Pathophysiology of the spinal cord injury

Omurilik yaralanmaların patofizyolojisi

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ABSTRACT
Spinal cord injury (SCI) causes significant morbidity and mortality leading to serious social problems. Although many studies conducted on it, any universal treatment protocol has not been accepted to date. Studies about treatment of SCI focused on two mechanisms. First is usage of neuroprotective agents and second are regeneration studies to improve axonal functions of injured spinal cord. Pathophysiological changes occurring after SCI has to be well understood in order to develop ideal treatment. J Clin Exp Invest 2014; 5 (1): 131-136

Key words: Spinal cord injury, pathophysiology

INTRODUCTION
The spinal cord injury (SCI) is characterized by the loss or degradation of motor, sensory and autonomous functions as a result of the wholly or partly damage in the spinal cord for reasons such as trauma. This injury is a very important public health problem which necessitates a life-long treatment and care costs besides labor and loss of income and which negatively affect patients, their family and the country’s economy with social and psychological problems [1,2]. More than half of the survivors from injury cannot return back to normal life [3]. On the other hand, the fact that the vast majority of spinal cord injuries are seen in healthy young adults who are between the ages of 15-25 is a serious social problem. Intensive efforts spent for treatment so far, although it contributes to the modern approach positively, a treatment protocol which is an effective and permanent as well as a universal one has not been developed yet [4-6]. That the adult central nervous system after injury is not regenerated is a major problem. For many years, many researchers have tried to find different methods on the pathophysiological mechanisms of acute SCI in order to improve neurological function [7]. Experimental studies on this subject showed that SCI that occurs after injury could worsen further after the trauma. Modern pharmacological treatment protocols being developed aims to reduce neuronal damage and aims to minimize the neurologic sequelae.

Epidemiology
The incidence of spinal cord injury in epidemiological studies in the United States has been reported to be 30 to 50 cases per year in a million, its prevalence has been reported to be 12,000 new cases per year [8]. The most common causes of SCI include motor vehicle accidents, sports and leisure injuries, work-related accidents, injuries from being beaten and falls at home [1]. These are more common in men especially in adults and in young adults. The causes of SCI vary by geographic regions.

A complete SCI occurred in 45% of the clinical picture after spinal cord trauma. 63% of spinal trau-
ma is cervical, 16% of it is thoracic and 20% of it is at the level of thoracolumbar vertebrae. While high cervical trauma caused tetraplegia, the traumas far below cause paraplegia. Tetraplegia and paraplegia are present at almost half of traumas [5,9-11].

In a study conducted in Turkey in 1992, the incidence of traumatic SCI has been reported to be 12.7 new cases in a million and totally 581 spinal cord injuries have been reported. Among these, the most common causes of spinal cord injuries are the motor vehicle accidents (48.8%), falls (36.5%), cutting injuries (3.3%), gunshot wounds (1.9%), and jumping into the water (1.2%). Male / female ratio is found to be 2.5 / 1, respectively [12].

SCI associated with underlying degenerative and pathological process such as osteoporosis are more common in women due to fall in future years, and ranks first among the reasons. Spinal cord injuries other than trauma widely include tumors (25%), spinal vascular diseases (25%), inflammatory diseases (20%), spinal stenosis (19%), and the less seen ones include surgical intervention, radiation myelopathy, neural tube defects and other causes [13].

Pathophysiology

The concept of two-step mechanism in SCI was introduced when, in the early 1900s, Allen showed that progressive damage occurred in animals with spinal cord injured [14,15]. It has been reported that the first one was primer-mechanical damage and the latter was secondary injury in which many factors triggered by these play a role.

1. Primer mechanical damage

The most common mechanism of human SCI is spinal cord compression which continue post beat [16]. Flexion, extension, dislocation or distraction forces related to rotation cause penetrating injuries, strains or tears in neural tissues and vascular structures. Other possible mechanical effects of bone structures are ligaments or the effects related to the compression which results from the hematomas in the spinal canal [15,17,18].

While bleeding in spinal cord trauma starts in early period, the interruption of blood flow occurs in a later period. Interruption of blood flow leads to hypoxia and ischemia local infarction. This, particularly, causes damage to the gray matter whose metabolic requirement is more. Neurons located in the damaged area are interrupted physically and myelin thickness is reduced. Also, edema and macrophages in the damaged area are other factors leading to deterioration of nerve transmission [19].

