

This model is not intended to mimic any specific neurosurgery operations. Instead, the goal is to produce a standard and reproducible model with certain amount of brain tissue loss and injury that will produce neuronal death, as well as BBB dysfunction leading to brain edema that occurs during routine neurosurgical operations in clinical practice.

Secondly, there is intraoperative bleeding that is controlled by packing and saline irrigation. Electrocoagulation is also used to control bleeding and to make incisions to gain access to deeper structures. There are variations in its usage in voltage, frequency, and duration of application.

Preliminary studies revealed that there is presence of localized edema around the operative site, in fact, surgically induced brain injury. This edema, indicated by brain water content calculated using standard methods, was present only in the ipsilateral frontal area, the area contiguous to the surgically induced brain injury. Time course performed experiments further revealed that this localized edema peaked at 24 hours, started declining after 3 days, and almost entirely resolved by 1 to 2 weeks after the procedure, thus mimicking a clinical situation appropriately. Further studies also revealed that there was a disruption of the BBB as indicated by standard methods such as IgG staining and Evans blue dye extravasation. In addition, using Nissl staining, we identified neuronal death in the area bordering the surgically induced brain injury. Moreover, a clear transition zone, that is, gradual

change from dead cells to viable cells, could be identified, thus enabling the extent of injury.

Brain injuries caused by lobe retraction were not considered because of variability in usage of retractors. Moreover, miniature instruments producing consistent pressure and stretch injuries seen with retractor usage are required for this particular brain injury component.

BRAIN RETRACTION, A NECESSARY TRAUMA IN NEUROSURGERY

Because effective surgical treatment for deep brain lesions, intracranial aneurysms, arteriovenous malformations, and cranial base tumors requires exposure that frequently can be obtained only by direct brain retraction, numerous animal models were proposed to measure this feature and to discover protective methods to be translated into intraoperative interventions that minimize the risk of brain retraction injury.

Brain retraction injury is caused by focal pressure (the retractor blade) on the brain, producing a local deformation of brain tissue for a finite period of time. Such a deformation causes a reduction or cessation of local perfusion (focal ischemia). It may also cause direct injury to brain tissue (neurons, their processes, and/or glia). Both the ischemia and the direct injury are probably dependent on the shape and number of the retractors as well as on the pressure and duration of the retraction.

Andrews and al. [2] review the published articles on brain retraction, principally during either brain tumor or intracranial aneurysm surgery and concluded retraction pressures used in clinical practice by neurosurgeons are usually in the range of 20 to 40 mm Hg. It has been suggested that the use of two small retractor blades may provide exposure equivalent to one large blade with a lower retraction pressure. He also used a swine animal model to mimic a major neurosurgical intervention, and to evaluate all the possibilities for neuroprotection, such as various therapeutical agents, hypothermia, hypotension or hyperventilation. He concluded his experiments proposing a protocol for any major brain intervention, combining judicious retraction, appropriate anesthetic and pharmacological

management, and aggressive intraoperative monitoring. Optimal brain retraction protection will most likely be afforded by a protocol that has several complementary beneficial effects: augmented blood flow, minimized calcium fluxes and excitotoxic injury, free radical scavenging, and decreased acidosis

OPERATIVE EXPOSURES PREVENTING SURGICALLY INDUCED BRAIN INJURY

Positioning the patient to minimize retraction and using intraoperative CSF drainage are practical and cost-effective ways to increase exposure. Extensive cranial base removal or craniofacial osteotomy may be essential to expose certain lesions. Positioning the patient so that gravity aids the exposure may reduce the need for direct brain retraction. Examples include the use of the sitting/semi sitting position to expose the supracerebellar/pineal region and the lateral decubitus position to approach ipsilateral midline and paramedian lesions. The use of cerebrospinal fluid (CSF) drainage, combined with the opening of the CSF cisterns, either by lumbar puncture or ventricular puncture, requires caution. Although CSF drainage has been reported to facilitate exposure while decreasing the brain retraction pressure required, significant neurological complications have been attributed to excessive CSF drainage.

