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MARKERS OF INFLAMMATION IN CRUSHING TRAUMA OF THE LOWER LIMBS

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Abstract. Crushing traumas are produced by high-energy traumatic agents and are thus characterized by severe and complex injuries, affecting all the structures of the involved limb. Vascular, bone or nerve injuries may occur, but the main characteristic of crushing is "rhabdomyolysis"- destruction of the skeletal muscles. If not treated before irreversible changes appear, the necrotic muscle will endanger not only the vitality of the limb, but also the life of the patient, due to systemic toxaemia. A complex interdisciplinary approach is thus necessary in order to insure the survival and recovery of the patient. Research has been done regarding objective monitoring criteria able to guide the treatment. Certain biochemical markers have been described as useful and the authors evaluate their clinical significance in patients with crushing trauma in a Level I Trauma Centre. The results of this retrospective study support the data presented in the literature regarding the correlation between the outcome of these patients and their biochemical profile.

Key words: biochemical markers, crushing trauma

Introduction

Modern traumatology faces the challenge of young patients with severe injuries generated by high-energy traumatic agents affecting not only parts of the skeleton but, due to physiopathological mechanisms, even the life of these patients. One of the most representative categories of such lesions is that of crushing trauma during which a limb (or limb segment) is injured by the traumatic agent while fixed on a hard surface.

After any trauma, the energy absorbed by the injured area represents the difference between the energy of the traumatic agent and the resistance of the injured structure. Because the hard surface plays the role of the counteraction, this is added to the energy amount previously discussed thus considerably increasing the effective energy responsible for the injuries [1, 2].

Due to this high energy, skeletal muscles are injured both directly (through immediate destruction of all the parts of the muscular fibres) as well as by indirect changes produced by:

- Disturbances in the microcirculation, and
- abnormal metabolic interactions between the muscle cells and the tissular fluids

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The common feature of all these situations is the **injury of skeletal muscle, which is called RHABDOMYOLYSIS [3];** through direct or indirect mechanisms, the local metabolism becomes anaerobic, including the glycolysis, which generates lactic acid, producing lactic acidosis.

Muscular ischemia also affects the function of the membrane pumps, which normally introduce potassium into the cells and extract sodium and water from the cells. Any of the situations impairing these pumps can affect these ions: potassium exits the cells, and sodium and calcium enter the cells, so the electric potential of the membrane is altered. Sodium also carries water, producing cellular oedema, which impairs the cellular respiratory processes, decreasing ATP synthesis and initiating lipid peroxidation, which results in the so called "free radicals".

Due to muscular destruction, all the compounds of the myocytes are dragged into the systemic blood flow, the most specific substance being myoglobin, which can be monitored both in blood and urine, as an indicator of the severity of the injury.

Besides the ion changes and myoglobin, the inflammatory syndrome is also responsible for the systemic effects of crushing trauma, described as "crushing syndrome". We must differentiate between the two entities: the "crushing trauma", representing the injury produced by a crushing mechanism, and the "crushing syndrome", which includes the systemic effects of the rhabdomyolysis produced by a crushing injury. The resulting substances harm the organs and systems, starting with the kidneys and the liver, continuing with the vital ones, until Multiple System and Organ Failure (MSOF) occurs. MSOF has the clinical appearance of shock and is lethal if the treatment and the body's reserves cannot compensate for it.[4]

The first affected are: the liver, which functions as part of the "cleaning" mechanism used by the body to get rid of useless or toxic products, and the kidneys, which are suffocated by high amounts of toxic products and by the other biochemical disturbances (acidosis, dyselectrolytemia, etc) and thus become dysfunctional [5]. Due to these aspects, the pathophysiology of crushing trauma has been thoroughly researched in order to guide the monitoring and therapeutic actions according to the characteristics of each patient.

Since inflammation is one of the factors involved in crushing, it is of great interest to the physicians treating these patients, not to mention that the inflammatory mechanism is one of the main triggers of coagulopathy in trauma [6, 7].

The inflammatory mechanism generates several substances; for some of them testing is widely available: ESR, leucocytes, fibrinogen, CRP. A more specific indicator of inflammation is Interleukine-6 (IL-6). It is not currently evaluated, mostly due to technical and financial circumstances, although it is considered to have a central role in acute inflammation, as it is responsible for the production of acute phase proteins [8, 9].

Also involved in chronic inflammation by stimulating T and B cells, IL-6 is mainly associated with the acute phase response, as its most important function is that of a pro-inflammatory cytokine, inducing the secretion of acute phase proteins: C-reactive protein (CRP), β2-fibrinogen, amyloid protein, haptoglobin, hemopexin [10,11]. The role of IL-6 was revealed to be even more complex when it was recently discovered that there is also an anti-inflammatory component to the action of IL-6 in both local and systemic acute inflammatory responses elicited by exposure to endotoxin, thus demonstrating that IL-6 is critical in controlling the extent of local and systemic acute inflammatory responses, particularly the level of proinflammatory cytokines in the local and systemic compartments [12, 13].

