DOI: 10.4149/BLL_2022_129

Bratisl Med J 2022; 123 (11)

806 – 812

CLINICAL STUDY

Postoperative pain management in geriatric patients after cholecystectomy and studies of glycemia and cortisol levels

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ABSTRACT

OBJECTIVE: The purpose of the study was to follow up the cortisol levels in relation to the postoperative pain intensity, its levels after treatment with opiate and non-opiate analgesics, and to monitor the relationship between the blood glucose and cortisol levels. Another goal was to optimize the postoperative analgesia of geriatric patients with the known combinations of analgesics.

METHODS: The cohort comprised 28 geriatric patients undergoing laparoscopic cholecystectomy. The patients were divided according to the intensity of postoperative pain into the groups with opiate and non-opiate analgesia. Furthermore, they were divided according to their physical condition (ASA classification) into two groups, ASA 2 and ASA 3. We evaluated three values of blood glucose levels, on the day before surgery, on the operative and the first postoperative days and those of cortisol on the day of surgery.

RESULTS: The patients had the blood glucose levels without significant deviation during the three days of measurements. The cortisol levels increased with the intensity of postoperative pain. High levels of cortisol were observed not only in the patients, who experienced acute pain after non-optimal postoperative analgesia, but also in those treated with strong opiates in the immediate postoperative period. The patients with mild pain intensity, treated with a combination of non-opiate analgesics, had the lowest values. The role of the patient's gender in both blood glucose and cortisol levels was not observed.

CONCLUSION: The cortisol levels have not corresponded so much with the assessment of acute postoperative pain as with the stress that was evoked in the patient due to hospitalization and fear of surgery. It is crucial to eliminate as much as possible all the stressors that can affect the cortisol levels and thus the blood glucose levels *(Fig. 6, Ref. 25).* Text in PDF *www.elis.sk*

KEY WORDS: cortisol, geriatric patient, blood glucose level, postoperative analgesia, laparoscopic cholecystectomy.

Abbreviations: ASA – American Society of Anesthesiologists, NRS – numerical rating scale, NSAID – non-steroid antiinflammatory drug

Introduction

Increasing life expectancies paired with age-related comorbidities resulted in the continued growth of the elderly surgical population. In this group, age-associated changes and decreased physiological reserve impede the body's ability to maintain homeostasis during times of physiological stress, with a subsequent decrease in physiological reserve. This can lead to age-related physiological and cognitive dysfunction resulting in perioperative complications (1). Elderly patients with coexisting diseases are at a greater risk for polypharmacy that can further complicate anesthetic management. Consequently, the importance of conducting a focused preoperative evaluation and identifying potential risk factors is strongly emphasized (2,3).

Acute postoperative pain is a significant trigger of the stress response. A large percentage of the patients experience fear of possible intense postoperative pain before surgery (4, 5). Cortisol is often referred to as the stress hormone. Its main role is to mobilize the body under stress, which is achieved mainly due to its effect on energy metabolism. Throughout the day, cortisol maintains blood glucose and suppresses nonvital organ systems to provide energy to an actively functioning brain and neuromuscular system. In addition to its paramount role in normal daily function, cortisol is the key player in the stress response. In the presence of a physical or psychological threat, cortisol levels surge to provide the energy and substrate necessary to cope with stress-provoking stimuli or escape from danger (6–8).

In this work, the geriatric patients undergoing a planned surgery, laparoscopic cholecystectomy under general anesthesia, were studied. We monitored the values of cortisol levels in relation to the postoperative pain intensity, the cortisol levels in treat-

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ment with opiate and non-opiate analgesics, and the relationship between the blood glucose and cortisol levels. The results are reported herein.

Material and methods

Patient selection criteria

We enrolled geriatric patients, who underwent the same type of surgery for laparoscopic cholecystectomy. Nature of the pain is reported to be somatic, visceral, and neuropathic (9). This information provides an opportunity for the preparation of sufficiently effective postoperative analgesia.

Another criterion was the selection of geriatric patients. Aging brings with it physiological changes that significantly affect the body's response to algic stimuli. Thus, optimally managed postoperative pain will greatly enhance the patient's convalescence.

Further, the patients were selected according to the criteria (10) of the American Society of Anesthesiologists (ASA). We selected a group of the patients in the ASA 2 (mild to moderate systemic disease for which the patient is operated on, or caused by another pathophysiological process without altering organ performance and function), and ASA 3 (serious systemic disease of any aetiology, limiting the patient) classifications.

