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Review Article

Oxidative Stress and Inflammatory Response in Traumatic Brain Injury: A Technical Review

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ABSTRACT

Traumatic brain injury is a major cause of mortality and morbidity world-wide. Outcomes in traumatic brain injury are related to the severity of injury which is dependent on the primary and secondary brain injury pathology. The primary brain injury lesions are directly related to the site of impact and include, lacerations, contusions and diffuse axonal injury. Secondary brain injury results from the biochemical and physiological cascades that occur after the primary brain injury. These changes can lead to a reduction in cerebral blood flow and cerebral perfusion resulting in cerebral ischaemia. In traumatic brain injury, the oxidative stress response leads to a reduction in the endogenous antioxidants and dysfunction of the blood brain barrier function. Immediately following traumatic brain injury, a catabolic process sets in resulting in alteration in the Na/K+ ATPase activity and the metabolic demand. These can cause metabolic uncoupling and a vicious cycle leading to tissue damage and necrosis due to oxidative stress. Following traumatic brain injury the reactive oxygen species are generated as a result of mitochondrial dysfunction, a dysfunction of the electron transport chain, glutamate excitotoxicity and activation of bradykinin. The bradykinin activates phospholipase A2, leading to the release of arachidonic acid which can serve as an additional source of free radicals and oxidative stress. The purpose of this review article was to illustrate the oxidative stress response in traumatic brain injury and to elaborate the importance of minimising this response in these patients. Management of traumatic brain injury should be directed at minimising, the oxidative stress response, as well as increasing the levels of endogenous anti-oxidants in these patients.

Keywords: *Traumatic brain injury, Oxidative stress, anti-oxidants.*

RÉSUMÉ

Les lésions cérébrales traumatiques représentent une cause majeure de mortalité et de morbidité dans le monde entier. Les résultats de ces lésions cérébrales traumatiques sont liés à la gravité des blessures qui dépendent à leur tour de la pathologie de la lésion cérébrale primaire ou secondaire. Les pathologies de lésions cérébrales primaires sont directement liées au site d'impact et comprennent entre autres, les lacérations, les contusions et les lésions axonales diffuses. Les pathologies de lésions cérébrales secondaires sont des cascades biochimiques et physiologiques qui se produisent après une lésion cérébrale primaire. Ces modifications peuvent conduire à une diminution du débit sanguin cérébral et la perfusion cérébrale entraînant une ischémie cérébrale. Dans une lésion cérébrale traumatique, la réponse au stress oxydatif conduit à une réduction des antioxydants endogènes et un dysfonctionnement de la fonction de barrière hémato-encéphalique. Immédiatement après la lésion cérébrale traumatique, un catabolisme des ensembles de procédé conduisant à une altération de l'activité de Na / K + ATPase et la demande métabolique. Ceux-ci peuvent provoquer le désaccouplement métabolique et un cercle vicieux conduisant à des lésions tissulaires et une nécrose due au stress oxydatif. Suite à une lésion traumatique du cerveau, des espèces réactives de l'oxygène sont générés à la suite d'un dysfonctionnement mitochondrial, un dysfonctionnement de la chaîne de transport d'électrons, excitotoxicité du glutamate et de l'activation de la bradykinine. La bradykinine active la phospholipase A2, conduisant à la libération de l'acide arachidonique qui peut servir comme une source supplémentaire de radicaux libres et le stress oxydatif. Le but de cette revue est d'illustrer la réponse au stress oxydatif dans les lésions cérébrales traumatiques et d'élaborer l'importance de minimiser cette réaction chez ces patients. La gestion d'une lésion cérébrale traumatique doit être adressée en vue de réduire au minimum la réponse au stress oxydatif, ainsi que l'augmentation des niveaux d'antioxydants endogènes chez ces patients.

Mots clés : *Les lésions traumatiques du cerveau, le stress oxydatif, des anti-oxydants.*

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INTRODUCTION

Oxidative stress involves enhancement in production of free radicals and strong oxidants as well as increased depletion of body stores of anti-oxidants following trauma or inflammation. It occurs when the level of toxic reactive oxygen species exceeds the level of endogenous anti-oxidants. These reactive oxygen species are produced by phagocytic cells in response to trauma or inflammation and can cause secondary neuronal damage or cerebral edema in patients with traumatic brain injury. Superoxide anions initiate cascades of arachidonic acid metabolism, leading to the formation of more superoxides and liberation of ferrous iron (Fe2+) from ferritin stores. Trauma is the commonest cause of oxidative stress (1-4).

Reactive oxygen intermediates include superoxide, hydroxyl radicals, hydrogen peroxide and hypochlorous acid and cause oxidative damage to cellular proteins and nucleic acids in addition to lipid peroxidation. Additionally the reactive oxygen species act as secondary messengers in the intracellular inflammatory pathway causing the consumption of endogenous anti-oxidants in oxidative stress and may lead to the development of multiple organ failure in polytraumatic patients (5).

Modulation of oxidative stress can increase the level of anti-oxidants, as shown in animal models. An understanding of the natural history in the human population is required in order to modulate oxidative stress. This research attempts to understand the natural history and treat oxidative stress in traumatic neurosurgical patients. It is based on the hypothesis that modulation of oxidative stress with neurosurgical and intensive care management will improve patient outcome after traumatic brain injury.

