Scientific Research Publishing

Open Journal of Anesthesiology, 2022, 12, 261-277
https://www.scirp.org/journal/ojanes
ISSN Online: 2164-5558
ISSN Print: 2164-5531

Effect of Local Wound Infiltration with Ketamine versus Dexmedetomidine Added to Bupivacaine on Inflammatory Cytokines, a Randomized Clinical Trial

Fatma A. El Sherif[1], Moaaz Tohamy[1*], Mohamed A. M. Mostafa[1], Suzan Adlan[2], Sahar Abdel-Baky Mohamed[1], Samar Mansour[3], Mahmoud M. Mohammed[4], Ahmad M. Abd El-Rahman[1]

[1]Anethesia, ICU, and Pain Management, South Egypt Cancer Institute, Assiut University, Assiut, Egypt
[2]Anesthesia, ICU, and Pain Management, National Cancer Institute, Cairo University, Cairo, Egypt
[3]Clinical Pathology, South Egypt Cancer Institute, Assiut University, Assiut, Egypt
[4]Surgical Oncology, South Egypt Cancer Institute, Assiut University, Assiut, Egypt
Email: *moaaz670@gmail.com

How to cite this paper: El Sherif, F.A., Tohamy, M., Mostafa, M.A.M., Adlan, S., Mohamed, S.A.-B., Mansour, S., Mohammed, M.M. and El-Rahman, A.M.A. (2022) Effect of Local Wound Infiltration with Ketamine versus Dexmedetomidine Added to Bupivacaine on Inflammatory Cytokines, a Randomized Clinical Trial. *Open Journal of Anesthesiology*, **12**, 261-277.
https://doi.org/10.4236/ojanes.2022.128024

Received: June 17, 2022
Accepted: August 28, 2022
Published: August 31, 2022

Abstract

Background: Ketamine or dexmedetomidine as an adjuvant to bupivacaine in local wound infiltration attenuated postoperative stress response, especially with ketamine in patients undergoing total abdominal hysterectomy. **Objectives:** Compare effect of local wound infiltration with ketamine or dexmedetomidine added to bupivacaine to bupivacaine alone on inflammatory cytokine response after total abdominal hysterectomy. **Methods:** Sixty female patients with endometrial carcinoma underwent total abdominal hysterectomy and scheduled to receive local wound infiltration before wound closure either with one of three; 40 ml of 0.25% bupivacaine alone (C Group) or with the addition of 2 mg/kg ketamine (K Group) or 2 μg/kg dexmedetomidine (D Group). After extubation, they were followed up for postoperative interleukin 6 (IL6), IL1β, IL10, and TNF-α levels were assessed at baseline, pre-infiltration, 6, and 24 h by blood samples obtained from each patient, hemodynamic variables, analgesic profile and side effects. **Results:** Inflammatory cytokines response was attenuated in K and D groups, evidenced by decreased mean pro-inflammatory cytokines IL6, TNF-α, and increased anti-inflammatory IL10 at 6 and 24 h postoperatively compared to pre-infiltration levels ($p \leq 0.01$) with preservation of IL1β at its preoperative level ($p > 0.05$). Attenuation was more in K and D groups than in the C group and was highest in the K group with decreased 1st request, total morphine consumption with-

out serious side effect. **Conclusion:** Local wound infiltration with ketamine or dexmedetomidine added to bupivacaine has a good postoperative analgesic profile and attenuated cytokines inflammatory response more than bupivacaine alone after total abdominal hysterectomy, with highest attenuation in ketamine group.

Keywords

Ketamine, Dexmedetomidine, Local Infiltration, Cytokines, Hysterectomy

1. Introduction

Oncology patients have immune function deficiency in which cellular immunity is inhibited by the stimulation and anesthesia during the peri-operative period due to (anesthetic techniques, operative trauma, stress response, pain, hypotension, hypothermia, blood transfusion, and hyperglycemia). Moreover, cellular immunity is closely related to infections after surgery, wound healing, and especially tumor metastasis. [1]

Immune changes occurring peri-operatively are primarily a result of surgical trauma and subsequent neuroendocrine responses, which play a central role in mediating the effect of surgery on the immune system. [2] [3]

Adaptive immunity consists of two types, humoral and cellular immunity which is linked to each other by a broad family of proteins called cytokines, which play an important role in immune cell activation, regulation, and communication. [4]

Interleukin-1β (IL1β), IL6, and TNF-α are the primary pro-inflammatory cytokines response to surgery. [3] The importance of IL6 as a reliable and particularly sensitive biomarker of inflammatory activation and a predictor of subsequent organ dysfunction and death has been indicated in numerous studies. [5] [6] IL10 is a potent anti-inflammatory cytokine that down-regulates the expression of Th1 cytokines. IL10 is capable of inhibiting the synthesis of pro-inflammatory cytokines like TNF-α, IL6, IL8, and IL1β. [7]

Single-shot local anesthetic infiltration (LAI) is a commonly used method for reducing postoperative pain. [8] [9] Regional anesthesia has the advantage of preventing noxious stimuli from reaching the central nervous system and, therefore, can attenuate the surgical stress response [10].

Ketamine or dexmedetomidine as an adjuvant to bupivacaine in local wound infiltration attenuated postoperative stress response, especially with ketamine in patients undergoing total abdominal hysterectomy. [11] Owing to the postoperative stress attenuation effect of local wound infiltration of ketamine and dexmedetomidine, we hypothesized that they attenuate the postoperative inflammatory cytokine response.

In this study, we aimed to compare the effect of local wound infiltration with

ketamine or dexmedetomidine added to bupivacaine to bupivacaine alone on inflammatory cytokine response after total abdominal hysterectomy.

2. Patients and Methods

The local ethics committee of South Egypt Cancer Institute, Assuit University, Assuit, Egypt approved this randomized study. Written informed consent was obtained from all participating patients. This study was registered at https://www.clinicaltrials.gov/ with identifier No: NCT03164590.

Sixty female cancer patients with endometrial carcinoma, ASA class I-II with ages 18 - 60 years, and weight 50 - 90 kg scheduled for total abdominal hysterectomy with low midline vertical incision were included in the study. Patients with known drug allergy to any of the study drugs, significant cardiac, respiratory, renal or hepatic diseases, coagulation disorders, and those with psychiatric illnesses that would interfere with perception and assessment of pain were excluded.

Preoperatively, patients were taught how to evaluate their pain intensity using the visual analog scale (VAS), scored from 0 - 10 (where 0 = no pain and 10 = worst pain imaginable), and how to deal with patient-controlled analgesia (PCA) device. Electrocardiogram (ECG), noninvasive blood pressure and pulse oximetry were applied upon arrival to the operative room. Then an intravenous line was introduced, and a two ml blood sample was obtained from each patient to assess baseline levels of inflammatory cytokines (IL 1β, IL6, IL10, and TNF-α) before induction of anesthesia.

No pre-medications were administered to patients of all groups. General anesthesia was induced with intravenous fentanyl 1 μg/kg, propofol 2 mg/kg, and rocuronium 0.6 mg/kg and maintained with sevoflurane in 50% oxygen/air mixture and rocuronium 0.1 mg/ kg. Intravenous (IV) fluids were administered. Towards the end of the surgery, another two ml blood sample was obtained from each patient to assess the levels of inflammatory cytokines immediately before wound infiltration. Local wound infiltration was performed intra-operatively before skin closure by the surgeon who was blinded to the investigational drug identity, which was prepared by the hospital clinical pharmacist in a sterile syringe. Patients were randomly assigned using an online research randomizer (http://www.randomizer.org) into three groups (20 patients each):

Ketamine (K) group: 20 patients received local wound infiltration with 40 ml of bupivacaine 0.25% + 2 mg/*kg* ketamine in two divided doses *i.e.* 20 ml on each side of the incision line.

