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Influence of the Level, Severity and Phase of Spinal Cord Injury on Hematological and Biochemical Parameters

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Abstract

Spinal cord (SC) injury is a neurological emergency that results in complications increasing in number and severity according to the level of the injury. Systemic response after SC injury may alter hematological and biochemical parameters. The present study was designed to investigate the effect of the lesion depending on its level and severity in order to provide a prognosis during its acute (24 hours post injury) and subacute (15 days post injury) phases. We hypothesized that hematologic and biochemical parameters will depend directly on the site, severity and phase of the lesion. Rats were subjected to T1 (high) or T11 (low) severe or moderate SC injury. Rats that were anesthetized but did not receive surgical procedure were used as controls. Blood samples were obtained 24 hours and 15 days post injury for acute and subacute analysis respectively. Results show that in both acute and subacute phases, the level of injury is not related to hematological alterations, in contrast, severity interferes with the normal blood cell count, hematocrit and hemoglobin concentrations. Regarding biochemical values, neither level, nor severity of injury are related to changes. It is worth mentioning that on the subacute phase almost all of the altered variables, that appeared during the acute stage of injury, tend to return to their normal values. The variation on both hematological and biochemical parameters may also be caused by hemorrhage, liver damage and inflammatory responses due to secondary mechanisms inflicted by SC injury. These findings help to understand the pathophysiology observed after injury and provide data that contribute to improve the initial management and the design of future therapies after SC injury.

Keywords: Animal model; Biochemical changes; Blood cell count; Contusion; Hematological changes; Inflammatory responses; liver damage; Metabolism; Spinal cord injury

Introduction

Spinal cord (SC) injury is a frequent phenomenon, it mostly affects males between 18 and 32 years old, however in developed countries there seems to be another peak at age of 65, possibly due to longer life expectancies. The global prevalence of people living with SC injury oscillates between 236 and 4187 cases per million; the annual incidence ranges between 12.1-57.8 cases per million. In developing countries, motor vehicle accidents were reported to be the main cause of-injury in 41.4% of patients, while unintentional falls represented 34.9% of patients. Regarding mortality, age is one of the main factors. Nevertheless, it is known that other circumstances can interfere with the course of the lesion, such as inadequate early management, lack of spinal stability and non-treated complications. SC injury can result in permanent loss of motor and sensitive functions below the level of lesion, as a consequence of direct injury or indirect damage of the surrounding bones, tissues, or blood vessels [1-4]. Common pathologies related to SC injury include pressure ulcers, depression, sleeping disorders, and autonomic dysfunction; all of which have a direct negative impact in the quality of life and their latter contributing to cardiovascular diseases, leading to an increase in morbidity and mortality [5-8]

SC injury pathophysiology can be divided into two main events: first, there is a mechanical interruption involving axons and synapses causing partial disconnection of ascending and descending nervous tracts. The following event is mediated by secondary mechanisms such as ischemia, edema, ionic imbalances, inflammatory response, mitochondrial dysfunction, metabolic inhibition and lipid peroxidation. All these alterations might lead to cell dysfunction and death of neuronal, glial and endothelial cells [3].

After SC injury -specially above T1 level, there is a decrease in sympathetic performance, resulting in hemodynamic instability that leads to loss in circulatory volume and cardiac output which is clinically manifested as hypotension and alterations in heart rate [9]. This sympathetic disturbance also results in delayed gastric emptying, dyspepsia and intestinal motility disruption, affecting the gastrointestinal system [10]. Respiratory and urinary systems may also be affected depending on the level of injury. If rostral, it is likely to cause respiratory failure by muscle paralysis [11,12]. On a caudal level of injury there is a higher risk of bladder dysfunction which may proceed to upper urinary tract infections [13]. Disruption of homeostatic blood flow as a result of decreasing sympathetic tone in vessels, generates a significant reduction of perfusion in skin, spleen, liver and muscles [14-16]. These changes might be responsible for modifying hematological and biochemical parameters which are important variables when evaluating the clinical status of the lesion.