2. Secondary mechanical damage

It is a damage which is started by primary injury and in which many pathophysiological mechanisms are defined when it develops in the hours and days after injury [7]. The main pathological process underlying all of these mechanisms is lack of energy due to impaired perfusion at the cellular level and ischemia [20-23]. It has been reported that ischemia begins immediately after traumatic SCI and if not treated, it deteriorates in the first 3 hours and continues for at least 24 hours [7]. After SCI, in spinal cord, there are many changes including hemorrhage, edema, demyelination, the formation of cavities with axonal and neuronal necrosis and a series of pathological changes which ended with infarction. Increased levels of glutamate, excitotoxicity, oxidative damage, ischemia, Ca++ dependent nitric oxide production, and free radical damage and lipid peroxidation in cell membranes are the contents of the secondary injury cascade [18,24,25]. However, many studies indicate that the spinal cord has a remarkable capable of healing capacity. In order that progressive tissue can pass in front of necrosis in this healing, the most important factor is to ensure proper blood flow. SCI is not only a pathology remaining in the injury in area but the spinal cord. By being affected by local injuries in spinal cord, neurons in descending pathways in the brain exhibit pathological chain of events from atrophy to apoptosis or necrosis [23]. Well vascularized astrocytic environment allow the axons to regenerate in the regions if the spinal cord injuries [26]. Therefore, understanding the mechanisms of the secondary injury, which can cause neuronal death after injury, stands as the most important issue in implementing advanced therapies [27]. Mechanisms that cause secondary damage to occur are held in two parts as systemically and local effects [2,7].

Systemic factors

Systemic factors that play roles in acute SCI are hypotension due to neurogenic shock, decreased cardiac output and respiratory failure [18,28]. In this case, metabolites and oxygen are prohibited to reach the tissues they need [18,23,28,29]. Drop in systemic blood pressure must absolutely be brought under control in a patient in spinal shock. Because the perfusion pressure is directly connected to the systemic blood pressure, the damage to the spinal cord is exacerbated. Therefore, a problem which may arise in the cardiopulmonary system may increase the severity of SCI by corrupting spinal cord perfusion. On the other hand, in order to avoid intramedullary hyperemia and hemorrhage, it has been
said that blood pressure should be kept only in normotensive levels [18]. Post-traumatic hypotension occurring immediately after the injury may take days or even months. In animal models with spinal cord trauma, normotension has been provided with blood transfusion and dopamine, thus, blood flow to the spinal cord has been able to be increased but because local microcirculation is damaged, spinal cord functions haven’t been improved [18,30].

**Local vascular effects**

It is known that severe SCI causes substantial decrease in blood supply and ischemia begins right after the trauma [7]. Systemic hemodynamic changes are reflected to blood flow in the spinal cord which’s otorespiration was disrupted. For this reason systemic hypotension and hypoxia further deteriorates the ischemia formed by spinal injury [31]. Ischemia, causes lack of energy by unsatisfactory transport of glucose and oxygen to the tissues resulting in decrease in ATP stores [32]. The exact causes of post-traumatic ischemia has not been fully understood. Focal narrowing of sulcal arterioles and intramedullary capillaries, fragmentation, aneurysmal dilatation or occlusion have been exhibited in experimental studies [20,22]. Kaptanoğlu et al demonstrated progressive vascular damage in spinal cord contusion injury model for the first time by using Evans blue technique. In this study there was 76% increase in uptake of Evans blue in the injury area at 24th hour compared to those at 2nd hour [33]. Decreased pH of the tissue due to lactic acidosis, congestion and venous stasis due to accumulation of fibrin and platelets, capillary endothelial damage, edema, petechial hemorrhages, vasoactive cytokines are some of the causes of ischemia. As a result, the system shifts to anaerobic respiration. Ischemia and subsequent triggering of anaerobic respiration leads to many of the pathological processes [18,34]. The proteinaceous leak through the intrinsic spinal cord veins, leads to edema at the site of injury and peripheral tissues [31]. Edema, causes relatively increased spinal cord pressure and this leads to disruption of local blood flow of the spinal cord [35]. In a study conducted by Kaptanoğlu et al. magnesium was found to reduce edema and vascular permeability ultrastructurally in spinal cord injuries [36].

**Ionic mechanisms**

After spinal cord trauma, abnormalities in the concentration of the electrolyte and gradient changes were observed [37]. In humans with 4-aminopyridine chronic SCI has increased axonal message and showed a recovery sign in moderate levels. This effect of 4-aminopyridin has been shown in cats with SCI by blocking the fast K+ channels [38]. On the other hand, ischemia-reperfusion injury leads to a significant increase in formation of glutamate and free radical. The destruction of the blood-spinal cord barrier can be prevented by antagonism of glutamate in endothelium. It has been shown that Glutamate receptor blockers improve neurological outcomes in an experimental SCI [7,39,40]. Mg+ is believed to decrease its by-products of lipid peroxidation with the indirect effect resulting from antagonism of glutamate [33]. The role of Ca ++ ion in the cell death is thought to be the most. Ca++ ions leads to promote the cell damage by activating phospholipases, proteases and phosphorylases in the cell. On the other hand, in the experimental spinal cord studies, calcium channel blockers were also tested in order to prevent secondary injury. There are many studies showing that these agents improve blood flow to the spinal cord and have a positive effect on healing [18,41-43]. It has been shown that, after SCI, dopamine, adrenaline, nimodipine, and dextran increase blood flow and promote neurological recovery [18,44].