The purpose of this paper is to describe patients with crushing trauma from the point of view of the systemic inflammatory response in order to verify the hypothesis that we could use the inflammatory tests in predicting the outcome of the patients.

Material and Methods

The authors retrospectively evaluated 38 patients that treated in a Level I Trauma Centre (The Clinical Emergency Hospital of Bucharest) during 01.06.2012-01.01.2015 for trauma produced by a crushing mechanism. The purpose of this analysis was to evaluate the importance of the inflammatory tests for the treatment and monitoring decisions in patients with crushing trauma.

The inclusion criteria were:

- the mechanism "crushing trauma" was established as part of the diagnosis either at admission or at discharge,
- skeletally mature patients (above 18 years of age)
- the affected segment was the shank or/and the thigh; injuries of the foot have a considerably smaller systemic impact and are therefore irrelevant to the subject of this paper
- informed consent was obtained according to the rules and regulations of the hospital
- the medical records of the patient were complete and appropriate for evaluation

a MESS score of 6 or less, therefore only cases with salvageable limb segments (otherwise, the indication would have been amputation)

The patients were evaluated using the following criteria:

I. Demography and epidemiology: age, gender, aetiology and injury site

II. Time elapsed between trauma and treatment initiation

III. The evolution of the inflammatory markers:

a. ESR (Erythrocyte Sedimentation Rate),

b. leucocytes,

c. fibrinogen,

d. C Reactive Protein (CRP),

e. IL-6 (Interleukin-6).

Results

I. Demography and epidemiology

The analysis regarding age and gender (Fig.1) showed that:

- Males are more frequently affected by crushing than females, presumably because they can be more easily involved in high-energy trauma due to their life style.

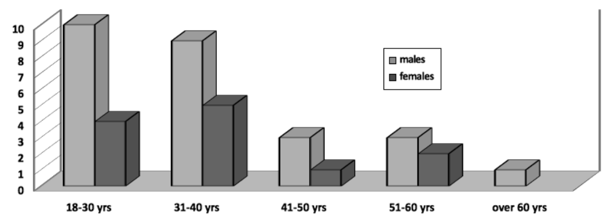

Fig.1. Demographic analysis of the study group

- Most of the patients were between 20-40 years old, therefore young patients, probably due to the same reason as mentioned before. This is particularly important since the severity of these trauma cases results in prolonged immobilisation and therefore missing work, generating substantial costs for the society, let alone the psychological impact upon the patients and their families.

As for the aetiology of the crushing trauma in the study group, most of the injuries (79%) resulted from traffic accidents (30/38 cases) while the rest were due to work accidents (2/38 cases- 5.2%) and accidental crushing (6/38 cases).

Regarding the injured site, most of the patients (34/38 cases, 89.4%) had unilateral injuries, while 4 patients had associated injuries – 1 with bilateral shank crushing and 3 with shank + ipsilateral thigh involvement.

II. Regarding the time elapsed between trauma and treatment initiation, the following must be underlined:

As presented in Figure 2, most of the patients were admitted to our hospital during the first 12 hours after trauma (33/38 cases - 86.8%). The fact that there were still 5 other patients who arrived later than 12 hours after crushing suggests that certain improvements regarding the emergency protocols are to be taken into consideration. This is because, due to the facts previously mentioned, the longer the time until the systemic dysfunctions are corrected, the bigger the probability for systemic complications to develop.

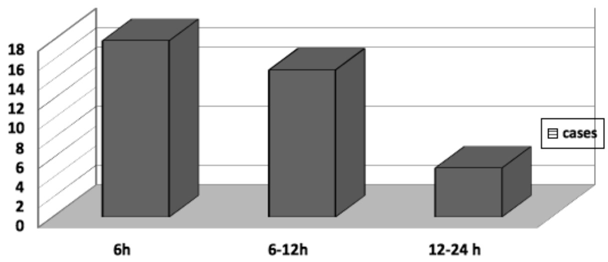

Fig.2. Demographic analysis of the study group

Regardless of the moment of arrival in our hospital, the patients followed the same protocol, with two main components:

1. Multidisciplinary evaluation, and
2. Local and general treatment

As presented in the medical records, initial evaluation included:

- Local evaluation of the injury site by a team consisting of senior surgeons from: orthopaedics-traumatology, vascular surgery, plastic surgery
- General clinical evaluation mandatorily including that of an anaesthesia - intensive care senior (specialist or consultant)
- Imaging evaluation of the injured limb: X-ray of the injured segment and adjacent joints, as well as X-rays of other injured segments; all the patients were required to get a pulmonary X-ray.
- ECG
- When other systems or organs were also injured, supplementary tests were indicated, such as echography or CT scan
- urinalysis and urine culture

