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Effects of Clonidine versus Midazolam premedication on postoperative pain in patients undergoing elective spinal neurosurgery. Prospective randomized study

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Abstract

Many preoperative, intraoperative and postoperative interventions and management strategies are available and continue to evolve for reducing and managing postoperative pain. Different pharmacologic actions of preanaesthetic medication may be desirable depending upon specific perioperative conditions such as patient selection, surgical procedure or anaesthesia type. Benzodiazepines are probably still most frequently used, although a variety of pharmacological premedication is available. Among these choices, alpha-2 agonists offer useful effects that make these drugs an interesting alternative for preanesthetic medication.

Objective. *This study evaluates the effect of clonidine in comparison to midazolam premedication on postoperative pain.*

Material and method. *In a prospective study, effects of clonidine (0,15 mg orally) and midazolam (7,5 mg orally) administered 60-90 minutes prior to estimated anaesthesia induction time were investigated in 40 ASA physical status I or II patients, with age between 18 and 75 years. The severity of postoperative pain was assessed immediately after the procedure 2nd, 6th, 12th and 24th hours after surgery using the visual analog scoring system (VAS score). Also, the total dose of administered analgesics during 24 hours after surgery and the interval between the surgery and the first request of analgesic were compared between the two groups.*

Results. *Postoperative pain VAS during 24 hours after the surgery was significantly lower in clonidine group (Group C) compared to the midazolam group (Group M): Group C – 1.33 points, Group M – 2.3 points. The meantime between surgery and the first request of analgesic in clonidine group was of longer duration compared in midazolam group: Group C – 3.22 hours, Group M – 4.53 hours.*

Conclusion. *Clonidine premedication reduces the severity of postoperative pain in patients undergoing elective spinal neurosurgery. Clonidine administration did not delay postoperative recovery.*

Keywords: premedication, clonidine, benzodiazepines, midazolam, postoperative pain

INTRODUCTION

The practice of pharmacological premedication in anaesthesiology was initiated soon after ether and chloroform were introduced as general anesthetics in the middle of the 19th century. Opioids and anticholinergics were the first drugs used for anesthetic premedication, and then barbiturates. The main effects of premedication was described at that time within a pro-

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tocol adopted by *Royal Victoria Hospital*: sedation, to shorten the period of induction, lessen the amount of general anaesthetic needed, without interfering with the depth of anaesthesia, to avoid post-operative nausea, to procure a longer period of insensibility to pain (10).

The current practice of anesthetic premedication has evolved into a generalized scheme that incorporates several aspects of patient care: decreasing preoperative anxiety, blocking intraoperative noxious stimulus, minimizing postoperative adverse effects of anaesthesia and surgery. However, the ideal of premedication is as illusory as using an ideal anesthetic technique. Rational use of premedication should be justified by: patient status, pre-existing medication, type of surgery, anesthetic agents and techniques used.

A variety of preanaesthetic medication may be used, although benzodiazepines are probably still most frequently preferred. Another alternative to benzodiazepines, because of the anxiolytic and sedative effects is represented by alpha-2 agonists.

The present study was designed to evaluate the effect of clonidine premedication in comparison to midazolam on postoperative pain.

MATERIAL AND METHOD

After approval of the Clinical Emergency Hospital Ethics Committee and written informed consent, 40 patients ASA physical status I or II, with age between 18 and 75 years, scheduled for elective spinal neurosurgery, were enrolled for this prospective randomized study. The patients were randomized (1:1) into two groups: Group C and Group M. On the day of surgery 60-90 minutes prior to estimated anaesthesia induction time, Group C received clonidine (0.15 mg orally) and Group M was premedicated with midazolam (7.5 mg orally). On arrival at the operating room, all patients were continuously monitored with EKG, non invasive blood pressure monitor, pulsoximetry. For induction of anaesthesia fentanyl 1-3 μg/kgc and propofol 1.5-2 mg/kgc were administered. Muscle relaxation for tracheal intubation was obtained by using succinylcholine 1mg/kgc and maintained with rocuronium 0.6 mg/kgc. Anaesthesia was maintained with sevoflurane and intraoperative analgesia was assured with fentanyl.

Cumulative doses of fentanyl administered for anaesthesia were recorded at the end of the surgery. All patients were evaluated with the Aldrete postanaesthesia recovery scoring system in order to asses the post anesthesia recovery of the neuro-cognitive, respiratory and cardiocirculatory functions. The severity of postoperative pain was assessed immediately after the procedure 2nd, 6th, 12th and 24th hours after surgery using the visual analog scoring system (VAS score). Also, the total dose of administered analgesics during 24 hours after surgery and the interval between the surgery and the first request of analgesic were compared between the two groups. Postoperative analgesia was provided by using a multimodal approach: paracetamol, nonsteroidal anti-inflammatory drugs (Ketoprofen), synthetic opioids (Tramadol).

RESULTS

Statistical analysis was performed using SPSS. Results are presented as mean ± standard error of mean (SEM) for parametric data. One way analysis of variance ANOVA was used to test for differences between groups.

Patients characteristics and intraoperative data

Patients in Group C were younger than patients in Group M: Group C: 40.8 ± 3.2 years; Group M: 38.3 ± 2.7 years, (P< 0.01; see Table 1). Cumulative doses of fentanyl administered during anaesthesia did not differ significantly between groups (P=0.034): Group M: 352.5 ± 51.6 μg; Group C: 330 ± 50 μg. Aldrete score showed a median of 8 points in both groups.

