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THE EFFECT OF A SMALL DOSE OF KETAMINE ON POSTOPERATIVE ANALGESIA AND CYTOKINE CHANGES AFTER LAPAROSCOPIC CHOLECYSTECTOMY

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Abstract: *Background and objectives:* In this study we assesed the effect of a small dose of ketamine on the production of TNFα, IL-1β and IL-6 and the postoperative pain in patients undergoing laparoscopic cholecystectomy.

Methods: Fifty patients undergoing laparoscopic cholecystectomy were randomized in two equal groups. Patients in the ketamine group after induction in anesthesia received ketamine – 025 mg/kg^{-1}. At the same time patients from the control group received sodium chloride. Postoperatively, the pain was assessed with VAS at periods of 30 min at 1, 2, 4, 8, 18, 24 and 48 hours. TNFα, IL-1β and IL-6 were evaluated before surgery at 4, 18 and 24h after the operation.

Results: Differences of mean values of TNFα and IL-1β between the two groups in the postoperative period were not significant. Mean values of IL-6 in the investigated group A were significantly lower than the mean values of IL-6 in the investigated group B after the 4th hour (p = 0.00990), after the 18th hour (p = 0.00133) and as after the 24th hour following surgery (p = 000860). the difference in pain intensity

according to the VAS scale was also statistically significantly smaller in group A after 30 min, 1,2,8 and 12 hours after surgery.

Conclusions: The addition of a small-dose of ketamine in patiens undergoing laparoscopic cholecystectomy resulted in attenuation of secretion of TNFα, IL-1β, IL-6 and reduction of postoperative pain.

Key words: ketamine, postoperative pain, proinflammatory cytokines.

Introduction

Laparoscopic surgery has an established place in modern general surgical practice, and provides many benefits over open surgery in patients, including reduction of hospitalization and recovery time, less postoperative pain, a better cosmetic outcome, a lower risk of incisional hernias, and an earlier return to normal activities [1]. However, the pneumoperitoneum itself is not a safe procedure, as evidenced by several structural and functional alterations observed after its use [2–4]. Surgery and anaesthesia elicit a characteristic response involving the metabolism, induction of synthesis and release of acute-phase proteins such as C- reactive protein (CRP), an increase in circulating concentrations of stress hormones (cortisol and catecholamines) and synthesis and release of various mediators, e.g. cytokines [5]. The inflammatory cytokines, such as tumour necrosis factor (TNFα), interleukin-1 (IL-1β) and interleukin-6 (IL-6) are all considered to be important mediators of the pathophysiological changes associated with surgery.

In animals, interleukin-1 (IL-1β) has been reported to be a potent activator of the hypothalamic-pituitary axis and it has been suggested that IL-1β also acts directly on the hypothalamus to induce the release of norepinephrine [6]. Plasma IL-6 levels rise after surgery and this rise reaches its peak between 6 and 12 hours after operation. It has been shown to be proportional to the severity of surgical injury and it is considered to be a sensitive indicator of surgical trauma [7–8]. Plasma IL-6 level is greater after hip replacement than after cholecystectomy [7]. After abdominal surgery, increased IL-6 levels were demonstrated without a simultaneous increase in IL1β and TNFα [9], while cardiopulmonary bypass has been associated with increased blood levels of IL-6 [10], as well as IL1β and TNFα [11]. Interleukin-6 is a very important inflammatory cytokine in the physiology of nociception and the pathophysiology of pain [12].

Effective pain management may affect the immune responses during the postoperative period. An attempt to diminish deleterious side-effects of the opiates on the immune system could be achieved by the addition of drugs with marked analgesic activity capable of attenuating pain stimuli and therefore

allowing reduction of the dosage of opiates. Ketamine, a neurotransmitter acting as an N-methyl D-aspirate receptor antagonist, has been shown to enhance the effect of morphine in control of perioperative pain. Cherry and colleagues have achieved reduction in morphine dosage and pain score by the addition of ketamine, with a direct relationship between ketamine dosage and pain score [13]. Similar results have been observed in patients undergoing knee or abdominal surgery [14]. In patients who received a small dose of ketamine and underwent coronary artery bypass and abdominal hysterectomy, Roytblat and colleagues have reported a decrease in serum IL-6 [15, 16].

The present study was designed to assess the postoperative pain and immunomodulatory effect of a sub-anesthetic dose of ketamine on the serum production of tumour necrosis factor (TNFα), interleukin-1 (IL-1β) and interleukin-6 (IL-6) in patients undergoing laparoscopic cholecystectomy.