Dexmedetomidine (D) group: 20 patients received local wound infiltration with 40 ml of bupivacaine 0.25% + 2 μg/kg dexmedetomidine in two divided doses *i.e.*, 20 ml on each side of the incision line.

Control (C) group: 20 patients received local wound infiltration with 40 ml of bupivacaine 0.25% in two divided doses *i.e.*, 20 ml on each side of the incision line.

After wound closure and adequate reversal of muscle relaxant effect and extubation, all patients were transferred to the post-anesthesia care unit (PACU). The postoperative patients' heart rate, noninvasive arterial blood pressure, respiratory rate, and oxygen saturation were monitored for the first 24 hrs. Hypotension, defined as a 15% decrease in the systolic blood pressure from baseline (preoperative measurements), was treated with an intravenous bolus of ephedrine 0.1 mg/kg. Bradycardia, defined as a decrease in the heart rate of 20% or more from baseline, was treated with intravenous atropine 0.01 mg/kg.

A blinded resident collected data; the presence and severity of pain at rest and on movement (coughing) were assessed using a 10 cm visual analog scale (VAS). If the VAS was ≥ 3, rescue analgesia was started by 0.1 mg/kg IV morphine bolus. Followed by patient-controlled analgesia (PCA), with a concentration of morphine of 1 mg/ml (each button push delivers a bolus of 1 ml, with a 5-minute lockout interval, with no background infusion) continued for 24 hrs. Two further blood samples (2 ml each) were obtained from each patient at 6 and 24 hrs postoperatively to assess inflammatory cytokines levels.

Side effects like nausea, vomiting, hypotension, bradycardia, chest pain, respiratory depression (respiratory rate below 8/minute), sedation, and psychological complications (hallucination, dissociative effects, delirium) were recorded all over the 24 h and treated accordingly. The duration of ICU and hospital stay were also recorded. The four blood samples [baseline (before anesthesia induction), pre-infiltration, 6 and 24 h] were collected in plasma tubes containing ethylenediamine-tetra-acetic (EDTA), centrifuged and stored at −20˚C for assessment of serum concentrations of cytokines (IL1β, IL6, IL10, and TNF-α) by a blinded investigator. Human premixed Muti assayed serum cytokines-Analyte Kit, Luminex Assay (LXSAH-10®; R&D systems, Minneapolis, MN, USA).

3. Statistical Analysis

Our primary outcome measure was the IL6 level (pg/ml) in the first 24 h. Secondary outcome measures were the levels of inflammatory cytokines (IL 1β, IL10, and TNF-α), visual analog scale at rest and movement (VASR-M), 1st request and total dose of morphine consumption incidence of side effects and ICU stay.

Sample size calculations were based on data from previous literature on changes on the levels of IL6 [12]. To detect a minimal difference of 1 SD in the IL6 levels in between, and within the study groups, it was calculated that 18 patients per group were required for the study to have a of 80% and a type I error of 0.05, using a confidence interval (CI) of 95%.

To compensate for dropouts, we recruited 20 patients in each group to account for random errors and additional comparisons.

All data were collected by Microsoft Excel program then analyzed with Statistical Package for the Social Sciences software (SPSS®) version 17 (IBM, Chicago, IL). Data were presented as number, percentage, mean (SD), median (range).

Chi-Square test was used to compare qualitative variables as (ASA class and side effects). One sample Kolmogorov-Smirnov normality test was used to test the distribution of quantitative variables to select accordingly to the type of statistical testing to use; parametric or nonparametric. The test showed that our data were not normally distributed, and nonparametric tests were used for statistical analysis. Kruskal-Wallis Test was used to compare the quantitative variables between three groups, and further analysis was done by the Mann-Whitney test to compare every two groups. Wilcoxon signed-rank test was used to compare pre and post-follow-up in the same group. A P-value of < 0.05 was considered statistically significant.

4. Results

The participating flow chart illustrated in (Figure 1). Regarding the demographic data (age, weight, and ASA) of the enrolled patients, there was no significant difference between the three studied groups ($p > 0.05$) (Table 1).

There was a significant decrease in mean IL6 level (pg/ml) in K group (81.07 ± 52.18) and D group (93.97 ± 61.26) respectively compared to C group (119.56 ± 66.29) at 6 h; ($p \leq 0.046$), and at 24 hrs in K group (75.44 ± 53.86) and D group (86.50 ± 55.67) respectively compared to C group (125.88 ± 74.99) ($p \leq 0.034$). Also, in each group, there was a significant decrease when comparing 6 and 24 hrs time points postoperatively to the pre-infiltration levels in K, D, and C groups ($p \leq 0.009$) but the lowest level was in K group (Table 2, Figure 2).

There was a significant difference in the mean levels of IL10 and TNF-α (pg/ml) between the three groups when compared all together ($p < 0.001$) at 6 and 24 h postoperatively but not in IL1β (Table 2, Figure 3). Comparing the IL10 levels at 6 and 24 h to the pre-infiltration levels, there was a significant increase in K and D groups ($p \leq 0.001$) (Table 2, Figure 4).

There was a significant decrease in the TNF-α levels at 6 and 24 h in K, D and C groups when compared to the pre-infiltration level and the lowest level was in K group ($p \leq 0.002$) (Table 2, Figure 5).

There was a significant reduction in median VAS-R score in-group K starting immediately postoperatively, at 2, 4, 6, 8 and 24 h compared to group C. In addition, there was a significant reduction in median VAS-R score in-group D starting immediately postoperatively up to 8 h compared to group C ($p \leq 0.05$). There was no significant difference between group K and group D in the median postoperative VAS-R score at any time point (Figure 6).

Also median VAS-M score, there was a significant reduction in median VAS-M in group K starting at 2 h postoperatively till 24 h compared to group C and a significant reduction in median VAS-M in group D starting at 2 and 4 h postoperative compared to group C with no significant differences between group K and group D at any time point (Figure 7).

PCA morphine consumption was significantly reduced in group K 5 mg (5 - 20 mg) and group D 10mg (5 - 15 mg) compared to group C 15 mg (5 - 20 mg)

