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Preoperative Clonidine or Levobupivacaine – Effect on Systemic Inflammatory Stress Response

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A B S T R A C T

With perioperative pain control it is possible to supervise immune system, release of inflammation mediators, and influence on treatment outcome. Use of analgetics before the pain stimulus (preventive analgesia) obstruct development of neuroplastic changes in central nervous system, and reduces pain. Investigation hypothesis was that preoperative epidural clonidine is more efficient in blockade of systemic inflammatory stress response comparing to levobupivacaine. Patients were allocated to three groups, according to preoperative epidural use of clonidine, levobupivacaine or saline (control group). Before operation, 1 h after the beginning, 1 h, 6 h, 12 h and 24 h after the operation following parameters were analyzed: interleukine-6, C-reactive protein and leukocyte count. There were no significant differences between groups in age, gender, body mass index and operation time. In preoperative clonidine group, we found significant reduction in interleukine-6 levels throughout investigation time, compared to preoperative levobupivacaine group and control group. Also, C-reactive protein was significantly lower at the end of investigation, compared to other two groups. Leukocyte count was lower, and within the normal range in all investigation times only in preoperative clonidine group. We demonstrated significant difference that support importance of clonidine central effect on pain pathways and systemic inflammatory blockade.

Key words: *clonidine, levobupivacaine, systemic inflammatory stress response, epidural analgesia*

Introduction

Postoperative period is associated with an increased production of cytokines, which augment pain sensitivity. Use of analgesics for immunomodulation can improve patient recovery[1].

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[2,3]. 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. 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[4,5].

Clonidine is an α_2-adrenergic agonist with 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. According to recent investigations clonidine lowers proinflammatory cytokine level, and prevents hypersensitization acting through adrenoreceptors alpha-2A[6]. Investigation of *Wu et al.* reported reduced postoperative pain level, analgesics consumption and IL-1RA, IL-6 and IL-8 levels during and after operation, associated with preoperative epidural clonidine treatment[7]. This results

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contribute to clonidine attenuating systemic inflammatory stress response. According to *Nader et al*. preoperative administration of clonidine reduced TNF-alpha level in plasma and cerebrospinal fluid[8]. Preoperative epidural clonidine was superior to intravenous route in postoperative pain control and immune stress response blockade in investigation of *Novak-Jankovic et al.*, which benefit to his central effect[9].

Levobupivacaine is novel long-acting local anesthetic, S-enantiomer of bupivacaine, with identical anesthetic potency[12,13]. When administered intraperitonealy or by local infiltration of operation site, levobupivacaine produced analgesia and reduction of proinflammatory cytokines[14–16]. Investigations of epidural and intrathecal levobupivacaine provide evidence for improved postoperative analgesia with reduced analgesic consumption[18,19]. But, it remains unknown if that analgesia is sufficient enough to blockade inflammatory stress response during perioperative time.

The aim of the present study was to investigate hypothesis that preoperative administration of epidural clonidine is more efficient in systemic inflammatory stress response blockade 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. The study included 42 patients undergoing colorectal resection surgery. According to the perioperative risk of anesthesia and operation, study patients were classified as ASA (American Society of Anesthesiologists) physical status I or II. Exclusion criteria were diabetes mellitus, renal and liver insufficiency, autoimmune disease, corticosteroid and immunosupressive use, and operation time exceeding six hours.

Patients were randomized into three groups: preoperative epidural clonidine (Group 1), preoperative epidural levobupivacaine (Group 2) and preoperative epidural saline as a control group (Group 3). On the day before the operation, patients were informed on the perioperative procedure, especially of introducing an epidural catheter for pain therapy. Before the operation, a 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), 7 mL of 0.25% levobupivacaine (Chirocaine®, Abbott S.p.A.) or saline. 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 vecuronium 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: interleukine-6 (IL-6), C-reactive protein (CRP) and leukocyte count (L).