Scant information is known about the association of this massive systemic response with its influence in clinical hematological and biochemical changes while considering diverse injury parameters we hypothesize that these parameters will be altered depending on the site, severity and phase of the injury; therefore in the present work, the effects of the level, severity and phase after SC injury were assessed, regarding preselected hematological and biochemical variables; which

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are relevant to predict the evolution of the injury during its acute (24 hours after SC injury) and subacute (15 days after SC injury) phases.

Methods

Study design and animal care

Two independent experiments were conducted in 80 adult (three months old) female Sprague- Dawley rats, weighing 200-220 g. In the first experiment (n=40), rats with SC contusion were studied for hematological and biochemical changes 24 h after injury. In the second one (n=40), the same parameters were analyzed in a group of rats with SC contusion 15 days after injury. For each experiment, animals were allocated into five groups (8 per group; see Table 1 for further description of the distribution of rats into groups): (1) Rats that were only anesthetized were used as the control group (with no surgical procedure, i.e. naïve), (2) high severe injury (HSI) at T1 level, (3) high moderate injury (HMI) at T1 level, (4) low severe injury (LSI) at T11 level, and (5) low moderate injury (LMI) at T11 level. Animals were matched for age and weight. All rats were housed in groups of two, under a light- and temperature-controlled room. To minimize stress, all animals were handled at least twice a day, starting 7 days prior to surgery. Sterile beds and filtered water were replaced daily. Animals also received manual bladder expression twice a day until recovery of sphincter control. Efforts were made to minimize both animal suffering and number of rats used. Animal care was provided in accordance with the ethical guidelines of our institution, which are equivalent to the National Institutes of Health (US) Guide for the Care and Use of Laboratory Animals.

Postoperatively, 1 mg/kg of gentamycin was administered once a day through subcutaneous-injection for 1 week (in the subacute group). Animals were carefully monitored for any signs of disease. Animals with overt signs of bladder or respiratory infections (e.g. hematuria, stertors or breathing complications) were excluded from the study. At the end of each experiment all animals were euthanized with an overdose of pentobarbital, to prevent them from suffering.

Spinal cord injury

Rats were anesthetized with ketamine (50 mg/kg) and xylazine (10 mg/kg). Thirty minutes later, animals were subjected to laminectomy at T1 or T11 segment respectively, in order to expose the spinal cord. A 10 g rod was then dropped onto the laminectomized cord from a height of 50 mm (severe injury) or 25 mm (moderate injury), using the NYU impactor (NYU, New York, USA), a weight drop device shown to inflict a well-calibrated contusive injury of the SC [17]. In all cases, the effectiveness of the injury was evaluated by verifying the site and size of the hematoma, as well as the data obtained from the computer linked to the impactor device. Only animals with a BBB (Basso, Beattie and Bresnahan) score of 0 (zero), 24 hours post injury were included in the study.

Blood sampling

Blood samples (approximately 0.50 mL/sample) were obtained through cardiac puncture, 24 hours (acute phase), or 15 days (subacute phase) post injury. Samples were collected in vials containing ethylenediaminetetraacetic acid for hematological analysis or heparin for biochemical studies. Hematological parameters: hematocrit, hemoglobin, leucocytes, erythrocytes and platelets were obtained using the Sysmex XE2100 equipment, a complete micro-centrifugal method for blood cell analysis [18-20]. Biochemical parameters: glucose, urea, creatinine, albumin, globulin and Aspartate Aminotransferase (AST) were obtained using Hitachi ISE900 Modular; an accurate, conservative and automated method to determine laboratory tests [21].

Statystical analysis

Data was analyzed using the GraphPad Prism 3.0 software. One-way ANOVA followed by Tukey's test was used to analyze data with Gaussian distribution. Data with no Gaussian distribution was studied using a Kruskal-Wallis followed by a Mann-Whitney U test. *P* value<0.05 was considered statistically significant.

