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Spine

Neuroprotective effects of infliximab in experimental spinal cord injury

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Abstract

Background: The aim of the study is to assess the effects of infliximab, a TNF-α receptor blocker, in a spinal cord clip compression injury model.

Methods: Clip compression injury model was used for producing spinal cord injury on 32 adult, male Wistar rats (Gazi University Animal Research Laboratory, Ankara, Turkey). After exposing the vertebral column between T7 and T10, total laminectomy was performed with the assistance of a high-speed drill and a surgical microscope. The dura was left intact. Spinal cord injury was performed on all rats with application of a 70-g closing force aneurysm clip for 1 minute. The rats were randomly allocated into 4 groups. Control group received no further therapy, whereas the other 3 groups received methylprednisolone (30 mg/kg intraperitoneal), infliximab (5 mg/kg subcutaneous), and a mixture of these 2 agents. All rats were killed 72 hours later, and the level of lipid peroxides in traumatized spinal cord tissue were measured as thiobarbituric acid-reactive material and determined using the method of Mihara and Uchiyama (Determination of malonaldehyde precursor in tissue by thiobarbituric acid test. *Anal Biochem* 1978;86(1):271-8).

Results: Treatment with infliximab and methylprednisolone decreased MDA levels in rats with spinal cord injury with a statistically significant difference. In addition, combined therapy achieved a more profound decrease in tissue MDA levels, which was also statistically significant.

Conclusions: Infliximab is found as effective as methylprednisolone on spinal cord clip compression injury. Moreover, the combination of these 2 agents demonstrated higher efficacy suggesting a synergistic effect between these 2 agents. However, further studies regarding functional and behavioral analyses as well as biochemical markers are required.

Keywords: Infliximab; Neuroprotective agents; Spinal cord injury; TNF-α

1. Introduction

Within the last 2 decades, many researches have focused on pathophysiology of acute SCI to find methods to restore neurologic function [18,45]. It has been hypothesized that acute injury leads to 2 different, interrelated mechanisms of damage to the spinal cord—the primary mechanical injury and a subsequent secondary injury because of additional damaging process after the initial injury [12,13]. Among these mechanisms, secondary injury draws much attention because of its susceptible nature to the pharmacological intervention [19,21-24,44]. There have been many studies investigating pharmacological agents such as methylprednisolone, melatonin, erythropoietin, magnesium, mexiletine, and naloxone, which protect or reduce secondary injury after experimental SCI [19,21-24].

Neutrophils are believed to play an important role in the pathogenesis of secondary injury [1,3,11,17,32,43,48]. Neutrophils, in addition to their functions as phagocytes,

Abbreviations: CNS, Central nervous system; IL, interleukin; MDA, Malondialdehyde; SCI, Spinal cord injury; TNF-α, Tumor necrosis factor α.

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release histolytic enzymes, reactive oxygen species, and proinflammatory factors, which lead to further tissue necrosis and inflammation [3,17,32,43,48]. Free radicals, inflammation, and many other factors lead to apoptosis and play an important role in neuronal and glial cell damage and destruction [2,7,29,36].

As the first identified member of the cytokine family, TNF-α is believed to have important roles in triggering and sustaining inflammation in different diseases such as rheumatoid arthritis, inflammatory bowel disease, and acute pancreatitis [6]. For this particular role, TNF-α has been targeted in various studies [6,30] as well as in experiments of spinal cord injury [41].

Infliximab (Remicade, Schering-Plough, Berlin) is a novel drug approved for management of some inflammatory diseases. It is a chimeric monoclonal antibody for TNF-α and binds to both soluble and transmembrane forms of TNF-α. By inhibiting TNF-α, infliximab reduces concentrations of TNF and other inflammatory mediators and impede lymphocyte migration to the inflammation site [28,31].

On the other hand, with their antioxidant and membrane-stabilizing characteristics, steroids can be useful in spinal cord injury [14-16]. The effects of methylprednisolone are thought to be mediated through its antiinflammatory properties or its direct effects on vascular permeability and edema [26]. According to a Cochrane Review [4], after spinal cord trauma, "high-dose methylprednisolone steroid therapy is the only pharmacological therapy shown to have efficacy when it can be administered within 8 hours of injury."

This study was conducted to evaluate the neuroprotective effects of infliximab in an experimental spinal cord injury model and to compare the results with a widely used agent, methylprednisolone.

