ORIGINAL RESEARCH PAPER

VOLUME-6 | ISSUE-5 | MAY - 2017 | ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

Effect of various doses of oral clonidine premedication on intra and postoperative analgesic requirements - A randomized control study.

Anaesthesiology

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ABSTRACT

Introduction:

Premedication can reduce intra and postoperative opioid requirements without affecting hemodynamics. In this study, various doses of oral clonidine used to assess intraoperative fentanyl requirement, postintubation mean arterial pressure, postoperatively time taken for first analgesic dose and postoperative total analgesic requirement for first 24 hours.

Methods and Material:

Institutional ethical committee approval and written informed consent obtained and studied for 2 years. 200 patients divided into 4 groups. Group P, C2, C3 and C4 received tablet ranitidine 150mg, oral clonidine 2µg/kg, 3µg/kg and 4µg/kg respectively 90 minutes preoperatively. Postoperatively, patients received Inj Paracetamol 1 gm i.v. if NRS score was ≥ 5. Post intubation mean arterial pressure, intraoperative bradycardia, total fentanyl used, and time taken for first request of analgesic, postoperative analgesic requirement for 24 hrs were recorded.

Results:

Intraop fentanyl and postoperative analgesic requirements were significantly greater in placebo group compared to clonidine group ($p<0.05$). Significant rise in mean arterial pressure was noted after postintubation period with prolonged time to reach baseline readings in placebo group than clonidine group ($p<0.05$). Low incidence of bradycardia and prolonged postoperative analgesia was observed in group C2 when compared to other clonidine groups.

Conclusion:

Oral clonidine (3µg/kg) premedication reduces intraoperative fentanyl and postoperative analgesic requirement.

KEYWORDS:

clonidine, premedication

Introduction:

Various classes of drugs with different routes of administration are practiced to achieve the stable hemodynamics during perioperative period. [1] These drugs can be used as premedications due to various effects like, antianxiety, antisialogogue and sedative effects. Clonidine is 2 adrenergic agonist which also has the property of augmenting the effects of anesthetic drugs. It is one of the ideal preanesthetic drugs as it reduces the laryngoscopic pressure and surgical stress response. This can be used either intravenous or oral route as a preanesthetic medication. An important aspect of medical health care is to provide cost effective treatment. [2] It is wise to use a premedication which not only decreases intraoperative anesthetic and analgesic requirement but also should have minimal or no perioperative side effects. Our aim was to evaluate total intraoperative opioid use, postoperative pain score, time taken to request for the first analgesic dose and 24hr postoperative analgesic requirements in patients undergoing surgeries under general anesthesia after premedicating with different doses of oral clonidine.

Materials and methods:

After obtaining institutional ethical committee approval and written informed consent this study was conducted. This study was conducted for 2yrs with a total sample of two hundred patients. A computer generated randomization was carried out and four groups consisting of 50 patients in each were created. In this study neither the subjects nor the investigators were aware of the group allocation. Group P (Placebo) received oral tablet ranitidine 150 mg, Group C2, C3 and C4 received oral clonidine 2 µg/kg, 3 µg/kg and 4 µg/kg body weight respectively. Intraoperative hemodynamics, postoperative pain score, time of the first request of analgesic and total postoperative analgesic requirement for 24 hrs are noted. The inclusion criteria was patients aged between 16-60 years of either sex, ASA (American society of anesthesiologists) class I or II, elective general surgeries under general anaesthesia (GA) were included in this study. Patients who were not willing to participate, suspected difficult airway, known neurological, endocrine, renal, cardiovascular diseases or allergic to study drugs were excluded from the study. All the patients included in the study were taught about numerical rating scale (NRS) and kept nil by mouth at least for 6 hrs preoperatively. The study drug was administered 30 min prior to the induction with sips of water. Baseline hear rate, noninvasive blood pressure were recorded preoperatively. A standard general anesthesia technique was used for all the patient i.e preoxygenation for 3 min, Inj Midazolam 0.05mg/kg, Inj Fenatnyl 1mcg/kg, Inj Thiopentone 5mg/kg, Inj Vecuronium 0.1mg/kg was administered and intubated with proper size cuffed endotracheal tube. The anesthesia was maintained with oxygen and nitrous oxide (1:1), Isoflurane as inhalational agent of choice with end tidal concentration of 0.8 and controlled ventilation was done (end tidal carbon dioxide concentration was maintained between 35 to 45 mm Hg). During intraoperative period, noninvasive blood pressure and heart rate and total amount of fentanyl used were noted. Any rises in the heart rate by 20% above the base line were supplemented with Inj Fentanyl. Once the surgery is completed the patient is extubated after the reversal. All the patients were monitored for postoperative pain using numerical rating scale for 24 hrs. Patients having episode

of intraoperative bradycardia (heart rate <60/min from base line) and hypotension (fall in MAP < 20% from base line) were treated with Inj Atropine 0.6mg IV and IV fluid bolus (0.9% normal saline) respectively. Postoperatively patients having NRS score equals to or more than five received Inj Paracetamol 1gm intravenously but not exceeding 3gm in 24hrs.

