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Attenuation of systemic inflammatory stress response after preoperative analgesia with clonidine compared to levobupivacaine-a randomised clinical trial

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Abstract

***Background and Purpose**: Use of analgetics before the pain stimulus (preventive analgesia) obstruct development of neuroplastic changes in central nervous system, and reduces pain. Furthermore, preventive analgesia can block harmful central nervous system response and inflammation as an early consequence of operation as well. Investigation hypothesis is that preoperative central clonidine will reduce systemic inflammatory stress response better than levobupivacaine.*

***Materials and Methods:**. Patients were allocated to three groups, according to preoperative epidural use of 5 μg/kg clonidine (n=17), 0.25% levobupivacaine (n=12) or saline as control group (n=13). Before operation, 1 h after the beginning, 1 h, 6 h, 12 h and 24 h after the operation following parameters were analyzed: procalcitonin (PCT), interleukine-6 (IL-6), C-reactive protein (CRP) and lactate.*

***Results:** There were no significant differences between groups in age, gender, body mass index and operation time. We demonstrated significant reduction in PCT, IL-6, CRP and lactate levels in preoperative clonidine group, compared to preoperative levobupivacaine group and controle group. Conclusion. These results support importance of clonidine central effect on pain pathways and systemic inflammatory stress response blockade.*

INTRODUCTION

Investigations showed that rising production of prostaglandine E2 and interleukin-6 at central sites is an important component of surgery induced inflammatory response in patients. Postoperative period is associated with an increased production of cytokines, which augment pain sensitivity. Use of analgesics for immunomodulation can improve patient recovery *(1, 5, 9)*.

Preventive analgesia is based on the concept that the occurrence of strong pain stimulus, hyperexcitation and hyperalgesia are possible to prevent by early blockade of pain pathways *(1, 2)*. Prolonged pain stimulus leads to secondary neuroplastic changes in the central nervous system, known as central sensitization, resulting in exaggerated response to afferent pain stimulus and amplification of pain (hyperalgesia). Administration of analgesics before the pain stimulus or surgical trauma, prevents harmful central nervous system response and inflammation as an early consequence of operation as well *(3, 4)*. In order to achieve success, preventive analgesia should meet two important

conditions, i.e. complete suppression of the afferent pain stimulus and adequate duration in the early postoperative course *(4)*.

Clonidine is an a_2-adrenergic agonist with known sedative, analgesic and hemodynamic properties. It inhibits transmission of nociceptive stimuli in the dorsal horn of the spinal cord, acting on the inhibitory descending pathways *(5, 6)*. Nader et al. showed that preoperative peroral administration of clonidine reduced TNF-alpha level in plasma and cerebrospinal fluid *(7)*. Investigation of Wu et al. reported reduced IL-1RA, IL-6, IL-8 and postoperative pain levels during and after operation, associated with preoperative epidural clonidine treatment *(8)*.

Investigations of long-acting local anesthetic levobupivacaine administered by epidural and intrathecal route provide evidence for improved postoperative analgesia with reduced analgesic consumption *(10, 11, 12, 13)*. But, it remains unknown if that analgesia is sufficient enough to blockade inflammatory stress response during perioperative time.

The aim of the present study is to investigate hypothesis that preoperative administration of epidural clonidine will attenuate systemic inflammatory stress response better than epidural levobupivacaine. The study was designed to compare clonidine and levobupivacaine, and than both with the control group.

MATERIALS AND METHODS

The investigation was carried out in the double-blinded manner, with due approval from the institution Ethics Committee and an informed consent from all study subjects.

Inclusion criteria were patients with well-defined colorectal carcinoma, without spread of malignant disease, confirmed by colonoscopy and computerized tomography (CT), body mass index (BMI) under 30, and perioperative risk for anesthesia and operation, classified as ASA (American Society of Anesthesiologists) physical status I or II. Exclusion criteria were diabetes mellitus, renal insufficiency (kreatinin level>120μmol/L), liver insufficiency (bilirubin level>20 μmol/L, aspartat-aminotransferase>35 i.j./L, alanin-aminotransferase>35 i.j./L), autoimmune disease, corticosteroid and immunosupressive use, and operation time exceeding six hours.