The study focusses on clinically applicable methods for the management of oxidative stress and the associated inflammatory pathological changes in traumatic brain injury patients.

Traumatic brain injury is a major cause of morbidity and mortality world wide. Mortality may exceed 40% in patients with severe traumatic brain injury (6). Traumatic brain injury may be focal or diffuse and may result in primary and secondary brain injury with associated derangement in cerebral blood flow and metabolism. The physiological responses in traumatic brain injury involve activation of cellular, humoral and tissue pathways (7-10). The main stay of therapy in traumatic brain injury is aimed at preventing or treating elevated intracranial pressure (11).

Traumatic brain injury (TBI) management guidelines have helped in reducing morbidity and mortality. Intracranial pressure and cerebral perfusion pressure management strategies have resulted in improved clinical outcomes in patients with traumatic brain injury (8). Primary brain injury occurs at the moment of impact while secondary brain injury results from complex pathological processes leading to cerebral ischemia and intracranial hypertension (6, 10). Following traumatic brain injury there is a reduction in the cerebral blood flow in the first 12-24 hours, this can result in cerebral ischemia especially in the first 3 hours of trauma (12, 13). Severe head injury results in a poor clinical outcome, with a mortality index of 35-40% in the United States. The secondary brain injury complex cascades lead to brain edema, inflammation of neural tissue and neural cell death (14-16).

Outcomes in traumatic brain injury (TBI) are dependent on several factors including, intracranial pressure (ICP), cerebral perfusion, metabolic function and oxygenation. Measurements of ICP, cerebral blood flow and cerebral perfusion pressure are necessary in order to avoid hypoperfusion, hyperperfusion or hypoxia as these factors reveal the state of cerebral oxygen consumption (10, 17, 18). Management of cerebral tissue oxygenation has been shown to help in the control of ICP and improvement on the outcomes of patients with TBI (19).

Several biochemical and physiological changes occur in traumatic brain injury especially in patients with moderate to severe head injury. These factors involve changes in oxidative stress and cause release of free radicals. These changes influence the intracranial pressure through changes in cerebral perfusion leading to cerebral ischemia, brain edema and neuronal damage (20, 21).

The superoxide radical ($O_2^{\bullet-}$) is involved in neuronal tissue damage through formation of hydroxyl radicals ($^{\bullet}OH$) and peroxynitrite ($ONOO^-$) radicals. The peroxynitrite ($ONOO^-$) radicals are formed from combination of superoxide radical with nitric oxide. NADPH oxidase is involved in the generation of superoxide ($O_2^{\bullet-}$) radicals in cells. High levels of NADPH oxidase are found in the cerebral cortex and in the hippocampus (22-24). Enhanced microglial activation, NADPH oxidase activity and superoxide radical generation in traumatic brain injury plays a major role in oxidative stress damage leading to neuronal tissue damage through release of inflammatory cytokines in patients with head injury (25, 26).

Partial pressure of oxygen in brain tissue PBO_2 directed therapy in patients with severe TBI has resulted in a reduction in mortality and morbidity among head injury patients (27). Brain tissue directed therapy sets a PBO_2 of 20 as the lower limit in order to avoid cerebral hypoxia and ischemia. PBO_2 monitoring may help complement ICP and CPP monitoring in traumatic brain injury (28-31).

Following head injury there is activation of inflammatory and anti-inflammatory cascades. Not much has been done to evaluate the interaction of traumatic brain injury,

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oxidative stress and inflammatory changes and their impact on the clinical outcomes in patients with TBI.

The objective of this paper was to review relevant and recent scientific publications on traumatic brain injury and oxidative stress. This paper was organized in different sections with emphasis being placed on the problems facing neurosurgeons such as epidemiology of brain trauma, oxidative stress and inflammatory changes in traumatic brain injury, management of traumatic brain injury and outcomes in patients with head injury.

EPIDEMIOLOGY OF TRAUMATIC BRAIN INJURY

Traumatic brain injury results in altered consciousness, seizures, focal neurological deficits and confusion following blunt or penetrating injury to the head. In the united states (US) and developed countries TBI is a major cause of morbidity and mortality among individuals younger than 45 years (32, 33). Traumatic brain injury is categorized into mild, moderate or severe based on the severity of the head injury. About 3.6% of patients with head injury die annually in the United States (34)**.** The epidemiological studies on TBI have great limitations and can be fraught with many shortcomings. Major causes of traumatic brain injury in the United States include falls (28%) automobile accidents (20%) and assaults (9%) according to data from the National Center for Injury Prevention and Control (33, 35). The general incidence of TBI in developed countries is 200 per 100,000 individuals at risk per year. In Johannesburg, South Africa, studies on traumatic brain injury reported an incidence of 360 per 100,000 in the category of patients aged 15-24 years old (36). According to North American studies 180-300/100000 children with traumatic brain injury are seen each year, this is lower than the findings from South African studies. Males are more likely to suffer from traumatic brain injury compared to females, with an estimated gender ratio of 4:1-5:1 being noted in South Africa (34, 36).