The cohort consisted of 28 geriatric patients, of which 16 were males and 12 females. Fifteen patients were included in the ASA 2 and 13 in ASA 3 classifications, respectively.

Methodology

Patients were admitted on the day before surgery, when standard preoperative investigations were performed. The blood pressure, pulse and the blood glucose levels taken at the same time period (17:00 hours) were recorded in the monitoring protocol. We evaluated three values of blood glucose levels, on the day before surgery, on the operative and the first postoperative days. The patients received premedication according to the workplace practices.

The operation was performed under a general anesthesia. At the beginning of anesthesia, the anesthetics Propofol, the analgesics Sufentanil, and the muscle relaxant Atracurium (Tracrium) were administered intravenously to the patients. The anesthesia was further performed by the inhalation of Sevoflurane (Sevoran). After completing operation and stabilizing the patients from the anesthesiology point of view, we proceeded to assess the intensity of pain according to the numerical rating scale (NRS). This evaluates the pain intensity from 0 to 10 (11). The number 0 means no pain, the number 10 the worst imaginable pain. These values, together with the blood pressure and pulse values measured at that time, were recorded in the monitoring protocol. According to the value of pain intensity, the patients were prescribed postoperative analgesia.

According to the type of postoperative analgesia chosen, we divided the patients into two groups. The first group consisted of the patients requiring opiate analgesics due to the intensity of postoperative pain. We used the opiate analgesics Sufentanil or Piritramid (Dipidolor) for the pain relief. The second group comprised patients, who reported only mild postoperative pain. They were administered non-opiate analgesics. The well-proven triple combination of analgesics Diclofenac (Almiral or Akis), Paracetamol Kabi, and Midazolam (Novalgin) were used. In the postoperative period, both groups of the patients were monitored for the blood pressure and pulses at the 4 hours intervals. The pain intensity and their analgesic treatment was continuously monitored according to a precisely determined schedule. In addition, the blood samples for measuring the cortisol levels (on the day of surgery) were taken together with the control postoperative laboratory samples at the same time (17:00 hours). We chose venous blood sampling to monitor the hormone levels. It was important to adhere to the collection schedule due to the fluctuating levels of cortisol during the day.

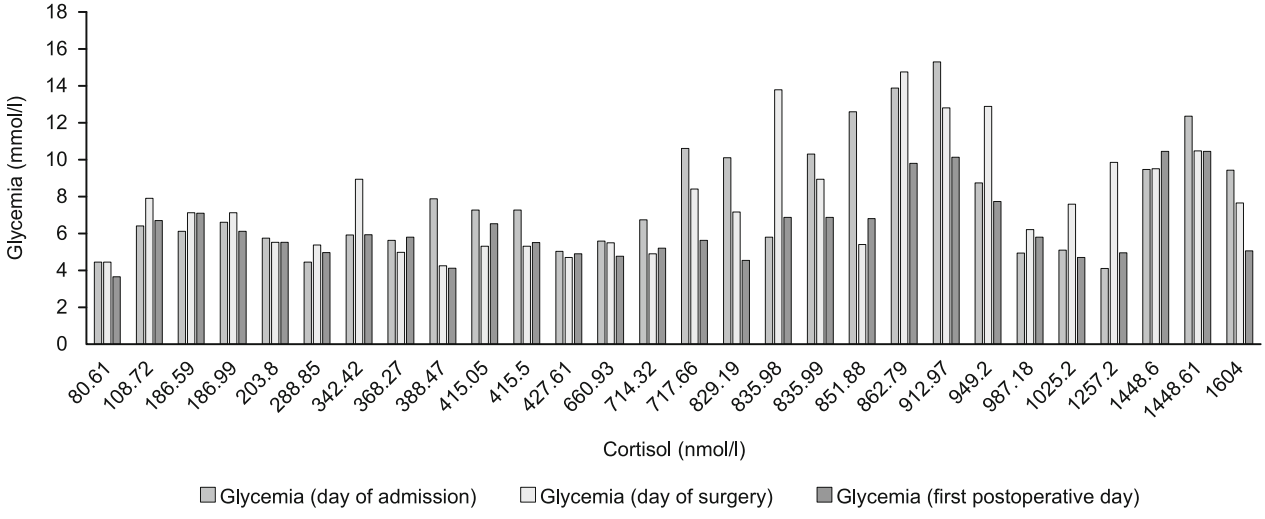

Fig. 1. Glycemia and cortisol levels in the cohort (16 males and 12 females); cortisol values taken on the day of surgery.