Results:

No statistical significant differences noted between all the groups with respect to demographic parameters or gender wise distribution (Table 1).

Table 1: Demographic data

	Group P (n=50)	Group C2 (n=50)	Group C3 (n=50)	Group C4 (n=50)
Sex (M /F)	17(34%) / 33(66%)	19(38%) / 31(62%)	18(36%) / 32(64%)	16(32%) / 34(68%)
Age (Yrs)	38.62 ± 11.4	35.18 ± 12.7	40.12 ± 10.4	35.84± 10.11
Weight (Kgs)	50.18 ± 10.3	52.74 ± 8.2	51.68 ± 9.4	54.14 ± 8.8

The mean arterial pressure was recorded at various interval is shown in table no 2.

Table 2: Comparison of mean arterial pressure at various time intervals

	Group P		Group C2		Group C3		Group C4	
	Mean ± SD	P-Value	Mean ± SD	P-Value	Mean ± SD	P-Value	Mean ± SD	P-Value
Preinduction	93.96 ± 8.14		88.44 ± 7.53		87.56 ± 7.10		87.82 ± 7.04	
Postintubation 1 min	110.2 ± 7.19	< 0.0001 (HS)	97.62 ± 7.01	0.0001 (HS)	94.76 ± 8.17	0.0001 (HS)	94.64 ± 6.38	0.0001 (HS)
3 min	105.1 ± 5.64	< 0.0001 (HS)	93.9 ± 4.64	0.0001 (HS)	92.14 ± 11.18	0.0033 (HS)	90.28 ± 5.92	0.0002 (HS)
5 min	100.54 ± 5.66	< 0.0001 (HS)	88.2 ± 4.89	0.7991 (NS)	86.56 ± 9.57	0.4129 (NS)	86.82 ± 6.30	0.1031 NS
10 min	89.46 ± 4.53	< 0.0001 (HS)	83.96 ± 5.99	0.0001 (HS)	82.54 ± 9.37	0.0022 (HS)	82 ± 6.97	
15 min	91.26 ± 5.49	0.0054 (HS)	82.6 ± 5.95	0.0001 (HS)	80.52 ± 8.00		81.38 ± 7.41	
30 min	87.52 ± 5.82	< 0.0001 (HS)	81.92 ± 6.52	0.0001 (HS)	81.24 ± 6.96		79.18 ± 7.00	
S= significant, HS =Highly significant, NS = Not significant								

In placebo group one minute after the laryngoscopy, mean arterial pressure increased from the pre-induction values, which was highly significant (P-value < 0.0001). MAP returned to the preinduction value at 10 min of intubation. In clonidine groups one minute after the laryngoscopy, there was highly significant increase in mean arterial pressure (P < 0.01), which remained significantly higher till 3 minutes in all the clonidine groups (P < 0.01). At 5 minutes the MAP were comparable with preinduction in clonidine groups (P > 0.05). These differences between placebo group and clonidine groups remained statistically highly significant at all the times after intubation (P < 0.01). There was no statistically significant change in mean arterial pressure at 5th minute from with pre-induction values among the clonidine groups. MAP remained significantly lower at 10, 15 and 30 minutes compared to its preoperative values in clonidine group.

Intraoperative bradycardia: In Group I, Group II C2, C3 and C4 it was 0%, 6%, 12% and 16% respectively. The incidence of intraoperative bradycardia was highest in C4 group and seen in 18% of patients.

The total amount of fentanyl usage in all the groups is shown in table 3.

Table 3: Comparison of total intraoperative fentanyl usage between the groups.

GROUP (mean±SD) mcg/kg	GROUP	MEAN DIFFERENCE	p VALUE
PLACEBO (2.18±0.48)	C2	0.24	<0.001 (S)
	C3	0.48	<0.001(S)
	C4	0.50	<0.001(S)
C2	PLACEBO	-0.24	<0.001(S)
	C3	0.23	<0.01(S)
	C4	0.02	<0.001(S)
C3	PLACEBO	-0.48	<0.001(S)
	C2	-0.23	<0.001 (S)
	C4	0.02	>0.05 (NS)
S= significant, NS = Not significant			

Placebo group shows statistically significant results when compared to other clonidine groups. Group C2 shows statistically significant results when compared to group placebo and C3 and C4 groups. Clonidine C3 group shows statistically significant results when compared to placebo and C 2 but not significant with group C4.

Table 4 shows the time of first request of analgesic dose in all the groups. The duration is more in all the clonidine groups when compared to placebo group. Among clonidine group, the group C4 has highest duration i.e mean duration of 175.9 min suggesting prolonged duration of analgesia.

Total utilization of Inj Paracetamol in placebo group was higher and statistically highly significant when compared to clonidine group during first 24 hrs (p<0.00001) (Table 4). Among the clonidine groups (Table 5), requirement of total dose of Inj Paracetamol in C2 group i.e. 1.44 ±1.03 was statistically significantly while comparing with C3 and C4 groups (p<0.05). While comparing C3 and C4 groups there was no significant requirement of total dose of Inj Paracetamol (P> 0.05) was observed.