2. Materials and methods

2.1. Rat model

Thirty-two male, adult Wistar rats weighing between 250 and 300 g were used in this study. Animals were kept under constant laboratory conditions of 18°C to 21°C room temperature, a 12-hour light-dark cycle, and were allowed free access to food and water. All experiments were approved by our institutional review board and performed in accordance with the local guidelines to minimize animal discomfort.

2.2. Anesthesia and surgical procedure

Anesthesia was induced by intramuscular administration of 50 mg/kg of ketamine hydrochloride (Ketalar, Pfizer, Istanbul, Turkey) and 10 mg/kg of xylazine (Rompun, Bayer, Istanbul, Turkey). The rats were numbered with ear tags. Their midbacks were shaved and cleaned with 10% of polyvinylpyrrolidone/iodine. Using aseptic technique and a surgical microscope, a midline incision was made along the spinal processes of T5 and T12. Fascia was opened sharply, and paravertebral muscles along the T7 and T10 vertebrae were dissected bilaterally. After exposing the vertebral column between T7 and T10, total laminectomy was performed with the assistance of a high-speed drill and a surgical microscope. The dura was left intact. Spinal cord injury was performed on all rats with application of a 70-g closing force aneurysm clip (Yasargil FE 721, Aesculap, Istanbul, Turkey) for 1 minute. The wounds were closed in layers after the operation. Paraplegia was observed in all rats after the operation. Until the end of the experiment protocol (72 hours), the animals' bladders were manually voided twice a day, and they were housed in a temperature-controlled room where food and water were provided ad libitum.

2.3. Description of groups

The rats were randomly allocated into 4 groups as follows: a control group (group 1) of 8 rats in which only laminectomy and trauma were performed, but no treatment was given; a steroid group (group 2) of 8 rats in which 30 mg/kg of methylprednisolone was administered immediately after spinal trauma; an infliximab group (group 3) of 8 rats in which animals received 5 mg/kg of subcutaneous infliximab immediately after spinal trauma; and a mixed therapy group (group 4) in which 8 rats received both 5 mg/kg of subcutaneous infliximab and 30 mg/kg of methylprednisolone.

2.4. Sacrificing of animals and sample preparation

Rats were killed by overdose pentobarbital after 72 hours. Spinal cords at the injury site were excised for a length of 2 cm; 1 cm rostrally and 1 cm caudally to the injury site. Tissue samples were immediately stored in a −20°C freezer for assays of MDA.

2.5. Determination of lipid peroxidation in traumatized spinal cord tissue

The level of lipid peroxides in traumatized spinal cord tissue were measured as thiobarbituric acid-reactive material and determined using the method of Mihara and Uchiyama [33]. Malondialdehyde has been identified as the product of lipid peroxidation that reacts with thiobarbituric acid to give a red species absorbing at 535 nm. The assay procedure for lipid peroxide in spinal cord tissue was set up as follows. Tissues were homogenized in 10 volumes (wt/vol) of cold 1.5% of KCl. One half a milliliter (0.5 mL) of homogenate was mixed with 3 mL of 1% of H_3PO_4 and 1 mL of 0.6% of thiobarbituric acid. The mixture was then heated in boiling water for 60 minutes. After cooling, the color was extracted into 4 mL *n*-butanol, and the absorbance was recorded at 535 and 520 nm. Using tetramethoxypropane as the standard, tissue lipid peroxide levels were calculated as nanomoles per gram of wet tissue.

Table 1
Malondialdehyde values of the experimental groups

Groups	Mean	SD	Median	Minimum	Maximum
Control (group I)	77.875	21.93700	88.0000	35.00	95.00
Steroid (group 2)	53.750	22.68889	46.5000	30.00	87.00
Infliximab (group 3)	50.375	13.09239	54.0000	24.00	65.00
Mixed therapy (group 4)	32.8750	8.83883	33.5000	19.00	47.00

Kruskal-Wallis χ^2, 14.248; *df*, 3; $P = .003$.

2.6. Statistical evaluation

Comparison among groups was done with Kruskal-Wallis analysis of variance and the Mann-Whitney *U* test. Results are expressed as mean ± SD, median, and range. Significance was approved when *P* values were less than .05.

3. Results

The MDA levels of the groups as arithmetic means ± SD are demonstrated in Table 1. The MDA levels were highest in the control group (77.8 ± 21.9) and lowest in the mixed therapy group (32.8 ± 8.8). Comparison of the MDA values of the groups with Kruskal-Wallis variance analysis revealed statistical significance ($P = .003$).