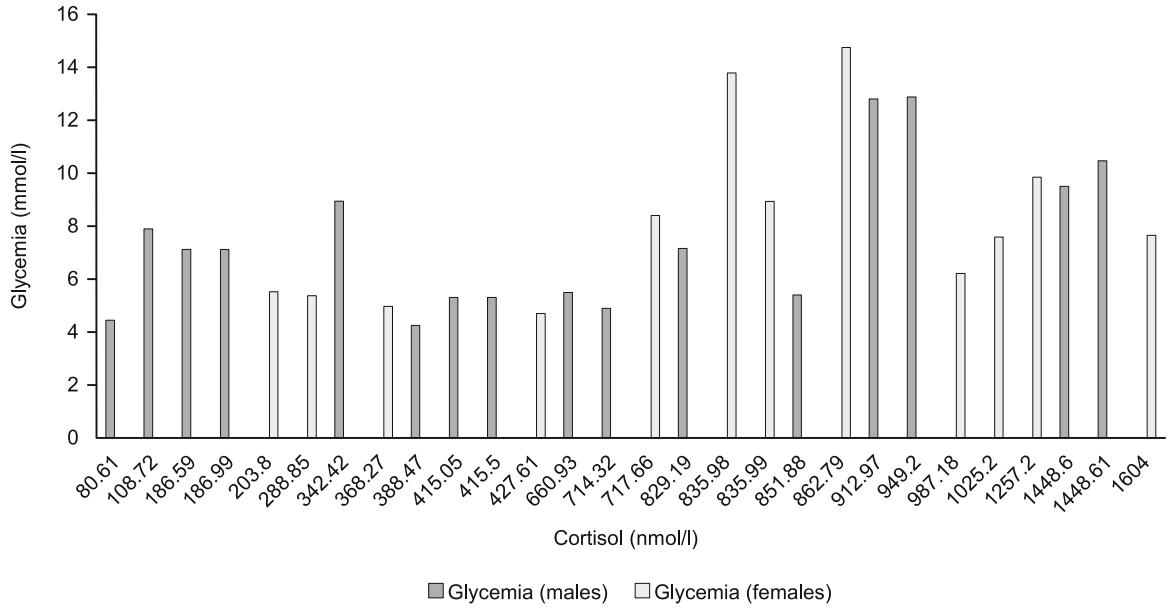

Fig. 2. Glycemia and cortisol levels in the patient cohort on the day of surgery.

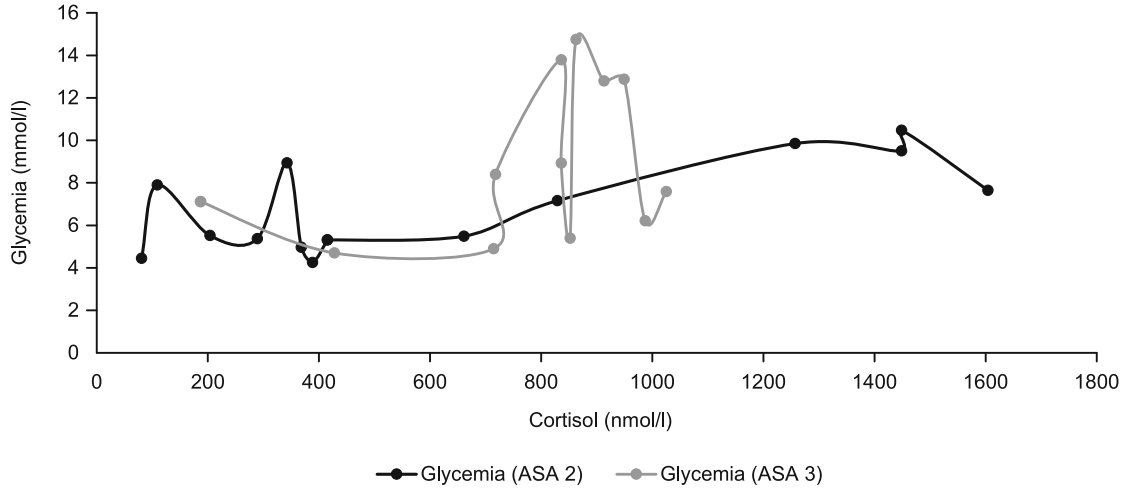

Fig. 3. Glycemia and cortisol levels in the patients with ASA 2 and ASA 3 classifications (https://www.asahq.org) on the day of surgery.