Methods

Fifty patients, ASA grade I or II, undergoing elective laparoscopic cholecystectomy were recruited at the University Anaesthesiology, Reanimation and Intensive Care Medicine Clinic within the period from August 2010 to November 2010. Severe hepatic, renal, cardiovascular or psychological disorders, malignant disease, immune system disorders, alcoholism or an inability to understand the study protocol were exclusion criteria. The day before surgery the patients were introduced to the concept of the visual analog scale (VAS) consisting of a 100-mm line ranging from "no pain" to "strongest possible pain".

The patients were premedicated with diazepam 5–10 mg given orally 90 min before operation and with i.v. administration of midazolam 2–3 mg upon arrival at the operating theatre. Anaesthesia was induced by i.v. administration of fentanyl 2–3 μg/kg^{-1}, propofol 1–2 mg/kg^{-1}, atracurium 0.5 mg/kg^{-1}, and maintained with nitrous oxide mixtures with oxygen and sevofluorane. All patients were mechanically ventilated with 12–14 breaths per minute and the tidal volume of 8–10 ml per kilogram of body weight. The end-tidal carbon dioxide concentration was maintained between 35 ± 45 mmHg.

The patients were randomized into two equal groups. Group A (ketamine group) comprised 25 patients who after 5 minutes of the induction of anaesthesia received racemic 025 mg/kg^{-1} ketamine. The dose of ketamine was chosen according to previous experience [16]. Group B (control group) consisted of 25 patients who received a similar volume of isotonic sodium chloride 5 minutes after induction of anesthesia. In the recovery room all patients were monitored for one hour, after which time the patients were returneda to the ward.

Analgesia in the postoperatrive period was provided with i.v. administration of 100 mg ketoprofen. If the patient was still not comfortable or had a

pain score of more than 30 mm according to the visual analog scale (VAS), we administered IV 100 mg tramadol. Postoperatively, the patients were interviewed about the severity of pain according to a visual scale (VAS) at periods of 30 min., 1, 2, 4, 8, 18, 24 and 48 hours.

Immunological assays

Venous blood samples (10 ml) from the peripheral vein were collected before surgery and 4, 18 and 24 h after operation. Blood samples were centrifuged at 4000 rpm for 5 min at 4°C. Serum was separated within 30 minutes to 2 hours from taking the blood sample, to prevent loss of activity, enzymatic degradation and inactivation of cytokines (some of the factors that cause clotting may cause activation of cytokines/receptors). Until the time of performing the analysis, serum samples were stored at -70°C. The concentration of proinflammatory cytokines was quantified using enzyme-linked immunosorbent assays (ELISA) (GE Healthcare, Amersham^{TM}).

The assay system was based on utilization of two different types of antibodies. The first antibodies were attached to the solid phase of the test (96 well microplates) and had a great affinity for interleukin found in the sample. The second antibody was specific for different epitopes of the interleukin. This antibody, the so-called detection antibody, was linked to the enzyme biotin. "Amplifier solution" was added to this complex, which represented a conjugate chain of dextran. This amplification reagent bound a large number of molecules of HRP (horseradish peroksidase). The binding of antibodies became evident when the enzyme bound to the second antibody reacted with the added substrate 3.3; 5.5 tetra-methyl benzedin (TMB). After a while the reaction was stopped by adding sulfuric acid. Finally, a reading of the colouring was made using the ELISA reader on 450 nm. The normal range for TNFα, IL-1β and IL-6 are 0, 9–4,9 pg/mL, 0–1,5 pg/mL and = 0–14,9 pg/mL.

Statistical analysis

Statistical analysis was performed with the Statistical Package of the Social Sciences (SPSS) for Windows. All values were shown as a mean ± (SD). For parametric data (serum concentration of the TNFα, IL-1β and IL-6) groups were compared with analysis of variance (ANOVA) and the Student t-test for dependent and independent samples. For attributive date we used Friedman ANOVA and the Mann-Whitney U Test. A value of $P < 0.05$ was regarded as significant.

Results

A total of 25 examinees who underwent laparascopic cholecystrectomy by adding ketamine (group A, n = 25), and 25 examinees undergoing laparasco-

pic cholecistectomy without added ketamine (group B, n = 25) were analased in this study. The mean age of the examinees in group A was 58 ± 10 years, while in group B it was 55 ± 12 years, and the analysis showed that there was no statistically significant difference (Student t-test: p = 0.3417) (Table 1). As for the gender, an almost identical number of men and women were included in both groups (Mann-Whitney: p = 0.8083) (Table 1). The average body weight of the investigated group A was 78 ± 17 kg, and in group B it was 79 ± 13 kg. The analysis showed that concerning this parameter, there was no significant difference (Student t-test: p = 0.8163) (Table 1).