Results

Effect of SC injury on hematological parameters

During the acute phase, hematocrit (Ht), hemoglobin (Hb), erythrocyte (Ert), and leukocyte (Lkt) levels were significantly lower in animals subjected to SC injury as compared to naïve rats (Table 2). This effect was more evident in severe injuries. The level of injury (high or low) did not evoke any effect on these parameters, there was no significant difference between groups. There was an increase in the number of platelets after injury; however, it was not statistically significant (p>0.05; One-way ANOVA, followed by Tukey's test). There was not significant relationship between the severity or level of injury upon the final number of platelets (Table 2).

At fifteen days post injury (subacute phase), (Table 3) Ht, Hb, Ert and Lkt reached their normal levels, only in animals with severe SC contusion the levels of Ht, Hb and Ert remained significantly reduced (p<0.05 One-way ANOVA followed by Tukey's test) as compared to the naïve group. The level of injury was not significantly implicated in the changes observed in these parameters. The amount of Lkt presented by the injured groups was very similar to naïve rat levels, although the

Rats included in both experiments (n=80)	Experiment 1, acute phase (n=40)	Control Group 1 (n=8)
		HSI 1 (n=8)
		HMI 1 (n=8)
		LSI 1 (n=8)
		LMI 1 (n=8)
	Experiment 2, subacute phase (n=40)	Control Group 2 (n=8)
		HSI 2 (n=8)
		HMI 2 (n=8)
		LSI 2 (n=8)
		LMI 2 (n=8)

Table 1: Distribution of rats per group.

	Naïve (mean ± SD)	HSI (mean ± SD)	HMI (mean ± SD)	LSI (mean ± SD)	LMI (mean ± SD)
Hematocrit (%)	41.86 ± 1.93	31.8 ± 1.13 *p= 0.01 ◊p= 0.03	35.02 ± 0.5 *p= 0.03	32.2 ± 1.7 *p=0.01 ◊p= 0.03	37.9 ± 2.1 *p= 0.04
Hemoglobin (g/dL)	14.7 ± 0.65	10.5 ± 0.6 *p= 0.03 ◊p= 0.04	12.3 ± 1.6 *p= 0.04	11.8 ± 0.5 *p= 0.03 ◊p= 0.04	13.4 ± 1.0 *p= 0.04
Leucocytes (10^3/L)	9.4 ± 0.7	5.1 ± 0.2 *p= 0.03 ◊p= 0.04	6.2 ± 0.2 *p=0.03	5.6 ± 0.1 *p= 0.03 ◊p= 0.04	6.6 ± 0.4 *p= 0.04
Erythrocytes (10^6/L)	6.6± 0.3	5.0 ± 0.3 *p= 0.04 ◊p= 0.04	5.4 ± 0.6 *p= 0.03	5.1 ± 0.2 *p= 0.02 ◊p= 0.04	6.2 ± 0.4 *p= 0.04
Platelets (10^3/L)	460 ± 63	508 ± 132	533 ± 104	615 ± 99	726 ± 196

* p <0.05 vs naïve group; One way ANOVA followed by Tukey´s test
◊ p <0.05 vs corresponding moderately injured group; Student´s t test

Table 2: Hematological parameters at 24 hours post injury.

	Naïve (mean ± SD)	HSI (mean ± SD)	HMI (mean ± SD)	LSI (mean ± SD)	LMI (mean ± SD)
Hematocrit (%)	46.2 ± 2.1	34.9 ± 7.04 *p= 0.03	42.2 ± 3.5	41.37 ± 2.1 *p= 0.04	43.7 ± 8.5
Hemoglobin (g/dL)	15.5 ± 0.4	11.6 ± 2.5 *p= 0.04	13.8 ± 2.1	13.1± 1.2 *p= 0.04	13.90 ± 1.7
Leucocytes (10^3/L)	10.1 ± 5.3	13.6 ± 3.36	7.9 ± 2.9	11.3 ± 7.8	7.5 ± 3.4
Erythrocytes (10^6/L)	7.2 ± 0.3	6.1 ± 0.4 *p=0.03	6.7 ± 1.4	6.3 ± 0.5 *p= 0.04	6.3 ± 1.7
Platelets (10^3/L)	451 ± 117.9	1013 ± 331 *p= 0.001	828.9 ± 254 *p= 0.02	1162 ± 307 *p= 0.001	950 ± 134 *p= 0.01

*p <0.05 vs naïve group. One-way ANOVA followed by Tukey´s test

Table 3: Hematological parameters at 15 days post injury.