On the first postoperative day, the patients were monitored according to the standard postoperative protocols. The pain intensity, blood pressure and pulses were monitored. The analgesic treatment was indicated according to a well-defined schedule. In this postoperative period, none group of the patients were given the opiate analgesics. In addition to blood pressure and pulses, the blood glucose value was recorded in the monitoring protocol. This was taken again at the same time period (17:00 hours).

Results

Relationship between blood glucose and cortisol levels

The fact that the blood glucose level will fluctuate at higher values during hospitalization could be expected due to the stress that hospitalization and the operation itself represent (12). Therefore, we focused on measurements of blood glucose levels during the three days, on the day of admission, on the day of operation, and on the first postoperative day. In the individual patients, we have not observed significant differences in the blood glucose values during these days (Fig. 1). The patients who had higher blood glucose values maintained them during all three days of our measurements.

Only 39 % of the total number of the patients came to the hospital with the blood glucose levels within the normal range up to 5.6 mmol/l (Fig. 1). None of the patients under study was treated for any form of an impaired glucose tolerance, and therefore, it was a high presumption of the normal blood glucose levels.

Further, we searched for a possible connection between the values of both cortisol and blood glucose levels and their relation-

ship to gender on the day of surgery. However, no statistically significant differences were found. The blood glucose values were found above the limit of 5.6 mmol/l in 62.5 % of male and 66 % female patients, respectively (Fig. 2).

Another data we followed up in the assessment of blood glucose versus cortisol levels was the relationship with the ASA classification of the patients. As can be seen (Fig. 3), patients belonging to the ASA 2 group exceeded the upper limit of the normal blood glucose level (5.6 mmol/l) in 40 % of the total number of the group, while in the ASA 3 patients this accounted for up to 71.4 % of the group. It appears that physical condition according to the ASA classification had an effect on the cortisol levels and related blood glucose values of the patients on the day of surgery. Thus, the ASA 3 patients managed surgical stress significantly worse than the ASA 2 patients.

The relationship between both the cortisol and blood glucose levels of the patients in the cohort was processed by the method of linear regression. The linear dependence on increasing cortisol and blood glucose levels was clearly demonstrated (data not shown).

Relationship between cortisol levels and postoperative pain intensity

We measured the cortisol levels of the patients in the early evening hours of the operating day (17:00 hours), when the values according to the circadian rhythm should be lower. As many as 71.3 % of the patients reported mild (64.3 %) to moderate (7.1 %) pain after surgery. Approximately one-third of the patients (28.6 %) characterized the pain intensity as severe immediately after surgery (Fig. 4). There was an increase in the cortisol levels between groups of the patients with mild to moderate pain (more significant in males). In contrast, there was a decrease in the levels of patients with moderate and severe pains.

Thus, 31.2 % of males experienced severe postoperative pain compared with 25 % of females. A slight decrease in cortisol levels among the patients with moderate and severe postoperative pain can be attributed to the fact that the perception of pain intensity is strictly individual for each patient. It depends on many factors

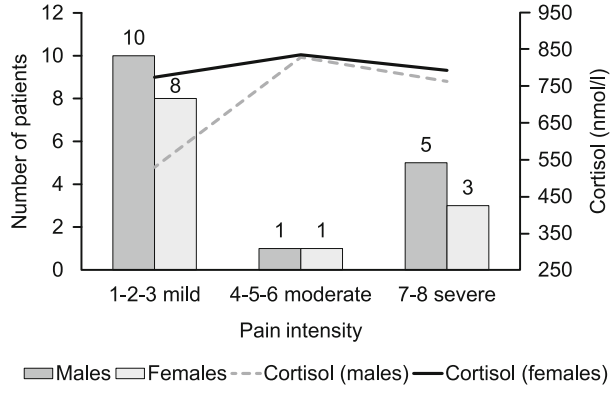

Fig. 4. Dependence of cortisol levels on the pain intensity in the patient cohort on the day of surgery; pain intensity numerical scale according to (11).