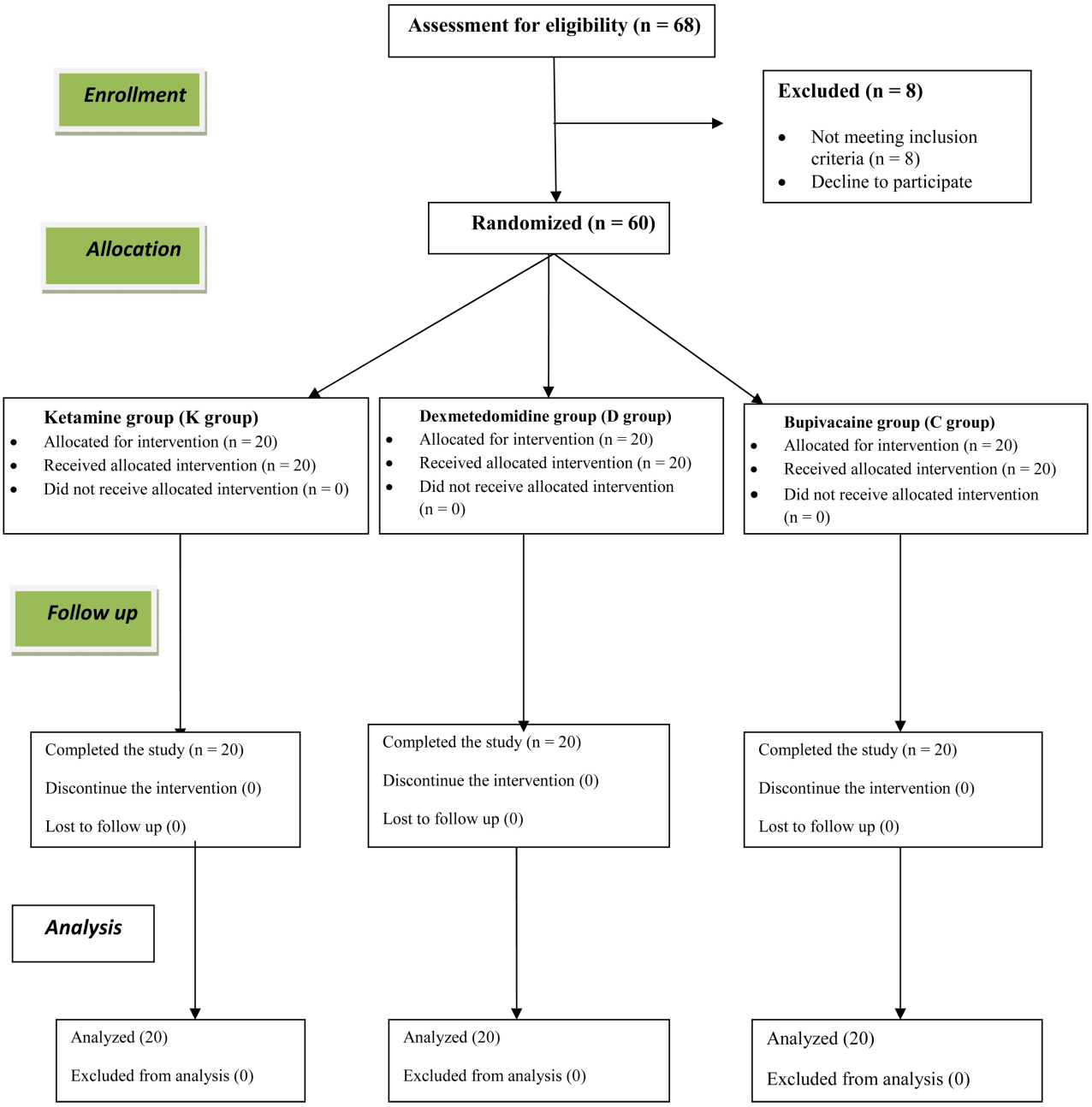

Figure 1. Patients flow diagram.

with no significant difference between K and D groups (p = 0.441) (Table 3). Time to the first request of rescue analgesia was significantly prolonged in group K 6 (2 - 12) h) and group D 6 (2 - 12) h compared to group C 4 (2 - 8 h) (p < 0.026) (Table 3).

The mean postoperative duration of ICU stay was in K group (1.10 ± 0.31 days), D group (1.15 ± 0.37 days) and C group (1.35 ± 0.59 days) and the hospital stay were in K group (3.80 ± 0.52 days), D group (3.85 ± 0.59 days) and C group (4.05 ± 0.22 days) with no significant differences (p > 0.05).

Three patients (15.0%) had nausea in group C compared to two (10%) in K

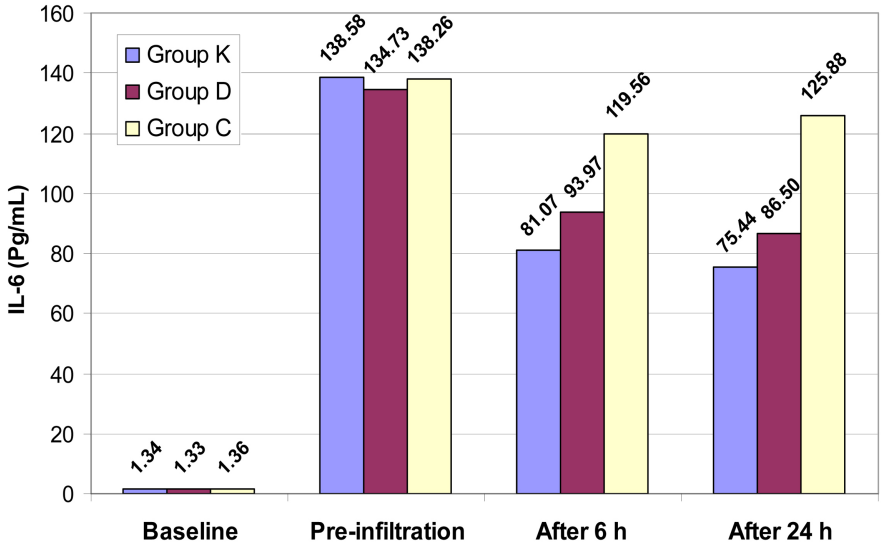

Figure 2. Changes in the level of interleukins (IL6) in (pg/mL) during the 24 hrs post-operatively. Group K: ketamine group; Group D: dexmetedomidine; Group C: control group. Data are presented as mean and SD; the number marked on the column was the standard deviation; After 6 or 24 hours indicates 6 and 24 hours after local infiltration postoperatively; baseline, before induction of anesthesia; Pre-infiltration: just before local infiltration and after induction of anesthesia.

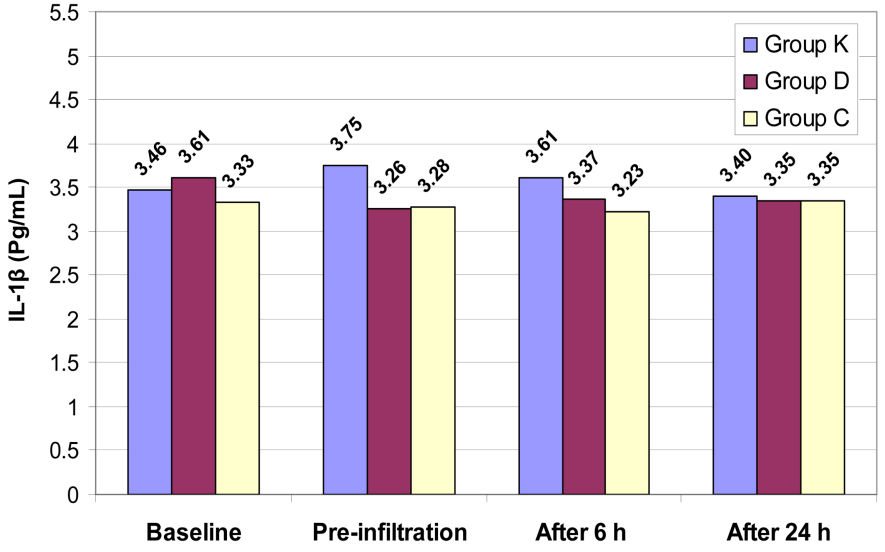

Figure 3. Changes in the level of interleukins (IL1β) in (pg/mL) during the 24 hrs post-operatively. Group K: ketamine group; Group D: dexmetedomidine; Group C: control group. Data are presented as mean and SD; the number marked on the column was the standard deviation; After 6 or 24 hours indicates 6 and 24 hours after local infiltration postoperatively; baseline, before induction of anesthesia; Pre-infiltration: just before local infiltration and after induction of anesthesia.

group and 1 (5.0%) in D group. Vomiting occurred in 2 (10%) patients in both C and K groups while only in 1 (5.0%) patient in D group. Only one patient had hypotension in group D. No significant differences observed in the incidence of the other side effects including sedation between the three studied groups.