According to a computer generated randomisation list, 50 patients were randomly assigned for one of three intervention groups. Eight patients were dropped out; one could not have the epidural catheter placed. Finally, 42 patients concluded the study (clonidine group, n=17; levobupivacaine group, n=12, controle group, n=13). On the day before the operation, patients were informed on the perioperative procedure, especially of introducing an epidural catheter for pain therapy. Epidural catheter was inserted at the Th10-L1 level (BRAUN Perifix 20 G catheter, winged 18 G Tuohy needle). Correct positioning was tested using 2 ml 2% lidocaine. Patient was observed for 5 minutes for the development of sensory blockade changes.

One hour prior to skin incision patients received 5 μg/kg of clonidine [Catapres®, Boehringer Ingelheim, Germany] or 7 mL of 0.25% levobupivacaine [Chirocaine®, Abbott S.p.A., Italy] or saline. Epidural catheter insertion and drug administration were performed by the anesthesiologist, who was not involved in the anesthesia maintenance. The operation was performed under general anesthesia using midazolam (0.15 mg/kg), fentanyl (2 μg/kg) and vecuronium (0.1 mg/kg) to facilitate endotracheal intubation, and sevoflurane, nitrous oxide 50% in oxygen, boluses of fentanyl and muscle relaxant for maintenance. After the surgery and recovery from anesthesia, patients were transferred to intensive care unit for continuous monitoring of vital functions and homeostasis. On their demand, upon the pain complaint all patients received boluses of epidural morphine 0.06 mg/kg diluted in 20 mL of isotonic saline.

Before operation (T0), 1 h after the beginning (T1), 1 h (T2), 6 h (T3), 12 h (T4) and 24 h (T5) after the operation following parameters were analyzed: procalcitonin (PCT), interleukine-6 (IL-6), C-reactive protein (CRP) and lactate.

The PCT level was measured using a semi-quantitative immunochromatographic rapid test (BRAHMS PCT-Q, Diagnostica, Berlin, Germany). All samples were centrifuged and examined using 6 drops of serum with enclosed dropper pipette into the cavity of the kit. After 30 minutes at room temperature the PCT concentration range of the sample was determined. A PCT concentration ≥0.5 ng/ml can be seen as a reddish band; the color intensity is directly proportional to the PCT concentration. The validity of the test was checked in comparison of the control band. The PCT ranges were as follows: slightly elevated PCT = 0.5 ng/ml, moderately elevated >0.5 ng/ml, markedly elevated PCT ≥2 ng/ml and severely elevated PCT ≥10 ng/ml.

Measurement of IL-6 was performed with enzyme-linked immunosorbent assay (ELISA), using commercially available kits (Bender MedSystems GmbH, Vienna, Austria). The study of CRP was determined by immunoturbidimetric method on the Olympus AU2700 analyzer (Tokyo, Japan).

A randomisation schedule was computer generated by a biostatistician (not otherwise involved in the study). Statistical analysis was performed using SPSS 15.01 Statistical Package (SPSS Inc, Chicago, IL, USA). Kolmogorov-Smirnov test was used to determine intragroup distribution. For quantitative variables with normal distribution one-way analysis of variance (ANOVA) and

TABLE 1
Patient's characteristics (X±SD).

	Clonidine group	Levobupivacaine group	Control group	P
Age (yr)	64.69±7.779	66.00±8.496	65.08±9.041	0.905
Gender				
Male / Female	11 / 6	7 / 5	8 / 5	0.941
BMI (kg/m^2)	25.65±3.90	25.42±2.867	25.69±2.634	0.975
BSA (m^2)	1.94±0.233	2.04±0.265	2.00±0.173	0.437
Operation time (min)	173.82±30.492	150.00±34.902	168.77±32.527	0.149

*P<0.05

Pearson correlation were used. When ANOVA yielded P<0.05, Scheffe's multiple comparison test was used. Data were expressed as Mean±SD. Variable without normal distribution (PCT) was analyzed with nonparametric Kruskal-Wallis test and Spearman correlation. Data was expressed as median (25th–75th percentile). Qualitative data were compared using the χ^2 test. Statistical significance was set at P<0.05.