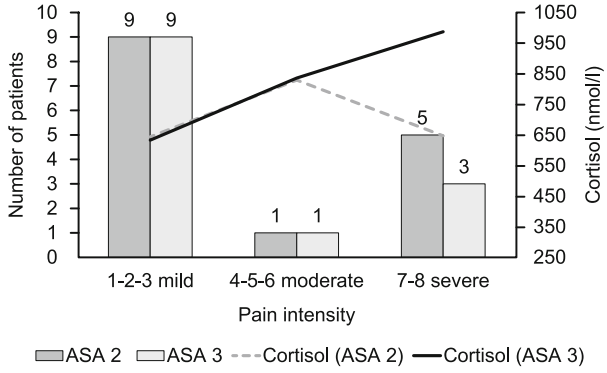

Fig. 5. Dependence of cortisol levels on the pain intensity in patients with ASA 2 and ASA 3 classifications (https://www.asahq.org) on the day of surgery; pain intensity numerical scale according to (11).

and it is very subjective, despite the patient´s attempts for objectivity. Therefore, the cortisol levels with respect to the pain intensity may differ in some patients.

We also studied the effect of the patient's physical condition on the perception of pain intensity after surgery (Fig. 5). In the group of patients according to the ASA 2 classification, the experience with mild, moderate, and severe postoperative pain was 60.0 %, 6.7 % and 33.3 % respectively. The cortisol curve has increased gradually between the patients with mild to moderate pain intensity. After reaching the peak, a decrease was noted between the patients with moderate to severe pain. The patients with the ASA 3 experienced mild, moderate, and severe pain in 69.2 %, 7.7 % and 23.1 % respectively. There was a steady increase in cortisol levels towards pain intensity among the groups.

In the ASA 2 group, the pain perception intensity has not followed the cortisol levels of all the patients. In contrast, a clear dependence between the cortisol levels and postoperative pain intensity was shown in the ASA 3 group. It appears that the patients belonging to ASA 3, having severe systemic diseases, were able to better identify and/or characterize the intensity of postoperative pain.

Cortisol levels in treatment with opiate and non-opiate analgesics

The patients were classified according to the intensity of postoperative pain into two groups. The first group consisted of the patients, who were given strong opiate analgesics (Sufentanil or Dipidolor in combination with Paracetamol) during the continuing analgesia. These patients accounted for 14.3 % of the cohort (opiate group). The second group consisted of patients, who were administered a combination of non-steroid antiinflammatory drugs (NSAID) with Paracetamol and Midazolam in the immediate postoperative period. These patients comprised up to 85.7 % of the group and were designated as the non-opiate group. Some patients of the latter (37.5 %) reported moderate to severe postoperative pain that developed despite the treatment with the non-opiate analgesics. The opiates (Piritramide) have been indicated to relieve the

