

Impact of anesthesia method on cortisol and interleukin-6 concentration changes during and after laparoscopic colorectal surgery

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Background. The surgical-stress-induced release of hormones, such as catecholamines (norepinephrine and epinephrine), adrenocorticotrophic hormone (ACTH), and cortisol, via the autonomic nervous system and the hypothalamic-pituitary-adrenal axis (HPA) mediates inhibitory effects on immune functions. Pain management may influence the immune response in the postoperative period. The goal of the present study was to examine to what extent postoperative pain management modulates the surgery-induced alterations of the immune response, specifically, interleukin-6, cortisol and C reactive protein (CRP); to compare effects of two pain management techniques, based on NSAID and continuous epidural infusion of a local anaesthetic and morphine mixture.

Materials and methods. Local Bioethics Committee's approval was received, patients ASA I–III scheduled for laparoscopic colorectal surgery (LCS) were randomised to receive general anesthesia (GA, N = 27) or combined general anesthesia with epidural analgesia (EA, N = 26). Anesthesia was induced with propofol, fentanyl and atracurium and maintained with sevoflurane. The EA group received the first dose of 3 mg epidural morphine with 0.25–0.125% bupivacaine mixture 20–30 min before surgery and continuous epidural infusion of bupivacaine 0.25% and 5 mg of a morphine mixture for postoperative analgesia. The GA group received intravenous fentanyl and morphine during surgery, and NSAID for postoperative pain management. There were 5 cases when laparoscopy was converted to open surgery due to surgery findings, these cases made the third-conversion group (CG) with further maintenance intended analgesia type. Pain was evaluated using the visual analogue scale (VAS) after anaesthesia and 24 hours later. Venous blood samples for cortisol and interleukin-6 were taken preoperatively before induction of anaesthesia (baseline), after surgery and 24 hours after baseline. Venous blood samples for CRP were checked after 1, 2, 3, 4, 6 days after surgery. Collected data were stored in the data base and were analysed using SPSS for Windows Version 19.0. The data were analysed using the Mann-Whitney U test and Student's t test for comparison of 2 groups and ANOVA for comparison of more than two groups. The Bonferroni adjustment was used to detect pairwise differences between the groups. The Chi-square test was used to determine differences between categorical variables. Differences between the groups were considered statistically significant at $p < 0.05$.

Results and discussion. There were statistically significant differences between the groups in pain score after surgery ($p < 0.001$) and 24 hours later ($p < 0.000$) and in bowel motility after anaesthesia ($p < 0.001$). In EA group bowel motility was observed in 96.2% of patients after surgery and lasted more than 24 hours despite of infusion of local anesthetic mixture with morphine. In the GA group only in 55.6% of cases bowel motility was observed after anaesthesia. No differences in bowel motility was determined between the groups 24 hours later. We determined statistically significant differences in cortisol value after surgery comparing EA and GA groups ($p < 0.003$) and also between three groups, despite the duration of anaesthesia statistically significant longer in the EA group. The highest cortisol value was determined in the conversion group. The interleukin-6 concentration differences were found significantly relevant comparing the EA group with CG and also comparing the GA group with CG ($p < 0.000$). Studying complications associated with intestinal anastomosis permeability using non-parametrical test some association between interleukin-6 concentration after 24 hours and anastomosis problems ($p < 0.039$) was determined. No differences in CRP findings between EA and GA groups during the 6-day postoperative period were determined.

Conclusions. Combined general anesthesia with epidural analgesia warrant better pain control after LCS and attenuate stress response reducing secretion of cortisol and interleukine-6.