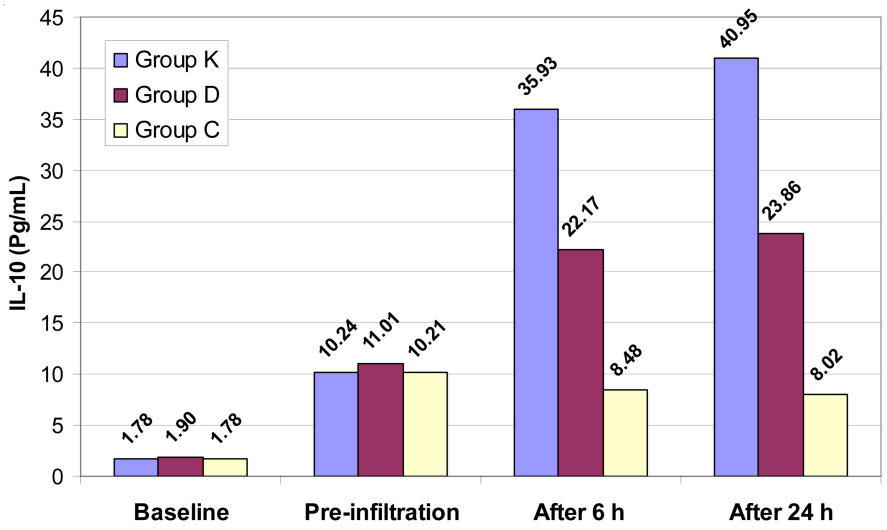

Figure 4. Changes in the level of interleukins (IL10) in (pg/mL) during the 24 hrs post-operatively. Group K: ketamine group; Group D: dexmetedomidine; Group C: control group. Data are presented as mean and SD; the number marked on the column was the standard deviation; After 6 or 24 hours indicates 6 and 24 hours after local infiltration postoperatively; baseline, before induction of anesthesia; Pre-infiltration: just before local infiltration and after induction of anesthesia.

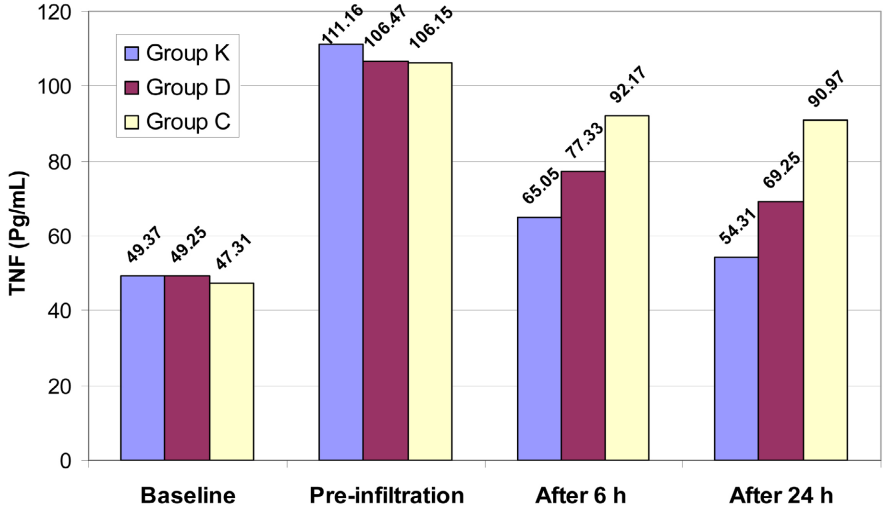

Figure 5. Changes in the level of interleukins (TNFα) in (pg/mL) during the 24 hrs post-operatively. Group K: ketamine group; Group D: dexmetedomidine; Group C: control group. Data are presented as mean and SD; the number marked on the column was the standard deviation; After 6 or 24 hours indicates 6 and 24 hours after local infiltration postoperatively; baseline, before induction of anesthesia; Pre-infiltration: just before local infiltration and after induction of anesthesia.

5. Discussion

We compared the effect of local wound infiltration of bupivacaine alone or bupivacaine mixed with ketamine or dexmedetomidine on the inflammatory response following total abdominal hysterectomy. The inflammatory response was reduced, evidenced by a decrease in the proinflammatory cytokines (IL6 and

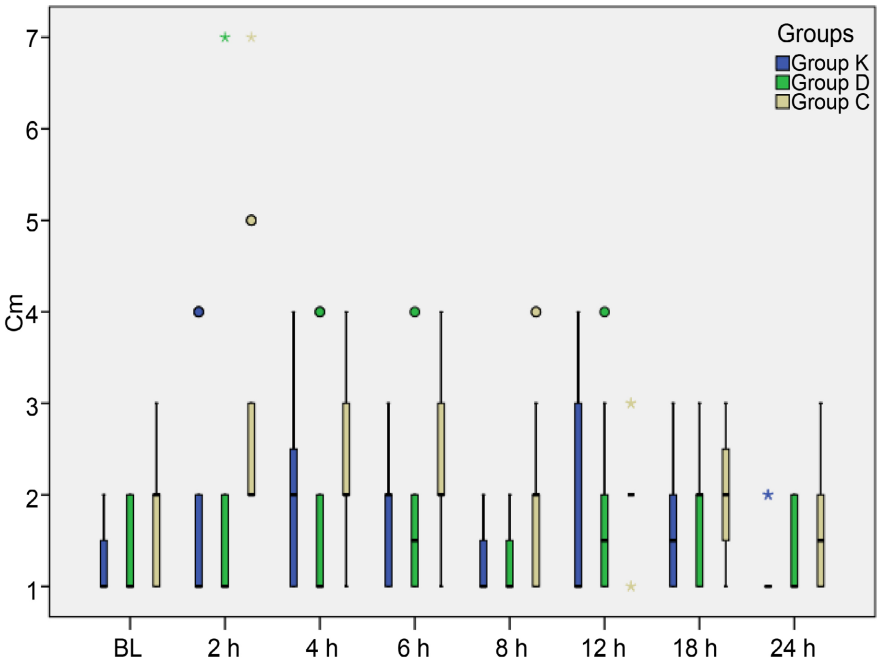

Figure 6. Visual analogue scale at rest between the three studied groups (VAS-R) in the 24 hours postoperatively after local wound infiltration with the studied medication. Group K: ketamine group; Group D: dexmetedomidine; Group C: control group. (I) Whisper indicated standarddeviation. *indicated significant difference between groups. Bl: base line value before anesthesia induction.