OXIDATIVE STRESS AND THE INFLAMMATORY RESPONSE

Traumatic brain injury induces a cascade of inflammatory and oxidative stress changes whose pathological nature is part of the secondary brain injury mechanisms. In traumatic brain injury there is activation of polymorphonuclear leucocytes, macrophages and the complement system resulting in increased generation of reactive oxygen species. In these patients episodes of hypoxia and shock cause release of endothelin-1 and scavenging of nitric oxide leading to vasoconstriction which worsens the hypoxia and ischemia. This process activates the release of inflammatory mediators including TNF-α. A consequence of the oxidative and inflammatory pathology is neuronal tissue injury and a decrease in the anti-oxidant activity (37, 38). **Figure 1** summarises the main mechanisms (ischaemia, hypoxia, macrophages, complement factors, interleukin 6 and interleukin 10 that increase the levels of reactive oxygen species and decrease levels of anti oxidants) that induce oxidative stress in traumatic brain injury. Trauma induces oxidative stress. Early and intensive management of traumatic brain injury and associated oxidative stress, improves the anti-oxidant status and should result in better clinical outcomes in these patients. Systemic stress including trauma causes a depletion of hepatic glutathione stores and endothelium derived relaxation factors (EDRF) such as nitric oxide and prostaglandins. The anti-oxidant capacity of nitric oxide is achieved by, inhibition of cysteine protease, inhibition of iron-induced generation of hydroxyl radicals via the Fenton reaction as well as interruption of the lipid peroxidation chain reactions and augumentation of anti-oxidant abilities of reduced glutathione (39). During phagocytosis neutrophils release lysozymes along with oxidative enzymes both of which can cause neuronal damage and aggrevate the inflammatory pathology. However anti-oxidants mechanisms exist to protect the host and limit tissue destruction. These mechanisms involve glutathione peroxidase, catalase, vitamine E, ascorbate and superoxide dismutase (40, 41).

PATHOPHYSIOLOGY OF OXIDATIVE STRESS

In traumatic brain injury there is increased cell membrane permeability as well as anaerobic glycolysis leading to increased lactic acid production. The ATP stores become depleted and the energy dependent ion pumps fail. The resulting catabolism activates lipid peroxidases, proteases and phospholipases with generation of free radicals (10). Trauma is the commonest cause of oxidative stress. Oxidative stress causes depletion of endogenous anti-oxidants due to free radical assault. The effects of these have been shown to aggravate the clinical effects in polytrauma patients and may even be associated with multi organ failure (3, 5, 42, 43). Management of traumatic brain injury should be aimed at avoiding hypotension and cerebral ischemia. Cerebral hypoperfusion leads to cerebral ischemia with associated metabolic disturbances. The mechanism by which cerebral ischemia occurs involves mechanical distortion, hypoperfusion, and changes related to nitric oxide and cholinergic neurotransmitter deficiencies. Biochemical changes leading to neuronal inflammation and neuronal cell death are responsible for secondary brain injury (44-46). In traumatic brain injury, vasospasms occur from day 2-15. The mechanisms are related to reduced potassium channel activity, reduced availability of nitric oxide and a reduction in cyclic guanosine monophosphate (CGMP) in vascular smooth muscle. There is prostaglandin induced vasoconstriction and free radical formation (44, 47-50).

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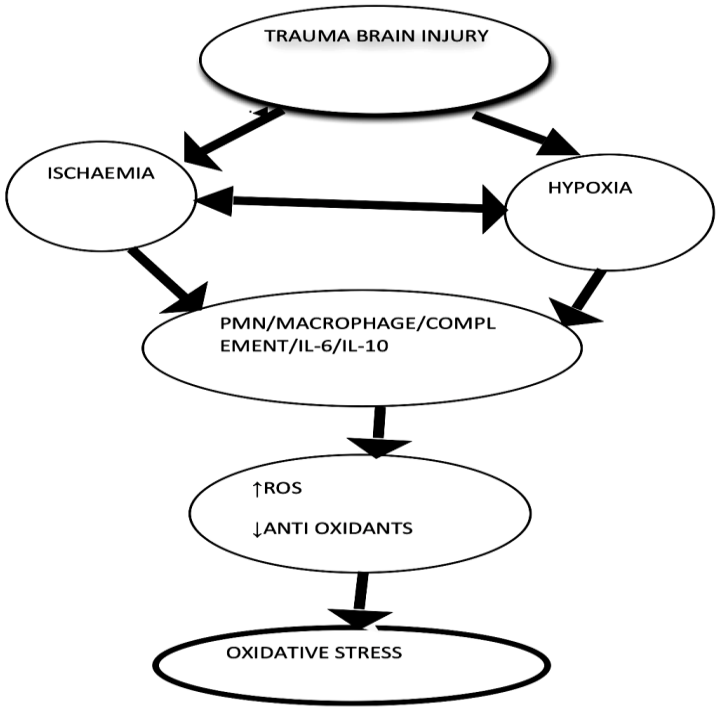

FIGURE 1: SCHEMATIC PRESENTATION OF TBI AND OXIDATIVE STRESS.

In traumatic brain injury there is release of excitatory amino acid neurotransmitters including glutamate and aspartate. These excitatory amino acids act on the N-methyl-D-aspartate channels, causing an increase in cell membrane permeability and intracellular calcium as well as sodium activation of calcineurin and calmodulin leading to neural tissue damage (10, 44, 51, 52).