Hyperventilation has serious drawbacks in the form of decreased CBF and increased alkalosis. If hyperventilation is used in conjunction with significant brain retraction, nimodipine perioperatively should be considered.

Brain resection is an inelegant means of gaining exposure and should be resorted to only after the techniques above have been exhausted. However, in a very few situations, it may be the safest way to accomplish the surgical goal. Brain retraction should be limited to 15 minutes maximum at a pressure of less than 40 mm Hg, with a 5-minute recovery period between retractions. The use of multiple, narrow blades may be less injurious than a single, wide blade. The advent of stereotactic craniotomy has reduced the amount of retraction required to approach many lesions. A micromanipulator for the brain spatula

represents an intraoperative equivalent of the stereotactic tower holder of the strain gauge retractor, and the results obtained in the laboratory suggest its effectiveness during the surgery.

Because experience has clearly demonstrated the deleterious effect of excessive brain retraction, resection of brain tissue is frequently employed in certain neurosurgical procedures (e.g., the gyrus rectus approach to the anterior communicating artery region and lateral cerebellar resection for large masses in the cerebellopontine angle). Other invasive, if not destructive, techniques have been developed to facilitate exposure of the cranial base region: petrous bone resection (possibly together with the division of the sigmoid sinus or the sacrifice of hearing) and orbitofrontal osteotomy. To maximize the clinical efficacy of operative management for many tumors, aneurysms, and arteriovenous malformations, it is important to employ all possible techniques to minimize the brain injury that may result from the need for adequate exposure.

Electrophysiological monitoring should be a part of procedures involving significant brain retraction unless the region of brain undergoing retraction is not amenable to the available monitoring techniques.

Brain electrical activity monitoring

It has been well established that brain electrical activity, both spontaneous (EEG) and evoked potentials (EP), is altered and then lost at a CBF level above the of permanent brain injury. An approximately linear relationship between SSEP amplitude and CBF has been observed in primates. Monitoring the EEG has the advantage of being a measure of the depression of cerebral metabolism by agents such as barbiturates and etomidate, but may not be as effective as EP at detecting deep, white-matter ischemia.

Brain stem auditory EP (BAEP) and SSEP (including brain mapping with arrays placed on the cortical surface) have been used for cerebroprotective monitoring under general anesthesia, particularly during complex surgery for intracranial aneurysms and arteriovenous malformations and surgery for tumors near the sensorimotor cortex. For extensive cranial base procedures, all three monitoring techniques (EEG, BAEP, and SSEP) have been used concurrently. With

NEUROPROTECTION AGAINST SURGICALLY INDUCED BRAIN INJURY

an experienced team, intraoperative BAEP or SSEP mapping or monitoring can be performed with little operative or perioperative delay. Stimulating earphones or electrodes are applied while the anesthesia is being induced and the lines are placed; EP acquisition requires only a minute or so during which electrocautery and other sources of interference must not be used. Monitoring brain electrical activity can be a very useful aid to cerebral protection.

Blood flow monitoring

Although there are many methods of focal CBF measurement that can be used in the laboratory, intraoperative CBF measurement that is feasible for monitoring brain retraction ischemia has been elusive. Only laser-Doppler and thermal diffusion measurements of CBF have become accepted techniques for neurosurgical operating room use. There are a number of technical difficulties with laser-Doppler flowmetry that make it difficult for routine intraoperative use: the probe must not be placed over a superficial vessel, which yields falsely elevated CBF readings, the probe must not move during the procedure, and the effects of changes in hematocrit (e.g., with bleeding, hemodilution, or with mannitol, ambient lighting, temperature, etc.), are uncertain. Thermal diffusion flowmetry is also subject to limitations, particularly the uncertain effects of changes in temperature.

Transcranial Doppler blood velocity monitoring has also been used intraoperatively during craniotomy. Not only is it physically challenging to perform transcranial Doppler monitoring on hemispheric vessels during surgery, as opposed to monitoring velocities in the contralateral hemisphere, with current technology, the spatial resolution of transcranial Doppler is insufficient to be a reliable monitor of the focal ischemia resulting from brain retraction.