ASA I classification was recorded in 15 (60%) patients in group A and in 14 (56%) patients in group B, while in the other 10 (40%) patients from group A and 11 (44%) patients from group B, ASA classification II was recorded, and the differences were not statistically significant (Mann-Whitney: p = 0.7787) (Table 1).

Table 1

Mean values and per centages of examinees in investigated groups A and B according to investigated variables and significance of differences

Variables	**A group – (Ketamine group)**	**B group – (Control group)**	**Significant differences (p)**
Age (yr.)	Mean ± std.dev. 58 ± 10	Mean ± std.dev. 55 ± 12	0.3417
Sex (M/F)	12 (48%) / 13 (52%)	13 (52%) / 12 (48%)	0.8083
Weight (kg)	Mean ± std.dev. 78 ± 17	Mean ± std.dev. 79 ± 13	0.8163
ASA I / II	15 (60%) / 10 (40%)	14 (56%) / 11 (44%)	0.7787

*significant difference

As to the mean values of IL-1β, IL-6 and TNFα in the four periods, we made an analysis between both investigated groups. Thus it was found that concerning the IL-1β and TNFα there were also no statistical differences between the two groups in the four time periods.

As to IL-6, the mean values in the investigated group A were statistically significantly lower than the mean values of IL-6 in the examinees from group B, after 4 hours (Studentt-test; p = 0.0099), after 18 hours (Student t-test; p = 0.0013) as well as 24 hours after the end of the operation (Studentt-test; p = 0.0086) (Table 2).

Table 2

Mean values of IL-1β, IL-6 and TNFα in examinees of investigated groups A and B and significance of differences

Variables		A group – (Ketamine group)		B group – (Control group)		Significant differences (p)
		Mean	**Std. Dev.**	**Mean**	**Std. Dev.**	
IL–1β	before op,	1.141	0.326	1.293	0.379	0.1345
	after 4 h	1.207	0.301	1.265	0.262	0.4793
	after 18 h	1.178	0.274	1.210	0.231	0.6535
	after 24 h	1.972	3.398	1.167	0.214	0.2429
IL–6	before op,	1.742	0.908	2.332	2.904	0.3370
	after 4 h	**4.637**	**4.026**	**14.508**	**17.929**	**0.0099***
	after 18 h	**10.797**	**9.185**	**25.889**	**20.147**	**0.0013***
	after 24 h	**9.352**	**7.897**	**20.258**	**18.272**	**0.0086***
TNFα	before op,	0.169	0.028	0.228	0.292	0.3194
	after 4 h	0.165	0.025	0.607	2.223	0.3245
	after 18 h	0.175	0.026	0.285	0.319	0.0933
	after 24 h	0.226	0.171	0.179	0.032	0.17801

*significant difference

The pain level according to VAS scale was followed up in both groups 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 18 hours and 24 hours after the operation.

The analysis according to Friedman ANOVA (in the group) showed that there were statistically significant differences in pain intensity according to the VAS scale in the early postoperative period in the examinees from group A (ANOVA Chi Sqr: = 145.0 df = 8 p = 0.000001) and in the examinees from group B (ANOVA Chi Sqr: 174.8 df = 8 p = 0.000001).

The analysis according to the Mann-Whitney U Test showed that the differences in pain intensity according to the VAS scale were statistically significantly lower in group A 30 min. (p = 0.000001), 1 hour (p = 0.0019), 2 hours (p = 0.000001), 8 hours (p = 0.0104) and 12 hours after the operation (p = 0.0004) but there were no differences in pain intensity according to the VAS scale after 4 hours (p = 0.0667), 18 hours (p = 0.9845), 24 hours (p = 0.6276) and after 48 hours (p = 1.0). (Table 3 and Figure 3.)