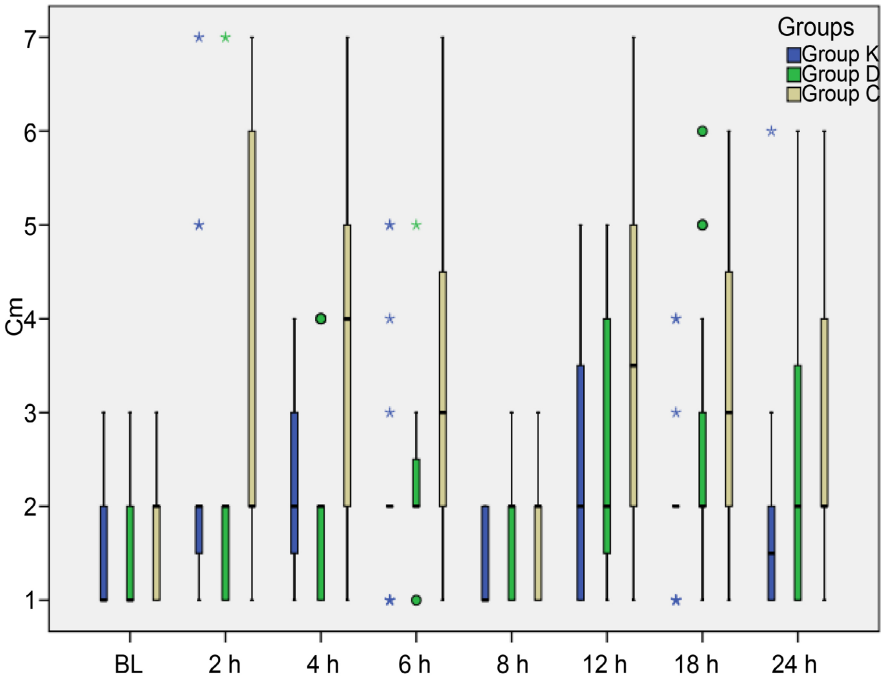

Figure 7. Visual analogue scale at movement between the three studied groups (VAS-M) in the 24 hours postoperatively after local wound infiltration with the studied medication. Group K: ketamine group; Group D: dexmetedomidine; Group C: control group. (I) Whisper indicated standard deviation. *indicated significant difference between groups. Bl: base line value before anesthesia induction.

Table 1. Demographic data of the studied groups.

	Group K (n = 20)	Group D (n = 20)	Group C (n = 20)	P-value[1]	P-value[2]	P-value[3]	P-value[4]
	Mean ± SD	Mean ± SD	Mean ± SD				
Age (years)	48.85 ± 4.70	48.20 ± 4.86	48.60 ± 5.08	0.894	0.644	0.817	0.796
Weight (kg)	72.65 ± 8.44	73.40 ± 8.08	73.50 ± 8.08	0.926	0.818	0.684	0.914
ASA score:							
ASA I	8 (40.0%)	9 (45.0%)	10 (50.0%)	0.817	0.749	0.525	0.752
ASA II	12 (60.0%)	11 (55.0%)	10 (50.0%)				

Data presented mean ± SD and No (%): ASA (American Society of Anesthesiologist). Group K: ketamine group; Group D: dexmetedomidine; Group C: control group. P-value[1]: p value comparing the three groups all together. P-value[2]: p value comparing group K to group D. P-value[3]: p value comparing group K to group C. P-value[4]: p value comparing group D to group C.

Table 2. Changes in the level of interleukins (pg/mL) (IL1β, IL6, IL10 and TNF-α) during the 24 hrs postoperatively.

		Group K (n = 20)	Group D (n = 20)	Group C (n = 20)	P-value[1]	P-value[2]	P-value[3]	P-value[4]
		Mean ± SD	Mean ± SD	Mean ± SD				
IL-1	**Baseline**	3.46 ± 3.11	3.61 ± 2.87	3.33 ± 3.02	0.798	0.735	0.797	0.482
	Pre-infiltration	3.75 ± 2.65	3.26 ± 2.50	3.28 ± 2.86	0.401	0.304	0.213	0.725
	After 6 h	3.61 ± 3.01	3.37 ± 2.44	3.23 ± 2.92	0.655	0.968	0.516	0.351
	P-value[5]	0.185	0.490	0.122				
	After 24 h	3.40 ± 2.55	3.35 ± 2.55	3.35 ± 3.01	0.798	0.808	0.473	0.745
	P-value[6]	0.051	0.872	0.432				
IL-6	**Baseline**	1.34 ± 0.20	1.33 ± 0.18	1.36 ± 0.26	0.986	0.892	0.935	0.892
	Pre-infiltration	138.58 ± 92.07	134.73 ± 75.35	138.26 ± 74.42	0.987	0.914	0.946	0.882
	After 6 h	81.07 ± 52.18	93.97 ± 61.26	119.56 ± 66.29	0.125	0.499	**0.028***	**0.046***
	P-value[5]	**0.000***	**0.000***	**0.000***				
	After 24 h	75.44 ± 53.86	86.50 ± 55.67	125.88 ± 74.99	**0.032***	0.337	**0.013***	**0.034***
	P-value[6]	**0.000***	**0.000***	**0.009***				
IL-10	**Baseline**	1.78 ± 0.89	1.90 ± 0.97	1.78 ± 1.04	0.779	0.675	0.715	0.507
	Pre-infiltration	10.24 ± 8.84	11.01 ± 8.94	10.21 ± 8.96	0.863	0.715	0.871	0.598
	After 6 h	35.93 ± 14.07	22.17 ± 17.71	8.48 ± 8.33	**0.000***	**0.001***	**0.000***	**0.000***
	P-value[5]	**0.000***	**0.001***	**0.015***				
	After 24 h	40.95 ± 10.90	23.86 ± 11.22	8.02 ± 7.04	**0.000***	**0.000***	**0.000***	**0.000***
	P-value[6]	**0.000***	**0.001***	**0.008***				
TNF	**Baseline**	49.37 ± 38.71	49.25 ± 37.92	47.31 ± 38.27	0.922	0.892	0.705	0.776
	Pre-infiltration	111.16 ± 46.16	106.47 ± 48.27	106.15 ± 47.89	0.926	0.725	0.745	0.989
	After 6 h	65.05 ± 38.15	77.33 ± 27.59	92.17 ± 21.09	**0.018***	**0.044***	**0.011***	**0.032***
	P-value[5]	**0.002***	**0.000***	**0.000***				
	After 24 h	54.31 ± 32.81	69.25 ± 37.88	90.97 ± 32.37	**0.003***	**0.058**	**0.002***	**0.025***
	P-value[6]	**0.000***	**0.000***	**0.000***				

Data presented mean ± SD Group K: ketamine group. Group D: dexmetedomidine group. Group C: control group. P-value[1]: p value comparing the three groups all together. P-value[2]: p value comparing group K to group D. P-value[3]: p value comparing group K to group C. P-value[4]: p value comparing group D to group C. P-value[5]: p value comparing level at 6 hrs to the pre-infiltration level. P-value[6]: p value comparing level at 24 hrs to the pre-infiltration level. *Significant P-value.

Table 3. Total postoperative morphine consumption (mg) and first request of rescue analgesia (hr) in the 24 hours postoperatively after local wound infiltration with the studied medication.

	Group K	Group D	Group C	P-value[1]	P-value[2]	P-value[3]	P-value[4]
First request:							
Mean ± SD	6.71 ± 4.00	6.06 ± 3.40	3.70 ± 1.75	0.026*	0.711	0.020*	0.021*
Median (Range)	6 (2 - 12)	6 (2 - 12)	4 (2 - 8)				
Total morphine dose:							
Mean ± SD	7.94 ± 4.70	8.33 ± 3.43	14.00 ± 3.48	0.000*	0.441	0.000*	0.000*
Median (Range)	5 (5 - 20)	10 (5 - 15)	15 (5 - 20)				

Group K: ketamine group; Group D: dexmetedomidine; Group C: control group. P-value[1]: p value comparing the three groups all together. P-value[2]: p value comparing group K to group D. P-value[3]: p value comparing group K to group C. P-value[4]: p value comparing group D to group C.