When the groups were compared using post hoc Mann-Whitney *U* test, results were as follows. When the control group was compared with the steroid, infliximab, and mixed therapy groups, the results were statistically significant ($P = .031$, $P = .027$, and $P = .003$, respectively). In addition, comparison of the steroid group and the infliximab group separately with the mixed therapy group revealed statistically significant difference ($P = .031$ and $P = .016$, respectively). However, there was no statistically significant difference between the steroid group and the infliximab group ($P = .916$).

4. Discussion

Traumatic injuries to the CNS including the spinal cord cause tissue damage through direct, primary, and indirect secondary mechanisms. Secondary damage leads to a large number of cellular, molecular, and biochemical events that result in tissue necrosis and functional deficit because of disruption of cell membranes [8] and alterations in both blood flow and metabolism [39]. One of these events leading to preventable damage is the local inflammatory response at the injury site.

Active inflammatory response and the hemorrhage with release of Fe and hemoproteins at the injury site lead production of reactive oxygen radicals and cytotoxic edema. Ultimately, these factors contribute to lipid peroxidation and ischemia [5,46].

The central nervous system consists of largely of lipids and is damaged easily by free radical-induced lipid peroxidation [40]. Lipid peroxidation is recognized as one of the main pathophysiologic mechanisms involved in secondary damage [10], and MDA, which is formed from the breakdown of polyunsaturated fatty acids, serves as an important and reliable index for determining the extent of the peroxidation reaction [19,34,38]. In fact, most efforts aiming neuroprotection after spinal cord injury are intended to counteract early lipid peroxidation [10].

Interactions between the activated neutrophils and the endothelial cell linings at the injury site play important roles in secondary mechanisms, and it was proven that inhibition of these interactions markedly reduce the severity of injury [41,43].

Tumor necrosis factor α is a potent proinflammatory cytokine that is released by monocytes, macrophages, and T lymphocytes. Tumor necrosis factor α binds to 2 receptors present on many types of cells as follows: type 1 TNF-α receptor (also known as p55) and type 2 TNF-α receptor (also known as p75) [20]. Cytokines, particularly TNF-α, contribute to activated leukocyte-induced endothelial cell damage not only by activating neutrophils but also by increasing the expression of endothelial leukocyte adhesion molecules such as E selectin, by which activated neutrophils adhere to the endothelial cell surface [25,35]. In addition, Zheng et al [50] have demonstrated that TNF-α can directly cause endothelial cell damage in the absence of neutrophils.

Many authors have studied the relationship between TNF-α and the neuronal injury. Wang et al [47] have demonstrated increased TNF-α levels in injured spinal cord tissues. Yakovlev and Faden [49] have demonstrated that spinal cord impact in rats caused an elevation of TNF-α messenger RNA levels at the site of trauma 30 minutes after the injury, and the severity of injury was proportional to the level of the TNF-α message. Similarly, Taoka et al [42] have found that the level of TNF-α in traumatized spinal cord tissue was significantly increased after compressive trauma, with a peak seen 4 hours after the trauma.

Infliximab, a novel TNF-α inhibitor, is widely used for many clinical and experimental conditions. Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and psoriasis are approved indications for clinical use of infliximab [27]. Olmarker et al [37] have demonstrated selective inhibition of TNF-α by intraperitoneal application of infliximab blocked both the early focal and the later general pain behavior induced by the experimental disk herniation in rats. In a uveitis model, Demir et al [9] have demonstrated that infliximab suppresses the synthesis of IL-1, IL-6, IL-8, and TNF-α.

On the other hand, methylprednisolone is the only agent proven to have positive effects after spinal cord injury. It is known that early administration of methylprednisolone after spinal injury decreases lipid peroxidation, stabilizes intracellular and extracellular Ca^{+2} current, decreases neurofilament degeneration, increases the spinal blood flow,

decreases Na^+ and water retention in lesion, and prevent K^+ loss [51].

Results of our study demonstrated spinal cord MDA levels of rats in the treatment groups decreased after administration of infliximab, methylprednisolone, or both, and the difference was statistically significant. In addition, comparison of the steroid and infliximab groups with the mixed therapy group revealed statistically significant difference. Considering the insignificant difference between the infliximab and steroid groups, this can be interpreted as infliximab and methylprednisolone have synergistic effects on spinal cord injury, in means of lipid peroxidation. Although both agents decrease the MDA levels in the injured spinal cord, their combination provide more profound decrease in tissue MDA levels.