Statistical analysis was performed using the one-way analysis of variance (ANOVA). Statistical significance was set at $p<0.05$. Results were expressed as Mean ± SD.

Results

There were no significant age, gender and body mass index differences among the groups of patients relative to pharmacokinetic and pharmacodynamic drug patern. Duration of operations were similar. In the preoperative clonidine group, we found significant reduction in IL-6 levels throughout investigation time, compared to preoperative levobupivacaine group and control group of patients (Table 1). Statistical differences were comfirmed at investigation times T1, T2, T3, T4 and T5 (Table 2).

CRP was significantly lower at the end of investigation, compared to other two groups (Table 3). Statistical difference was found in T5 (Table 4). Also, in preoperative clonidine group leukocyte count was lower, and within the normal range in all investigation times, com-

TABLE 1
INTERLEUKINE-6 LEVELS

GROUP	Mean	SD
Group 1 IL-6 (pg/mL) /T0	0.05	0.123
IL-6 (pg/mL) /T1	0.394	0.8105
IL-6 (pg/mL) /T2	8.941	2.3369
IL-6 (pg/mL) /T3	18.865	3.3339
IL-6 (pg/mL) /T4	16.571	3.6107
IL-6 (pg/mL) /T5	12.512	4.9777
Group 2 IL-6 (pg/mL) /T0	0.36	1.026
IL-6 (pg/mL) /T1	2.092	2.7064
IL-6 (pg/mL) /T2	20.817	13.9161
IL-6 (pg/mL) /T3	39.167	13.1461
IL-6 (pg/mL) /T4	29.817	11.5760
IL-6 (pg/mL) /T5	23.342	12.5872
Group 3 IL-6 (pg/mL) /T0	0.38	0.985
IL-6 (pg/mL) /T1	2.546	2.7440
IL-6 (pg/mL) /T2	55.277	16.4381
IL-6 (pg/mL) /T3	79.623	12.0297
IL-6 (pg/mL) /T4	71.985	11.2838
IL-6 (pg/mL) /T5	57.715	16.3108

TABLE 2
DIFFERENCE IN INTERLEUKINE-6 LEVELS

	Sum of Squares	df	Mean Square	F	Sig.
IL-6 /T0					
Between Groups	1.034	2	0.517	0.859	0.431
Within Groups	23.468	39	0.602		
Total	24.503	41			
IL-6 /T1					
Between Groups	39.133	2	19.567	4.206	0.022
Within Groups	181.431	39	4.652		
Total	220.564	41			
IL-6 /T2					
Between Groups	16393.055	2	8196.528	58.545	0.000
Within Groups	5460.141	39	140.004		
Total	21853.196	41			
IL-6 /T3					
Between Groups	27505.957	2	13752.979	140.578	0.000
Within Groups	3815.429	39	97.832		
Total	31321.386	41			
IL-6 /T4					
Between Groups	23614.539	2	11807.269	143.429	0.000
Within Groups	3210.529	39	82.321		
Total	26825.068	41			
IL-6 /T5					
Between Groups	15710.306	2	7855.153	57.458	0.000
Within Groups	5331.764	39	136.712		
Total	21042.070	41			

*$P<0.05$

TABLE 3
C-REACTIVE PROTEIN LEVEL

GROUP	Mean	SD
Group 1 CRP (mg/L) /T0	10.229	5.4844
CRP (mg/L) /T1	10.682	3.9480
CRP (mg/L) /T2	12.582	6.0067
CRP (mg/L) /T3	19.853	10.7765
CRP (mg/L) /T4	24.190	11.5140
CRP (mg/L) /T5	45.500	21.5873
Group 2 CRP (mg/L) /T0	7.667	5.9344
CRP (mg/L) /T1	32.375	61.0644
CRP (mg/L) /T2	42.492	69.6184
CRP (mg/L) /T3	37.917	52.8670
CRP (mg/L) /T4	43.050	53.2230
CRP (mg/L) /T5	108.400	33.4547
Group 3 CRP (mg/L) /T0	6.308	6.5084
CRP (mg/L) /T1	14.338	31.2970
CRP (mg/L) /T2	19.354	30.4888
CRP (mg/L) /T3	30.815	32.7972
CRP (mg/L) /T4	49.190	37.9290
CRP (mg/L) /T5	115.377	25.0041

