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Both clonidine and metoprolol modify anesthetic depth indicators and reduce intraoperative propofol requirement

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Abstract
Purpose. Beta-blockers have been used in the past to decrease the depth of anesthesia, but the results are conflicting. However, beta-blockers are known to suppress electroencephalographic activities. This study was carried out to assess the effect of metoprolol on anesthetic depth indicators. We also compared the effect of metoprolol in reducing propofol requirements.
Methods. Ninety healthy adult patients undergoing peripheral nerve injury repair were enrolled in three groups to receive either: a tablet containing clonidine 200 μg, a tablet containing metoprolol tartrate 100 mg, or a placebo; 1 h prior to surgery. Standard anesthesia technique was followed. The bispectral index was monitored to guide propofol infusion and was maintained between 40 and 60. The total duration of anesthesia and surgery, and the total propofol consumption, were noted.
Results. Demographic variables were comparable in all three groups. Significantly less propofol was consumed by patients in the clonidine and metoprolol groups in comparison to that in the placebo group ($P < 0.001$). Heart rate and mean blood pressure values differed significantly in the placebo group in comparison to the values in the other two groups.
Conclusion. Our study showed that, like clonidine, metoprolol attenuated the hemodynamic response to intraoperative stimuli and also had a sparing effect on the propofol dose requirement.

Key words Propofol · Metoprolol · Clonidine · Bispectral index

Introduction

To suppress intraoperative stress responses and thereby prevent perioperative cardiac complications, beta-blockers are being used increasingly. However, there have been conflicting reports on the effects of beta-blockers on the depth of anesthesia. Johansen [1], in his study, found that electroencephalographic activity was significantly suppressed by esmolol, but could not find a definite mechanism for the cortical suppression by esmolol. In contrast, Berkenstadt and colleagues [2] did not find that esmolol reduced the bispectral index (BIS) in their study. Atenolol has been shown to reduce anesthetic requirements without modifying anesthetic depth indicators in elderly patients [3]. Unlike atenolol and esmolol, there are no studies available regarding the effects of metoprolol on anesthetic depth. This prospective randomized, controlled, blinded study was carried out to evaluate the effects of metoprolol on intraoperative hemodynamic variables and the bispectral index as anesthetic depth indicators. We also compared the effect of metoprolol in reducing the propofol requirement with that of clonidine, which has been shown to reduce intraoperative propofol consumption in a previous study [4].

Patients, materials, and methods

This was a prospective randomized control study conducted in 90 healthy adult patients. Inclusion criteria were patients undergoing peripheral nerve repair surgery, adult patients of either sex (18–60 years), and American Society of Anesthesiologists (ASA) physical status I and II. We excluded patients with cardiopulmonary disorders, those with any systemic illness, patients on beta-blockers, those with neuropsychiatric disorders, women who were pregnant and patients with known sulfite sensitivity and allergy to eggs or soyabean oil.

After we had obtained approval from the institutional ethics committee and informed consent from the patients, they were divided into three groups, of 30 each, by the use of computer-generated block random-

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ization numbers. Patients receiving a tablet containing metoprolol tartrate 100 mg were considered as group I; those patients who received a tablet containing clonidine 200 μg were considered as group III; the remaining patients, who received placebo, formed the control group and were designated as group II. The test drug was given to the nurse concerned to administer, and patients were not informed about which drug they were receiving. The drugs were administered orally 1 h before the induction of anesthesia. Inside the operating theater, baseline heart rate (HR), mean blood pressure (MBP), and bispectral index (BIS) values were noted. General anesthesia was induced with fentanyl ($2\ \mu g \cdot kg^{-1}$) and propofol was administered until there was a loss of verbal response. The airway was secured with a laryngeal mask airway (LMA) of appropriate size. Anesthesia was maintained with propofol infusion (Terufusion syringe pump, model STC- 523; Terumo, Tokyo, Japan) at a rate adjusted to maintain the BIS between 40 and 60, and nitrous oxide and oxygen at a 2:1 ratio. The smoothing rate of the BIS was kept at 30 s. All patients received fentanyl ($1\ \mu g \cdot kg^{-1} \cdot h^{-1}$) as an analgesic. Intraoperative monitoring included ECG, noninvasive blood pressure measurement, pulse oximetry, capnometry, inspired gases, and airway pressure (Datex Engstrom AS/3; Helsinki, Finland). BIS was monitored with the help of a BIS sensor (Version 4.0 A-2000; Aspect Medical Systems, Newton, MA, USA). All parameters were recorded at 15-min intervals, and the mean value at the end of each hour was taken for comparison among the groups. Mean blood pressure (MBP) and HR were maintained within 20% of baseline by using the vasopressor mephentermine and atropine as and when required. Propofol infusion was continued until the skin sutures were completed to maintain the target BIS. The total duration of anesthesia and of surgery, and the total propofol consumption were noted. Intraoperative and postoperative complications were noted and patients were interviewed 2 h after surgery for recall of any intraoperative events. The emergence time, defined as the time of stopping the propofol infusion and removal of the LMA, was noted for all patients. Groups were decoded after statistical analysis. All statistical analyses were done using analysis of variance (ANOVA) and Scheffe's post-hoc analysis tests. P values of less than 0.05 were considered significant.