Key words: laparoscopic colorectal surgery, cortisol, interleukin-6, epidural analgesia

INTRODUCTION

The postoperative period is associated with neuroendocrine, metabolic and immune alterations, which are the combined result of tissue damage, anesthesia, postoperative pain, and psychological stress. Suppression of immune defense mechanisms was demonstrated in the postoperative period. Such immune compromise could affect the postoperative infection rate, healing process, and the rate and size of tumor metastases disseminated during surgery (1). Pain management may influence the immune response in the postoperative period. Several pain management techniques are frequently used in the postoperative period. These techniques include traditional systemic administration of opiates on a regular schedule or on demand (IOR), patient-con-

trolled intravenous analgesia (PCA), and continuous epidural analgesia (CEA) or patient control epidural analgesia (PCEA). The PCEA technique is usually based on a mixture of local anesthetics and opiates. Such a mixture allows to reduce the dose of opiates while increasing the efficiency of the postoperative analgesia. In addition, local anesthetics have an antiinflammatory effect of their own, and in this way they may also contribute to the attenuation of the postoperative pain (2). After major surgical procedures, there is an early hyperinflammatory response with release of the proinflammatory tumor necrosis factor, interleukin-1 and interleukin-6 cytokine, neutrophil activation and microvascular adherence, and uncontrolled polymorphonuclear and macrophage oxidative activity. This ultimately results in significant cell-mediated immunosuppression marked by

monocyte deactivation, decreased microbicidal activity of phagocytes, and an overall imbalance between proinflammatory and antiinflammatory cytokines and immunocompetent cells (3). Epidural analgesia may reduce infectious complications by reducing lymphocyte suppression, attenuating proinflammatory cytokines, and by increasing surgical wound oxygen tension to promote healing (1, 4), although such positive effects may be negated by the more extensive inflammatory response from more extensive surgery (5, 6). General anesthesia accompanied by surgical stress is considered to suppress immunity, presumably by directly affecting the immune system or activating the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system. Proinflammatory cytokines, such as IL-1, IL-6, and tumor necrosis factor (TNF)-from monocytes and macrophages and lymphocytes activated by surgical stress can stimulate the HPA. Therefore, the neuroendocrine system and proinflammatory cytokines and antiinflammatory cytokines synergistically augment their suppressive effects in the perioperative immune system. Interleukin-6 (IL-6) is an important mediator of the acute phase response and a sensitive marker of tissue damage (7). The surgical-stress-induced release of hormones such as catecholamines (norepinephrine and epinephrine), adrenocorticotrophic hormone (ACTH) and cortisol via the autonomic nervous system and the HPA mediates inhibitory effects on immune functions (8, 9). The antiinflammatory effects of anesthetics may be beneficial in situations involving ischemia and reperfusion injury or the systemic inflammatory response syndrome (10). Awareness of these immunological properties is helpful for daily anesthetic management.

The goal of the study was to examine to what extent postoperative pain management regime modulates the surgery-induced alterations of the immune response, specifically, interleukin-6, cortisol and C reactive protein; to compare effects of two pain management techniques, based on NSAID and continuous epidural infusion of local anaesthetic and morphine mixture.

MATERIALS AND METHODS

Patients, anesthesia and perioperative analgesia techniques

Having received the Vilnius Regional Biomedical Research Ethics Committee approval, participa-

