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Effects of Clonidine Preemptive Analgesia on Acute Postoperative Pain in Abdominal Surgery

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A B S T R A C T

Preemptive analgesia refers to blockade of afferent nerve fibers before a painful stimulus, which prevents or reduces subsequent pain even beyond the effect of the block. The aim of the study was to compare the effect of clonidine used before and at the end of operation on pain control in abdominal surgery. A total of 77 patients admitted for colorectal surgery were randomly classified into three groups: epidural clonidine before operation, epidural clonidine at the end of operation, and control group. After the operation on patient demand, analgesia with boluses of epidural morphine was instituted. The parameters of postoperative pain level using VAS score (visual analog scale), sedation and analgesics consumption were determined as outcome measures at 1, 2, 6, and 24 h of the operation. Clonidine administered before operation provided lowest pain scores at 6 and 24 h ($p<0.05$). Clonidine administered at the end of operation had low pain scores at 1 and 2 h, with a significant pain breakthrough thereafter (6.93±1.66 at 6 h and 4.04±2.39 at 24 h) compared with the group administered clonidine before operation (3.60±2.94 and 3.71±1.82). Clonidine administered before operation provided less sedation ($p<0.05$) and a significantly lower use of analgesics ($p<0.05$). Blockade of nociceptive stimulus using the centrally acting α_2-adrenergic agonist clonidine before the onset of pain stimulus resulted in reduced pain levels, sedation and analgesic requirement.

***Key words**: epidural analgesia, patient-controlled analgesia, postoperative pain, pain measurement, clonidine*

Introduction

Preemptive 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). The administration of analgesics before the pain stimulus or surgical trauma prevents this harmful central nervous system response to injury and inflammation as an early consequence of operation[2–4]. In order to achieve success, preemptive analgesia should meet two important conditions, i.e. complete suppression of the afferent pain stimulus and adequate duration in the early postoperative course[1]. Also, attributing improved pain control to the preemptive analgesic effect requires comparison of the prestimulus (preemptive) therapy with identical therapy administered after the stimulus. Otherwise, comparison of groups with no post-stimulus analgesic administration would merely assess the effect of total analgesic dose increment.

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. Thus, clonidine modulates the release of serotonin and norepinephrine, and blocks the transmission of pain[5].

Experimental evidence indicate central mechanisms that are involved in preemptive clonidine analgesia. Kita

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et al. demonstrated the α_2 adrenoreceptors in the region above the mesencephalon to contribute significantly to clonidine analgesia and hemodynamic stabilizing effects[6].

Kawasaki et al. investigated the action of clonidine on glutaminergic transmission, pointing to the involvement of α_2 adrenoceptors. Clonidine inhibits transmission to the gelatinous substance neurons through the activation of α_2 adrenoceptors. This could contribute to at least a part of the inhibitory modulation of pain sensation[7].

Our search through the literature revealed no study comparing preincisional and postincisional treatment with clonidine as a sole analgesic. The aim of the present study was to assess the efficacy of preemptive clonidine treatment. The study was so designed as to compare the preincisional and postincisional treatment, and then both with the control group.

Materials and Methods

The investigation was designed as a randomized and placebo controlled study, with due approval from the institution Ethics Committee and an informed consent from all study subjects. The study included 77 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 and the operation time exceeding six hours.

Patients were randomized by a blind observer into three groups: epidural clonidine before operation, epidural clonidine at the end of operation, and epidural saline before operation as a control group. On the day before the operation, patients were instructed how to complete the visual analog scale (VAS) and 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.

Epidural clonidine was administered as a bolus dose of 5 μg/kg, diluted in 20 mL of isotonic saline 45 min prior to skin incision or at the end of operation. Control group received epidural saline 45 min prior to skin incision. The operation was performed under general anesthesia using midazolam (0.15 mg/kg), fentanyl (2 μg/kg) and rocuronium (0.6 mg/kg) to facilitate endotracheal intubation, and sevoflurane, nitrous oxide 50% in oxygen, boluses of fentanyl and rocuronium 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. Pain score variables at rest measured on 0–100 VAS and sedation scores measured on a five point scale (1=wide awake, 2=drowsy, 3=dozing, 4= mostly sleeping, 5=only aroused by tactile stimulation) were obtained at 1, 2, 6 and 24 h postoperatively. In addition, the cumulative use of analgesics was assessed at the end of the study period.