Following TBI, cells are attacked by oxidative stress factors including hypoxia and cytokines. A consequence of this is a free radical response and overproduction of reactive oxygen species like hydrogen peroxide and hydroxyl radicals, which may cause oxidative tissue damage and cerebral ischemia. The free radicals attack components of the cell including lipids, proteins and nucleic acids (49, 50, 53). The increased production of superoxide anions during hypoxia and the reperfusion that occur initiate the cascade of arachidonic acid metabolism resulting in the formation of more superoxide anions (4, 54, 55).

The hydroxyl radical is from reactions involving hydrogen peroxide. Both the hydroxyl radical and molecular oxygen react with poly-unsaturated fatty acids causing structural and functional changes leading to fatty acid peroxyl radical formation. These radicals react with other lipids, proteins, or nucleic acids to initiate the electron transfer cascade and associated oxidative changes causing base hydroxylation, DNA strand breakage, lipid peroxidation and cell death (50, 53).

Reactive oxygen species cause cell damage by lipid peroxidation, whose effects result in increased cell membrane permeability. Hydroxyl radicals react with poly unsaturated fatty acids forming carbon centered lipid radicals which interact with molecular oxygen to generate peroxy radicals. The peroxy radicals are then converted to lipid hydroperoxides through extraction of hydrogen atoms from methylated carbons causing further propagation of lipid chain peroxidation. Lipid hydroperoxides decompose following interaction with iron complexes and form alkoxyl and peroxyradicals. Whereas iron propagates this cascade, the presence of tocopherol terminates it (56-58).

Oxidative stress is a disturbance in the equilibrium status of pro-oxidant/anti-oxidant systems in intact cells and accounts for much of the negative consequences of secondary brain injury (50, 53). Tissue injury in traumatic brain injury can be attributed to peroxynitrite ($ONOO^-$), which is formed by a combination of nitric oxide (NO) radical and superoxide radical. Normally the release of oxygen-derived free radicals is under the control of cellular anti-oxidant systems. However when the capacity of anti-

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oxidant systems is exceeded in head injury, neuronal tissue damage results (53, 59-61).

Free superoxide radicals ($O_2^{\bullet-}$) released in traumatic brain injury cause neuronal damage through formation of hydroxyl ($^{\bullet}OH$) and peroxynitrite ($ONOO^-$) radicals. The amelioration of NADPH oxidase activity in traumatic brain injury results in increased superoxide radical generation and neuronal damage (22, 62). Markers of oxidative damage following traumatic brain injury include 4-hydroxynonenal (4-HNE), 8-hydroxydeoxyguanosine (8-OHdG) and phosphor kitone (P-H2AX) (63).

HOST RESPONSE TO OXIDATIVE STRESS

Vitamin E and C (ascorbic acid) are helpfull in inactivating free radicals, especially the lipid radicals. Glutathione peroxidase is active in scavenging free radicals particularly the peroxides (64, 65). Tocopherol inactivates the lipid peroxyl radical forming a tocopherol radical and lipid peroxide. The tocopherol radical is in turn inactivated by ascorbate leading to regeneration of tocopherol and the formation of ascorbate radical. Alterations occur in the ascorbate radical leading to the formation of ascorbate and dehydroascorbate. The dehydroascorbate is subsequently reduced by GSH to form ascorbate and oxidized glutathione (66, 67).

ANTI-OXIDANTS IN HUMANS

Anti-oxidants protect human or host tissues against uncontrolled oxidation. In humans anti-oxidants can be water soluble or lipid soluble. Water soluble anti-oxidants include ascorbate, uric acid, bilirubin and thiol proteins and glutathione. Lipid soluble anti-oxidants include α and γ-tocorphenol, carotenoids, ubiquinol and lycopene. The anti-oxidant process involves compartmentation, detoxification, repair and utilization. Compartmentation involves spartial separation of potentially harmfull substrates as well as distribution of anti-oxidants in the body. Detoxification breaks down anti-oxidants to non toxic substrates (68). Repair involves oxidative changes while utilization involves degradation of peroxidized and denatured lipids and proteins (68, 69).

MANAGEMENT AND OUTCOMES OF TRAUMATIC BRAIN INJURY

Management of traumatic brain injury involves maintaining hemodynamic equilibrium, avoidance of hypotension and hypoxia, optimization of cerebral perfusion and oxygenation as well as control of the intracranial hypertension and avoidance of secondary brain insults. Early management of traumatic brain injury requires optimization of oxygenation and cerebral perfusion. Consistent application of protocols in the management of traumatic brain injury have resulted in a reduction in mortality and improved clinical outcome in these patients (70, 71).

Current management of traumatic brain injury not only involves monitoring the intracranial pressure and brain tissue oxygenation but also initiation of brain tissue oxygen directed therapy to correct and treat the effects of hypoxia in addition to the intracranial pressure management and cerebral protective measures (72).

Intracranial Pressure

Management of traumatic brain injury not only involves monitoring of intracranial pressure (ICP) and brain tissue oxygenation but also optimization of cerebral perfusion pressure (CPP), mechanical (hyper-) ventilation, oxygenation and therapy to reduce intracranial pressure (ICP), as well as pharmacological intervention to reduce excitotoxicity and neuronal tissue damage. This current approach in management of traumatic brain injury has resulted in reduction in mortality and improvement in outcomes among head injury patients (27, 73).