TABLE 4
DIFFERENCE IN C-REACTIVE PROTEIN LEVEL

	Sum of Squares	df	Mean Square	F	Sig.
CRP /T0 Between Groups	119.687	2	59.844	1.695	0.197
Within Groups	1376.951	39	35.306		
Total	1496.638	41			
CRP /T1 Between Groups	3564.286	2	1782.143	1.311	0.281
Within Groups	53020.878	39	1359.510		
Total	56585.164	41			
CRP /T2 Between Groups	6574.790	2	3287.395	1.971	0.153
Within Groups	65046.086	39	1667.848		
Total	71620.876	41			
CRP /T3 Between Groups	2404.532	2	1202.266	1.030	0.366
Within Groups	45510.156	39	1166.927		
Total	47914.688	41			
CRP /T4 Between Groups	5157.901	2	2578.951	1.990	0.150
Within Groups	50543.877	39	1295.997		
Total	55701.778	41			
CRP /T5 Between Groups	45090.397	2	22545.198	32.243	0.000
Within Groups	27270.003	39	699.231		
Total	72360.400	41			

*$P<0.05$

pared to other two groups (Table 5). Statistical differences were found at T2, T3, T4 and T5 (Table 6).

Discussion

Patients undergoing major surgical resection for cancer are at high risk for postoperative infectious complications, due to excessive inflammatory stres response on surgery and anesthesia. They may benefit from early and efficient perioperative analgesia, in order to attenuate this response. Studies of preoperative analgesia in major colorectal surgery patients were predominantly investigating postoperative pain level and analgesics consumption. Therefore, it is not known if analgesic potency is sufficient for inflammatory response blockade. Clonidine was usually used alone, or in combination with local anesthetics and opioids. Several attempts have been made to compare epidural and systemic administration of clonidine. Compared to intravenous administration, epidural clonidine seems to be more potent[20]. Reduction in the clonidine requirement when administered by epidural route provided indirect evidence for the main site of its analgesic action.

In our study, clonidine was administered by epidural route in dose of 5 μg/kg. We found that IL-6 level in-

TABLE 5
LEUKOCYTE LEVEL

GROUP	Mean	SD
Group 1 L (10^9/L) /T0	7.759	1.3224
L (10^9/L) /T1	8.076	3.2223
L (10^9/L) /T2	9.006	2.8800
L (10^9/L) /T3	9.953	2.9260
L (10^9/L) /T4	9.171	2.0551
L (10^9/L) /T5	9.671	2.6902
Group 2 L (10^9/L) /T0	7.344	1.0529
L (10^9/L) /T1	8.317	1.6118
L (10^9/L) /T2	10.142	2.9503
L (10^9/L) /T3	11.875	2.7496
L (10^9/L) /T4	12.675	3.1037
L (10^9/L) /T5	11.100	2.9505
Group 3 L (10^9/L) /T0	7.348	1.8031
L (10^9/L) /T1	10.231	5.7366
L (10^9/L) /T2	15.000	7.1200
L (10^9/L) /T3	13.592	4.3316
L (10^9/L) /T4	13.685	4.6481
L (10^9/L) /T5	12.669	3.6504

creases in all groups, with highest level at 6 h (T3). These elevations were significantly less pronounced in preoperative clonidine group compared to levobupivacaine and control group. It is known that IL-6 is proinflammatory cytokine, his level is indicative for inflammatory response in perioperative period, and it increases proportionally to severity of inflammation. Our results are comparable to literature that investigate changes of IL-6 in systemic inflammatory stress response and sepsis[7,21,22,29,32]. In our study, CRP was significantly lower at the end of investigation, compared to levobupivacaine and control group (45.5 mg/L vs. 108.4 and 115.4 mg/L). Regarding the literature, CRP is less sensitive marker for systemic inflammatory stress response than cytokines and procalcitonin[23–27]. Nevertheless persistent CRP elevation over 100 mg/L is predictive for infectious postoperative complications[23].

