TRAUMA AND BURNS

Trauma is any sort of injury, including the emotional trauma of divorce or the physical trauma of a broken hip. In this chapter, we will talk mostly of physical trauma even though emotional trauma is also known to deplete glutathione. Motor vehicle accidents, work injuries and falls are common examples of accidental trauma. Intentional trauma includes everything from gunshot wounds to surgical procedures. Burns may be caused by heat, chemicals or radiation. Radiation burns are discussed in chapter 2, and sunburn and UV (ultraviolet) burns in chapter 21.

Glutathione, antioxidant protection, immune defenses, and oxidative stress play an important role in all of these conditions. High or low levels of GSH have a significant effect on the susceptibility, tolerance and degree of injury, as well as the recovery time and outcome.

PHYSICAL TRAUMA

Until this century, traumatic injury was the major cause of death in human beings. In North America today, trauma has fallen to third place behind heart disease/stroke and cancer, but in some economic groups – especially poor urban male populations – trauma remains at the forefront.

Any critical illness depletes glutathione reserves. In a recent article from the journal Critical Care Medicine, F. Hammarqvist shows that intensive care patients suffered an approximate 40% loss of glutathione compared with healthy individuals. M. Kretzschmar from Germany followed patients with multiple injuries in an intensive care unit, from admission to discharge or death. He found the more severe the injuries, the higher the degree of oxidative stress and depletion of glutathione defenses. An Irish team led by C. Kilty suggests the measurement of glutathione S-transferases could be a useful indicator of general organ damage.

A Harvard Medical School team led by M.K. Robinson showed that lab animals artificially depleted of glutathione were dramatically more prone to death and complications of blood loss (hemorrhagic shock). Their results suggest that treatment of trauma should include some way to maintain glutathione levels. This would decrease the likelihood of multi-system organ failure in the event of shock.

The role of oxidative stress and glutathione metabolism in brain and neurological tissue injuries has been the focus of much research. Head injuries often damage the crucial blood-brain barrier, and subsequent circulatory problems lead to swelling and fluid buildup in the brain. Free radicals mediate some of the complex “secondary injuries” seen in this type of trauma. Efforts to prevent post-injury complications are a crucial part of treatment in emergency and critical care management.

Glutathione metabolism counteracts the damage caused by these oxyradicals. Increases in glutathione peroxidase activity following neurological trauma have been well documented. If injury is severe or complicated, these resources may become eventually

depleted. Canadians B.H. Juurlink and P.G. Paterson of the University of Saskatchewan suggest that nutritional interventions with GSH-precursors can maximize antioxidant defenses, and that such strategies should be pursued aggressively.

E.F. Ellis's team at the Department of Pharmacology and Toxicology with the Medical College of Virginia, tested the use of NAC against concussion after trauma to the brain. They discovered that NAC given prior to or shortly after the brain injury could prevent some of the consequences of oxidative circulatory compromise. At Ohio State University, J.H. Lucas and D.G. Wheeler showed a similar protective effect of glutathione on spinal cord injury. Using the GSH-precursors gamma-glutamyl-cysteine and OTZ elevated glutathione levels increased spinal neuron survival after physical trauma.

R. Wagner and R.R. Myers of the University of California developed an interesting therapy for nerve injury and sciatic inflammation and presented it in the journal "Pain". They were able to decrease the pathological consequences of sciatic nerve injury by using the drug NAC to raise GSH levels. Pre-treated subjects responded best. The longer the delay in administering NAC after injury, the less effective was the treatment.

Surgery is intrusive and disrupts a patient's anatomy. It leads to a host of physiological adjustments. Although from the surgeon's pint of view this is a controlled procedure with end-point objectives, from the body's point of view, it is traumatic. Just like recovery from accidental trauma, the outcome of the operation depends on the patient's prior defenses, fitness, and immune status.

Surgery releases billions of free radicals into the body. These severely tax the patient's antioxidant defenses and poor surgical outcomes seem to go hand-in-hand with low antioxidant levels. As the cell's primary intracellular antioxidant, glutathione is drawn from stores in the liver and skeletal muscles and dispersed to reduce the damage. The result of major surgery may be whole-body glutathione depletion. Articles from the American Journal of Physiology as well as the Annals of Surgery describe a fall in glutathione levels of 40% after abdominal surgery. This may increase the patient's susceptibility to cellular oxidative injury.