	Naïve (mean ± SD)	HSI (mean ± SD)	HMI (mean ± SD)	LSI (mean ± SD)	LMI (mean ± SD)
Glucose (mg/dL)	151.2 ± 26	166 ± 16	173 ± 17	181± 16	174 ± 19
Urea (mg/100 mL)	28.6 ± 3.1	38.2 ± 4.5 *p= 0.03	48 ± 8.8 *p= 0.02	38.6 ± 6.7 *p= 0.03	44.6 ± 7.2 *p= 0.02
Creatinine mg/100 mL)	0.4 ± 0.04	0.5 ± 0.04 *p= 0.04	0.6 ± 0.2 *p= 0.03	0.6 ± 0.03 *p= 0.03	0.5 ± 0.18 *p= 0.04
Albumin (mg/100 mL)	4.5 ± 0.1	4.3 ± 0.04 *p= 0.04	4.2 ± 0.2 *p= 0.03	4.2 ± 0.05 *p= 0.03	4.1 ± 0.2 *p= 0.03
Globulins (mg/100 mL)	4.5 ± 0.13	4.1 ± 0.1 *p= 0.03	4.2 ± 0.1 *p= 0.03	4.1 ± 0.2 *p= 0.03	4.3 ± 0.1 *p= 0.04
AST IU/mL	132.6 ± 21.5	295.6 ± 46.5 *p= 0.01	341.8 ± 42.1 *p= 0.001	268 ± 53.7 *p= 0.01	260 ± 68.2 *p= 0.01

*p <0.05 vs naïve group. One-way ANOVA followed by Tukey´s test

Table 4: Biochemical parameters at 24 hours post injury.

quantity of Lkt was slightly lower in rats with SC moderate injuries, the difference was not statistically significant (p>0.05 One-way ANOVA followed by Tukey´s test). The number of platelets was significantly increased in all four groups with SC injury when compared to control group (p<0.05, One-way ANOVA followed by Tukey's test). The increase of levels in these cells was similar in all studied groups (Table 3), and was significantly higher than those presented by the similar groups throughout the acute phase (p<0.03, One-way ANOVA). Finally, comparing Ht, Hb, Ert, and Lkt values presented in subacute phase to those present in the acute one, it was confirmed that these parameters returned to normal in most of the groups. HMI and LSI showed a significant increase in values as compared to the similar groups during the acute phase (HMI: Ht p=0. 01, Hb p=0.05, Lkt p=0.05, Ert p=0.04; LSI: Ht p=0.001, Hb p=0.3, Lkt p=0.05, Ert p=0.02; Kruskal Wallis followed by Mann Whitney U test). Only in the case of Lkt, animals with HSI presented a significant recovery in the subacute phase when compared to those of the acute stage (p=0.01 Mann Whitney U test).

Effect of SC injury on biochemical parameters

Throughout the acute phase, almost all biochemical parameters were altered (Table 4). The slight elevation of glucose in SC injured rats during this period, was not statistically significant (p>0.05, One-way ANOVA followed by Tukey´s test). Albumin and globulins were significantly diminished in SC injured rats in contrast to naive animals (p<0.05). Urea and creatinine, concentrations were significantly increased at this time point. AST also presented a significant increase in the blood of SC injured animals as compared to naive rats (p<0.05). All of these biochemical changes were similar for all studied groups with no additional effects regarding severity and level of lesion.