**Free radicals**

To maintain cell viability, it is important to prevent the generation of intense free radicals [45]. The effectiveness of anti-oxidative defense mechanisms was reduced by aging and it was shown to be have a significant effect on the pathophysiology of SCI. In studies of experimental SCI carried on old and young rats two week mortality was 20% and 50% in young and old rats, respectively [46]. Free radical scavenger agents such as, Cyclosporin A[15], EPC-K1 [47], vitamin E and selenium [16] are shown to be useful for SCI. Kaptanoğlu et al. showed that melatonin, Mexiletine, erythropoietin, thiopental and propofol inhibit the lipid peroxidation after SCI [48-50].

**Opiate receptors**

An experimental study showed a marked release of endogenous opioid peptides locally in spinal cord injuries [23]. Preventing progressive tissue damage by opiate receptor blockade suggested that endogenous opioids might have a role in the pathophysiology of secondary injury. Faden et. al reported that post traumatic hypotension, spinal cord blood flow and the patient’s clinic was improved by a non-selective opioid antagonist, naloxone, after acute SCI [51]. The most affected opioid is dynorphin in human spinal cord injuries and the severity of the
trauma and dynorphin levels has been reported to be correlated [52].

Inflammatory response

Inflammatory response is initiated within hours by peripheral immune cells such as macrophages, neutrophils, and T cells after SCI and reaches maximum level in a few days [53,54]. This response is observed as the endothelial damage, the release of mediators of inflammation, vascular permeability, edema formation, migration of peripheral inflammatory cells and activation of microglia. Macrophages, and neutrophils play a role in the growth of the lesion and tissue damage. Macrophages and microglia play a role in inflammatory reactions and secondary pathological changes by the release of cytokines (TNF, IL-1, IL-6, IL-10). Inflammatory mediators such as bradykinin, prostaglandins, leukotrienes, platelet activating factor and serotonin accumulate at the lesion site in injured spinal cord. Additional cytokines, chemokines, nitric oxide, oxygen and expression of nitrogen species in response to inflammatory cytokines accelerate the central nervous system inflammatory response [54]. In two independent SCI model, 30 minutes after traumatic injury iv administration of systemic IL-10 resulted in systemic decreased inflammation. IL-10 is neuroprotective, and improves motor function [54].

Excitatory amino acids

NMDA receptors is thought to have a directory role in excitatory neurotransmission of the spinal cord [55]. In connection with this the NMDA receptor blockade has been shown to have a protective effect against secondary damage to traumatic and ischemic models [2]. With the administration of NMDA antagonists significant neurological improvement and significant decrease in edema occur [56]. This group receptors can be blocked by Mg++ [57]. Likewise, administration of AMPA antagonists have been reported to reduce injured area and cause functional improvement [58].

Glutamate is the major excitatory neurotransmitter in the central nervous system. Neuronal damage caused by excessive activation of glutamate receptors was detected by Olney et al. and defined as excitotoxicity [28]. Excitatory amino acids, glutamate and aspartate, rise within minutes after SCI [59]. After experimental SCI, concentration of extracellular excitatory amino acid in the spinal cord reach to the toxic levels within 15 minutes and maintain its toxicity as well as 120 minutes [23]. Extracellular excitatory amino acids are quite toxic for the neurons in spinal cord.

Apoptosis

Presence apoptosis is shown after traumatic SCI of human being which is triggered by release of cytokines, inflammatory injury, free radical injury and excitotoxicity [28,60,61]. Apoptotic cell death is observed after 3 hours to 8 weeks after traumatic SCI. Apoptosis occurs around lesion center as well as Wallerian degeneration area of descending and ascending white matter tracts [60]. Experimental studies have shown that apoptosis in oligodentrocytes aggravates demyelination occurring after a few weeks of injury. Crowe et al. have defined the oligodentrocytic changes in SCI for the first time [62]. In addition it’s thought that apoptosis adversely affects the outcome by increasing neuronal loss [28]. Some authors advocate that apoptosis in microglia worsens secondary inflammatory injury [61]. Experimental studies support that SCI exaggerates caspase activation [28]. Caspases are triggered by signals activating apoptosis and play an active role in all three pathways of apoptosis [63].

Apoptotic cell death occurs in all cellular components of the spinal cord (neurons, astrocytes, oligodentrocytes, and microglia). Neuronal protection is essential since neurons of the spinal cord have no reproduction capability [3]. Although glia has regeneration potential, inhibiting the glial death support the neuronal protection by two similar mechanisms. First, glia provides neurotrophic and metabolic support to injured neurons, which needs this support for recovery. Second, glia removes apoptotic mediators such as cytokines, free radicals released from dying cells, which are toxic to adjacent cells [3].

CONCLUSION

There are many experimental studies have been conducted and also still ongoing to understand pathophysiology of SCI. However, as a result of these studies an ideal treatment model to apply on human beings has not been developed yet. Clarifying the pathophysiology of SCI will contribute significantly to determine the optimal treatment.

REFERENCES