Differences in pain scores, sedation and need of analgesics were evaluated using the one-way analysis of variance (ANOVA). When ANOVA yielded $p<0.05$, Scheffe's multiple comparison test was used in combination with Dunnett-C test. Alternatively, data were analyzed using Mann-Whitney U test. Statistical significance was set at $p<0.05$. Results were expressed as X±SD.

Results

There were no significant age and body weight differences among the groups of patients relative to pharmacokinetic and pharmacodynamic drug patern (Table 1). Duration of operation were similar. We found significant differences in pain scores among the groups. In the group of patients administered epidural clonidine before operation, a significant reduction in postoperative VAS scores was observed at 6 h and 24 h as compared with the other two groups (3.60±2.94 and 3.71±1.82, respectively). Also, this group showed lowest VAS scores throughout the study period (highest VAS score was 3.71 at 24 h). In the group of patients administered epidural clonidine at the end of operation, a significant reduction in postoperative VAS scores was observed at 1 h and 2 h (0.26±0.59 and 0.89±1.31, respectively), and a significant increase in VAS scores at 6 h and 24 h (6.93±1.66 and 4.04±2.39, respectively). The highest VAS scores throughout the study period were measured in the control group (Table 2).

Clonidine produced sedation in both groups, however, the sedative effect was significantly more pronounced in the group of patients administered epidural clonidine at the end of operation. There was no sedation effect in the control group (Table 3). All patient were extubated at the end of surgery.

TABLE 1
SUMMARY OF TREATMENT GROUPS

Group	N	Age (yr)	Weight (kg)	Duration of surgery (min)
Epidural clonidine before operation	25	59.24±10.74	73.88±7.40	155±33.91
Epidural clonidine at the end of operation	27	64.41±11.10	65.59±10.00	158±36.94
Control group	25	60.40±11.43	73.92±13.91	169±37.23

TABLE 2
VAS SCORES

VAS scores	Epidural clonidine before operation	Epidural clonidine at the end of operation	Control group	p
1 h	1.44±2.60	0.26±0.59	6.48±3.07	0.00000
2 h	3.08±3.50	0.89±1.31	5.29±3.63	0.00017
6 h	3.60±2.94	6.93±1.66	6.08±2.14	0.00000
24 h	3.71±1.82	4.04±2.39	5.60±2.00	0.00790

*p<0.05

TABLE 3
SEDATION LEVEL

Sedation level	Epidural clonidine before operation	Epidural clonidine at the end of operation	Control group	p
1 h	2.60±0.82	3.44±0.85	2.80±1.26	0.01343
2 h	1.88±0.73	2.67±0.83	2.28±0.98	0.01214
6 h	1.68±0.56	1.74±0.90	1.64±0.81	0.86541
24 h	1.96±0.35	1.89±0.51	1.84±0.62	0.88379

*p<0.05

TABLE 4
POSTOPERATIVE CONSUMPTION OF EPIDURAL MORPHINE

Morphine consumption mg/24h	Epidural clonidine before operation	Epidural clonidine at the end of operation	Control group	p
X±SD	8.40±3.74	11.11±4.24	18.00±6.45	0.00000

*p<0.05

The use of postoperative epidural morphine boluses on patient demand was significantly reduced in the group of patients administered epidural clonidine before operation (Table 4).

Discussion

Studies comparing preincisional and postincisional treatment in the field of preemptive analgesia in lower abdominal surgery were predominantly using local anesthetics and opioids. Clonidine was usually used in combination with these analgesics. When preemptive treatment was instituted using epidural and intrathecal route, it resulted in better postoperative pain relief compared with intravenous administration.

Lavand'homme et al. compared intraoperative intravenous and epidural treatment with a combination of local anesthetics, opioids and clonidine, and found that epidural analgesia provided effective preventive analgesia after major abdominal surgery[8]. In contrast, Holthusen et al. used intravenous preincisional clonidine in combination with morphine and ketamine in patients undergoing transperitoneal tumor nephrectomy. This multireceptor approach failed to exert a clinically relevant effect[9].