Blood samples were tested for:

- Complete blood count (CBC) – erythrocytes, leucocytes, platelets
- Coagulation tests: PT, APTT, INR
- Inflammatory standard tests: ESR, Fibrinogen, C Reactive Protein
- Standard metabolic tests: glucose, urea, creatinine, AST, ALT, GGT, proteins, albumin, ions (sodium, potassium), total and direct bilirubin
- Enzymes specific for crushing: LDH, CK and CKMB for differential diagnosis of increased CK levels

Following initial evaluation, urgent surgery was indicated IN ALL the cases, as crushing is characterized by severe injuries that require immediate treatment. Besides the orthopaedic team, some cases also required the involvement of plastic surgeons (15 cases) or vascular surgeons (4 cases), due to associated injuries. Since the treatment of crushing injuries is not the purpose of this paper, this is not going to be presented in detail, but briefly summarized instead:

- Large exploratory fasciotomy with complete access to all the muscular spaces of the involved segment
- Vascular and nerve exploration
- Haemostasis
- Evaluation of the muscles, with thorough excision of all devitalized tissues
- Bone stabilization by external fixation after excision of devitalized fragments
- Treatment of associated injuries
- Bone coverage (at least temporary)

The patients were monitored both for local and systemic outcome. Local monitoring of the crushing site included recording the aspect of the musculo-skeletal injury both initially and during secondary debridement. Systemic monitoring included the previously mentioned tests as well as serum and urinary myoglobin, diuresis and creatinine clearance.

It must be underlined that secondary debridement was repeated many times due to the fact that disturbances of the microcirculation induce secondary muscular necrosis requiring repeated necrectomies.

The parameters that were monitored for this research were:

a. ESR (Erythrocyte Sedimentation Rate)
b. leucocytes
c. fibrinogen
d. C Reactive Protein (CRP)
e. IL-6 (Interleukin -6)

The evolution of these parameters in the study group is shown in Figures 3-7. Note that the actual values obtained are compared to the normal level, so what is shown on the graphs is not the absolute value, but the ratio between the value in study group and the mean normal value. Therefore, level 1 on the vertical axis of the graph means that the value in the study group matched the mean normal value, 2 on the vertical axis means that levels obtained were twice as high as the normal value, 3 means three times as high, and so on.

The monitoring sequence included the following moments illustrated on the horizontal axis of the graphs: the moment of admission - (1), the end of surgery - (2), then daily until the 7th day after surgery (D2-D7), then days 10 (d10), 14 (d14), 18 (d18), 21 (d21), 28 (d28).

The values of the ESR (Fig. 3) started to decrease on D3, but with a smooth curve, with persistently high values until the third week after trauma. This is in contrast to the number of leucocytes (Fig. 4), which had a more rapid positive response, with mean normal values 2 weeks after the initial trauma.

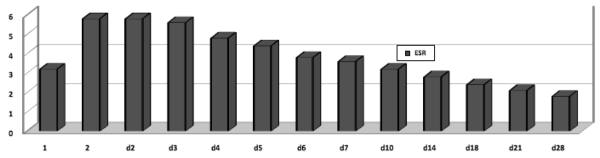

Fig. 3. ESR variation in patients with crushing trauma

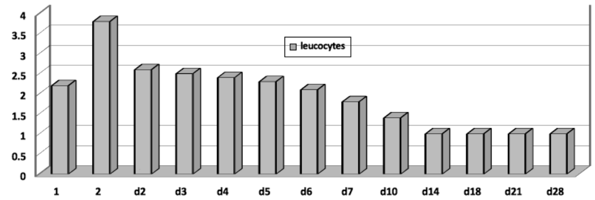

Fig. 4. Leucocyte levels within the study group

Compared to these two parameters, the levels of CRP increased more brutally and decreased abruptly starting from D5; this approximates the so-called “the acute inflammatory” stage after trauma and it seems that CRP defined this period better than other inflammatory tests in this study group.

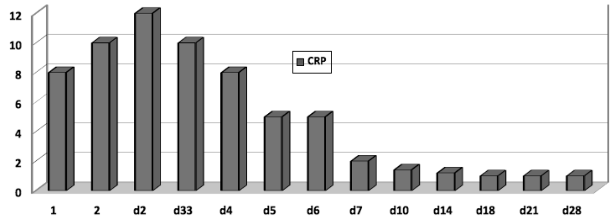

Fig. 5. C Reactive Protein in the study group

Fibrinogen decreased smoothly starting from D4 with a trend somewhat parallel to that of CRP, getting back to normal 2 weeks after trauma.