Results

All patients completed the study and data from these patients were analyzed. Demographic variables were comparable in all three groups. The preinduction BIS value and duration of surgery were also comparable. However, total propofol consumption differed among the groups (Table 1). Significantly less propofol was consumed by patients in groups I and III in comparison to that in group II ($P < 0.001$). HR and MBP values in group II differed significantly from those in the other two groups. Groups I and III had comparable HR and MBP values at baseline as well as at successive intervals (Table 2). Three patients in the clonidine group (group III) required mephentermine to maintain blood pressure. Atropine was administered to two patients in the metoprolol group (group I) to maintain the HR. The emergence times were comparable in all the groups. There were no postoperative complications and none of the patients had free recall of any intraoperative event.

Discussion

Various studies have stated the advantages of perioperative beta-blockade, but few studies have evaluated the interaction between beta receptor antagonists and anesthetic requirement or anesthetic depth, as indicated by BIS in our study. Coloma and colleagues [5], in their study, compared esmolol and remifentanil infusions with respect to their effects on intraoperative hemo-

Table 1. Demographic and surgical data

	Metoprolol (group I; $n = 30$)	Control (group II; $n = 30$)	Clonidine (group III; $n = 30$)	P value
M:F	26:4	30:0	30:0	
Age (years)	29.9 ± 8.9	26.7 ± 8.0	30.7 ± 7.7	0.14
Weight (kg)	63.8 ± 10.9	66.8 ± 12.1	61.2 ± 9.4	0.14
Duration of surgery (min)	245 ± 15.9	242 ± 15.9	244 ± 15.4	0.25
Total propofol (g)	1.53 ± 0.4*	2.0 ± 0.7	1.33 ± 0.6*	
Emergence time (min)	4.5 ± 3	5 ± 2	5 ± 2.5	0.5
Baseline BIS value	98.2 ± 0.7	98.2 ± 0.8	98.0 ± 1.2	0.65

*$P < 0.001$ compared to the control group
Values are means ± SD
n, Number of patients; BIS, bispectral index

Table 2. Intraoperative hemodynamic parameters in three study groups

	Metoprolol (group I; $n = 30$)	Control (group II; $n = 30$)	Clonidine (group III; $n = 30$)
Heart rate (beats min^{-1})			
Baseline	70.5 ± 7.9**	78.8 ± 14.1	71.0 ± 10.2*
1 h	66.1 ± 5.6**	74.9 ± 9.0	67.9 ± 10.1**
2 h	66.9 ± 7.5**	73.2 ± 8.3	66.0 ± 9.7***
3 h	66.6 ± 7.5*	71.5 ± 8.5	64.9 ± 9.6**
4 h	66.0 ± 6.0**	73.2 ± 10.9	65.6 ± 10.6***
Mean blood pressure (mmHg)			
Baseline	85.8 ± 12.9*	92.7 ± 7.4	83.2 ± 12.6**
1 h	78.4 ± 7.6***	86.2 ± 6.1	77.2 ± 8.2***
2 h	79.1 ± 8.4***	89.1 ± 7.7	77.2 ± 6.9*
3 h	78.7 ± 7.8***	89.9 ± 6.3	79.6 ± 5.9*
4 h	80.6 ± 7.8***	90.1 ± 5.9	80.1 ± 7.1**

