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# CCL2/MCP-1 level in serum of acute pain syndrome patients with wounds sustained in combat

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**ABSTRACT**

**Background:** The aim of our study was to examine the relationship between the inflammatory response and the pain response by determining the level of C-C motif chemokine ligand 2 (CCL2)/mono-cytechemoattractant protein-1 (MCP-1) in the serum of patients with combat injuries in the perioperative period with different methods of analgesia.

**Materials and methods:** The study involved 24 servicemen with gunshot wounds to extremities of various localizations due to a mine or explosive mechanism. The patients were divided into 2 groups: group 1 (n = 12)–received standard general anesthesia (with intravenous infusion of 0.005% fentanyl, morphine 1%), group 2 (n = 12)–combination of general anesthesia and infiltration anesthesia of the wound with 0.5% bupivacaine.

**Results:** The plasma CCL2/MCP-1 level in the patients prior surgery averaged 19.15 ± 6.80 pg/ml pg/ml; ($p < 0.05$). After 12 hours in patients from group 1 there was an increase in the level of CCL2/MCP-1 in the blood plasma (3.1 times), $p < 0.05$, and 9.5 times 24 hours after surgery. In group 2 there wasn't an increase in inflammatory markers after 12 hours, but after 24 hours after surgery, plasma CCL2/MCP-1 level significantly increased 3.3 times ($p < 0.05$). In the preoperative period the pain intensity ranked by the visual analog scale 7.8 scores, in the postoperative period, the degree of pain intensity was quantitatively the lowest in group 2.

**Conclusions:** MCP-1 biomarker levels may be an indicator of the intensity of the inflammatory process and pain in the perioperative period. The CCL2/MCP-1 level is significantly influenced by the type of anesthesia.

**Keywords:** mono-cytechemoattractant protein-1, perioperative pain, military, local anesthetic

## INTRODUCTION

Treatment of combat wounded with severe burns and concomitant traumatic injuries requires coordinated interaction of surgical, resuscitation and evacuation forces [1]. These patients are a huge challenge for the entire medical system due to the severity of the injuries amid active hostilities that make it impossible to evacuate quickly before emergency care is provided. In the structure of total sanitary losses in the military conflicts, the victims of the surgical profile are 75%, and among them the number of victims with limb injuries ranges from 54 to 75% [2].

Pain is one of the most common symptoms due to which fighters seek medical attention. The level of pain they feel usually reaches 7-8 points on the visual analog scale (VAS). Because primary care includes stabilization of the cardiovascular and respiratory systems, assessment of multiple and severe injuries, pain assessment may not always be incorrect, so treatment of pain may be delayed, leading to chronic pain [3]. This creates the preconditions for a detailed study of the mechanisms of pain physiology and its treatment with the implementation of the results in clinical practice [4].

According to international studies, biomarkers of acute and chronic pain indicate a stable relationship between pain intensity and the level of proinflammatory mediators in the serum of both animals and humans [4, 5]. Most known mediators of inflammation cause pain by binding to nociceptors located in the peripheral nervous system [4-7]. According to the data, the C-C motif chemokine ligand 2 (CCL2), also known as mono-cytechemoattractant protein-1 (MCP-1) can attract monocytes to develop inflammation, infection, pain and ischemia in the affected area [8, 9]. Therefore, the participation of this chemokine in the development of acute and chronic pain due to inflammatory cells is likely and requires further study.

The aim of the study is to examine the relationship between the inflammatory response and the pain response by determining the level of CCL2/MCP-1 in the serum of patients with combat injuries in the perioperative period with different methods of analgesia.

**Table 1.** Demographic indicators of both research groups

| The level of MCP-1 in the blood plasma of patients | Time to determine the level of MCP-1 after surgery | |
|---|---|---|
| | In 12 hours | In 24 hours |
| Before surgery (n = 24) | 19.15 ± 6.80 pg/ml* | |
| Group 1 (n = 12) | 53.67 + 9.12 pg/ml | 165.57 + 15.32 pg/ml |
| p | < 0.05 | < 0.05 |
| Group 2 (n = 12) | 29.67 + 8.18 pg/ml | 58.18 + 7.68 pg/ml |
| p | < 0.05 | < 0.05 |

Note. *A significant difference in the level of MCP-1 before surgical operation

## MATERIALS AND METHODS

Ethical approval for this study (protocol number 2 on 2 March 2022) was provided by the institutional Ethical Committee [10].

The study was a prospective, single-center, randomized controlled trial conducted in March and April in 2022 according to the Declaration of Helsinki. Each subject of the study was provided with all the details about medical procedures and with the opportunity to discuss any questions with healthcare professionals and then signed a detailed form of informed consent to conduct the research.