tion in the study was offered to patients during the study period scheduled for laparoscopic colorectal surgery (LCS) at the Centre of Abdominal Surgery Vilnius University Hospital Santariskiu Clinics. Patient's consents to participate in the study were obtained. 58 patients of I-III physical classes according to the American Society of Anaesthesiologists (ASA) classification were randomly divided into two groups to receive general anaesthesia (GA group, N = 27) and following postoperative analgesia based on NSAID or combined general anesthesia with continuous epidural analgesia (EA group, N = 26) in the perioperative period for more than 24 hours. Both groups of patients received the same premedication, prevention of nausea and vomiting, non-steroidal anti-inflammatory drugs (NSAIDs), induction of anesthesia with propofol, muscle relaxation with atracurium, and maintenance of anesthesia was given with sevoflurane. The depth of anesthesia was monitored using entropy. An epidural catheter was placed in EA group patients via the Th₁₀₋₁₁ or Th₁₁₋₁₂ interspaces and was advanced 4 cm cephalad. The position of the epidural catheter was tested with 1 mg/kg lidocaine, 2%. The EA group patients received an epidural mixture of 10 ml bupivacaine (0.25%) plus morphine 2–3mg 20–30 min before induction of anesthesia and the following boluses of bupivacaine 0.125 to 0.25%. The EA group received continuous epidural infusion of bupivacaine 0.25% and 5 mg morphine mixture for postoperative analgesia. The GA group received intravenous fentanyl and morphine during surgery, and NSAID for postoperative pain management. Both groups were monitored for vital signs and the depth of anaesthesia in the same way. The colloids, and, if insufficient, intravenous ephedrine were administered to ensure haemodynamics. Venous blood samples for cortisol and interleukin-6 were taken preoperatively before induction of anaesthesia (baseline), after surgery and 24 hours after baseline. Venous blood samples for CRP were checked in 1, 2, 3, 4, 6 days after surgery. There were 5 cases when laparoscopy was converted to open surgery due to surgery findings, these cases made the third-conversion group (CG, N = 5) with further maintenance intended analgesia type. Pain was evaluated using the visual analogue scale (VAS) after anaesthesia and 24 hours later.

Statistical analysis

Collected data were stored in the data base and were analysed using SPSS for Windows Version 19.0. Continuous data were summarized by using descriptive statistics – number of cases, mean, standard deviation, median, and range (minimum and maximum). Categorical variables were summarized by using frequency (counts) and proportions. Differences in mean values between the groups were analyzed with the Mann-Whitney U test and Student's t test for comparison of 2 groups and ANOVA for comparison of more than two groups. Bonferroni adjustment was used to detect pairwise differences between groups. The Chi-square test was used to determine differences

between categorical variables. Differences between the groups were considered statistically significant at $p < 0.05$.

RESULTS

The GA and EA groups were similar in the body weight, body mass index, age, ASA groups and duration of surgery (Table 1).

We determined statistically significant differences in cortisol value after surgery (Table 2) comparing EA and GA groups ($p < 0.003$) and also among three groups, despite the duration of anaesthesia statistically significant longer in the EA group. The highest cortisol value was determined

Table 1. Characteristics of the patients according to the postoperative pain management group

	Group GA	Group EA	P value
Body mass index*	67.78 (10.90)	67.51 (10.97)	ns
Body mass*	24.03 (2.68)	24.54 (3.16)	ns
Age*	62.22 (7.82)	65.08 (13.18)	ns
Bowel motility after operation	55.6%	96.2%	0.001
Bowel motility 24 h later	96.3%	96.2%	ns
Pain score after surgery (VAS)*	1.48 (1.70)	0.23 (0.82)	0.001
Pain score 24 h later (VAS)*	3.19 (1.98)	0.46 (0.65)	0.000
Morphine consumption (surgery)*	15.56 (6.41)	2.96 (0.20)	0.000
Morphine consumption (postoperatively)*	1.48 (4.56)	4.69 (0.68)	0.001
Anesthesia duration, min*	197.96 (61.82)	220.19 (44.06)	0.047
Surgery duration, min*	165.37 (59.90)	175.58 (44.21)	ns
Anastomotic permeability	14.8%	11.5%	ns

GA – general anaesthesia group, EA – continuous epidural analgesia group; ns – no statistically significant differences.

*Values are expressed as mean (standard deviation(SD)).

