

EFFICACY OF ORAL CLONIDINE VERSUS DIAZEPAM AS A PREMEDICATION AND AS AN ADJUNCT TO GENERAL ANESTHESIA IN SELECTIVE UPPER ABDOMINAL SURGERY

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Abstract

Background: Preanesthetic medication lessens preoperative anxiety, provides amnesia for preoperative and perioperative events and maintains hemodynamic stability by attenuating autonomic reflexes.¹ Use of α -2 adrenoreceptor agonist like clonidine has a lot of advantages as a premedication agent due to the wide spread distribution of α -2 receptors throughout the central nervous system and rest of the body.

Aim : To assess the efficacy of oral clonidine versus diazepam as a premedication and as an adjunct to general anesthesia in selective upper abdominal surgery

Methodology: A comparative study was done on 50 patients in our hospital for duration of two years. The patients were divided into two groups of 25 each. Group I patients received 0.2 mg/kg of diazepam orally and patients in Group II received 3.5 micgm/kg of clonidine orally. Pre-anesthetic examination involved the overall assessment and selection of patients for the study. Sedation was measured by using a five graded scale. Subjective assessment for dizziness, nausea, headache and dryness of mouth was performed. Base line heart rate and blood pressure were recorded after fixing ECG leads and blood pressure cuff using noninvasive Hewlett Packard Blood Pressure monitor.

Results : Sedation level among the clonidine group was grade 3 which is found to be statistically significant when compared to the diazepam group. The heart rate, systolic BP, diastolic BP and the MAP are statistically significantly lower among the clonidine group of patients when compared to the diazepam group at almost all the time intervals during the induction of anesthesia. The requirement of isoflurane among the clonidine group was only 0.5% when compared to 1% among diazepam group and the duration of analgesia was 8.83hrs in clonidine group whereas it was only 5.08hrs in diazepam group.

Conclusion : The administration of oral clonidine is a simple and cost effective form of premedication in patients undergoing upper abdominal surgeries results in improved perioperative haemodynamic stability and reduction in anaesthetic requirements. In addition, it also reduces the post-operative analgesic requirements.

Introduction

Preanesthetic medication lessens preoperative anxiety, provides amnesia for preoperative and perioperative events and maintains hemodynamic stability by attenuating autonomic reflexes.¹ Use of α -2 adrenoreceptor agonist like clonidine has a lot of advantages as a premedication agent due to the wide spread distribution of α -2 receptors throughout the central nervous system and rest of the body. Clonidine reduces sympathetic activity, the incidence of shivering,² dries up secretions; minimizes fluctuations in the hemodynamic profile during anesthetic induction³ and decreases anesthetic requirements for both opioid and volatile anesthetics.⁴ Premedication with oral clonidine provides significant benefits for preoperative anxiety and analgesia. Clonidine can be given via oral, intramuscular, intravenous, intrathecal and epidural routes.

Clonidine is rapidly absorbed after oral administration. It reaches a peak plasma concentration within 60-90 minutes. The bioavailability of the drug is about 75-95%. About 20-40% of the drug is bound to protein. 50% of the drug is metabolized in the liver to inactive metabolites which are excreted in the urine and the half life is about 12-33 hours. As clonidine is lipid soluble, it penetrates the blood-brain barrier to reach the hypothalamus and medulla. It does not require transformation into another substance prior to its action⁵

Clonidine synchronously decreases the cold-response threshold while slightly increasing the sweating threshold thus suggesting that it acts on the central thermoregulatory system rather than preventing shivering peripherally⁶

Premedication with clonidine blunts the stress response to surgical stimuli and the narcotic and anaesthetic doses are also reduced. In addition, clonidine increases cardiac baroreceptor reflex sensitivity to increase in systolic blood pressure, and thus stabilises, blood pressure.⁷ These characteristics suggest that clonidine may be useful in the anaesthetic management of patients undergoing upper abdominal surgeries. Accordingly, this study was designed to evaluate the effects of oral clonidine premedication in comparison with diazepam on haemodynamic response and modulation of post-operative pain in patients undergoing selective upper abdominal surgeries.

Aim

To assess the efficacy of oral clonidine versus diazepam as a premedication and as an adjunct to general anaesthesia in selective upper abdominal surgery

Methodology

A comparative study was done on 50 patients in our hospital for duration of two years. The patients were divided into two groups of 25 each. The patients were included in the study with the following inclusion criteria

1. Patients between the age of 18-60 years.
2. Patients coming for elective cholecystectomy or minicholecystectomy.
3. Body weight above 40 Kgs.
4. Patients in physical status ASA I or II.

Patients with cardiovascular, respiratory or renal disease, patients taking drug treatment known to affect the blood pressure, heart rate or hormonal response and patients with the blood pressure of more than 100 mm Hg of diastolic pressure were excluded from the study.