The study involved 24 servicemen with gunshot, mine and explosive wounds to extremities of various localizations due to a mine or explosive mechanism injuries received for treatment in March-April 2022 at the Military Medical Clinical Center of the Central Region and the Clinical Center for Thermal Injury and Plastic Surgery. At this clinical center, patients received highly specialized medical surgical care. All patients were SARS-CoV-2 negative, anti-epidemic measures were followed. Patients with suspected infection until receiving the PCR test were managed according to the protocol of the management of the disease of COVID-19 [11-13].

Previously, the wounded patients received care at the secondary and tertiary levels of medical care underwent primary surgical treatment of wounds, fasciotomy, extra focal osteosynthesis, and intensive care (antibacterial, analgesic, and symptomatic). All affected servicemen were men of working age (from 18 to 60 years old), average age 33.0 ± 5.3 years. Injuries of the upper extremities were observed in 9 cases (37.5%), of which multiple–4 (44.4%); injuries of the lower extremities were observed in 12 cases (50%), of which multiple–5 (41.66%); injuries of the upper and lower extremities were observed in 3 patients (12.5%). Injuries were accompanied by bone fractures in 7 patients (29.1%), damage to the main vessels in 4 patients (16.6%), nerves in 3 patients (12.5%).

We did not include patients with comorbidities (diabetes, cardiovascular disease, hereditary diseases), or any acute or chronic inflammatory processes, including inflammatory processes of the skin and subcutaneous fat.

Patients were divided into 2 groups depending on the chosen methods of perioperative analgesia: group 1–12 patients who underwent general anesthesia by method of total intravenous anesthesia (TIVA + intravenous infusion of opioid analgesic fentanyl 0.005%, morphine 1%), group 2–12 patients who underwent general anesthesia and infiltration anesthesia of the wound with a local anesthetic bupivacaine 0.5%.

Evaluation of the effectiveness of analgesia was performed on the basis of monitoring of hemodynamic parameters, dynamic evaluation of stress response markers. One hour before surgery and in the postoperative period (12 and 24 hours after surgery), patients filled out a pain diary, where they were asked to characterize the pain syndrome using a VAS, assessing the dynamics of the presence and degree of pain.

To determine the level of CCL2 / MCP-1 in patients, venous blood was taken in vacutainers with EDTA 1 h before surgery, 12 h and 24 h after surgery. Plasma was obtained from selected blood samples by centrifugation at low speed, followed by freezing and storage at -80 °C until use.

The level of CCL2/MCP-1 in the plasma of patients was determined using a kit for specific enzyme-linked immunosorbent assay, manufactured by Elabscience, USA, according to the manufacturer's protocol. The results were evaluated by the degree of absorption of the test samples using a microplate reader Humareader (Germany) with a wavelength of 450 nm. The minimum detectable concentration was 1 pg/ml.

Statistical processing of the obtained data was performed using the software package Statistica 6.0 for Windows and the licensed version of BioStat. Differences between the obtained indicators were considered statistically significant at $p < 0.05$ using Student's t-test for bound or unbound samples.

The relationship between CCL2/MCP-1 and VAS values was assessed by using Pearson's interval (proportional) correlation coefficient (r). The correlation was found to be very strong ($r > 0.9$), strong ($0.9 < r < 0.8$), moderate ($0.8 < r < 0.7$), and weak ($0.7 < r < 0.5$) correlation. The correlation was considered statistically significant at $p < 0.05$.

## RESULTS

This study investigated the biomarker of inflammation, namely CCL2/MCP-1, in patients requiring surgical treatment (multiple staged surgical treatments with necrectomy (as indicated) and wound healing with antiseptics in the operating room) and assessed the level of inflammatory response depending on the methods of anesthesia. The obtained levels of the studied biomarker of inflammation in certain periods of the early postoperative period are shown in **Table 1**.

The results of studies revealed an increase in the level of CCL2/MCP-1 in the plasma of patients in the group 1 (3.1 times) 12 h after surgery, compared with this group before surgery ($p < 0.05$, **Table 1**). Moreover, 24 h after surgical treatment of patients using standard methods of general anesthesia, the level of the studied chemokine significantly increased 9.5 times compared to the data obtained before surgery ($p < 0.05$).