During the subacute phase (Table 5), glucose remained slightly elevated in SC injured rats with no significant difference when compared to naïve animals or to the similar groups in the acute phase. Urea and creatinine levels returned to normal values; however, albumin and globulins remained significantly lower than the naive group (p<0.05, Kruskal Wallis followed by Mann- Whitney U test). AST continued to be significantly increased during this period. The severity or level of injury did not interfere with results obtained throughout this phase. When we evaluated urea, creatinine, albumin and globulins in both phases (acute and subacute), a significant reduction in values from all the groups of subacute phase was found (HSI: urea p=0.05, creatinine p=0.05, albumin p=0.03, globulins p=0.01; HMI: urea p=0.04, creatinine p=0.02, albumin p=0.04, globulins p=0.01; LSI: urea p=0.05, creatinine p=0.03, albumin 0.02, globulins p=0.001; LMI: urea p=0.05, creatinine p=0.05, albumin p=0.03, globulins p=0.001; Kruskal Wallis followed by Mann Whitney U test). In the case of AST the values presented in the subacute phase were always significantly higher than those observed during the acute stage (HSI: p=0.02, HMI: p=0.05, LSI: p=0.01, LMI: p=0.01; Mann Whitney U test).

Discussion

Spinal cord injury-is a devastating condition with lifetime lasting sequels. Although the initial injury may only last a few seconds, a complex cascade of events arises, causing further damage [22]. Clinical consequences depend directly on the level of injury; in the matter that high injuries may lead to tetraplegia, while low injuries result in paraplegia [10]. It is important to consider the severity of the injury, since it may be associated to tissue degeneration and functional recovery.

In the present study, we demonstrate that SC injury caused changes in hematological and biochemical parameters. Regarding hematological disturbance, we observed an overall decrease on hematocrit, hemoglobin and erythrocyte count in all injured animals; being HSI and LSI the groups with more cell level decrease.

	Naïve (mean ± SD)	HSI (mean ± SD)	HMI (mean ± SD)	LSI (mean ± SD)	LMI (mean ± SD)
Glucose (mg/dL)	160.7 ± 44.4	180 ± 34.3	176 ± 34.08	1801 39.2	170 ± 48.16
Urea (mg/100 mL)	28.6 ± 2.8	34 ± 8.8	32.1 ± 7.4	33.8 ± 8.3	35.6 ± 9.4
Creatinine mg/100 mL)	0.5 ± 0.08	0.43 ± 0.05	0.41 ± 0.01	0.51 ± 0.04	0.45 ± 0.2
Albumin (mg/100 mL)	4.8 ± 0.1	3.2 ± 0.4 *p= 0.02	3.5 ± 0.3 *p= 0.03	3.4 ± 0.2 *p= 0.03	3.4 ± 0.4 *p= 0.03
Globulins (mg/100 mL)	3.1 ± 0.3	2.3 ± 0.2 *p= 0.03	2.6 ± 0.5 *p= 0.04	2.6 ± 0.3 *p= 0.04	2.2 ± 0.4 *p= 0.02
AST IU/mL	136.7 ± 57	408.2 ± 96 *p= 0.001	407.7 ± 101 *p= 0.001	417.5 ± 139 *p= 0.001	452 ± 112 *p= 0.001

*p <0.05 vs naïve group. Kruskal Wallis followed by Mann-Whitney U test

Table 5: Biochemical parameters at 15 days post injury.

The presence of anemia has been reported during the acute phase of SC injury even during the absence of detectable blood loss [23]. After SC injury there is an inflammatory response accompanied by hemorrhage mainly due to the disruption of the microvasculature of the spinal cord, this can persist for up to 48 hours after injury [24]. Greater blood loss can be, manifested by lower levels of hematocrit, hemoglobin and erythrocyte counts. Also, a severe injury is commonly associated with a critical inflammatory response and thus with high levels of TNF-alpha, IL-1beta and IL-6 [25]. Together, these findings suggest that the inflammatory response is a possible cause of the variation in the hematological parameters, especially those found in severe SC injury.