The patients were then randomly divided into two groups :

Group I patients received 0.2 mg/kg of diazepam orally and patients in Group II received 3,5 micgm/kg of clonidine orally 90 minutes before induction of anaesthesia.

Pre-anaesthetic examination involved the overall assessment and selection of patients for the study. If the patient was considered fit for study, he was assigned to one of the two groups. Heart rate and blood pressure were recorded. The visual analogue scale for anxiety scoring was explained to the patient (zero scoring for no anxiety and 100 scoring for fear of death). The preoperative day's anxiety was recorded.

Before taking the patient to the operating table the following were assessed in the two groups of patients.

1. Sedation: Using a five graded scale. .
2. Subjective assessment of dizziness, nausea, headache and dryness of mouth.

Base line heart rate and blood pressure were recorded after fixing ECG leads and blood pressure cuff using noninvasive Hewlett Packard Blood Pressure monitor. Intravenous infusion started in a peripheral vein.

Induction and intubation were carried out in the following steps:

1. 2.5% thiopentone in 50mgm increments intravenously every 15 seconds until the eye lash reflex disappeared.
2. Patients breathed spontaneously a gas mixture of 66% nitrous oxide, 33% oxygen and 0.5% isoflurane for 2 minutes.
3. The occurrence of involuntary muscle movements, breath holding, laryngospasm, hiccups and coughing were noted.

4. Fentanyl 2mcg/kg and vecuronium 0.1mg/kg were given and ventilation assisted.
5. The vocal cords were sprayed with Lignocaine and then tracheal intubation was done
6. The heart rate and blood pressure were recorded every 2 minutes after the administration of thiopentone for 15 minutes.

Maintenance of anaesthesia in both groups included a balanced anaesthetic of nitrous oxides, oxygen and isoflurane. No additional doses of narcotics were given. The heart rate and blood pressure were noted every 5 minutes for 1 hour and every 10 minutes till the end of anaesthesia. If the blood pressure increased more than 30% of baseline, the inspired concentration of isoflurane from the flutec vaporizer was increased to 1%. The amount of fluids administered was recorded. At the end of surgery the neuromuscular blockade was reversed with atropine and neostigmine.

All the patients in both the groups were seen and interviewed by the investigator 24 hours after the surgery. Analgesics were given in the post-operative period only when the patient had complained of pain. The data were analysed using SPSS version 16 chi-square test and T test were used for deriving the statistical inference.

Results

Table 1 : Distribution of various parameters among the study population

Parameters	GROUP I (Diazepam) N = 25	GROUP II (Clonidine) N = 25
Age (Mean±SD)	43.19±12.9	39.95±11.9
Body weight (Mean±SD)	54.81±11.8	58.95±9.9
ASA - I	22 (88%)	20 (80%)
ASA - II	3 (12 %)	5 (20%)
Duration of surgery in Hrs (Mean±SD)	2.84±0.744	2.45±0.25
Minichole	12 (48 %)	18 (72%)
Cholecystectomy	13 (52%)	7 (28%)

Table 1 shows the various physical parameters measured among the study population in both the groups. Age, body weight, ASA, type of surgeries, duration of surgery are almost similar in both the clonidine group as well as in the diazepam group. All the 50 patients had undergone either minichole or cholecystectomy operation only.

Table 2 : Effect of sedation among the study population

Grading for sedation	GROUP I Diazepam (N=25)	GROUP II Clonidine(N=25)
Grade 1 – Alert	7 (28%)*	3 (12%)
Grade 2 - Drowsy but easily aroused by verbal command	4 (16%)	3 (12%)
Grade 3 - Sleeping and arousable by verbal command	11 (44%)	19 (76%)*
Grade 4 - Sleeping, not arousable by verbal command but arousable by light tactile stimulation	3 (12%)	0
Grade 5 - Sleeping and difficult to arouse by tactile stimulation	0	0

*P<.05 (by applying chi-square test)

Table 2 shows the various grading of sedation among both the groups after injecting the respective drugs. It is inferred from the table that majority of the patients sedation level among the clonidine group was grade 3 which is found to be statistically significant when compared to the diazepam group. In diazepam group 7 patients were in grade I level of sedation compared to only 3 patients in the clonidine group. So clonidine gives an ideal sedation to the patients neither too low nor too high when compared to that of diazepam.

Table 3 : Heart rate and blood pressure measurements among the study population during the induction of anesthesia.