In turn, in patients of the group 2 there were no significant quantitative changes in the level of CCL2/MCP-1 in the plasma of patients 12 hours after surgery, compared with this indicator in the group before surgery (**Table 1**). However, one day after surgery, CCL2/MCP-1 significantly increased 3.3 times

**Table 2.** Distribution of patients depending on the level of pain on a VAS

| Pain intensity on VAS (points) | Preoperative period | Postoperative period | | | |
|---|---|---|---|---|---|
| | | Group 1 | | Group 2 | |
| | | In 12 hours | In 24 hours | In 12 hours | In 24 hours |
| 1-4 mild pain, abs. (%) | 0 patients (0.0%) | 3 patients (25.0%) | 6 (50.0%) | 2 (16.5%) | 8 (66.6%) |
| 5-7 moderate pain, abs. (%) | 10 patients (41.6%) | 7 patients (58.3%) | 5 (41.6%) | 8 (66.6%) | 4 (33.3%) |
| 8-10 severe pain, abs. (%) | 14 patients (58.8%): Severe pain 43.3% & very severe 15.5% | 2 (16.6%) | 1 ( 8.3%) | 2 (16.6%) | 0 (0.0%) |

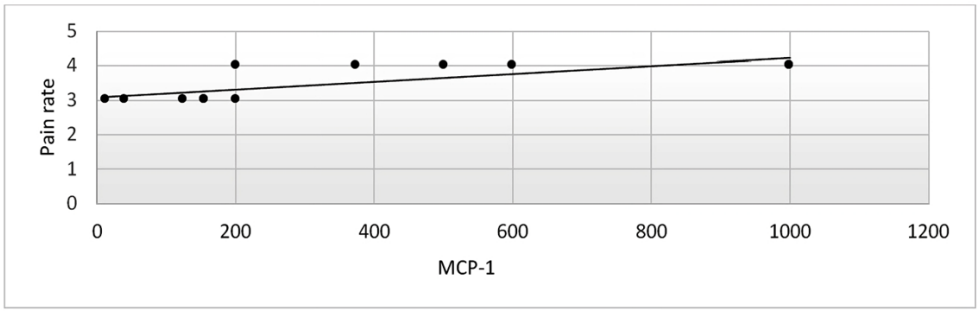


**Figure 1.** The Pearson correlation coefficient (r = 0.56775) between the plasma CCL2/MCP-1 level and VAS scores of pain intensity in the group 1 (Source: Authors' own elaboration)

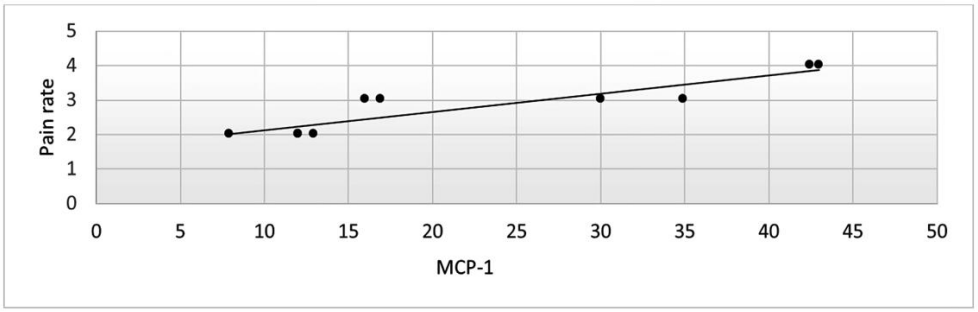


**Figure 2.** The Pearson correlation coefficient (r = 0.816519) between the plasma CCL2/MCP-1 level and VAS scores of pain intensity in the group 2 (Source: Authors' own elaboration)

compared to the values of the studied chemokine before surgery ($p < 0.05$).

When studying the dynamics of the pain syndrome, it was found that in the preoperative period, the level of pain on the VAS averaged 7-8 points and almost did not differ in the study groups. The majority of patients reported severe pain (45.8%), some patients had moderate (41.6%) and very severe (12.5%) pain, which was accompanied by weakness, sleep disturbances, and severe anxiety. After 12 h of the postoperative period in patients of the group 1–7 patients (58.3%) experienced moderate pain, which negatively affected mood, anxiety and disturbed sleep, 2 patients (16.6%) from the group 1 experienced severe pain, who required opioid analgesics and caused severe discomfort, patients in group 2–8 patients (66.6%) experienced moderate pain, and 2 patients (4.3%) experienced severe pain, according to the VAS (8-10 points). After 24 hours in the study groups, patients experienced mild pain of varying intensity that did not require additional analgesia and 2 patients (87.5%) of the group 1 had moderate pain that affected general mood and sleep and 1 patient had severe pain. 4 patients of the group 2 had moderate pain of 5-7 points on VAS (**Table 2**).

An investigation into the relationship between MCP-1 levels as an objective stress marker and the subjective pain ratings reported by patients using the VAS.The coefficient correlation of these parameters and subjective assessment of pain ranged from different methods of analgesia from 0.8 to 0.2 ($p < 0.05$), which corresponded from a high to moderate degree of correlation at all stages of the study (**Figure 1**).