RESULTS

There were no significant differences in age, gender, body mass index (BMI), body surface area (BSA) and duration of operation among the groups of patients (Table 1). In preoperative clonidine group, PCT levels remain unchanged, compared to preoperative levobupivacaine group, where PCT inceased at the end of investigation. Statistical differences were found at investigation times T3, T4 and T5 (Table 2).

IL-6 levels were significantly lower in preoperative clonidine group throughout investigation time, compared to preoperative levobupivacaine group. Statistical differences were comfirmed at investigation times T1, T2, T3, T4 and T5 (Table 3). CRP levels were significantly lower in clonidine group compared to levobupivacaine group at T5 (Table 4). Lactate levels were significantly lower in clonidine group compared to levobupivacaine group in investigation time T0, and compared to controle group in investigation times T1, T2, T3 and T4 (Table 5).

DISCUSSION

Patients undergoing major surgical resection are at high risk for postoperative infectious complications. They may benefit from early and efficient perioperative analgesia in order to attenuate systemic inflammatory stress response *(17, 18)*. Epidural clonidine was superior to in-

TABLE 2.
Procalcitonin (PCT) levels.

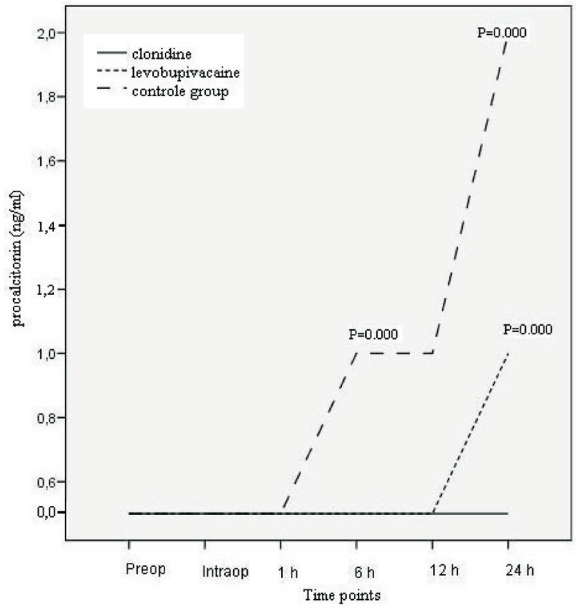


TABLE 3.
Interleukine-6 (IL-6) levels.

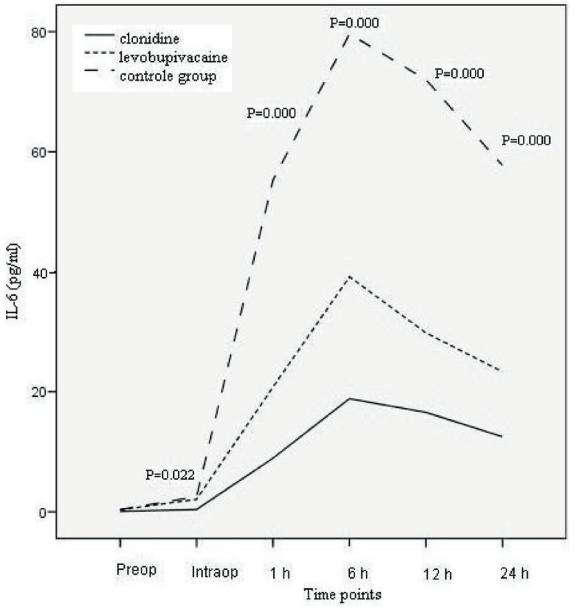


TABLE 4.
C-reactive protein (CRP) levels.