Although focal CBF monitoring could be very useful to protect against brain retraction ischemia, at the present time, the available techniques are probably neither sufficiently accurate nor practical for routine intraoperative use.

Retractor blade pressure monitoring

Two basic types of retractor blade pressure monitoring have been used in brain retraction research, both in the laboratory and intraoperatively. The first is n

air-tight plastic sleeve fits over the tip of a retractor blade, with opposing electrodes on the retractor tip and the sleeve between the tip and the brain surface. A pump causes the air pressure within the sleeve to cycle with the contact and the release of the electrodes.

Other studies have used a strain gauge attached to the brain retractor spatula. The strain gauge is reliable and inexpensive. If strain gauges are attached to both sides of the retractor blade, the effects of temperature changes on the calibration are obviated.

ANESTHESIOLOGY PROTECTION

Anesthetic agents

Isoflurane, often in combination with nitrous oxide and a narcotic such as fentanyl, is probably the most widely used anesthetic agent for intracranial procedures. It has been well studied in ischemia, hypotension, and hypocapnia. Isoflurane has been tried recently as a cerebroprotective agent in neurosurgical procedures.

Propofol is an intravenous anesthetic used for intracranial procedures. One advantage of propofol may be more reliable intraoperative SSEP recordings (better signal-to-noise ratio) than with isoflurane/nitrous oxide/fentanyl. Propofol was found to be more cerebroprotective than nitrous oxide/fentanyl in a rat model of incomplete cerebral ischemia. Propofol also decreased brain retraction pressure during clinical neurosurgical procedures in comparison with a control anesthesia of isoflurane/nitrous oxide/fentanyl. However, it also caused a larger decrease in blood pressure, thus resulting in a reduction in cerebral perfusion pressure in the region of retraction.

Barbiturates have been used for intraoperative cerebral protection. Knowledge of the effects of barbiturates on intraoperative electrophysiological monitoring is essential. It has been shown that intraoperative pentobarbital increases latencies in both BAEP and SSEP. The latency increase is particularly important in interpreting the central conduction time.

Etomidate, an intravenous imidazole anesthetic, is a potential cerebral protection agent that has been used intraoperatively. Its advantages over barbiturates include a relative lack of cardiodepression and a rapid

recovery from anesthesia, but direct comparison of the cerebroprotective effect of etomidate versus barbiturates has yet to be performed.

Hyperventilation, induced hypotension, and induced hypertension

Hyperventilation is frequently used to decrease brain volume and thus to improve exposure with minimal retraction. However, CBF decreases as well, and the net result on local cerebral perfusion pressure may be detrimental. Hyperventilation causes alkalosis, which has recently been shown to be detrimental to cultured cortical neurons undergoing hypoxic or excitotoxic injury.

Several groups have investigated hypotension and/or hypocapnia in large animal models while monitoring various combinations of the following: brain electrical activity (EEG and/or SSEP), CBF, and measures of cerebral metabolism. Because many neurosurgeons have had the impression that induced hypotension is particularly detrimental in conjunction with brain retraction or temporary vessel occlusion, intraoperative-induced hypotension is probably less commonly used now than previously. Induced hypertension as a cerebroprotective measure during temporary vessel occlusion in aneurysm surgery has recently been advocated.

Hypothermia

The cerebroprotective effects of hypothermia have been utilized in two ways: deep hypothermia for cardiopulmonary bypass and circulatory standstill (20°C), and mild hypothermia (32°C). Deep hypothermia requires cannulation of the femoral vessels and extracorporeal circulation and runs a significant risk of coagulopathy. For certain extremely difficult aneurysms, however, it may represent the only feasible way of obtaining sufficient exposure.

Mild hypothermia represents a compromise that may prove to be of considerable benefit in many cases. Although the cooling and warming protocols place a burden on operating room personnel, and recovery and extubation may be delayed an hour or two, mild hypothermia has fewer complications than deep hypothermia. The magnitude of the cerebroprotective benefit of mild hypothermia is probably substantial, but its role in relationship to other intraoperative

cerebroprotective interventions remains to be established (105).