Infliximab and methylprednisolone are agents that have wide clinical use. With the results of our study demonstrating positive and synergistic effects of these 2 agents on SCI, we think that new sights are opened for further experiments, even experiments on human subjects with SCI.

Further studies are required with large cohorts evaluating functional and behavioral aspects of SCI rather than biochemical marker changes are required for definitive results that may have clinical impacts.

References

[1] Balentine JD. Pathology of experimental spinal cord trauma. II. Ultrastructure of axons and myelin. Lab Invest 1978;39(3):254-66.

[2] Bao F, Chen Y, Dekaban GA, Weaver LC. An anti-CD11d integrin antibody reduces cyclooxygenase-2 expression and protein and DNA oxidation after spinal cord injury in rats. J Neurochem 2004;90(5): 1194-204.

[3] Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. JAMA 1982;247(12):1707-14.

[4] Bracken MB. Steroids for acute spinal cord injury. Cochrane Database Syst Rev 2002(3):CD001046.

[5] Carlson SL, Parrish ME, Springer JE, Doty K, Dossett L. Acute inflammatory response in spinal cord following impact injury. Exp Neurol 1998;151(1):77-88.

[6] Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med 2001;344(12):907-16.

[7] Crowe MJ, Bresnahan JC, Shuman SL, Masters JN, Beattie MS. Apoptosis and delayed degeneration after spinal cord injury in rats and monkeys. Nat Med 1997;3(1):73-6.

[8] Demediuk P, Saunders RD, Clendenon NR, Means ED, Anderson DK, Horrocks LA. Changes in lipid metabolism in traumatized spinal cord. Prog Brain Res 1985;63:211-26.

[9] Demir T, Godekmerdan A, Balbaba M, Turkcuoglu P, Ilhan F, Demir N. The effect of infliximab, cyclosporine A and recombinant IL-10 on vitreous cytokine levels in experimental autoimmune uveitis. Indian J Ophthalmol 2006;54(4):241-5.

[10] Diaz-Ruiz A, Rios C, Duarte I, Correa D, Guizar-Sahagun G, Grijalva I, Madrazo I, Ibarra A. Lipid peroxidation inhibition in spinal cord injury: cyclosporin-A vs methylprednisolone. Neuroreport 2000;11(8): 1765-7.

[11] Ducker TB, Kindt GW, Kempf LG. Pathological findings in acute experimental spinal cord trauma. J Neurosurg 1971;35(6):700-8.

[12] Faden AI, Simon RP. A potential role for excitotoxins in the pathophysiology of spinal cord injury. Ann Neurol 1988;23(6):623-6.

[13] Fehlings MG, Tator CH, Linden RD. The relationships among the severity of spinal cord injury, motor and somatosensory evoked potentials and spinal cord blood flow. Electroencephalogr Clin Neurophysiol 1989;74(4):241-59.

[14] Hall ED. Inhibition of lipid peroxidation in CNS trauma. J Neurotrauma 1991;8(Suppl 1):S31-40 discussion S1.

[15] Hall ED. Lipid antioxidants in acute central nervous system injury. Ann Emerg Med 1993;22(6):1022-7.

[16] Hall ED. The neuroprotective pharmacology of methylprednisolone. J Neurosurg 1992;76(1):13-22.

[17] Hamada Y, Ikata T, Katoh S, Nakauchi K, Niwa M, Kawai Y, Fukuzawa K. Involvement of an intercellular adhesion molecule 1-dependent pathway in the pathogenesis of secondary changes after spinal cord injury in rats. J Neurochem 1996;66(4):1525-31.

[18] Holtz A, Nystrom B, Gerdin B, Olsson Y. Neuropathological changes and neurological function after spinal cord compression in the rat. J Neurotrauma 1990;7(3):155-67.

[19] Ildan F, Polat S, Oner A, Isbir T, Gocer AI, Tap O, Kaya M, Karadayi A. Effects of naloxone on sodium- and potassium-activated and magnesium-dependent adenosine-5¢-triphosphatase activity and lipid peroxidation and early ultrastructural findings after experimental spinal cord injury. Neurosurgery 1995;36(4):797-805.