* $P < 0.05$ compared to the control group; ** $P < 0.02$ compared to the control group; *** $P < 0.01$ compared to the control group
Values are means ± SD
n, Number of patients

dynamic stability and early recovery after outpatient laparoscopic surgery, when administered as IV adjuvants during desflurane anesthesia. They found that both drugs were associated with frequent "postanesthesia care unit bypass" rates (78%–81%), short times to "home readiness" (119–120 min), excellent patient satisfaction (81%–85%), and rapid resumption of normal activities (2.6–3.2 days). Zaugg and colleagues [6], in their study, stated that perioperative beta-blockade conferred several advantages, including decreased analgesic requirements, faster recovery from anesthesia, and improved hemodynamic stability.

Our study showed that, like clonidine, metoprolol attenuated the hemodynamic response to perioperative stimuli and also had a sparing effect on the propofol dose requirement. This finding suggests that the use of metoprolol may result in increased anesthetic depth. Previous studies [5, 6] have indicated that beta receptor antagonists not only block cardiovascular stress responses after noxious stimuli but that they also increase the antinociceptive component of anesthesia. The mechanism of the antinociceptive effect remains unclear. One explanation may be a central antinociceptive effect of beta adrenoceptor blockers. Consistent with this hypothesis is the finding that intravenous esmolol decreased nociceptive behavior in rats after formalin injection [7]. Noxious stimulation is transmitted through the spinal cord, brain stem reticular formation, and thalamus to the cerebral cortex, where it evokes an EEG arousal response. Beta adrenoceptors are present in various parts of the reticular activating system, particularly in the medial septal region of the basal forebrain [8]. The infusion of beta adrenoceptor agonists elicits enhancement of the behavioral and EEG indices of waking in animals [8]. Conversely, the infusion of beta receptor antagonists decreases EEG indices of arousal [8]. Similarly, in humans, the infusion of isoprenaline [9] or epinephrine [10] causes clinical signs of arousal associated with increases in BIS. These findings suggest that noxious stimulation during the perioperative period increases central catecholamine concentration, and that beta receptor antagonists such as metoprolol and esmolol prevent an increase in the BIS response to noxious stimuli by blocking beta receptors within the reticular formation. The pharmacokinetics of metoprolol also support this hypothesis. Unlike esmolol and atenolol, metoprolol is highly lipophilic and readily crosses the blood-brain barrier; its concentration in cerebrospinal fluid has been reported to be 78% of the plasma concentration.

Another explanation for this may be an alteration of propofol pharmacokinetics by metoprolol. Like clonidine, metoprolol also reduces cardiac output, leading to a decrease in propofol clearance as a result of decreased hepatic blood flow. In agreement with our study, patients beta-blocked with atenolol required less fentanyl and isoflurane than unblocked control patients to produce similar BIS values. Metoprolol acts on peripheral beta receptors in the heart. Thus, use of this drug results in sympatholysis; that is, this drug has, the ability to block the sympathetic arm of the nervous system. Reduction in cardiac output and HR due to sympathetic inhibition results in lower blood pressure. Hence, in our study, metoprolol like clonidine, decreased systolic, diastolic, and MBP values, and this decrease was significant when compared to control-group findings. From their study to determine the influence of cardiac output on plasma propofol concentrations during constant infusion in swine, Kurita et al. [11] concluded that blood propofol concentrations during propofol infusion anesthesia were affected by cardiac output, which changes easily in response to several factors, including inadequate

anesthetic depth and the administration of inotropic agents or adrenergic beta antagonists.

There are certain limitations in our study. Unlike the studies carried out by Kurita et al. [11], and Morris and colleagues [4], we did not measure the plasma propofol concentration and so cannot eliminate a potential pharmacokinetic interaction of the beta-blockers with propofol. Moreover, metoprolol, by attenuating the hemodynamic responses to perioperative noxious stimuli, may have prevented the increase in cardiac output that would normally lead to the redistribution of blood flow, with a resultant fall in the effect–site concentration of propofol and increase in BIS. Further studies are required to assess the exact mechanism of action of beta-blockers on the potentiation of the hypnosis component of anesthesia. The optimal dose, timing, and method of administration of different beta-blockers during anesthesia need to be determined to obtain the maximum advantage of these adjuvant anesthetic drugs.

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