Normally, leukocyte count increases in the postoperative period as a result of inflammatory response to anesthesia and surgery. In the preoperative clonidine group, we found leukocyte count within normal range compared to other two groups. This contribute to clonidine effect on inflammatory stress response blockade.

Conclusion

Using the centrally acting α_2-adrenergic agonist clonidine before the pain stimulus has set in resulted in better systemic inflammatory stress response blockade compared to levobupivacaine. From the clinical point of view, this effect can contribute to faster postoperative recovery, which may be a worthwhile advantage to postoperative patients.

TABLE 6
DIFFERENCE IN LEUKOCYTE LEVEL

	Sum of Squares	df	Mean Square	F	Sig.
leukocytes /T0 Between Groups	1.725	2	0.862	0.425	0.657
Within Groups	79.191	39	2.031		
Total	80.916	41			
leukocytes /T1 Between Groups	38.309	2	19.155	1.267	0.293
Within Groups	589.615	39	15.118		
Total	627.924	41			
leukocytes /T2 Between Groups	282.993	2	141.496	6.595	0.003
Within Groups	836.799	39	21.456		
Total	1119.791	41			
leukocytes /T3 Between Groups	98.592	2	49.296	4.317	0.020
Within Groups	445.294	39	11.418		
Total	543.886	41			
leukocytes /T4 Between Groups	170.655	2	85.328	7.689	0.002
Within Groups	432.795	39	11.097		
Total	603.450	41			
leukocytes /T5 Between Groups	66.385	2	33.192	3.485	0.041
Within Groups	371.463	39	9.525		
Total	437.848	41			

*$P<0.05$

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PRIJEOPERACIJSKA PRIMJENA KLONIDINA ILI LEVOBUPIVAKAINA – UČINAK NA SUSTAVNI UPALNI ODGOVOR ORGANIZMA

SAŽETAK

Potpunom kontrolom perioperacijske boli možemo nadzirati odgovor imunosnog sustava i oslobađanje medijatora upale, čime izravno utječemo na ishod liječenja. Primjena analgetika prije nastanka bolnog podražaja (preventivna analgezija) spriječava razvoj neuroplastičnih promjena u središnjem živčanom sustavu, te može smanjiti razinu boli. Hipoteza istraživanja je da prijeoperacijska epiduralna primjena klonidina značajno učinkovitije blokira bol i sustavni upalni odgovor organizma u odnosu na levobupivakain. Bolesnici su razvrstani u tri skupine, obzirom na prijeoperacijsku epiduralnu primjenu klonidina, levobupivakaina ili fiziološke otopine (kontrolna skupina). Prije operacije, 1 h nakon početka operacije, te 1 h, 6 h, 12 h i 24 h nakon operacije analizirani su parametri: interleukin-6, C-reaktivni protein i leukociti. Između ispitivanih skupina nije bilo statistički značajne razlike u dobi, spolu, tjelesnoj masi i trajanju operacije. U skupini s klonidinom prije operacije dokazane su statistički značajno najniže vrijednosti interleukina-6 tijekom cijelog vremena ispitivanja, u usporedbi s skupinom s levobupivakainom prije operacije i kontrolnom skupinom ispitanika. Dokazane su značajno najniže vrijednosti C-reaktivnog proteina na kraju ispitivanja, u usporedbi s druge dvije skupine ispitanika. Vrijednosti leukocita su tijekom cijelog vremena ispitivanja značajno najniže i unutar normalnih granica jedino u skupini s klonidinom prije operacije. Istraživanjem su dokazane statistički značajne razlike, koje potvrđuju važnost centralnog učinka klonidina na puteve boli i blokadu upalnog odgovora organizma.