A relatively new surgical device – the laparoscope – is a tube with a fiberoptic cable through which the surgeon can see into and work within a body cavity. Tools are attached to the end of the laparoscope and procedures are performed through small surgical holes in the patient's body. This reduces cutting, recovery time and hospital stays for many patients. The difference in trauma induced by conventional surgery and laparoscopic surgery is measurable. A team of Hungarian surgeons noted oxidative stress and GSH levels in two such groups of patients undergoing gall-bladder removal. The laparoscopic group showed significantly lower values of oxidation and less depletion of GSH-systems than the open-surgery group.

Glutathione not only protects us from oxidative stress, it also bolsters immune response, controls and balances the inflammatory response and helps synthesize and repair proteins

involved in the healing process. This knowledge has stimulated research into the use of GSH enhancing strategies to improve and accelerate wound repair.

Plastic surgeons from the University of Michigan, Ann Arbor showed that depleted glutathione levels lead to delayed wound healing and poor repair. Biochemists from the Max Plank Institute in Germany showed that while healing, skin wounds initially increase their production of glutathione peroxidase in order to fight free radical formation. As healing progresses GSH levels fall. Pharmacologists from the Central Drug Research Institute in India demonstrated a 60-70% depletion of glutathione peroxidase and glutathione S-transferase levels in skin wounds after several days healing. Understanding these mechanisms at play, Van der Laan described in an article in the Journal of Surgical Research how NAC infusion could reduce tissue injury and shorten the repair period of crush injuries.

An important consideration in all surgery is disruption of blood flow to tissues (ischemia). When blood flow is re-established (reperfusion) there is a burst of free radical formation in the affected region that may affect the survival of those tissues. The Australians K.R. Knight and K. MacPhadden found that NAC, the glutathione precursor was able to decrease the amount of reperfusion injury in skin flaps. Potential applications are being investigated in cardiac surgery to avoid reperfusion injury.

BURNS

Heat or thermal burns consist of a complex series of events involving initial injury, physiological adjustments to circulatory and fluid changes, hematological and immunological responses, and an elaborate healing process. Death from heat burns is often delayed. Days after a burn, patients may die from circulatory shock, a result of loss of fluids from the burn. Weeks after a burn, patients may succumb to overwhelming infection (sepsis) because of the breakdown in their immune defenses.

Burn specialists have long known that oxidative stress can be dramatic in severe burn patients. Lipid peroxide levels, a good measure of free radical damage, are consistently high. Glutathione and its related enzyme activities are impaired. This has initiated research into the use of antioxidants to protect the cell from further damage.

A German team of pediatric surgeons conducted a two-year study on children with burns and severe inflammatory diseases. They managed to correct parameters of oxidative stress in these patients using selenium substitution, which raised glutathione peroxidase. They found this a valid supportive therapy for such conditions. Other nutritionists have increased selenium delivery through TPN (Total Parenteral Nutrition or intravenous nutrition) or through tube feeding, where food is supplied directly to the stomach or intestines.

One phenomenon of the early post-burn period is a drop in hemoglobin (red blood cell count). Scientists have questioned why. A team from Varna Medical University showed that burns depleted the glutathione and antioxidant defenses of the red blood cell itself. Oxidative byproducts accumulated, leading to destruction of these cells. They suggest

that adequate antioxidant therapy might prevent this complication, as long as it is begun early enough.

A Japanese team led by Y. Kasanuma from the Environmental Health Sciences Division of Tohuku University of Medicine investigated the effects of mild heat injury on oxidative stress. Rather than burning tissue, they exposed animals to mild chronic heat exposure (35^0C, 95^0F). They showed that chronic exposure to high temperatures causes oxidative damage and that GSH-related anti-oxidative systems play an important role in defending against this damage.

A recent study published in the journal "Burns" by D. Konukoglu was aimed at the use of NAC to treat burns. Researchers were able to decrease levels of lipid peroxidation and increase GSH levels. Using antioxidant supplementation (GSH, vitamin C and NAC) to raise glutathione levels, several Boston studies published in the Journal of Burn Care Rehabilitation and in Shock, showed that they could reduce mortality from 60% to zero in animals suffering third degree burns. This is strong evidence that oxidation contributes to post-burn mortality.

CONCLUSION

Surgery, burns, trauma and shock are all complex events, consisting of a series of biochemical, anatomical, physiological and immunological responses. Oxidative stress and the release of free radicals is an inevitable part of the initial injury, the subsequent inflammatory reactions and the healing processes. Glutathione is an integral part of our body's mechanism to minimize damage and promote healing. It acts both as an antioxidant and as a support for the immune system.

The value of antioxidant supplementation and nutritional support has historically been underestimated, but new approaches to this problem are under development and attitudes are changing. Strategies to maintain or increase glutathione enzyme systems have been beneficial in preliminary trials and show much promise in the treatment of major trauma, surgery and burn management protocols.

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