In the course of the subacute phase, hematological parameters presented a significant recovery, especially in moderately injured groups. In animals subjected to a severe injury, hematological values remained significantly lower compared to naïve animals. In this case, inflammation is one of the main factors linked to the decrease in normal blood cell count.-Studies have reported that TNF restricts hematopoietic stem cell activity, possibly leading to a decrease in hematocrit, hemoglobin and erythrocyte count [26]. It has also been demonstrated that elevated levels of cathecolamines (particularly norepinephrine), may lead to a reduction in erythroid progenitor colony growth. This persistent hyper-adrenergic state can develop after severe traumatic SC injury, and it can last for approximately 10 days resulting in bone marrow dysfunction [27].

Twenty four hours after injury white blood cell count also presented a reduction in all injured groups, being more evident in rats with severe SCI. This could be a consequence of neutrophil and monocyte migration from blood to the injured area, especially during the early acute phase, as well as to the hemorrhage due to trauma [28]. Platelet count at 24 hours post injury presented an overall increase in all injured groups, however it was not statistically significant. Nevertheless, during the subacute phase there was a significant increase of blood platelets in all injured groups, predominantly in severe SC injury. Thrombocytosis can develop as a consequence of a reactive process, and in many cases it may appear as a response to elevated endogenous levels of IL-6, other cytokines, or catecholamines, associated with inflammatory conditions, acute blood loss and other stress situations [29].

Regarding biochemical parameters, glucose presented a slight but not significant elevation in SC injured rats; this finding concurs, in some way, with previous studies [30]. Glucose increase could be the result of the reduction in metabolic rate after SC injury [31]. Additionally, a significant increase in urea and creatinine was observed. It is worth mentioning that after SC injury there is a decrease in microvascular blood flow that affects several organs, such as the kidney. This situation would explain the increase of urea and creatinine 24 hours post-injury. Previous studies have already reported renal failure in the acute phase of SC injury [32]. Noteworthy, fifteen days after injury the parameters returned to their normal values.

Liver impairment after SC injury has already been described [33,34]. Throughout this study, we found liver damage manifested by an increase in aspartate aminotransferase (AST), which presented an increase in all injured groups 24 hours post-injury. A possible mechanism of liver damage after SC injury is the reduction in microvascular blood flow, that leads to hepatic hypoperfusion caused by the spinal shock that takes place shortly after SC injury [16]. Hepatic hypoperfusion, manifests with increased transaminases in serum, and decreased liver functions, such as drug metabolism [35,36]. Fifteen days post injury, AST levels persisted higher than normal. Approximately 60-76% of individuals with SC injury present hepatic dysfunction, experiencing an increase in serum transaminases for at least 2 months after injury [37]. The nature of hepatic dysfunction after SC injury is still unknown; however, it has been suggested that inflammatory cells may participate in liver damage [38].

Albumin and globulin levels were lower in injured rats compared to control groups. Hypoalbuminemia presents 24 hours after injury as a postoperative complication and it has been associated with acute inflammatory reactions that promote capillary leak; this can be exacerbated by the release of inflammatory mediators such as TNF [39]. Likewise, the persistent reduction in albumin at day 15 post injury can be related to a decrease of albumin synthesis, which could be secondary to liver damage [40]. The levels of globulins depend also on hepatic function; thereby, liver damage could also explain its reduced concentrations. There is also a decrease in the concentration of these proteins, affected by inflammatory responses [41].

Collectively, our results show that hematological and biochemical parameters are indeed affected by SC injury. Nevertheless, only in the case of Ht, Hb, Ert and Lkt, the severity of the injury complicated these hematological parameters. The level of injury did not provoke any additional effects. All studied parameters were altered during the acute phase but most of them presented a trend to recovery throughout the subacute phase of SC injury. The results presented in this study contribute to the management of SCI demonstrating that severe injuries present the most altered parameters; therefore, thorough attention must be paid to these patients. Furthermore, these results contribute to a better comprehension of the acute phase, which is also the critical stage in the management of the patient. Likewise, altered parameters at the acute phase, may recover in most cases. These findings provide a better understanding on the pathophysiology of SC injury in experimental models and should be considered for future research studies.

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