Table 2. Interleukin-6 and cortisol changes perioperatively

	Group GA	Group EA	Conversion group	P value
Interleukin-6 before surgery, ng/l*	2.97 (1.76)	3.78 (3.60)	4.54 (0.83)	ns
Interleukin-6 after surgery, ng/l*	10.90 (9.45)	11.22 (7.14)	44.80 (48.18)	<0.000
Interleukin-6 24 h later, ng/l*	52.20 (197.56)	61.78 (215.31)	20.13 (9.48)	ns
Cortisol before surgery, nmol/l*	253 (79)	325 (134)	242 (200)	ns
Cortisol after surgery, nmol/l* (comparing 3 groups)	532 (220)	344 (212)	936 (1149)	GA vs EA – ns GA vs CG – ns EA vs CG – 0.006
Cortisol 24 h later, nmol/l*	165 (215)	117 (157)	259 (205)	ns
CRP 1 day after surgery*	128.6 (0)	64.0 (38.47)	–	ns
CRP 2 days after surgery*	62.07 (66.43)	42.62 (26.98)	–	ns
CRP 3 days after surgery*	137.3 (183.42)	39.0 (16.12)	–	ns
CRP 4 days after surgery*	54.81 (71.39)	52.09 (37.35)	–	ns
CRP 6 days after surgery*	34.61 (49.42)	53.54 (77.71)	–	ns

* mean (SD).

in the conversion group. The interleukin-6 concentration differences were found significantly relevant comparing the EA group with CG and also comparing the GA group with CG ($p < 0.000$). Studying complications associated with intestinal anastomosis permeability using the non-parametrical test association between interleukin-6 concentration after 24 hours and anastomosis problems ($p < 0.039$) was determined. No differences in CRP findings between EA and GA groups during the 6-day postoperative period were determined.

DISCUSSION

Surgery has major impact on patient homeostasis, expressed mainly by an immune response compromise (11). The unavoidable inflammatory response involves regional and systemic release of cytokines, hormones, acute-phase proteins, eicosanoids, and other substances by surgical manipulation-activated immune cells (11, 12, 13). Epidural analgesia is associated with a shorter duration of postoperative ileus, attenuation of the stress response, fewer pulmonary complications, improved postoperative pain control and mobility, and a quicker recovery from the patient's viewpoint. It does not reduce the incidence of anastomotic leak, intraoperative blood loss or transfusion requirement, duration of hospital stay, or risk of thromboembolism or cardiac morbidity compared with the use of conventional analgesia in unselected patients undergoing gastrointestinal surgery. There is evidence that for a subgroup of patients with a high risk of cardiac or pulmonary morbidity, thoracic epidural analgesia reduces hospital costs and stay after gastrointestinal surgery, and blockade at this level seems preferable for gastrointestinal operations (14). The present study shows that patients in the EA group exhibited reduced postoperative pain, reduced cortisol response to laparoscopic surgery, and attenuated proinflammatory cytokine interleukin-6 response to surgery. Interleukin-6 is an important mediator of the acute phase response and a sensitive marker of tissue damage (10). Our findings have links with this statement because some association between anastomosis permeability and rise of IL-6 24 hours after surgery ($p < 0.039$, non-parametrical test) was found. In the study, the tight correlation between the postoperative pain management type and postoperative infection or anastomotic permeability was not

determined. Proinflammatory cytokines are key mediators of illness symptoms (15); their attenuation in the PCEA group may have contributed to attenuated illness response, to reduced postoperative pain, and possibly to reduced risk of developing chronic pain. In the present study, better postoperative pain control in EA group, and lower cortisol after surgery were determined. In Beilin et al. (1) study, ex vivo production of the proinflammatory cytokines IL-1 and IL-6 was more increased in IOR and PCA with morphine groups compared with the PCEA group, especially at 24 hours after surgery. The patients of the first two groups were treated with opiates, whereas patients of the PCEA group were treated with a mixture of opiates and local anesthetics; this may account for the attenuated levels of proinflammatory cytokines in the PCEA group. Local anesthetics can reduce the postoperative inflammatory response in two ways: they block neural transmission at the site of tissue injury and thus may attenuate the neurogenic inflammation (16), or they have systemic anti-inflammatory properties of their own (17). Regarding the findings, it may be possible to attribute the reduced inflammatory using CEA, consisting of local anesthetics and opiates (1). In the above mentioned Beilin et al. (1) study, patients of the IOR and PCA groups have reported higher levels of pain while demonstrating larger production of IL-1 and IL-6. It has been argued that nociception and proinflammatory cytokines play a mutual up-regulatory role (21); thus, increased production of proinflammatory cytokines may contribute to more severe pain and vice versa. The proinflammatory cytokines IL-1 and IL-6 mediate hyperalgesia. IL-1 and IL-6 are involved in the mechanisms of allodynia and possibly in the development of postoperative neuropathic and chronic pain (22). The study confirms that epidural analgesia effectively reduces postoperative pain, decreases the endocrine response to surgery, and thus may attenuate surgery-induced immune alterations.