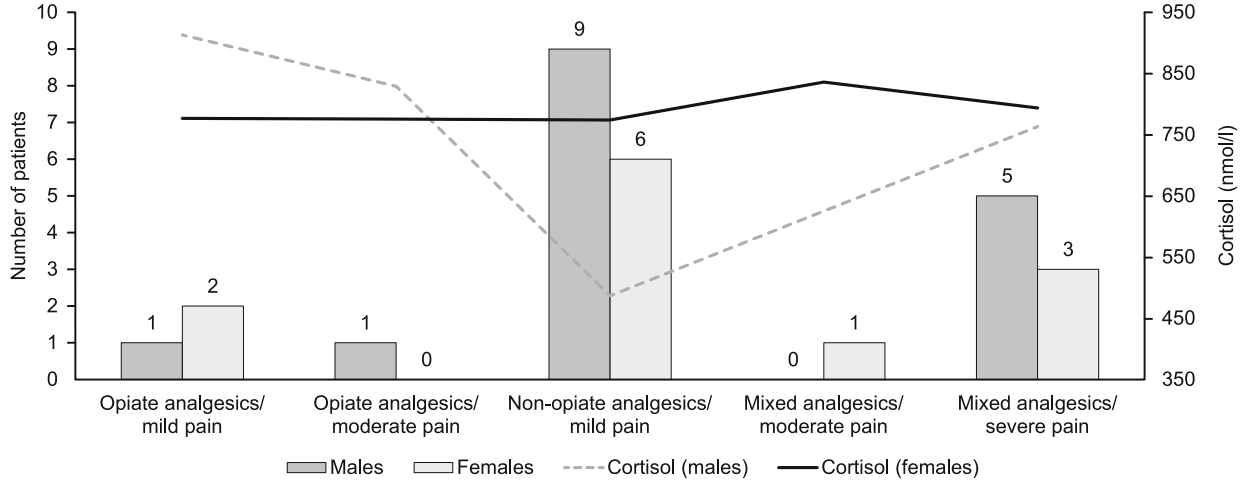

Fig. 6. Dependence of cortisol levels on the pain intensity according to the type of analgesic treatment; pain intensity numerical scale according to (11).

pain. This group of the patients was designated as the mixed group.

We observed differences in the monitoring of cortisol levels in the patients of all groups (Fig. 6). Most of the patients treated with a combination of non-opiate analgesics had mild pain that reflected lower cortisol levels in males only. In the opiate group with mild to moderate pain, males had cortisol levels higher than those of the non-opiate group. Females had these values almost unchanged. However, these patients represented only a small number of the cohort because the opiate analgesics are not among the drugs of the first choice for laparoscopic cholecystectomy. In the mixed group, the cortisol levels were quite comparable with those of the opiate group.

With respect to the patient´s gender, the lowest levels of cortisol were found in the male group of non-opiate analgesics (Fig. 6). In males, the opiate group had higher levels compared to the mixed group. Male patients reported mild to moderate pain in opiate, mild and moderate pains in the non-opiate groups, respectively. In the mixed group a severe pain was given. In females, the cortisol levels were quite steady in all the groups. The female patients reported mild pain in the opiate and non-opiate groups and moderate to severe pains in the mixed group.

However, the cortisol levels have not correlated with the pain intensity assessment. Males in the non-opiate group (35.7 %) developed an intense postoperative pain and the opiate analgesics were added to their treatment. In females, this group accounted for 40 %. It appears that gender differences in postoperative pain assessment were not significant in this case.

Discussion

Optimal analgesia after laparoscopic cholecystectomy is essential for reducing postoperative complications and improving patient recovery, and satisfaction. In this work we have focused on some of the most important factors that might influence the outcome of a successful analgesia.

It has been reported that the blood glucose levels in the patients fluctuated at higher values during hospitalization due to the stress that hospitalization and the operation itself represent (12). Thus, we focused on the measurements of patient´s blood glucose levels during the three days, i.e. on the day of admission, on the day of the operation, and on the first postoperative day, but no significant differences were found. Our assumption that glycemia could reach the highest values on the day of the operation was not confirmed for the given number of the patients. Most probably, the administration of a sufficient amount of opiates inhibits transmission of impulses from the trauma site and blocks the hypothalamus and pituitary function during the day of surgery (13). The patients who had higher blood glucose values maintained them during all three days of our measurements.

It has been reported (14) that female gender should be considered a risk factor for stress during a surgery. The evaluation of both cortisol and blood glucose levels of males and females on the day of surgery has, however, not shown statistically significant differences.

Our results strongly indicated an association between the patient's physical condition according to the ASA classification and the blood glucose and cortisol levels. The patients with severe systemic diseases that limit them (ASA 3) had higher blood glucose and cortisol levels than the ASA 2 patients on the day of surgery. Moreover, the dependence of glycemic levels on the cortisol values was clearly demonstrated by a method of linear regression in the whole group on the day of surgery.

Since blood glucose levels were above normal in most of the patients, we assume that the patients already experienced an acute stress on admission to the hospital. While sympathetic neurotransmitters regulate the initial phase of the acute stress response, the neuroendocrine response follows late, but with a longer effect. Approximately 15 minutes after the onset of stress, the cortisol levels rise systemically and remain elevated for several hours. The elevated cortisol levels mobilize glucose through gluconeogenesis and reduce peripheral glucose consumption (8).

In the evaluation of postoperative pain, we had to consider the geriatric age of patients in the group, which has certain specifics (15). Perception of the intensity of postoperative pain is related to the reduced function of individual organ systems, comorbidities of the patients and their chronic medication. Equally important are differences in the perception of age-related pain (16). Acute postoperative pain is a significant trigger of the stress response. A large percentage of the patients experience fear of possible intense postoperative pain before surgery (4, 5). The cortisol levels are affected not only by increased physical activity, but also by psychological pressure or the current mental state of the patients (17, 18).