TNF-α) and an increase in the anti-inflammatory cytokines (IL10) with the preservation of IL1β production at its preoperative level. The reduction was more evident in the ketamine group than in other groups without the development of significant side effects.

Wound infiltration with local anesthetics is a simple, effective, and cheap method of providing adequate postoperative analgesia without significant side effects. Wound infiltration seems not only to provide analgesia in lower abdominal surgery it might reduce the up-regulation of peripheral nociceptors that manifests as increased sensitivity to pain [13]. Moreover, it has been suggested that regional anesthetic techniques can reduce postoperative stress response. [14] Local wound infiltration with ketamine or dexmedetomidine added to bupivacaine had an opioid-sparing effect, delayed the first request of rescue analgesia, and attenuated the postoperative stress response especially with ketamine in patients undergoing total abdominal hysterectomy [11]. It may be logical to think that a reduction in stress response through better analgesia by using regional anesthetic techniques may reduce inflammation.

To the best of our knowledge, the effect of locally infiltrated ketamine or dexmedetomidine as adjuvants in wound infiltration on postoperative inflammatory response is not yet explored. In our study, the plasma levels of IL6, TNF-α, and IL10 increased markedly at the end of surgery just before wound infiltration compared to their baselines. The addition of ketamine or DEX decreased the elevation of IL6 and TNF-α with increased IL10 at six and 24 hrs postoperatively more than using bupivacaine alone. This highlights the local effect of ketamine or DEX on postoperative inflammatory response and the immune system in this group of already immunocompromised patients.

IL-6 is the "gold index," reflecting surgical stress, which plays an anti-inflammatory and proinflammatory role. [15] by activating the hypothalamic-pituitary-adrenocortical axis system in the process of stress reaction and immune response. [16] IL6 is a main proinflammatory cytokine produced as early as 2 - 4 h after tissue damage. Circulating IL6 levels appear to be proportional to

the extent of tissue injury during operation. [17] In particular, elevations of IL6 levels have been correlated with the subsequent development of postoperative complications. [18]

Those enforced the importance of IL6 than other cytokines and were chosen as our primary outcome.

Ketamine seems to exert a beneficial effect on the post-surgical immune response via several mechanisms, acting as an analgesic; it causes alleviation of pain, which by itself is a promoter of proinflammatory cytokine production. [19] Peripheral analgesic effect of ketamine may be easily explained by blocking of sodium and potassium currents in peripheral nerves. [20]

The analgesic effects of ketamine are generally believed to be mediated through the blockade of phencyclidine binding site of NMDA receptors of the nociceptive neurons. However, ketamine has also been reported to interact with opioid, monoamine, cholinergic, purinergic, and adenosine receptor systems. [21]

Ketamine, similar to local anesthetics, possesses anti-inflammatory effects without affecting local healing processes (blunting neutrophil activation but sparing endothelial production of cytokines) [22]. This is mediated by its effect on G-protein-coupled-receptor signaling, specifically Gg down regulation. [23] Moreover, a list of proposed mechanisms mediates the anti-inflammatory effects of ketamine including; inhibition of nuclear factor-κB and activator protein [24], inhibition of proinflammatory cytokine production (IL6 and TNFα) [25], inhibition of neutrophil functions [26], the release of adenosine [27], blockade of large-conductance KCa channels on microglia (BK channels), or inhibition of nitric oxide production in macrophages [28]. Ketamine also downregulates the proinflammatory enzymes cyclooxygenase 2 and inducible nitric oxide synthase and preserves the expression of the anti-inflammatory, heme-oxygenase-1 [29].

In accordance with us, Dale *et al.* [21] concluded that intraoperative ketamine significantly inhibited the early postoperative IL6 inflammatory response during major surgery. Beilin *et al.* [30] also reported that the addition of IV 0.15 mg/kg ketamine reduced the secretion of the proinflammatory cytokines IL6 and TNF-α in the early postoperative period up to 4 hrs. Remarkably, in our study, inflammatory response attenuation lasted for up to 24 hrs probably because the higher ketamine dose we used (2 mg/kg), despite the different route of administration.

In addition, Kawasaki *et al.* [31] reported that ketamine suppressed TNF-α and IL6 in whole human blood and directly suppressed proinflammatory cytokine production. Ketamine reduced IL6 and increased IL10 but not TNF-α after coronary arteries bypass grafting and may facilitate the production of anti-inflammatory mediators, as reported by Welters *et al.* [32]

The local analgesic effect of dexmedetomidine is caused by enhancement of the hyperpolarization-activated cation current, which prevents the nerve from returning from a hyperpolarized state to resting membrane potential for subsequent firing [33].

In our study, local wound infiltration of 2 μg/kg DEX at the end of surgery reduced the levels of the proinflammatory cytokines IL6, TNF-α, and increased anti-inflammatory IL10 with preservation of IL1β at its preoperative level more than using bupivacaine alone, but to a lesser extent than ketamine.

DEX has suppressing effects of inflammatory mediators via α2-adrenoceptor-mediated mechanism and necrosis factor κB (NFκB) this inhibition mechanism is responsible for the production of TNFα and IL6 (34). Recently, it has been demonstrated that DEX has the ability to activate phagocytosis [35].

In addition, DEX suppresses the sympathetic and stimulates the parasympathetic nervous systems [36] Stimulating the vagus nerve has an anti-inflammatory response [37] by suppressing peripheral cytokine release via macrophage nicotinic receptors and the cholinergic anti-inflammatory pathway. Therefore, DEX has beneficial roles for immune-compromised patients because of its effect on innate immunity activation and anti-inflammatory responses. [34]

Studying the effects of dexmedetomidine and α2-adrenergic receptor agonists on cytokines [38] [39] revealed that they modulate lipopolysaccharide-induced TNF-α production on macrophages [40]. Taniguchi *et al.* [41] showed that dexmedetomidine had an inhibitory effect on cytokine responses in endotoxemia. Memis *et al.* [42] found that dexmedetomidine infusion decreased cytokine production in sepsis and suggested a modulator effect of dexmedetomidine on cytokine production by macrophages and monocytes. Also, Tasdogan *et al.* [43] reported that dexmedetomidine infusion of one μg/kg over 10 minutes followed by a maintenance dose of 0.2 - 2.5 μg/kg/hr at the 24th hrs decreases TNF-α and IL6 levels up to 24th and 48th hrs. This means that high doses and long infusion time are required to achieve the same effect on the cytokine response. The local site of administration of dexmedetomidine is the main reason for the absence of side effects associated with its systemic use.

Our study might be limited by the short period of measuring inflammatory cytokines, and we recommend further researches measuring them for several postoperative days. In addition, despite the absence of systemic side effects like hypotension, bradycardia, and sedation, we think that this study is limited by a lack of measurement of serum levels of ketamine and dexmedetomidine, to rule out, confidently, their possible systemic effects.

6. Conclusion

Local wound infiltration with either ketamine or DEX added to bupivacaine has a good postoperative analgesic profile and attenuated inflammatory response compared to bupivacaine alone after total abdominal hysterectomy, with more attenuation in the ketamine group.

Data Sharing Statement

We are not planning to share any of the data with anyone.

Conflicts of Interest

None of the authors has conflict of interests.