CONCLUSIONS

Epidural analgesia in laparoscopic colorectal surgery effectively reduces postoperative pain and attenuates stress response reducing secretion of cortisol and interleukin-6.

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ANESTEZIJOS METODO ĮTAKA KORTIZOLIO IR INTERLEUKINO-6 SEKRECIJAI PERIOPERACINIŲ LAIKOTARPIŲ TAİKANT LAPAROSKOPINĘ KOLOREKTALINĘ CHIRURGIJĄ

Santrauka

Įžanga. Operacijos sukeliamas stresas paveikia neuroendokrininį organizmo atsaką – katecholaminų, AKTH, kortizolio sekreciją, uždegimą skatinančių ir slopinančių citokinių gamybą. Anestezijos komponentų bei būdų, mažinančių uždegimą, skatinančių citokinių gamybą, taikymas gali būti naudingas apribojant sisteminio uždegiminio atsako sindromo vystymąsi. Il-6 yra svarbus uždegimą skatinantis ūmios fazės citokinas ir audinių pažeidimo žymuo.

Tyrimo tikslas. Tiriant kortizolio ir interleukino-6 bei CRB pokyčius perioperaciniu laikotarpiu siekta nustatyti, kaip perioperacinės analgezijos būdas gali paveikti laparoskopinės kolorektalinės chirurgijos

sukeliamą stresą. Tyrimo metu taikyti du perioperacinės analgezijos metodai – NVNU ir epidūrinė vietinio anestetiko ir opioido infuzija.

Tyrimo medžiaga ir metodai. Regiono biomedicininė tyrimų etikos komitetui leidus, tyrime pasiūlyta dalyvauti ligoniams, kuriems tyrimo vykdymo laikotarpiu VUL Santariškių klinikų Pilvo chirurgijos centre buvo atliktos laparoskopinės storosios žarnos rezekcijos operacijos. Buvo tiriami 58 I–III fizinės klasės pagal Amerikos anesteziologų asociacijos klasifikaciją (ASA) ligoniai, atsitiktinės atrankos būdu suskirstyti į dvi grupes: bendros anestezijos (GA, N = 27) ir kombinuotos anestezijos su epidūrine analgezija (EA, N = 26). Abiejų grupių pacientams taikyta vienoda premedikacija, pykinimo, vėmimo profilaktika, nuskausminimas nesteroidiniais vaistais nuo uždegimo (NVNU), anestezijos indukcija intraveniniu anestetiku ir raumenų relaksantu, anestezijos palaikymui skiriamas tas pats inhaliacinis anestetikas Sevorane. Operacijos metu analgezija skirta pagal poreikį taikant skirtingus metodus: GA grupės pacientams skirti intraveniniai narkotiniai analgetikai (fentanilis, morfinas); EA grupės pacientams pagal poreikį epidūriškai buvo leidžiamas vietinio anestetiko bupivakaino (0,125–0,25 %) ir narkotinio analgetiko morfino mišinys. EA pacientams prieš anesteziją buvo kateterizuojamas epidūrinis tarpas krūtinės srityje. Buvo stebimos abiejų grupių gyvybinės funkcijos, taip pat tirtas kortizolis bei interleukinas-6 veniniame kraujyje prieš anestezijos pradžią, po operacijos ir praėjus 24 val. nuo pradinio tyrimo. CRB tyrimas kartotas pirmą ir šeštą pooperacinę parą. Siekiant užtikrinti hemodinamiką prireikus buvo skiriami koloidai, kai jų nepakakdavo, į veną buvo leidžiamas efedrinas. Tyrimo metu kai kurios laparoskopiskai pradėtos operacijos dėl radinių operacijos metu buvo užbaigtos atlikus laparotomiją, todėl buvo išskirta trečioji, konversijos, pacientų grupė (CG). Šios grupės pacientams perioperacinė analgezija tęsta pradžioje numatytu būdu. Visų grupių pacientų skausmas vertintas pagal vizualią analogų skalę (VAS) nuo 1 iki 10. Pooperaciniam epidūrinės grupės pacientų nuskausminimui nuolat buvo skiriama 0,25 % bupivakaino ir 5 mg morfino tirpalo infuzija. Pirmosios grupės pacientų skausmas buvo slopinamas nesteroidi-