In our cohort, we have confirmed the dependence of cortisol levels on the intensity of postoperative pain as reported elsewhere (4, 5). Generally, the cortisol levels increased with the intensity of postoperative pain. When monitoring the whole cohort of the patients, the increase in cortisol levels was the most intense among the patients with mild to moderate postoperative pain. After exceeding the level of 800 nmol/l, the cortisol levels did not increase significantly although some patients reported severe pain intensity after surgery.

The relationship between cortisol levels and pain intensity by gender has not been confirmed in contrast to the work of other authors (14), who reported that females experienced more surgical stress than males. The fact that the geriatric patients perceive and experience acute pain with certain specifics different from the rest of the population probably plays a role (19). It appears that both overall mental and physical condition of the patient and the individual level of pain perception rather than gender determine the assessment of postoperative pain.

When monitoring the cortisol levels and postoperative pain intensity in the patients with ASA 2 and ASA 3 classifications, there was a distinct development of cortisol levels to the postoperative pain intensity. While in the ASA 2 group, the cortisol levels increased most noticeably among the patients with mild to moderate pain, the situation was different in the ASA 3 patients. The patients with severe postoperative pain achieved the highest cortisol levels. It might be feasible to better identify and characterize the intensity of postoperative pain in this group of the patients.

An optimal postoperative pain relief is one of the basic requirements in the immediate postoperative period. A proper choice of the type and combination of analgesics, a precise titration and dosage, and finally the exact timing of administration of individual doses of analgesics, prevent development of acute postoperative pain. A continuous association of different types of anesthesia with the postoperative analgesia is also very important (20, 21).

In our cohort of patients, we also followed up their cortisol levels in treatment with the opiate and non-opiate analgesics. We have found that the cortisol levels did not correspond so much with the assessment of acute postoperative pain, in our case with NRS, but rather with the stress that is evoked in a patient due to hospitalization and fear of surgery. High levels of cortisol were found not only in the patients, who experienced severe postoperative pain after a postoperative analgesia that was not optimal, but also in the patients treated with strong opiates in the immediate postoperative period. The data reporting (16) that the patients given opiate analgesics had lower cortisol levels were not confirmed in our cohort. It is important to pay a sufficient attention not only to the treatment of postoperative acute pain, but also to the preparation of the patient before the operation. There is a need to eliminate as much as possible all stressors that may affect the cortisol levels.

The stress response results in the elevated cortisol levels (7, 8, 22). This stress hormone is then excreted to an increased extent together with catecholamines. Glucocorticoids and catecholamines affect the activity of individual organ systems in order to help the body to cope with the increased challenge. For geriatric patients, the acute stress represents an increased burden to the body, which is unable to manage optimally. This can affect the length of recovery as well as the patient mortality (23, 24).

In their work, Kwon et al (18) examined the cortisol levels in relation to the timing of surgery. Their result showed that the afternoon surgery was more suitable with respect to the postoperative recovery, wound healing, reduced production of inflammatory cytokines, and blood glucose levels. In the afternoon, the elevated cortisol levels returned earlier to the initial values. In another study, Özmen et al (25) compared the cortisol levels in postoperative analgesia using the local anesthetics (Bupivacaine) and the central opiate administration (Fentanyl). Results were more favourable for the local anesthetics, the patients had lower cortisol levels and reported less postoperative pain than with the centrally administered opiates. Thus, in order to reduce the patient's stress response, a thorough preoperative preparation is important that should focus not only on improving the patient's physical condition, but also on the patient's mental condition because the cortisol levels depend on both of these factors as has been shown in our work.

In conclusion, we have brought several pieces of evidence indicating that the monitoring of cortisol and blood glucose levels might be a useful tool in an improved management of the pre- and postoperative analgesia of geriatric patients. The levels of cortisol have not corresponded so much with the assessment of acute postoperative pain as with the stress that is evoked in patient due to hospitalization and fear of surgery. Therefore, it is important to eliminate as much as possible all the stressors that can affect cortisol levels and thus the blood glucose levels. Future trends in the postoperative pain management will include application of novel tools to individualize multimodal regimens for the patient and the type of surgery in order to better manage the acute postoperative pain.

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Received June 13, 2022.
Accepted July 6, 2022.