When assessing the level of pain and the level of CCL2/MCP-1 in the plasma of patients in the dynamics of the group 1 of studies revealed an outpacing increase in pain. Patients noted the maximum level of pain in the postoperative period 12 hours after surgery, while the maximum increase in CCL2/MCP-1 was recorded 24 hours after surgery (**Figure 1**). However, the maximum values of proinflammatory cytokines were associated with higher pain intensity according to VAS, with a correlation between moderate strength, r = 0.56775 ($p < 0.05$).

The group 2 observed almost the same level of proinflammatory markers CCL2/MCP-1 in the preoperative and postoperative periods, which increased significantly 3.3 times after 24 h, accompanied by a strong correlation between the degree of subjective assessment of pain for VAS, r = 0.816519, ($p < 0.05$) (**Figure 2**).

## DISCUSSION

Chemokines play an important role in the control of leukocyte activation and regulation of leukocyte transport in some immune-mediated and inflammatory diseases [14-18].

Improper chemokine expression can lead to leukocyte infiltrates and tissue damage. There is growing evidence that MCP-1 is an important participant in the inflammatory process of wound healing [18].

Our data showed a pronounced inflammatory response in patients of all study groups before surgery, which correlated differently in the postoperative period. These changes were to some extent modified by various anesthesia tactics. The results showed that significantly higher MCP-1 levels were observed in patients in the standard general anesthesia group, and lower rates were found in patients who combined general anesthesia with infiltration wound anesthesia with the local anesthetic bupivacaine 0.5%.

According to scientific sources, data on the effect of local anesthetic (lidocaine 2%) on the production of MCP-1 and induced MCP-1 activation of monocytes, may be important for understanding the interaction between local anesthetics and wound healing [19]. Local anesthetics (such as lidocaine, bupivacaine) are used in the treatment of patients with surgical wounds. The introduction of anesthetic into the surgical wound reduces the migration of leukocytes and metabolic activation in the wound area [20]. After topical application or infiltration of tissues, the concentrations of anesthetics in the tissues are usually in the millimolar range, and similar concentrations are present around the spinal nerves after epidural or spinal anesthetic administration. According to our study and the above, it can be assumed that local anesthetics attenuate MCP-1-induced activation of inflammatory cells. These results suggest that the effects of anesthetics on wound healing may act at least in part by modulating the production of MCP-1 and MCP-1-induced activation in inflammatory cells [18].

The development of pain is a sensory and emotional reflection of pathological processes in the body. The detected maximum increase in the assessed stress marker on average coincided in time with the maximum manifestations of pain. However, the correlation dependence in the groups was radically different: from strong correlation (r–0.8) in the second observation group to moderate correlation (r–0.5)–in the first group, which once again showed the diversity of neurophysiological processes of pain and psycho-emotional factors of pain perception and ability to regulate the influence of proinflammatory mediators by different methods of analgesia [19].

## CONCLUSIONS

Indicators of MCP-1 biomarker levels in the patient's blood in the hospital may be an indicator of the intensity of the inflammatory process and pain in the perioperative period and requires further detailed study.

The dynamics of CCL2/MCP-1 levels in the early postoperative period showed lower rates in patients of group 2 after 12 hours and 24 hours compared with group 1 ($p < 0.05$), which probably indicated a decrease in the inflammatory response when using local anesthetics in the wound.

Reducing pain syndrome (by the VAS) 2 times less (after 12 hours and 24 hours) indicates the effectiveness of the multimodal approach as the optimal method of perioperative analgesia in patients, which allows them to achieve adequate levels of analgesia compared to the use of only general analgesia methods.

According to the Pearson correlation between CCL2/MCP-1 markers rate and pain syndrome, the study group demonstrated a higher degree of correlation (r–0.816519, $p < 0.05$), proving the relationship between variables at high rates.

These results suggest that the effect of a local anesthetic on wound healing is at least partially correlated with the level of MCP-1 and MCP-1-induced activation in inflammatory cells, which usually requires further detailed research.

The level of CCL2/MCP-1 cytokines in the serum depends on many factors (choice of anesthesia, surgery, underlying pathology, comorbidities, etc.), and the lack of sound research on this issue leaves much room for study.

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**Ethical statement:** The authors stated that the study was approved by the Ethics Committees at the Vinnytsya Regional Clinical Hospital Vinnytsya Regional Council, Military Medical Clinical Center of the Central Region, and the Clinical Center for Thermal Injury and Plastic Surgery on 2 March 2022 with protocol number 2.

**Declaration of interest:** No conflict of interest is declared by the authors.

**Data sharing statement:** Data supporting the findings and conclusions are available upon request from the corresponding author.

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