Corticosteroids

Although corticosteroids are commonly used perioperatively in neurosurgical procedures involving brain retraction, particularly in patients with preoperative cerebral edema, there is no conclusive evidence that corticosteroids are cerebroprotective against focal brain ischemia.

Mannitol

Mannitol has many potentially beneficial effects during brain retraction: improved blood flow in the microcirculation; 2) free radical scavenging; and 3) decreased brain water content or edema. Mannitol has been shown to improve CBF and pH in regions of moderate ischemia, as well as regulating viscosity.

However, mannitol leads to significant, acute changes when administered in high doses, including hyponatremia, decreased hematocrit, and increased osmolality. Other detrimental effects include hypotension, acidosis, and hyperkalemia. Thus, Mannitol may be more cerebroprotective during brain surgery if it is administered in frequent, small doses (0.5 g/kg/h) or by a low-dose continuous infusion, rather than a bolus administration every 4 to 6 hours.

Nimodipine

The dihydropyridine calcium channel blocker, nimodipine, has been tried as a prophylaxis for cerebral ischemia caused by cerebral vasospasm after a subarachnoid hemorrhage and as a treatment for acute stroke. Nimodipine has undergone numerous trials in cerebral ischemia models; one frequent (but not universal) finding being that it usually elicits an increase in CBF during both the ischemic phase and the delayed hypoperfusion phase. Nimodipine has multiple, potentially beneficial effects for brain retraction ischemia: cerebral vasodilatation, amelioration of K⁺-induced vasoconstriction, antagonism of calcium entry into neurons via the L-channel, anticonvulsant properties, and reduction of acidosis. Although the data on nimodipine's effect on CBF with changes in PCO₂ (hyperventilation) are inconclusive, there are data to support the use of nimodipine for its cerebroprotective effect in the alkalosis induced by hyperventilation.

NEUROPROTECTION AGAINST SURGICALLY INDUCED BRAIN INJURY

The effects were investigated on animal models of mannitol plus nimodipine on cerebral blood flow (CBF) and evoked potentials (EP) ipsilateral and contralateral to brain retraction, in comparison with either agent alone, during both normoventilation and hyperventilation. Intravenous mannitol (2 g/kg over 15 min) and/or nimodipine (1 microgram/kg/min constant infusion) was administered. Mannitol plus nimodipine was superior both to controls and to either mannitol alone or nimodipine alone in preserving EP amplitude ipsilateral to retraction during both normoventilation and hyperventilation. Mannitol alone was effective in normoventilation at preserving EP, while nimodipine alone was effective in hyperventilation. No significant asymmetries in CBF or EP were seen with mannitol plus nimodipine in either normoventilation or hyperventilation. By five minutes post retraction CBF had returned to pre retraction values for all groups, and EP amplitude had returned also except for hyperventilated controls.

Dextromethorphan, a noncompetitive N-methyl-D-aspartate receptor antagonist, has been shown to be effective in small animal models of cerebral ischemia. Like nimodipine, dextromethorphan appears to be particularly effective in focal ischemia and may result in improved CBF in ischemic regions. Because of its efficacy in excitotoxic injury, dextromethorphan is currently under investigation in acute stroke patients and may offer intraoperative cerebral protection in addition to that offered by nimodipine. Dextromethorphan is an N-methyl-D-aspartate receptor antagonist with the advantages of safety and easy administration in humans.

Tromethamine, a weak base buffering agent, has been shown to be efficacious during prolonged hyperventilation, such as in the treatment of severe head injury. In experimental brain injury, it improves brain energy status (phosphocreatine to inorganic phosphate ratio), brain edema, and acidosis (in blood and probably brain as well). Tromethamine has been shown recently to ameliorate lactate acidosis after focal brain injury (128). Tromethamine may prove to be efficacious in conjunction with hyperventilation during neurosurgical procedures requiring lengthy brain retraction.

Tirilazad mesylate is a 21-aminosteroid antioxidant that appears to reduce tissue necrosis in ischemia with reperfusion, probably by decreasing free radical production. It is not clear whether tirilazad mesylate improves CBF in ischemia. Tirilazad mesylate is undergoing trials in acute ischemic stroke and in subarachnoid hemorrhage and may prove advantageous for intraoperative use.