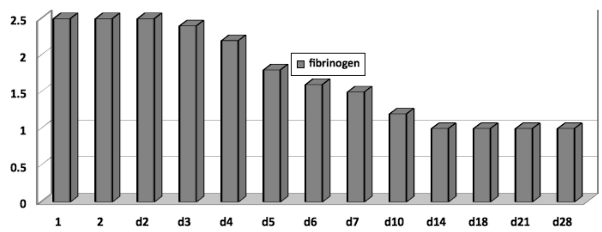

Fig. 6. Fibrinogen in the study group

In addition to standard inflammation tests, IL-6 was also measured in order to evaluate its capacity to reflect the inflammatory response and to compare this capacity to that of the other tests. In this study group, IL-6 levels were consistent with:

- The severity of the initial trauma (reflected by CRP as well)
- The persistence of the inflammatory syndrome until D5, when the level of IL-6 clearly decreases
- IL-6 reaches normal values (ratio 1) only after nearly 3 weeks, as additional proof of the severity of initial accident.

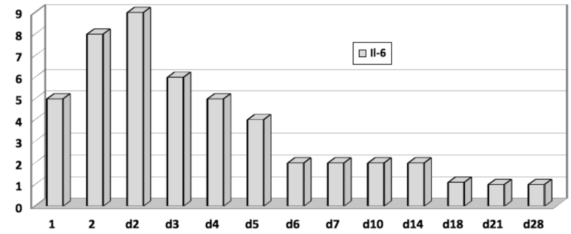

Fig. 7. Levels of IL-6 in the study group

An interesting matter is the comparative analysis of these parameters, which is shown in Fig. 8, showing different curves of variation, reflecting the way that each parameter is influenced by the trauma and by the treatment.

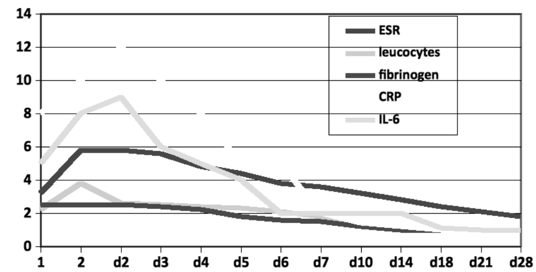

Fig.8. The comparative evolution of the parameters over time

Discussion

In concordance with the data from the literature, the inflammatory response in patients from this study group (monitored using the above described parameters) demonstrated the systemic impact of the severe initial trauma.

Regardless of the moment when the patient arrived at the hospital, all the parameters had abnormal values; the fact that they also had higher values after surgery than before needs to be discussed so as not to create any false impressions. Due to its severity, crushing trauma represents a surgical emergency and all the patients were operated on immediately after arriving at the hospital, while the disturbances induced by the trauma were still fully developing. Therefore the increase after surgery (for all the parameters) was caused to a much smaller extent by the surgical aggression and to a much larger extent by the initial trauma. Although it is only a hypothetical example, it could be said that had the patients not been operated on, the inflammatory markers would have definitely been higher than the values we found post-surgery.

The most abrupt response to trauma can be found in the trends of CRP and IL-6, which were also the slowest parameters to return to normal levels, thus reflecting in a more sensitive way the post-traumatic systemic impact. The first parameters to approach normal values are leucocytes and fibrinogen, which also have the smoothest curve, which might suggest that their reliability is debatable when using them as markers for the severity of trauma.

CRP and IL-6 are also the parameters which are most influenced by surgery, since they start to decrease immediately after the primary surgical debridement. In the study group, they have also been found to illustrate in the most direct manner the "acute inflammatory response", since their major disturbances last until D5 after trauma, corresponding to this period.

Although this study does not establish a correlation between the inflammatory tests and the onset of complications, it might suggest that, together with the specific tests for rhabdomyolysis, the analysed parameters (especially CRP and IL-6) should be monitored in patients with crushing trauma.

Conclusions

The inflammatory syndrome following trauma is well described in literature, as it is the main response of the human body to any attack. The intensity of the syndrome depends on the traumatic energy; it also reflects the impact of the trauma upon different organs and systems.

Despite the fact that crushing trauma is a localized injury, its general consequences are by far more severe, as they refer to systemic toxaemia. Myoglobin, products of anaerobic metabolism, as well as severe electrolyte disturbances (especially potassium and sodium) are responsible for renal failure and, in more severe cases, for MSOF and death.

One of the mechanisms that contribute significantly to these pathological events is the inflammatory syndrome, which, as shown in this paper, is influenced by the severity of the trauma and reflects the systemic impact of crushing. The clinical relevance of this conclusion is the necessity of including the inflammatory tests (especially CRP and IL-6) among the parameters that must be monitored. Their pattern reflects the state of the injured tissues and the outcome of the patients, thus providing the opportunity to anticipate and prevent the onset of vital complications.

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