Table 3

Mean values of VAS according to hours in examinees from A and B groups and significance of differences

VAS	A group – (Ketamine group)		B group – (Control group)		Significant differences (p)
	Mean	Std. Dev.	Mean	Std. Dev.	
30 min	**3.60**	0.86	**5.80**	0.65	0.000001*
1 h	**3.60**	0.50	**4.24**	0.59	0.0019*
2 h	**2.60**	0.50	**3.84**	0.47	0.000001*
4 h	**3.00**	0.57	**3.36**	0.57	0.0667
8 h	**2.52**	0.58	**3.04**	0.61	0.0104*
12 h	**2.28**	0.46	**2.92**	0.49	0.0004*
18 h	**2.04**	0.45	**2.04**	0.61	0.9845
24 h	**1.48**	0.51	**1.56**	0.50	0.6276
48 h	**1.20**	0.41	**1.20**	0.41	1.0

*significant difference

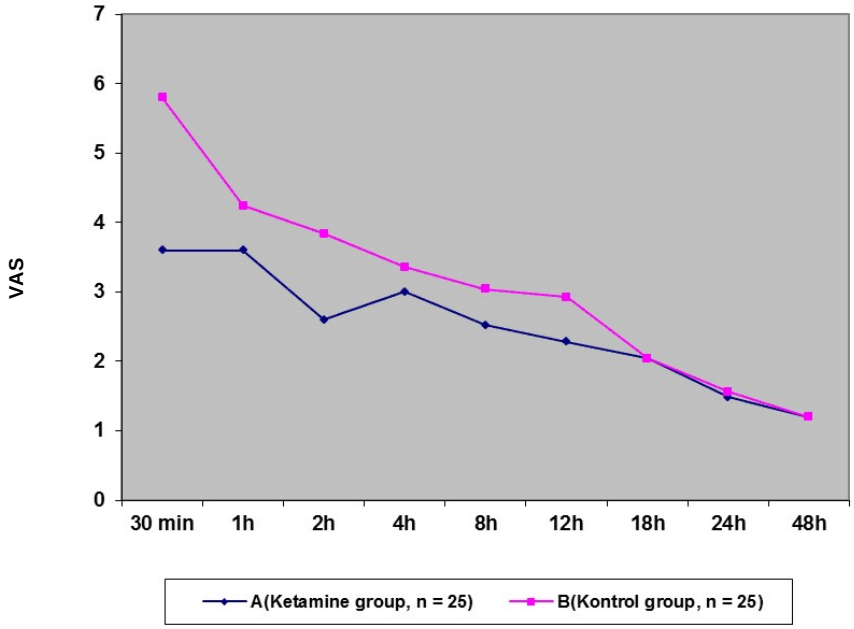

Figure 1 – Mean values of VAS according to hours in investigated groups A and B

Discussion

It is generally agreed that proinflammatory mediators, including cytokines, are to a great extent responsible for metabolic changes associated with injury and surgery. Inflammatory response is associated with the release of a number of proinflammatory cytokines and acute-phase protein. TNFα, IL-1β and IL-6 are major mediators of the acute-phase response in humans [17]. IL-6 is released to plasma in the early postoperative period. This has suggested that the magnitude of the damage of tissues may related to the ability of macrophages/monocytes and fibroblasts to release IL-6, but not TNFα and IL-1β. IL-6 is produced by lymphoid and nonlymphoid cells and affects regulation of T and B cells, IG secretion, acute phase inflammatory reactions and haematopoiesis. TNF-α is an enhancer of IL-6 secretion and is produced primarily by activated monocytes and macrophages. Anaesthetic methods may affect the cytokine response to surgery changing nervous and hormone pathways.

Opioid drugs and local anaesthetics seem to have little effect on the inflammatory component of the stress response [15, 18]. Increasing the dose of opioids during general anaesthesia had little effect on the IL-6 response [18]. Combining regional with general anaesthesia suppressed the endocrine and metabolic response but had little influence on IL-6 increases [19]. Although it is not known by what mechanism ketamine suppresses the IL-6 [15]. Total intravenous anaesthesia (TIVA) with propofol and alfentanil are known to suppress IL-6 production in abdominal hystectomy [20]. Helmy et al. investigated cytokine production in response to TIVA in patients undergoing open and laparascopic cholecystectomy [21]. In their study TNFα and IL-6 increased after open cholecystectomy, but this response was absent in laparascopic cholecystectomy [21].

Clements and Nimmo showed that the analgesic effect of ketamine occurred at a much lower plasma concentration (100 ng/ml) than the anaesthetic effects (700 ng/ml) [21]. In healthy volunteers, IV ketamine application in doses of 0.125 and 0.25 mg/kg increase the pain threshold. At this small dose, the incidence of side-effects does not seem to be clinically important [15]. Ketamine anaesthesia (2mg/kg) alone produces a dose-related increase in cardiovascular stimulation and psychomimetic disturbance after surgery. Decreasing the dose of ketamine can modify these side-effects [15].