MOLECULAR PATHWAYS PROVIDE FUTURE PROTECTIVE MEASURES

Besides proving a good anatomical base for sham surgeries, animal models also allow studying the cellular signaling mechanisms by performing molecular techniques on the affected brain tissue. Delineating the signaling pathways will elucidate the key molecular targets for potential neuroprotection against surgically induced brain injury.

Inhibition of Src tyrosine kinase

Preliminary experiments using inhibitors of key molecular targets, such as Src tyrosine kinase, have yielded very promising results. Src acts as a common signaling mediator involved in a broad spectrum of physiological responses, including gene transcription, adhesion regulation, and cell differentiation and survival [17]. Recent studies have shown that Src is activated by signals that increase intracellular Ca²⁺ concentration and that Src serves as a signaling protein for pathological mechanisms of neuronal degenerative disease, including ischemia and seizure. *In vitro* kinase assays have shown the ischemia/reperfusion-induced activation of Src [17], and it has been shown by immunoblotting with antibody against Tyr416 phosphorylated Src, that Tyr416 phosphorylation of Src is increased in the rat hippocampus following transient forebrain ischemia. These results, confirmed by the *in vivo* models, suggest that Src signaling is involved in microglial activation in response to ischemic injury.

PP1 is a selective inhibitor for Src tyrosine kinase [18], which is an upstream regulator of MAPKs. Src tyrosine kinase and the ubiquitous MAPKs are well implicated in brain injury resulting from different causes such as cerebral ischemia, trauma, and hemorrhage [19, 20] and have an important role in cerebral edema

[19, 21]. Inhibition of Src tyrosine kinase with PP1 reduces the expression of VEGF, protects the BBB, and reduces brain edema immediately after subarachnoid hemorrhage [22]; it also offers cerebral protection against stroke by influencing the VEGF-mediated vascular permeability and cerebral edema [18]. Treatment with PP1 was associated with decreased edema, decreased breakdown of the BBB, decreased expression of both vascular endothelial growth factor and phosphorylated extracellular signal-regulated kinase 1 and 2, and preservation of ZO-1 expression.

Erythropoietin

Erythropoietin was administered (5000 U/kg) intraperitoneally to a rat animal model on the day before surgery, the day of surgery, and for two postoperative days. EPO did not improve histological, immunohistochemical, or magnetic resonance imaging outcomes. The absence of EPO-related neuroprotection in this study was somewhat surprising, given the multitude of other models in which EPO functions as a neuroprotectant. It is possible that alternate administration methods, such as direct, intracavity EPO treatment, may result in improved anti-apoptotic outcomes. We conclude that tissue injury in surgery brain injuries involves BBB breakdown, edema, and apoptosis. Pretreatment with erythropoietin does not improve outcomes in this model, and may increase brain edema early after surgery.

17 β -Estradiol

Pretreatment with 17 β -estradiol reduces the size of acute (after 4 h) glutamate-mediated lesion by almost 47%. The pre-treatment with high doses of estradiol activates the production of lactate that has been shown to occur after cortical application of glutamate [23], suggesting that lactate may be an important effector of 17 β -estradiol. Although for many years lactate has been considered as a major detrimental factor in ischemic brain damage, many studies now suggest that lactate, produced by glycolysis mainly in glial cells during an anaerobic period, becomes the obligatory substrate for aerobic energy metabolism, in particular upon reoxygenation [24]. Glutamate uptake into astrocytes is conducted by specific glutamate transporters [25] and has been shown to stimulate

aerobic glycolysis inducing glucose utilisation and lactate production in vitro [26] and in vivo. Lactate is an efficient energy substrate for neurons and can fully substitute for glucose for oxidative metabolism [24]. Lactate produced in astrocytes and released in the ECF does not readily diffuse through membranes and therefore must be transported across them by monocarboxylate transporters, MCT1 and MCT2. The blockage of neuronal MTCs with 4-CIN abolished the neuroprotective effect of 17 β -estradiol by preventing lactate uptake into neurons. Lactate accumulates in extracellular space and can not be used as an energy supply. Therefore a large lesion is obtained that reflects the lack of energy for neurons in the penumbra.