Time	Heart rate		Systolic BP		Diastolic BP		MAP	
	Diazepam group (Mean±SD)	Clonidine group (Mean±SD)	Diazepam group (Mean±SD)	Clonidine group (Mean±SD)	Diazepam group (Mean±SD)	Clonidine group (Mean±SD)	Diaze Pam (Mean±SD)	Cloni Dine (Mean±SD)
0 Min	93±15	79.2±12*	130±12	116±14*	82±9	72±9*	99±8	87±10*
5 Min	96.2±14	81±13*	118±20	110±16*	80±10	70±10*	92±12	85±11*
10 Min	99±19	87±13*	114±11	102±14*	78±7	72±12*	90±9	82±13*

*-P<.05 (by applying T test)

Table 3 shows the heart rate and blood pressure measurements during the induction of anesthesia at 0, 5 and 10 minutes respectively. It is inferred from the table that the heart rate, systolic BP, diastolic BP and the MAP are statistically significantly lower among the clonidine group of patients when compared to the diazepam group at almost all the time intervals during the induction of anesthesia. So it is shown that clonidine seems to be hemodynamically more efficacious than diazepam.

Table 4 : Isoflurane requirement and duration of analgesia among the study groups

	Group I (Diazepam)	Group II (Clonidine)
isoflurane 0.5%	14 (56%)	22 (88%)*
Isoflurane 1%	11 (44%)	3 (12%)
Duration of Analgesia in Hrs (Mean±SD)	5.08±2.65	8.83±6.16**

*p<.05 (by applying chi-square test)

**p<.05 (by applying student T test)

Table 4 shows the requirement of isoflurane dosage and the duration of analgesia experience by both the groups. Among the clonidine group 88% of the patients required only 0.5% isoflurane for the maintenance of anesthesia when compared to 44% in the diazepam group and the difference was found to be statistically significant. Similarly the mean duration of analgesia among the patients in the clonidine group was 8.83 hrs whereas in the diazepam group it was only 5.08 hrs and the difference was statistically significant.

Discussion

Clonidine is rapidly absorbed after oral administration. Peak plasma concentration is rapidly achieved in 60-90 mins is highly lipid soluble, easily crosses blood-brain barrier and therefore may interact with alpha-adrenergic receptors at spinal and supraspinal sites within the central nervous system. In addition previous studies suggest that clonidine may also affect peripheral sensory nerves as a sole agent or in combination with local anaesthetics.

Clonidine has been demonstrated to inhibit neurotransmission in both A-delta and C nerve fiber which are theorized to mediate pin-prick, surgical pain. Finally Clonidine has been demonstrated to potentiate inhibitory effects of local anaesthetics on C fiber activity. Therefore Clonidine may exert its effects within the central nervous system at peripheral nerve roots by potentiation of effects of local anaesthetics.

We have compared our results with previous study which also showed the same results.^{8,9,10} The primary mechanism of Clonidine analgesia is via a non-opioid spinal action on central alpha 2 adrenergic receptor in the dorsal horn of spinal cord.

The analgesic effect of clonidine is mediated by the same central alpha₂ adrenoreceptors that mediated its hypotensive effects. Clonidine added to local anaesthetics enhances the effects of local anaesthetics on C fiber action potentials.^{11,12}

In last few years, many reports have permeated the anaesthesia literature addressing the desirable properties of alpha₂ agonists in the perioperative period.^{13,14} In adults 0.3 mg of oral clonidine produced sedation and anxiolysis. Carabine et al¹⁵ noted that higher doses had better sedative effect; 0.2 mg being effective for anxiolysis. In our study, clonidine treated groups had significantly superior sedation compared to diazepam group. Maximum sedation occurred at 90 minutes; this is understandable, considering the peak plasma concentration at 90 minutes following oral clonidine administration.

Comparable to previous study,¹⁶ in our study also, there was no significant change in respiratory frequency with clonidine premedication. In addition, there was no incidence of respiratory depression or desaturation postoperatively.

Hypertension and tachycardia were noticeable during the application of CO₂ pneumoperitoneum in the diazepam group. Patients premedicated with clonidine had more stable haemodynamics than those pre-treated with diazepam. Clonidine premedication effectively blunted the cardiovascular response to surgical stress, especially pneumoperitoneum. Compared with the baseline measurements, there was significantly less increase in heart rate and MAP in the clonidine group compared to the diazepam group and it is almost similar to the study done by Shivinder Singh et al¹⁷.

Various authors^{18,19} have noted a decrease in anaesthetic requirement in clonidine treated patients and it is almost in par with our study where the isoflurane requirement in the clonidine group was 0.5% and that of diazepam it was 1%.

Conclusion

The administration of oral clonidine is a simple and cost effective form of premedication in patients undergoing upper abdominal surgeries results in improved perioperative haemodynamic stability and reduction in anaesthetic requirements. In addition, it also reduces the post-operative analgesic requirements.

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