Management and treatment of ICP and CPP alone does not prevent hypoxic episodes in TBI, and so multimodality monitoring and treatment in TBI including PBO_2, CPP and ICP monitoring does help in reducing morbidity or mortality in TBI patients (74, 75).

Current therapy in traumatic brain injury not only aims at reducing the effects of primary injury but also the secondary brain injury consequences related to hypotension, hypoxia and elevated intracranial pressure (12, 76, 77).

Cerebral auto-regulation maintains cerebral perfusion and oxygenation and also plays a role in maintaining the intracranial pressure. Brain trauma foundation guidelines in the management of TBI have set a target CPP of 60-70 mmHg. Monitoring and management of intracranial pressure, cerebral oxygenation and cerebral perfusion pressure correlate well with better outcomes in TBI (78-81).

Therapy directed at maintaining brain tissue oxygenation (PBO_2) at 20 mmHg- 40 mmHg has been associated with reduction in morbidity and morbidity (27, 82). The therapeutic use of normobaric hyperoxia to counter act cerebral ischemia and facilitate cerebral oxidative metabolism has been documented to have beneficial effects in traumatic brain injury (83).

In addition to the above treatment modalities, surgical modalities to treat patients with traumatic brain injury including craniotomy, craniectomy to decompress, remove and treat the intracranial mass lesions have gone a long way in reducing morbidity and mortality in patients with TBI (11, 84, 85).

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Patients presenting with head injury with intracranial pathology especially subdural, extradural hematoma, intracerebral hematomas or associated hemorrhagic contusions and brain edema with mass effects including tonsilar or subfalcine herniation, ventricular effacement and midline shift should be surgically managed (11).

Traumatic brain injury management guidelines have defined criteria to help in management of patients with head injury; among the criteria for surgical evacuation of extradural hematoma include a volume of 30 Cm^3, or extradural hematoma (EDH) with Glasgow Coma Score (GCS) <9 with anisocoria, midline shift of >5 mm. Other criteria used in surgical management of intracranial traumatic mass lesions include, hematoma thickness greater than 10 mm for subdural hematoma (SDH), midline shift greater than 5 mm, with a GCS <9 and or a drop in GCS by more than 2 points or an increase in the ICP > 20 in patients who were being managed conservatively. Indications for surgery for traumatic parenchymal lesions include a low GCS <8, with a temporal contusion >20 Cm cubic, and midline shift >5 mm; for posterior fossa intracerebral hemorrhage (ICH) besides neurological deterioration indications for surgery also include cisternal effacement and obliteration of the fourth ventricle (11, 84-88).

Early management of traumatic brain injury requires that the oxygenation and cerebral perfusion be optimized. The systolic blood pressure should be maintained above 95 mmHg. Intracranial pressure monitoring should be carried out in patients with a low GCS particularly if the GCS is below 8. Various types of ICP monitors can be used and can include monitors in the subdural, epidural, intra-parenchymal spaces as well as the ventricular drains. Some studies have documented improved outcomes in patients with ICP monitoring when compared to those without ICP monitoring (89, 90).

Medical Intervention in TBI

In patients with moderate to severe head injury with elevated intracranial pressure, medical measures to decrease the intracranial pressure include head elevation to 30 degrees, administration of mannitol at 0.25-1 mg/kg or hypertonic saline 3% or 5% (91).

Hypertonic saline has been shown to restore the blood volume and to improve the outcome in patients with severe TBI. Several studies have shown beneficial effects of continuous hypertonic saline infusion in children with TBI (92). Beneficial effects of hypertonic saline, include reduction in ICP, expansion of intravascular volume, reduction in cerebral edema and improvement in cardiac contractility (93, 94).

Routine use of prophylactic mannitol in traumatic brain injury is not recommended (84). In patients with moderate to severe TBI where the ICP monitor is yet to be inserted, the use of mannitol should be reserved for those with signs of transtentorial herniation or progressive neurologic deterioration. Unwarranted use of mannitol may cause intravascular dehydration, hypotension, pre-renal azotemia and hyperkalemia (95).

Other fluids – aggressive fluid resuscitation to achieve euvolemia and minimize hypotension is a necessity in TBI. Use of a central venous pressure (CVP) line and maintaining of CVP at 8-10 mmHg is vital. In patients unresponsive to fluid resuscitation, the use of pressors to maintain systolic blood pressure above 90 mmHg is recommended. Isotonic fluids especially normal saline are preferred to achieve an adequate intravascular volume, anemia should be avoided and the hematocrit should be maintained above 30% (84).

Hypothermia

Induction of hypothermia is thought to reduce secondary brain injury in TBI by suppressing metabolism suppression and reducing inflammation and the release of free radicals, cytokines and excitatory amino acids (96, 97).

Moderate hypothermia at temperatures of 34-36 Celsius may be advocated for in the management of moderate to severe traumatic brain injury as it leads to a reduction in the ICP, cerebral metabolism and cerebral perfusion pressure and may lead to improved clinical outcomes in these patients (12, 98).