Higher concentration of lactate observed after 17 β -estradiol pre-treatment provides neurons with enough energy to survive after glutamate overstimulation. This increase in glutamate-stimulated lactate production may lead to neuroprotection as illustrated by the reduction of the volume of the lesion. The abolition of lactate production observed after 120 min in the presence of the anti-estrogen Tamoxifen suggests that the enhancement of glutamate-driven production of lactate by 17 β -estradiol is dependent on the estrogen receptors

Matrix metalloproteinase inhibition

This study describes the neuroprotective effects of MMP inhibitor-1 by preservation of BBB and attenuation of brain edema after SBI. On a rodent model of SBI, localized edema was observed in the brain tissue bordering the surgical injury after a disruption of BBB. The increase in BBB permeability, evaluated by IgG staining and MRI studies, was localized to the brain tissue surrounding the SBI, which compared well with the localized brain edema (ipsilateral frontal lobe). Increased MMP-9 and MMP-2 enzyme activities were seen in the brain tissue surrounding the SBI at time points corresponding to maximal brain edema. MMP-2 enzyme activity, although significant, was only mildly increased after surgical injury. Immunohistochemical evidence further suggested that the MMP-9, but not MMP-2 expression, increases in neurons and the recruited neutrophils in the brain tissue adjoining the SBI. Neutrophils have been implicated as a major cellular source of MMP-9

NEUROPROTECTION AGAINST SURGICALLY INDUCED BRAIN INJURY

after brain injury [27]. MMP-9 promotes BBB breakdown secondary to micro vascular lamina proteolysis leading to edema formation after brain injuries [1, 28]. Thus, increased MMP activity, especially that of MMP-9, could produce BBB disruption and lead to brain edema after SBI.

Inhibition of MMP-9 and MMP-2 enzymatic activity in the affected brain resulted in reduced brain edema and preservation of BBB. MRI studies further supported a neuroprotective role for MMP inhibitors as early as 3 hours after SBI. Although T2-weighted imaging showed accelerated edema formation at 3 hours after treatment, the contrast-enhanced T1-weighted imaging showed beneficial effects of MMP inhibitor-1 on BBB permeability, which translated into attenuation of brain edema at later stages.

Previously, it was thought that vascular engorgement or cerebral blood volume contributes to brain swelling after brain injury. However, recent clinical studies have shown that brain edema contributes to the brain swelling [29]. Brain water content is a good indicator of brain swelling resulting from the edema. A 1% increase in brain water content is equivalent to a 4.3% increase in tissue volume, which can cause raised intracranial pressure. Present findings show significant early neurological deficits over Days 1 to 3, which resolve over 1 to 2 weeks, paralleling the natural resolution of brain edema. In the untreated animals, MMP-9 activity persisted through day 3 after SBI even though the neurological deficits seemed to improve with natural resolution of brain edema. This persistent MMP-9 activity may likely be due to inflammatory changes after SBI. The MMP-9 levels, however, were reduced in MMP inhibitor-1-treated animals, suggesting that MMP-9 inhibition can decrease brain edema. MMP inhibitor treatment regimens decreased brain edema and BBB permeability. However, they did not show a significant difference in neurological scores between different groups. MMP inhibitor-1 has promise as a neuroprotectant by preserving the BBB and attenuating brain edema. This effect of MMP inhibitor-1 is mechanistically distinct from agents in current clinical practice, including osmotic agents, diuretics, and steroids. Drugs that are neuroprotective in this model such as MMP inhibitor-1 may enable more aggressive

surgical approaches, aid with surgery in anatomically confined regions of the cranial vault, and ultimately provide a greater margin of safety for patients.

CONCLUSION

Brain surgery is associated inevitable with a degree a brain injury, due to retraction, focal ischemia, hemorrhage or electrocoagulation. All these contribute to postoperatively complications or prolonged hospitalization periods. Therefore it is recommended for new complete protocols, combining surgical technical procedures, anesthesiology agents and modalities, and lately, involvement with molecular pathways associated to brain injury.

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