Postoperative pain assessment

During the postoperative period, VAS for pain was similar between the groups (see Table 2). However, patients premedicated with clonidine tended to display lower VAS values then midazolam patients per 24 hours (Group C: 1.33 points; Group M: 2.3 points).

TABLE 1. *Patient characteristics and intraoperative data. Two different premedication regimens were studied: midazolam (7,5 mg orally) or clonidine (150 μg orally) administered 60-90 de minutes prior to anaesthesia induction. (Data are given as mean ± SEM. Data are stastically significant: p<0.01)*

	MIDAZOLAM (*n=20*)	CLONIDINE (*n=20*)	P value
Age (years)	40.8 ± 3.2	38.3 ± 2.7	0.005
Gender (male/female)	12/8	11/9	
Fentanyl (μg)	352.5 ± 51.6	330 ± 50	0.034

TABLE 2. *The severity of postoperative pain was assessed immediately after the procedure (VAS 0) 2nd(VAS 2), 6th(VAS 6), 12th(VAS 12) and 24th(VAS 24) hours after surgery using the visual analog scoring system (VAS score). The one-way analysis of variance-ANOVA was carried out for comparison of pain scores*

	MIDAZOLAM (n=20)	***CLONIDINE (n=20)***	***P value***
VAS 0	*0.77*	*0.58*	*0.05*
VAS 2	*2.33*	*2.05*	*0.2*
VAS 6	*2.18*	*2.16*	*0.1*
VAS 12	*2.05*	*1.6*	*0.09*
VAS 24	*2.3*	*1.33*	*0.07*

Postoperative analgesia

The time interval between the elective neurosurgery procedure and the first request of analgesic was of longer duration in clonidine group, but data are not statistically significant (see table no.3, p> 0.01).

The analgetic demands were lower in Group C in comparison to Group M (see table no.4). The total dose of nonsteroidal anti-inflammatory drugs (Ketoprofen) was lower in Group C: 100.0 ± 7.9 mg; Group M: 160 ± 6.5 mg; data are statistically significant: p <0.01.

Also, the doses of paracetamol and opioids were lower in patients premedicated with clonidine, but data are not statistically significant : p> 0.01 in both groups (see Table 4).

TABLE 3. *Time interval between the elective neurosurgery and the first request of analgesic*

	MIDAZOLAM (n=20)	***CLONIDINE (n=20)***	***P value***
Time (h)	*3.22 ± 0.7*	*4.53 ± 1.25*	*0.049*

TABLE 4. *Analgesic demands per 24 h for Group M and Group C. Data are given as mean ± SEM, Data are statiscally significant: p<0.01.*

ANALGESIC AGENT Per 24 h	***MIDAZOLAM (n=20)***	***CLONIDINE (n=20)***	***P value***
Paracetamol (g)	*1.8 ± 0.8*	*1.35 ± 0.48*	*0.066*
Ketoprofen (mg)	*160 ± 6.5*	*100 ± 7.9*	*0.006*
Tramadol (mg)	*145 ± 5.4*	*120 ± 4.3*	*0.082*

DISCUSSION. LIMITS

The present study was designed to reflect routine clinical practice. Generally, preanaesthetic medication is usually prescribed depending on available drugs and a general consensus on the doses of clonidine and midazolam administered for premedication does not exist. Previous studies demonstrated that low-dose clonidine failed to attenuate stress response to laringoscopy (4), and high-dose clonidine (300 µg) increased incidence of hypotension (5). The doses chosen in our study represent standard low doses of clonidine and midazolam that have been shown to exert comparable premedication effects in a previous study (13).

Benzodiazepines inhibit anxiety, induce anterograde amnesia, minimal sedation. The main disadvantages of using benzodiazepines are the absence of analgesia, respiratory depression, greater sedation in elderly patients (11,12). Although administered for the sedative effect, benzodiazepines can produce paradoxical reaction: agitation and delirium (8,12).

An interesting alternative to benzodiazepines is represented by alpha-2 agonists. Alpha-2 adrenoreceptor agonists have been shown to induce sedation, anxiolysis, increase haemodynamic stability and attenuate adverse haemodynamic responses to surgical stress. Clonidine can be used to reduce the risk of perioperative cardiac mortality in patients undergoing noncardiac surgery when administered prophylactic (1,2). The present study was designed to evaluate the effect of clonidine premedication in comparison to midazolam.

Pain assessment through VAS is less time-consuming and easy to use (7). However, pain represents a complex issue and the subjective component must not be neglected.

The need for lower doses of ketoprofen in Group C may be explained by the secondary antinociceptive activity of ketoprofen which involves noradrenergic systems at spinal and supraspinal levels (5).

The results of our study indicate the advantages of using clonidine premedication in comparison to midazolam premedication in ASA I or II patients, but the results can not be extended in patients at cardiac risk.

CONCLUSION

Clonidine premedication reduces the severity of postoperative pain in patients undergoing elective spinal neurosurgery. Clonidine administration did not delay postoperative recovery.

Clonidine can be an alternative for premedication, but we consider that in order to appreciate the postoperative analgetic outcomes, further studies are needed to confirm the results.

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