Anti-Seizure Prophylaxis

Post-traumatic seizures may be classified as early or late if they occur within the first 7 days or after. Seizure prophylaxis may only help to prevent early post-traumatic seizures (99, 100). There is an increased risk for seizures in patients with subdural hematoma, epidural hematoma, depressed skull fracture, cerebral contusion, GCS <10, intracerebral hematoma, penetrating head injury, and patients who present with seizures during the first 24 hours after traumatic brain injury (84, 101). Usually phenytoin is used starting with a loading dose of 15-20 mg/kg IV loading dose followed by a daily dose of 100 mg every 8 hours for 7 days.

Mechanical Ventilation

Patients with severe TBI should be intubated and mechanically ventilated. Hypoxia should be avoided and the PCO_2 should be kept between 35-40 mmHg, the oxygen saturation (pulse oxymeter) should be kept above 95% (PaO_2 > 60%) (102).

Hyperventilation: in patients with moderate to severe TBI, management may include a reduction of the PCO_2 to 30-35 mmHg. This may reduce the ICP by 25% via

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vasoconstriction however prolonged hyperventilation to PCO_2 below 30 mmHg may lead to cerebral ischemia (103).

In acute settings where there is a rapid neurological deterioration due to cerebral edema, hyperventilation may be used for 15-30 minutes, however on such occasions the jugular venous oxygen saturation ($SjvO_2$) or brain tissue oxygen tension or saturation (PBO_2) measurements are recommended to monitor cerebral oxygenation and avoid cerebral ischemia (84, 104).

OUTCOMES

The Glasgow Coma Score (GCS) and in particular the motor component are major predictors of outcome in traumatic brain injury. There is an increasing probability of poor outcome with a decreasing GCS (105, 106). Studies reveal that the relationship between admission GCS score and mortality is exponential with a marked increase in mortality in patients with GCS < 9. The mortality among patients presenting with severe head injury is significantly high (107).

Hypotension is a major determinant and an independent predictor of outcome in severe TBI. Prolonged hypotension in TBI is associated with increased mortality (108, 109). Other predictors of outcome include hypoxia, age, pupillary abnormalities and CT classification. Traumatic brain injury is associated with an increased probability of poor outcome with increasing age of patients. Survival in patients with intracranial hematomas decreases with advancing age (110-112).

The pupillary size and light reflex are indirect measures of dysfunction to pathways subserving consciousness and, act as important clinical parameters in assessing outcome from traumatic coma. Patients with bilaterally reactive pupils after TBI have a significantly better outcome (113, 114).

Sedation and analgesia are necessary in TBI patients to minimize pain or noxious stimuli as well as agitation. Neuroprotective agents such as propofol and midazolam sedatives have been used in TBI to minimize any increase in intracranial pressure. The sedative analgesics commonly used in traumatic brain injury include morphine and fentanyl. The use of these agents to provide sedation and analgesia helps to decrease cerebral metabolism and oxygen consumption (115, 116). Thought high dose barbiturate therapy has been used to control intractable intracranial hypertension in TBI, it is associated with hypotension and does not have clear beneficial effects on long-term outcome (80).

METHODS OF OXIDATIVE STRESSS EVALUATION

Total Anti Oxidant Capacity in Plasma

The antioxidant potential determines the ability to withstand oxidative stress. The majority of methods to measure the anti-oxidant activity are inhibitory except for the ferric reducing anti-oxidant power (FRAP) and the total serum reducing capacity, which determine the total reducing capacity of antioxidants. Inhibitory methods are in two phases – in the first phase there is free radical generation while the second phase involves the addition of a sample, which scavenges the free radical.

The reducing methods measure the anti-oxidant ability of the serum against ferric iron (Fe3+) for FRAP assay and phospholipase A2. These reducing methods do involve generation of free radicals. The unit of anti-oxidant capacity is the Trolox which is defined as the millimolar concentration of a substance that has the same antioxidant capacity as a millimolar of Trolox (117).

Total Radical Trapping Potential (TRAP) Method

This method is used to evaluate the anti-oxidant status and was developed by Wayner (118). TRAP is defined as the number of molecules of peroxyradical trapped per liter of fluids. Total anti-oxidant activity determines the ability of the anti-oxidant to reduce chemiluminescence in the TRAP assay. It measures the induction times in the oxidation of lipid dispersion exposed to free radical assault under aerobic conditions (63, 118).

This method is based on thermal decomposition of the water soluble 2, 2 azinobis (2-amidopropane) hydrochloride (ABAP) yields peroxyradicals at a constant rate. Each molecule of Trolox , Hoffman-LaRoche, Basel Switzerland) α-tocopherol and phenolic anti-oxidants traps two peroxy radicals resulting in Trolox having a stoichiometric factor of 2.0 in the TRAP assay. The serum sample is mixed with linoleic acid to prevent the termination reaction of two newly generated peroxy radicals happening. Initiation of the reaction involves the addition of ABAP, following which monitoring is done until oxygen uptake is maximal. After the take up of 50% of the oxygen Trolox I added for calibration of the system. Total sample assay varies per oxidant capacity (118). TRAP measures the level of the following anti-oxidants – Uric acid, Protein sulfhydryl groups (-SH), α-Tocopherol, Ubiquinol-10 (119, 120).