Investigations of preincisional treatment with clonidine as a sole analgesic for abdominal surgery patients provide evidence that preemptive treatment (epidural and peroral) enhances the analgesic effect of opiates, resulting in reduced intraoperative and postoperative analgesic consumption[5,14]. In the study by Wu et al., preincisional epidural clonidine treatment compared with control group (preincisional saline) reduced perioperative cytokine response, postoperative pain at rest and movement, with faster return of bowel function[10]. De Kock et al. investigated antihyperalgesic effect of intrathecal clonidine in patients undergoing right colic resection. Spinal clonidine contributes to the reduction of secondary hyperalgesia in patients recovering from abdominal surgery. Patients received preincisional clonidine or bupivacaine, without comparing the analgesic effect with a postincisional group[11]. The design of the studies in the field did not allow the preemptive effect to be properly demonstrated because there was no comparison between the analgesic intervention before and after the surgical stimulus[1,16]

Several attempts have been made to compare epidural and systemic administration of clonidine. Compared to intravenous administration, epidural clonidine seems to be more potent[17,18]. Reduction in the clonidine require-

ment 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 did not observe side effects of epidural clonidine use such as respiratory depression, hypotension and bradicardia. Marinangeli et al. reported that doses of clonidine 3–5 μg/kg produced sufficient analgesia without higher degree of side effects[19]. Epidural clonidine analgesia begins within 30 min and lasts for 4–5 h. The group of patients who received clonidine at the end of operation showed very low VAS scores at 1 h and 2 h, when the concentration of clonidine was very high, followed by a pain breakthrough at 6 h with the highest VAS score measured in the study (6.93±1.66). The group of patients with preoperative clonidine administration showed continuously low VAS scores and a reduced incidence of postoperative hyperalgesia. Our results of improved preincisional clonidine analgesia could be compared with those reported by De Kock et al. We believe that it was the result of the clonidine central blocking the transmission of nociceptive stimuli along descending pathways. Postincisional treatment provided short-lasting analgesia and secondary hyperalgesia.

The sedative-hypnotic effects of clonidine are related to the inhibition of neural firing in the locus coeruleus, a brainstem nucleus located in the dorsal part of the medulla[20,21]. According to our findings, the sedative effect was considerably stronger in the group of patients receiving clonidine at the end of operation than in those with preoperative administration of clonidine, this because of the short time interval between the administration of clonidine and the first measurement.

Conclusion

This study has shown that preemptive analgesia may be achieved by epidural clonidine administration. Using the centrally acting α_2-adrenergic agonist clonidine before the pain stimulus has set in resulted in reduction of the pain level and consecutive analgesic requirement, in comparison with clonidine administration at the end of operation. The use of preemptive clonidine treatment resulted in lower sedation. From the clinical point of view, the balance between analgesia and side effects appears to be better with preemptive treatment, because the reduction in pain level and analgesic requirement is associated with a lower level of sedation, which may be a worthwhile advantage to postoperative patients.

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UČINAK PREEMPTIVNE ANALGEZIJE KLONIDINOM NA RAZINU AKUTNE POSLIJEOPERACIJSKE BOLI U ABDOMINALNOJ KIRURGIJI

SAŽETAK

Preemptivna analgezija podrazumijeva blokadu uzlaznih živčanih puteva prije nastanka bolnog podražaja, čime se sprječava ili smanjuje razina nastale boli. Cilj ove studije bila je usporedba učinka klonidina primjenjenog prije opera-

cije i na kraju operacije na smanjenje poslijeoperacijske boli. Ukupno 77 bolesnika predviđenih za operacijski zahvat u kolorektalnoj kirurgiji metodom randomizacije podijeljeno je u tri skupine: epiduralni klonidin prije operacije, epiduralni klonidin na kraju operacije i kontrolna skupina. Nakon operacijskog zahvata, na zahtjev bolesnika primjenjivana je epiduralna analgezija bolusima morfina. Kao mjere ishoda istraživanja, u vremenskom slijedu 1., 2., 6., i 24. sata od operacijskog zahvata proučavani su parametri razine poslijeperacijske boli korištenjem VAS ljestvice (vizualno analogna skala), sedacije i potrošnje analgetika. Klonidin primjenjen prije operacije iskazao je značajno niže vrijednosti boli u 6. i 24. satu ispitivanja ($p<0,05$). Klonidin primjenjen na kraju operacije imao je niže vrijednosti boli u 1. i 2. satu, s značajnim porastom razine boli nakon tog vremena (6,93±1,66 u 6. satu i 4,04±2,39 u 24. satu) u usporedbi s klonidinom prije operacije (3,60±2,94 i 3,71±1,82). Klonidin prije operacije iskazao je značajno nižu razinu sedacije ($p<0,05$) i manju potrošnju analgetika ($p<0,05$). Blokada nocicepcijskog impulsa primjenom centralno djelujućeg α_2-adrenergičkog agonista klonidina prije nastanka osjeta boli dovodi do smanjenja razine poslijeoperacijske boli, sedacije i potrebe za analgeticima.