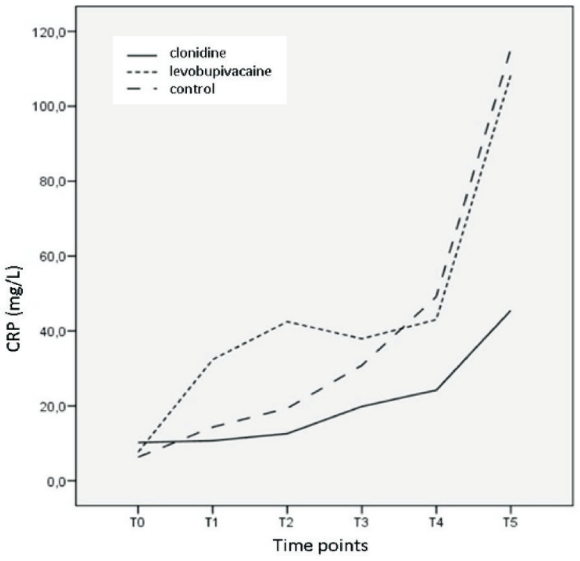
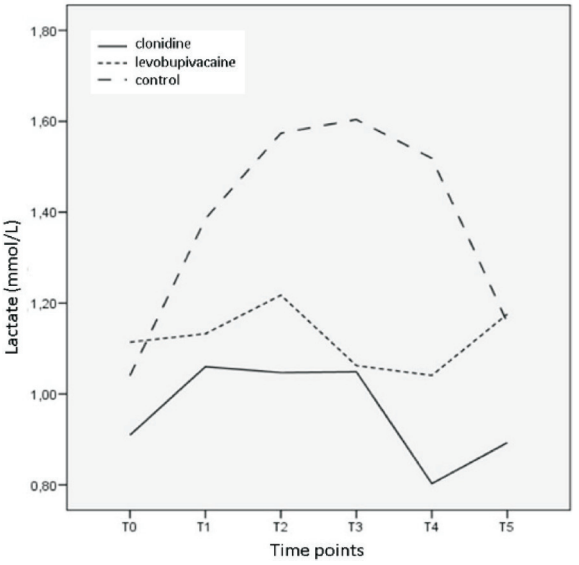


TABLE 5.
Lactate levels.



travenous route in postoperative pain control and immune stress response blockade in investigation of Novak-Jankovic et al., which benefit to his central effect *(5)*.

In our study, clonidine and levobupivacaine were administered by epidural route. We did not observe side effects or complications of epidural analgesia during investigation. Usually, elective surgery induces an increase in PCT after 2 h, rapidly increases between 6–8 h, with highest concentrations at 18 h. The magnitude of elevation is related directly to surgical trauma and inflammation *(3, 4)*. Postoperatively, PCT levels were increased in preoperative levobupivacaine and controle group, but remain unchanged in preoperative clonidine group. These results are similar to those of Sarbinowski et al. who emphasized importance of PCT as an early marker in differentiation of non-SIRS and SIRS patients following major oncological surgery *(18)*, as well as results of Watt *et al. (3)*.

Levels of IL-6 increases proportionally to severity of tissue trauma and inflammation within 1–3 h, with concentration peak at 6 h, and may remain elevated for 48–72 h. In our study levels of IL-6 were significantly higher in levobupivacaine group and controle group, with highest rise at 6 h (T3). The pattern of change of IL-6 was similar to that of PCT, and comparable to results of Mokart *et al. (19)* and Neunhoeffer *et al. (16)*. Levels of CRP and lactate were also lower in preoperative clonidine group, but it was much less prominent.

In conclusion, using the centrally acting a_2-adrenergic agonist clonidine before the pain stimulus has set in resulted in reduced systemic inflammatory stress response compared to levobupivacaine. From the clinical point of view, this effect can contribute to reduction of postoperative complications, which may be a worthwhile advantage to postoperative patients.

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