References

[1] Snyder, G.L. and Greenberg, S. (2010) Effect of Anesthetic Technique and Other Perioperative Factors on Cancer Recurrence. *British Journal of Anaesthesia*, **105**, 106-115. https://doi.org/10.1093/bja/aeq164

[2] Chrousos, G.P. (1995) The Hypothalamic-Pituitary-Adrenal Axis and Immune-Mediated Inflammation. *The New England Journal of Medicine*, **332**, 1351-1362. https://doi.org/10.1056/NEJM199505183322008

[3] Kennedy, B.C. and Hall, G.M. (1999) Neuroendocrine and Inflammatory Aspects of Surgery: Do They Affect Outcome? *Acta Anaesthesiologica Belgica*, **50**, 205-209.

[4] Colucci, D.G., Puig, N.R. and Hernandez Pando, R. (2013) Influence of Anaesthetic Drugs on Immune Response: From Inflammation to Immunosuppression. *OA Anaesthetics*, **1**, 21-38. https://doi.org/10.13172/2052-7853-1-3-1091

[5] Kanda, T. and Takahashi, T. (2004) Interleukin-6 and Cardiovascular Diseases. *Japanese Heart Journal*, **45**, 183-193. https://doi.org/10.1536/jhj.45.183

[6] Cruickshank, A.M., Fraser, W.D., Burns, H.J., Van, D.J. and Shenkin, A. (1990) Response of Serum Interleukin-6 in Patients Undergoing Elective Surgery of Varying Severity. *Clinical Science*, **79**, 161-165. https://doi.org/10.1042/cs0790161

[7] de Waal Malefyt, R., Abrams, J., Bennett, B., Figdor, C.G. and de Vries, J.E. (1991) Interleukin 10(IL-10) Inhibits Cytokine Synthesis by Human Monocytes: An Autoregulatory Role of IL-10 Produced by Monocytes. *Journal of Experimental Medicine*, **174**, 1209-1220. https://doi.org/10.1084/jem.174.5.1209

[8] Coughlin, S.M., Karanicolas, P.J., Emmerton-Coughlin, H.M., Kanbur, B., Kanbur, S. and Colquhoun, P.H. (2010) Better Late than Never? Impact of Local Analgesia Timing on Postoperative Pain in Laparoscopic Surgery: A Systematic Review and Meta Analysis. *Surgical Endoscopy*, **24**, 3167-3176. https://doi.org/10.1007/s00464-010-1111-1

[9] Einarsson, J.I., Sun, J., Orav, J. and Young, A.E. (2004) Local Analgesia in Laparoscopy: A Randomized Trial. *Obstetrics & Gynecology*, **104**, 1335-1339. https://doi.org/10.1097/01.AOG.0000146283.90934.fd

[10] Abbagh, A. and Elyasi, H. (2007) The Role of Paravertebral Block in Decreasing Postoperative Pain in Elective Breast Surgeries. *Medical Science Monitor*, **13**, CR464-CR467.

[11] Mohamed, S.A., Sayed, D.M., El Sherif, F.A. and Abd El-Rahman, A.M. (2018) Effect of Local Wound Infiltration with Ketamine versus Dexmedetomidine on Postoperative Pain and Stress after Abdominal Hysterectomy, a Randomized Trial. *European Journal of Pain*, **22**, 951-960. https://doi.org/10.1002/ejp.1181

[12] Othman, A.H., Ahmed, D.G., Abd El-Rahman, A.M., El Sherif, F.A., Mansour, S. and Aboeleuon, E. (2019) Effect of Preperitoneal versus Epidural Analgesia on Postoperative Inflammatory Response and Pain Following Radical Cystectomy: A Prospective, Randomized Trial. *The Clinical Journal of Pain*, **35**, 328-334. https://doi.org/10.1097/AJP.0000000000000679

[13] Kerr, D. and Kohan, L. (2008) Local Infiltration Analgesia. A Technique for the Control of Acute Postoperative Pain Following Knee and Hip Surgery. *Acta Orthopaedica*, **79**, 174-183. https://doi.org/10.1080/17453670710014950

[14] Bozkurt, P. (2002) The Analgesic Efficacy and Neuroendocrine Response in Pedia-

tric Patients Treated with Two Analgesic Techniques: Using Morphine Epidural and Patient Controlled Analgesia. *Pediatric Anesthesia*, **12**, 248-254. https://doi.org/10.1046/j.1460-9592.2002.00791.x

[15] El-Tahan, M.R., Mowafi, H.A., Al Sheikh, I.H., Khidr, A.M. and Al-Juhaiman, R.A. (2012) Efficacy of Dexmedetomidine in Suppressing Cardiovascular and Hormonal Responses to General Anaesthesia for Caesarean Delivery: A Dose Response Study. *International Journal of Obstetric Anesthesia*, **21**, 222-229. https://doi.org/10.1016/j.ijoa.2012.04.006

[16] Yang, X.H., Bai, Q., Lv, M.M., Fu, H.G., Dong, T.L. and Zhou, Z. (2017) Effect of Dexmedetomidine on Immune Function of Patients Undergoing Radical Mastectomy: A Double Blind and Placebo Control Study. *European Review for Medical and Pharmacological Sciences*, **21**, 1112-1116.

[17] Wei, M. (2001) Cytokine Responses and Anti-Inflammatory Strategies in Coronary Artery Bypass Grafting. Tampere University Press, Tampere.

[18] Baigrie, R.J., Lamont, P.M., Kwiatkowski, D., Dallman, M.J. and Morris, P.J. (1992) Systemic Cytokine Response after Major Surgery. *British Journal of Surgery*, **79**, 757-760. https://doi.org/10.1002/bjs.1800790813

[19] Beilin, B., Bessler, H., Mayburd, E., Smirnov, G., Dekel, A., Yardeni, I. and Shavit, Y. (2003) Effects of Preemptive Analgesia on Pain and Cytokine Production in the Postoperative Period. *Anesthesiology*, **98**, 151-155. https://doi.org/10.1002/bjs.1800790813

[20] Brau, M.F., Sander, F., Vogel, W. and Hempelmann, G. (1997) Blocking Mechanism of Ketamine and Its Enantiomers in Enzymatically Demylinated Peripheral Nerve as Revealed by Single-Channel Experiments. *Anesthesiology*, **86**, 394-404. https://doi.org/10.1097/00000542-199702000-00014

[21] Dale, O., Somogyi, A.A., Li, Y. and Shavit, Y. (2012) Does Intraoperative Ketamine Attenuate Inflammatory Reactivity Following Surgery? A Systematic Review and Meta-Analysis. *Anesthesia & Analgesia*, **115**, 934-943. https://doi.org/10.1213/ANE.0b013e3182662e30

[22] Hollmann, M.W. and Durieux, M.E. (2000) Local Anesthetics and the Inflammatory Response: A New Therapeutic Indication? *Anesthesiology*, **93**, 858-875. https://doi.org/10.1097/00000542-200009000-00038

[23] Hollmann, M.W., Herroeder, S., Kurz, K.S., Hoenemann, C.W., Struemper, D., Hahnenkamp, K. and Durieux, M.E. (2004) Time-Dependent Inhibition of G Protein-Coupled Receptor Signaling by Local Anesthetics. *Anesthesiology*, **100**, 852-860. https://doi.org/10.1097/00000542-200404000-00015

[24] Welters, I.D., Hafer, G., Menzebach, A., Muhling, J., Neuhauser, C., Browning, P. and Goumon, Y. (2010) Ketamine Inhibits Transcription Factors Activator Protein 1 and Nuclear Factor-kappaB, Interleukin-8 Production, as Well as CD11b and CD16 Expression: Studies in Human Leukocytes and Leukocytic Cell Lines. *Anesthesia & Analgesia*, **110**, 934-941. https://doi.org/10.1213/ANE.0b013e3181c95cfa