niais vaistais nuo uždegimo, o prireikus – tramadoliu arba morfinu į raumenis. Surinkti duomenys buvo laikomi kompiuterinėje duomenų bazėje ir apdoroti panaudojant *SPSS for Windows 19.0* versiją. Kiekybiniams rodikliams aprašyti buvo apskaičiuotas bendras stebėjimų skaičius (n), vidurkis, standartinis nuokrypis, mediana, minimali bei maksimali reikšmės. Kokybiniai rodikliai aprašyti pateikiant jų procentinę pasiskirstymą. Siekiant palyginti dviejų grupių kiekybinius rodiklius, buvo taikomas parametrinis Studento *t* kriterijus arba neparametrinis Mann-Whitney *U* kriterijus, kelių grupių palyginimui buvo naudojamas ANOVA testas. Lyginant dviejų kokybinių rodiklių tarpusavio sąsają taikytas chi kvadrato kriterijus. Skirtumai laikyti statistškai reikšmingi, jeigu paklaidos tikimybės reikšmė yra mažesnė nei 0,05.

Rezultatai. Laparoskopinių kolorektalinių operacijų metu nustatytas statistškai patikimai mažesnis ($p < 0,003$) kortizolio kiekis kraujyje, kai perioperacinei analgezijai taikomas epidūrinis skausmo malšinimas bupivakaino ir morfino mišiniu. Didžiausias kortizolio kiekis po operacijos nustatytas konversijos grupėje; praėjus 24 val. nuo pradinio matavimo statistškai patikimo skirtumo tarp grupių nenustatyta. Interleukino-6 koncentracija po operacijos skyrėsi tarp GA ir konversijos bei EA ir konversijos grupių ($p < 0,000$). Tiriant koreliaciją tarp diagnozuoto anastomozės pralaidumo ir interleukino-6 kiekio pokyčių praėjus 24 val. po pradinio tyrimo, sąryšis ($p < 0,039$) nustatytas neparametriniu testu, tačiau ANOVA testas to nepatvirtino. Per 6 pooperacines dienas nerasta reikšmingų CRB skirtumų tarp EA ir GA grupių. Nustatytas statistškai patikimai mažesnis skausmo intensyvumas EA grupėje vertinant iškart po operacijos ir po 24 val. ($0,23 \pm 0,82$ vs. $1,48 \pm 1,70$ iškart po operacijos ir $0,46 \pm 0,65$ vs. $3,19 \pm 1,98$ vėliau po operacijos).

Išvados. Kombinuota bendra anestezija su epidūrine analgezija patikimai mažina pooperacinį skausmą, uždegimą skatinančio neuroendokrininio atsako dydį, kortizolio ir interleukino-6 sekreciją laparoskopinių kolorektalinių operacijų metu.

Raktažodžiai: laparoskopinė kolorektalinė chirurgija, epidūrinė analgezija, kortizolis, interleukinas-6