[20] Kapadia MK, Rubin PA. The emerging use of TNF-alpha inhibitors in orbital inflammatory disease. Int Ophthalmol Clin 2006;46(2):165-81.

[21] Kaptanoglu E, Beskonakli E, Solaroglu I, Kilinc A, Taskin Y. Magnesium sulfate treatment in experimental spinal cord injury: emphasis on vascular changes and early clinical results. Neurosurg Rev 2003;26(4):283-7.

[22] Kaptanoglu E, Caner HH, Surucu HS, Akbiyik F. Effect of mexiletine on lipid peroxidation and early ultrastructural findings in experimental spinal cord injury. J Neurosurg 1999;91(2 Suppl):200-4.

[23] Kaptanoglu E, Solaroglu I, Okutan O, Surucu HS, Akbiyik F, Beskonakli E. Erythropoietin exerts neuroprotection after acute spinal cord injury in rats: effect on lipid peroxidation and early ultrastructural findings. Neurosurg Rev 2004;27(2):113-20.

[24] Kaptanoglu E, Tuncel M, Palaoglu S, Konan A, Demirpence E, Kilinc K. Comparison of the effects of melatonin and methylprednisolone in experimental spinal cord injury. J Neurosurg 2000;93 (1 Suppl):77-84.

[25] Klebanoff SJ, Vadas MA, Harlan JM, Sparks LH, Gamble JR, Agosti JM, Waltersdorph AM. Stimulation of neutrophils by tumor necrosis factor. J Immunol 1986;136(11):4220-5.

[26] Koc RK, Akdemir H, Karakucuk EI, Oktem IS, Menku A. Effect of methylprednisolone, tirilazad mesylate and vitamin E on lipid peroxidation after experimental spinal cord injury. Spinal Cord 1999; 37(1):29-32.

[27] Kuek A, Hazleman BL, Ostor AJ. Immune-mediated inflammatory diseases (IMIDs) and biologic therapy: a medical revolution. Postgrad Med J 2007;83(978):251-60.

[28] Kulmatycki KM, Abouchehade K, Sattari S, Jamali F. Drug-disease interactions: reduced beta-adrenergic and potassium channel antagonist activities of sotalol in the presence of acute and chronic inflammatory conditions in the rat. Br J Pharmacol 2001;133(2): 286-94.

[29] Liu XZ, Xu XM, Hu R, Du C, Zhang SX, McDonald JW, Dong HX, Wu YJ, Fan GS, Jacquin MF, Hsu CY, Choi DW. Neuronal and glial apoptosis after traumatic spinal cord injury. J Neurosci 1997;17(14): 5395-406.

[30] Maini RN, Taylor PC. Anti-cytokine therapy for rheumatoid arthritis. Annu Rev Med 2000;51:207-29.

[31] Markham A, Lamb HM. Infliximab: a review of its use in the management of rheumatoid arthritis. Drugs 2000;59(6):1341-59.

[32] Means ED, Anderson DK. Neuronophagia by leukocytes in experimental spinal cord injury. J Neuropathol Exp Neurol 1983;42(6): 707-19.

[33] Mihara M, Uchiyama M. Determination of malonaldehyde precursor in tissues by thiobarbituric acid test. Anal Biochem 1978;86(1):271-8.