Some studies report the recent discovery of the N-Methyl-D-Aspartate (NMDA) receptor which seems to play a role in pain transmission and according to other studies, ketamine binds to these receptors with a nonselective antagonism, reducing wound hyperalgesia. The analgesic efficacy of ketamine is linked to activation of NMDA receptors of the dorsal horn of the spinal cord [23]. NMDA receptors at the spinal level prolong and amplify the nocioceptive

response (wind-up phenomenon). Ketamine acts on nicotinic and muscarinic receptors; it blocks sodium channels in the peripheral and central nervous system and interacts with opioid receptors μ, δ and κ. Ketamine also acts as a noncompetitive antagonist at the phencyclidine receptor site in the NMDA receptor complex canal. This system is involved in the development and maintenance of secondary hyperalgesia after tissue injury [24].

Mathiesen LC et al. demonstrateda lack of preemptive analgesic effect of (R)-ketamine in laparascopic cholecystectomy [25]. Our study reports that the preemptive application of a low dose of ketamine has a significant improvement of postoperative analgesia in the first 8 hours after laparascopic cholescystectomy. This preemptive analgesic effect is already seen in other abdominal surgical procedures [17], anterior cruciate ligament repair [16, 28] and abdominal hysopterectomy [26, 27].

A small dose of ketamine, given before skin incision, decreases postoperative pain, reduces morphine consumption and delays the patient's request for analgesia after laparoscopic gynecological surgery [26]. Christophe Menifaux et al. observed that a single small dose of ketamine administered intraoperatively delays the first request for analgesic, produces a significant 50% morphine–sparing effect during the first 48 hours after knee surgery performed under arthroscopy, and facilitates knee mobilization at 24 hours [28]. Preemptive low-dose ketamine is able to produce adequate postoperative analgesia and increase the analgesic effect of tramadol [22]. Ketamine is the only NMDA antagonist approved by the Food and Drug Administration [29].

Some investigators have suggested that i.v. application of ketamine might have some advantages over epidural ketamine when administered with morphine in blocking nocioceptive sensitization [30]. Moreover, this beneficial effect may only be obtained after systematic administration [30].

Conclusion

In patients undergoing elective laparascopic cholecystectomy the addition of a small dose of ketamine (0.25 mg/kg^{-1}) after induction of anaesthesia resulted in attenuation a of the secretion of proinflammatory cytokines (TNFα, IL-1β, IL-6) during the first postoperative day. Preemptive use of ketamine as a potent noncompetitive NMDA antagonist can improve postoperative analgesia in the early postoperative period in these patients.

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Р е з и м е

ЕФЕКТ НА МАЛИ ДОЗИ НА КЕТАМИН НА ПОСТОПЕРАТИВНАТА АНАЛГЕЗИЈА И ЦИТОКИНСКИТЕ ПРОМЕНИ ПО ЛАПАРАСКОПСКА ХОЛЕЦИСТЕКТОМИЈА

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Во оваа студија ние го оценувавме ефектот на малите дози на кетаминот врз продукцијата на TNFα, IL-1β, IL-6 и постоперативната болка кај пациенти за лапараскопска холецистектомија.

Педесет пациенти за елективна лапараскопска холецистектомија беа поделени во две еднакви групи. Пациентите во кетаминската група, n = 25, по воведот во анестезија добија 0,25 mg/kg^{-1} кетамин. Во исто време пациентите од контролната група, n = 25, добија еднаков волумен на изотоничен натриум хлорид. Во постоперативниот период, болката се оценуваше според визуелно аналогната скала (ВАС) во период од 30 мин, 1, 2, 4, 8, 18, 24 и 48 часа. TNFα, IL-1β и IL-6 беа евалуирани пред започнување на хируршката итервенција, по 4, 18 и 24 часа по операцијата.

Разликите на средните вредности на TNFα и IL-1β помеѓу двете испитувани групи во постоперативниот период не се значителни. Средните вредности на IL-6 кај испитаниците од групата А се статистички значително пониски од средните вредности на IL-6 кај испитаниците од групата В по четвртиот час (p = 0,00990), по осумнаесеттиот час (p = 0,00133) како и по 24 часа од операцијата (p = 0,00860). Разликата во интензитетот на болката според VAS скалата е статистички значително помала кај групата А по 30 мин., 1, 2, 8 и 12 часа по оперативната интервенција.

Додавање на мали дози на кетамин по воведот во анестезија кај пациенти кај кои се изведува лапараскопска холецистектомија резултира со промени во

секрецијата на TNFα, IL-1β, IL-6, но и доведува до редуцирање на постоперативната болка.

Клучни зборови: кетамин, постоперативна болка, проинфламаторни цитокини.

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