The 2-2' Azinobis (3 etheyl benzothiazoline-sulfonic acid) method

The 2-2' Azinobis method uses spectrophotometry to measure the anti-oxidant capacity. Inhibition of the cation radical of 2-2' Azinobis by anti-oxidants forms the basis of this study (63). Anti-oxidants suppress the absorbance of 2-2' Azinobis. The 2-2' Azinobis free radical cation is formed through the reaction of ferrimyoglobulin radical species with 2-2' Azinobis. Methods for assay include

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inhibition assay using fixed time point, inhibition assay with reaction rate and decolorization assay as well as lag phase measurements (63, 117, 121-123).

A reduction of the total anti oxidant activity occurs in HIV positive patients and critically ill patients (117, 124-126). During analysis coefficients of variation (CV) are clear and good CV ranges are from 0.54%-1.59% for intra assay and from 3.6%-6.1% for inter assay (63, 117, 123).

Fixed times are required in reading the reaction times. Marked variations on the contributions of the anti oxidants occur following even slight changes on the reaction conditions. This method has a long lag phase and is greatly affected by temperature variations (123, 127). Hyperuricemia and hypouricemia can cause false positive and false negative results respectively. This method is highly dependant on substrate solubility variation (123, 127).

Oxygen Radical Absorbance Capacity (ORAC) Assay

This method is used in quantitative analysis of the oxygen radical absorbance capacity (ORAC) of antioxidants in serum. Beta-phycoerythrin (beta-PE) is used as an indicator protein. 2-2' azinobis (2-amidinopropane) dihydrochloride (AAPH) as a peroxyradical generator and 6 hydroxy-2,5,7,8 tetramethyl chroman-2 carboxylic acid (Trolox) is used as a control standard. Results are in ORAC units, and 1 ORAC unit equals the net protection produced by 1 microM Trolox. Anti oxidants including, vitamin C, beta carotene, uric acid, albumin and bilirubin as well as α- tocopherol are oxidized by the peroxyradical. A linear correlation exists between the ORAC value and the concentration of serum trolox, vitamin C, uric acid and bovine albumin (128-130).

The free radical trapping method in hypoalbuminaemia is inversely correlated to hyperlipidemia particularly in patients with nephrotic syndrome. A low anti-oxidant potential in hyperlipidemia is associated with an increased risk of cardiovascular diseases and may improve with consumption of fruits and vegetables (128-130).

Ferric Reducing Anti-Oxidant Power Method (FRAP)

This method evaluates the total anti-oxidant power. It assesses the ferric reducing potential of the sample. At a low PH reduction of ferric tripyridyltriazone to a ferrous state produces an intense blue colour which can be measured by the change in absorbance at 593 nm. The change in absorbance is proportional to the total reduction of the electron donating anti-oxidants in the reaction (127, 131).

The ferric reducing anti-oxidant power and ascorbate concetration (FRASC) is a modification of the FRAP method and quantifies three indices of anti-oxidant status; the total reducing (anti-oxidant) power, the absolute concentration of ascorbate, and the contribution of ascorbate to the total anti oxidant power of the sample (127, 131).

Advantages and Disadvantages of the FRAP Method

It is a direct test of anti-oxidant power and it does not use lag phase type of measurement (120, 131-133). The FRAP and FRASC methods use three indices of anti-oxidant status: the anti oxidant power, the absolute concentration of ascorbic acid and the relative contribution of ascorbic acid. Here the stoichiometric factors are constant, linearity is maintained, sample pre treatment is not required. This method is very sensitive and it can be reproduced easly (131).

The FRAP method and its FRASC modification have corrected for the high uric acid production and can be used for a wide range of biological fluids and demonstrate consistent results (127, 131). It does not measure sulfhydryl groups (SH) containing anti-oxidants especially plasma proteins. Anti-oxidants particularly ascorbate groups reduce ferric salts and may react with ferrous salts to further generate free radicals and could present an additional challenge during the study (127, 131).

The Total Reducing Capacity Studies

It was developed by Mayer et al and measures anti-oxidants in serum (134). During the study thiol labelled arachidonic acid is suspended in a buffer containing hydroxyethylpiperazine-N-2'-ethanesulfonic acid glycerol and triton-X-100. Equal volumes of the substrate is added to a microtiter plate and incubated at room temperature for 15 minutes. Bee venom phospholipase A_2(PLA_2) is the standard used. When coupled with monochrombimone serum free thiols (like glutathione) cause fluorescence which can be measured using a fluorometer and compared to standard. The interassay variation is >7% and the retrieval rate is >97%. The normal values range from 100-120ng/ml).

Glutathione System

Glutathione, an α-aminoacid and a tripeptide is formed from glycine, cysteine and glutamine. Glutathione functions as a catalyst, and is involved in metabolism and anti-oxidant activities. Significant oxidative stress causes depletion of red cell glutathione levels and reduces disulphide linkages in proteins and other molecules. It functions as a co-enzyme and is involved in trans-membrane transport of aminoacids (135-137).

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Glutathione has been found in various tissues including red cells, kidneys, liver, brain and spinal cord and oxidative stress causes a depletion of the glutathione especially in the red blood cells. Because of these accurate changes in the red blood cells, the red cell glutathione index is an important marker for oxidative stress. Glutathione protects against free radical assault (135, 137-145). Free radical production in trauma causes depletion of anti-oxidants in extracellular fluid with depletion of red cell glutathione stores. This causes increased production of oxidized glutathione (GSSG). Subsequent conversion back to reduced glutathione requires glutathione reductase and NADPH (66, 141, 146).