[34] Mizuno Y, Ohta K. Regional distributions of thiobarbituric acid-reactive products, activities of enzymes regulating the metabolism of oxygen free radicals, and some of the related enzymes in adult and aged rat brains. J Neurochem 1986;46(5):1344-52.
[35] Mulligan MS, Varani J, Dame MK, Lane CL, Smith CW, Anderson DC, Ward PA. Role of endothelial-leukocyte adhesion molecule 1 (ELAM-1) in neutrophil-mediated lung injury in rats. J Clin Invest 1991;88(4):1396-406.
[36] Nesic O, Xu GY, McAdoo D, High KW, Hulsebosch C, Perez-Pol R. IL-1 receptor antagonist prevents apoptosis and caspase-3 activation after spinal cord injury. J Neurotrauma 2001;18(9):947-56.
[37] Olmarker K, Rydevik B. Selective inhibition of tumor necrosis factor-alpha prevents nucleus pulposus-induced thrombus formation, intraneural edema, and reduction of nerve conduction velocity: possible implications for future pharmacologic treatment strategies of sciatica. Spine 2001;26(8):863-9.
[38] Qian H, Liu D. The time course of malondialdehyde production following impact injury to rat spinal cord as measured by microdialysis and high pressure liquid chromatography. Neurochem Res 1997;22 (10):1231-6.
[39] Rawe SE, Lee WA, Perot PL. Spinal cord glucose utilization after experimental spinal cord injury. Neurosurgery 1981;9(1):40-7.
[40] Schmidley JW. Free radicals in central nervous system ischemia. Stroke 1990;21(7):1086-90.
[41] Taoka Y, Okajima K. Spinal cord injury in the rat. Prog Neurobiol 1998;56(3):341-58.
[42] Taoka Y, Okajima K, Uchiba M, Murakami K, Harada N, Johno M, Naruo M. Activated protein C reduces the severity of compression-induced spinal cord injury in rats by inhibiting activation of leukocytes. J Neurosci 1998;18(4):1393-8.
[43] Taoka Y, Okajima K, Uchiba M, Murakami K, Kushimoto S, Johno M, Naruo M, Okabe H, Takatsuki K. Role of neutrophils in spinal cord injury in the rat. Neuroscience 1997;79(4):1177-82.
[44] Tator CH. Biology of neurological recovery and functional restoration after spinal cord injury. Neurosurgery 1998;42(4): 696-707 discussion-8.
[45] Tator CH, Fehlings MG. Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. J Neurosurg 1991;75(1):15-26.
[46] Usul H, Cakir E, Arslan E, Peksoylu B, Alver A, Sayin OC, Topbas M, Baykal S. Effects of clotrimazole on experimental spinal cord injury. Arch Med Res 2006;37(5):571-5.
[47] Wang CX, Nuttin B, Heremans H, Dom R, Gybels J. Production of tumor necrosis factor in spinal cord following traumatic injury in rats. J Neuroimmunol 1996;69(1-2):151-6.
[48] Xu JA, Hsu CY, Liu TH, Hogan EL, Perot Jr PL, Tai HH. Leukotriene B4 release and polymorphonuclear cell infiltration in spinal cord injury. J Neurochem 1990;55(3):907-12.
[49] Yakovlev AG, Faden AI. Sequential expression of c-fos protooncogene, TNF-alpha, and dynorphin genes in spinal cord following experimental traumatic injury. Mol Chem Neuropathol 1994;23(2-3): 179-90.
[50] Zheng H, Crowley JJ, Chan JC, Hoffmann H, Hatherill JR, Ishizaka A, Raffin TA. Attenuation of tumor necrosis factor-induced endothelial cell cytotoxicity and neutrophil chemiluminescence. Am Rev Respir Dis 1990;142(5):1073-8.
[51] Zileli M, Özer F. Pharmacological treatment in spinal cord injuries. In: Zileli M, Özer F, editors. Spinal cord and spine surgery. Izmir: Saray; 1997.

Commentary

Despite the great mountain of clinical and experimental studies from all over the world, the problem of solving the effects of a severe spinal cord injury remains widely without solution. More frustrating, unfortunately, is that the solution of such a problem, with its double component of primary and secondary injury, appears elusive and not near at hand, especially for primary injury. Therefore, the nature of the problem forces us to proceed slowly, adding only small steps to the hypothetical solution(s). This article moves in that direction and deals with the specific part of the problem related with the treatment of the secondary injury. Together with free radicals and many other factors, inflammation is an important cause of lipid peroxidation and neuronal and glial damage. Tumor necrosis factor α is a cytokine playing an important role as inflammatory agent that favors the migration of lymphocytes and the consequent secondary injury. The inhibitor of TNF-α, infliximab, could limit the secondary injury after spinal cord trauma. In this experimental study in rats, a midthoracic spinal cord injury was provoked using an aneurysmal clip. The rats were treated with infliximab or with methylprednisolone, or with both drugs. As it is known, methylprednisolone is a well-accepted antioxidant-antiinflammatory agent limiting secondary injury after spinal cord trauma. Three days after trauma, the spinal cords were collected to measure the levels of malondialdehyde (MDA), which is a product of lipid peroxidation. Lowering of the levels of MDA was similar after treatment with either infliximab or methylprednisolone but much more when both drugs were used together. This study was performed 72 hours after spinal cord injury; to know which could be the clinical effects of infliximab alone or associated with methylprednisolone remain to be elucidated. However, as noted above, small steps have been added by this study to the difficult chapter of spinal cord injury.

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