[25] Wu, G.J., Chen, T.L., Ueng, Y.F. and Chen, R.M. (2008) Ketamine Inhibits Tumor Necrosis Factor-Alpha and Interleukin-6 Gene Expressions in Lipopolysaccharide-Stimulated Macrophages through Suppression of Toll-Like Receptor 4-Mediated c-Jun N-Terminal Kinase Phosphorylation and Activator Protein-1 Activation. *Toxicology and Applied Pharmacology*, **228**, 105-113. https://doi.org/10.1016/j.taap.2007.11.027

[26] Weigand, M.A., Schmidt, H., Zhao, Q., Plaschke, K., Martin, E. and Bardenheuer, H.J. (2000) Ketamine Modulates the Stimulated Adhesion Molecule Expression on

Human Neutrophils *in Vitro*. *Anesthesia & Analgesia*, **90**, 206-212. https://doi.org/10.1097/00000539-200001000-00041

[27] Mazar, J., Rogachev, B., Shaked, G., Ziv, N.Y., Czeiger, D., Chaimovitz, C., Zlotnik, M., Mukmenev, I., Byk, G. and Douvdevani, A. (2005) Involvement of Adenosine in the Anti-Inflammatory Action of Ketamine. *Anesthesiology*, **102**, 1174-1181. https://doi.org/10.1097/00000542-200506000-00017

[28] Li, C.Y., Chou, T.C., Wong, C.S., Ho, S.T., Wu, C.C., Yen, M.H. and Ding, Y.A. (1997) Ketamine Inhibits Nitric Oxide Synthase in Lipo-Polysaccharide Treated Rat Alveolar Macrophages. *Canadian Journal of Anesthesia*, **44**, 989-999. https://doi.org/10.1007/BF03011971

[29] Ward, J.L., Adams, S.D., Delano, B.A., Clarke, C., Radhakrishnan, R.S., Weisbrodt, N.W. and Mercer, D.W. (2010) Ketamine Suppresses LPS-Induced Bile Reflux and Gastric Bleeding in the Rat. *The Journal of Trauma*, **68**, 69-75. https://doi.org/10.1097/TA.0b013e3181a8b3a7

[30] Beilin, B., Rusabrov, Y., Shapira, Y., Roytblat, L., Greemberg, L., Yardeni, Z. and Bessler, H. (2007) Low-Dose Ketamine Affects Immune Responses in Humans during the Early Postoperative Period. *British Journal of Anaesthesia*, **99**, 522-527. https://doi.org/10.1093/bja/aem218

[31] Kawasaki, T., Ogata, M., Kawasaki, C., Ogata, J., Inoue, Y. and Shigematsu, A. (1999) Ketamine Suppresses Pro-Inflammatory Cytokine Production in Human Whole Blood *in Vitro*. *Anesthesia & Analgesia*, **89**, 665-669. https://doi.org/10.1213/00000539-199909000-00024

[32] Welters, D., Feurer, M.K., Preiss, V., Muller, M., Scholz, S., Kwapisz, M., *et al.* (2011) Continuous S-(+)-ketamine Administration during Elective Coronary Artery Bypass Graft Surgery Attenuates Proinflammatory Cytokine Response during and after Cardiopulmonary Bypass. *British Journal of Anaesthesia*, **106**, 172-179. https://doi.org/10.1093/bja/aeq341

[33] Brummett, C.M., Hong, E.K., Janda, A.M., Amodeo, F.S. and Lydic, R. (2011) Perineuraldexmedetomidine Added to Ropivacaine for Sciatic Nerve Block in Rats Prolongs the Duration of Analgesia by Blocking the Hyperpolarization-Activated Cation Current. *Anesthesiology*, **115**, 836-843. https://doi.org/10.1097/ALN.0b013e318221fcc9

[34] Kawasaki, T., Kawasaki, C., Ueki, M., Hamada, K., Habe, K. and Sata, T. (2013) Dexmedetomidine Suppresses Proinflammatory Mediator Production Inhuman Whole Blood *in Vitro*. *Journal of Trauma and Acute Care Surgery*, **74**, 1370-1375. https://doi.org/10.1097/01586154-201305000-00028

[35] Sanders, R.D., Hussell, T. and Maze, M. (2009) Sedation & Immunomodulation. *Critical Care Clinics*, **25**, 551-570. https://doi.org/10.1016/j.ccc.2009.05.001

[36] Kamibayashi, T. and Maze, M. (2000) Clinical Uses of alpha2-Adrenergic Agonists. *Anesthesiology*, **93**, 1345-1349. https://doi.org/10.1097/00000542-200011000-00030

[37] Tracey, K.J. (2002) The Inflammatory Reflex. *Nature*, **420**, 853-859. https://doi.org/10.1038/nature01321

[38] Straub, R.H., Herrmann, M., Berkmiller, G., Frauenholz, T., Lang, B., Scholmorich, J. and Falk, W. (1997) Neuronal Regulation of Interleukin 6 Secretion in Murine Spleen: Adrenergic and Opioidergic Control. *Journal of Neurochemistry*, **68**, 1633-1639. https://doi.org/10.1046/j.1471-4159.1997.68041633.x

[39] Maes, M., Lin, A., Kenis, G., Egyed, B. and Bosmans, E. (2000) The Effects of Noradrenaline and alpha-2 Adrenoceptor Agents on the Production of Monocytic Products. *Psychiatry Research*, **96**, 245-253.

https://doi.org/10.1016/S0165-1781(00)00216-X

[40] Szelenyi, J., Kiss, J.P. and Vizi, E.S. (2000) Differential Involvement of Sympathetic Nervous System and Immune System in the Modulation of TNF-alpha Production by alpha2- and beta-Adrenoceptors in Mice. *Journal of Neuroimmunology*, **103**, 34-40. https://doi.org/10.1016/S0165-5728(99)00234-9

[41] Taniguchi, T., Kidani, Y., Kanakura, H., Takemoto, Y. and Yamamoto, K. (2004) Effects of Dexmedetomidine on Mortality Rate and Inflammatory Responses to Endotoxin-Induced Shock in Rats. *Critical Care Medicine*, **32**, 1322-1326. https://doi.org/10.1097/01.CCM.0000128579.84228.2A

[42] Memis, D., Hekimoğlu, S., Vatan, I., Yandim, T., Yuksel, M. and Sut, N. (2007) Effects of Midazolam and Dexmedetomidine on Inflammatory Responses and Gastric Intra-Mucosal pH to Sepsis, in Critically Ill Patients. *British Journal of Anaesthesia*, **98**, 550-552. https://doi.org/10.1093/bja/aem017

[43] Tasdogan, M., Memis, D., Sut, N. and Yuksel, M. (2009) Results of a Pilot Study on the Effects of Propofol and Dexmedetomidine on Inflammatoryresponses and Intra-abdominal Pressure in Severe Sepsis. *Journal of Clinical Anesthesia*, **21**, 394-400. https://doi.org/10.1016/j.jclinane.2008.10.010

Abbreviations

IL1β: Interleukin-1β; TNF-α: Tumor necrosis factor α; LAI: Local anesthetic infiltration; ASA: American Society of Anesthesiologists; VAS: Visual, analog scale; PCA: Patient-controlled analgesia; ECG: Electrocardiogram; PACU: Post-anesthesia care unit; ICU: Intensive care unit; SPSS: Social Sciences software; DEX: dexmedetomidine.