Measurement of Glutathione

Measurement of glutathione stores may include:

The use of spectrometer at wave length of 320 nm and the Ellmans reagent from fresh blood to Calculate the difference in the ratio of reduced and oxidized gluathione to reduced glutathione (147, 148).

The Reed method involves measurement of reduced glutathione (GSH), oxidized glutathione (GSSG) and other thiols by making derivatives of free thiols with iodo acetic acid. There is conversion of free amino groups to 2,4 dinitrophenyl derivatives. A method based on conjugation of glutathion S transferase catalyses a reaction between chlorbenzidine with glutathione to form S glutathion (a 2,4 dinitrophenyl compound) which has maximum absorbance at 340 nm forms the basis for the Asensi modification of the Brigelious method. The specimen is then pre-treated with trichloroacetic acid and the supernatant is stable for a week a -200 celcious.

The Brown and Armstrong method measures GSH. Metaphosphoric acid/EDTA and sodium chloride samples are added to fresh bloods for stablisation. This method is simply a modification of the Beutler method. The mixture formed is then centrifuged and the supernatant stored at -800 celcious (149, 150).

Enzymatic Assays

Superoxide dismutase converts superoxide radical into molecular oxygen and hydrogen peroxide. Catalase and Glutathione peroxidases convert hydrogen peroxide into water and in case of catalase into water and oxygen. Superoxide dismutase and catalase do not require cofactors while glutathione peroxidase does.

Glutathione reductase and glucose 6 phosphate dehydrogenase are co-enzymes that enable glutathione peroxidase to function effectively (151).

Superoxide dismutase has 3 iso enzymes that are highly compartmentalized. The cytosolic and nuclear copper and zinc containing superoxide dismutase and mitochondrial manganese containing superoxide dismutase and the extracellular superoxide dismutase. Catalases are found in the cytoplasm and the peroxisomes while Glutathione peroxidases are found in subcellular compartments including mitochondria and nuclear. Extracellular superoxide dismutase is distributed in tissues including the cerebrospinal fluid, ascetic fluid, plasma, kidney heart and lung (152).

The activity of these anti-oxidant enzymatic systems may be evaluated by enzymatic assays using spectrophotometry, or by using the native gel evaluation method or by immunohistochemistry. The enzymatic activity assay requires 10 fold more protein than the natural gel activity assay and gives a quantitative result while the native gel method gives a more qualitative result. Immunohistochemical analysis enable assessment of the anti-oxidant expression (153, 154).

In the immunohistochemical analysis, the immunofluorescence and immunogold methodologies are used to measure endogenous Catalase, Superoxide dismutase (SOD) and Glutathione peroxidase (GPx) levels. The disadvantage of the immunostaining method in Immunohistochemistry is that it does not measure the activity of the anti-oxidant proteins and cannot determine the subcellular location of the proteins.

Glutathione peroxidase has 5 iso-enzymes, it is protective against oxidative damage and suppresses the apoptosis induced by hydrogen peroxide. For glutathione peroxidase to function effectively it requires the following co-enzymes, glutathione reductase and glucose 6 phosphate dehydrogenase, several co-factors including reduced glutathione, NADPH and glucose 6 phosphate (155-157).

Lipid Peroxide Measurements

Free radical attack on polyunsaturated fatty acids results in formation of lipid peroxides. Thiobarbituric acid reaction forming malondialdehyde (MDA) from breakdown of lipid peroxides provides a clear measurement of lipid peroxides (158-160).

Another method for lipid peroxide measurements, involves evaluation of cholesterol oxidation products. Cholesterol oxidation leads to formation of cholesterol -3-5- dience 7-one as a major product in addition to cholesterol α and β epoxide a well as 7-ketocholesterol and 25 hydroxy cholesterol (161-163).

D- ROMS and Oxystress Method

This measures free radical products in plasma and was developed by Cesarone, Belcaro et al. (1999). It is based on the ability of transition metals to catalyze the breakdown of peroxides to free radicals (164). The Novel oxystress

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method measures the anti oxidant status. It measures the level of circulating free radicals and provides a picture of the oxidative status in the patient. It quantifies the hydrogen peroxide in urine and plasma that causes a colour change in the presence of thiobarbituric acid. This quantification is perfomed using a spectrophotometer at a wave length of 532 nm.

Urine Measurement of Oxidative Stress

Markers found in CSF, urine, or blood could be used as oxidative stress indices. Measuring oxidative damage in a clinical setting involves valuation of urinary metabolites such as F2-isoprostane (8-iso prostaglandin F2-α), urinary aldehydes, hydrogen peroxide and oxidants such as lipid peroxides and hydroxyl groups (165). Another method for assessment of urine peroxide involves the oxoglutarate oxidative decarboxylations (166, 167). Measurement of 8-oxoguanine in plasma or urine is an appropriate method for evaluation of oxidative stress. 8-oxoguanine an indicator of oxidative stress is a consequence of free radical assault on DNA (168).

CONCLUSION

Aggressive surgical and medical management of traumatic brain injury patients reduces the severity of oxidative stress and results in better clinical outcomes.

Competing Interest:

Authors declare that they have no competing interest.

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