Table no 4: Postoperatively time taken to request of first analgesic and total dose of paracetamol used for first 24 hrs.

	Group P	Group C2	Group C3	Group C4	
Duration Mean ± S.D (minutes)	90.4 ± 33.12	101.2± 55.23	160.3± 40.2	174.9 ± 30.31	
Inj PCM (Gm)	2 ± 1.143	1.44±1.03	0.96± 0.75	0.76 ± 0.55	p = <0.00001 (HS)
HS = Highly significant					

Table 5: Intergroup comparison of paracetamol requirements

GROUP		Mean difference	p value
PLACEBO	C2	0.56	<0.05 (S)
	C3	1.04	<0.001(HS)
	C4	1.2	<0.001(HS)
C2	PLACEBO	-0.56	<0.05 (S)
	C3	0.48	<0.05(S)

C3	C4	0.68	<0.01(S)
	PLACEBO	-1.04	<0.001 (HS)
	C2	-0.48	<0.05 (S)
	C4	0.2	>0.05 (NS)
S= significant, HS =Highly significant, NS = Not significant			

Discussion:

Various techniques and drugs have been tried to prevent or to treat the postoperative analgesia. All these modalities are not free from the side effects. It is important to adopt a method wherein the premedication that itself not only fulfills the criteria of anxiolysis, sedation and antisialogogue action but also should reduce the opioid requirements during intra and postoperative period. It is also important to select a drug which will not affect the perioperative hemodynamics significantly.

Clonidine an alpha 2 agonist has been used in different routes to prevent postop pain in various surgeries. This drug has gained interest due to multiple actions like anxiolysis, sedation and anesthetic sparing effect. [3,4] Due to good safety profile of this drug it is used in both pediatric and adults. [5- 8]

Use of preoperative clonidine as a premedicant has the effect of antisailogouge and anxiolysis which is good for the patient's well-being and decreases the postoperative pain per se. [9] The clonidine which was used preoperatively may have a pre-emptive analgesic effect and due to long elimination half life the postoperative analgesic requirement are less. [10]

Time of request for analgesic dose in placebo group (90.4 ± 33.12) was earlier when compared to clonidine group [C2 (101.2 ± 55.23), C3 (160.3 ± 40.2) and C4 (174.9 ±30.31)]. Similar results have been observed in Sing S et.al where in the request of first dose of analgesia was made in placebo and clonidine group (150mcg) was 100.4 ± 24.3 and 185 ± 34.4 respectively. [8] However among the clonidine groups request of analgesia was prolonged in group C3 when compared to group C1 indicating prolonged duration of analgesia in C3 in comparison with C1 group.

The intraoperative use of fentanyl in placebo group was higher (2.18 ±0.48 mcg/kg) and statistically significant compared to clonidine groups ($p < 0.05$).

In a study by the author Mariappan et.al, the comparison of oral clonidine and intravenous dexmedetomedine was made. In this study the author observed overall fentanyl (mcg/kg) requirement intraoperatively was 3.14± 0.93(mean ± SD), while in our study it was 1.93± 0.2, 1.7±0.2, 1.68±0.2 in group C2, C3 and C4 respectively. The mean body weight in the above study among clonidine group was 60.21±6.7. The mean body weight among the groups C2, C3 and C4 were 52.74±8.2, 51.68±9.4, 54.14±8 respectively. This explains why the fentanyl requirement was less in our study in comparison with the study conducted by Mariappan et.al. [11]

The total dose requirement of Inj Paracetamol as a rescue analgesia in placebo group was higher as compared to the clonidine group. Among the clonidine group the total paracetamol used in the group C2 was statistically significant when compared to the C3 and C4 group. Between the C3 and C4 group there was no statistically significant difference in utilization of the Inj Paracetamol, indicating that the oral dose 3mcg/kg is effective to provide post operative analgesia for first 24 hrs. In a similar study conducted by singh et al, the rescue analgesia was given to 72 % in first 24hrs. In our study the 80% of the patients received Inj Paracetamol in placebo group. This higher percentage is mainly due to patients underwent open surgeries in our study whereas in Singh et al the study was done on laparoscopic cholecystectomy. [8]

In a study the author used oral clonidine (5mcg/kg) and studied the effects on heart rate. Incidence of the bradycardia was 26% in case of when compared to control group (13%). [12] In our study the incidence of the bradycardia has been seen 0%, 8%, 14% and 18% in placebo, C2, C3 and C4 groups respectively. This lower incidence could be due to lower dose used in our study groups. The result shows that, the incidence of bradycardia increases as the dose of the oral clonidine increases. This entire patient's heart rate was normalized after administering Inj Atropine 0.6mg i.v. The lowest heart rate recorded was 35/min in group C3.

Oral clonidine when used as premedicant, enhances the quality of pain relief and substantially prolongs the duration of analgesia when compared to placebo group. Our results suggest that use of oral clonidine as premeditation can be used to reduce intraoperative and postoperative opioid needs and defer it's side effects.

Conclusion:

Oral clonidine at various doses in comparison with placebo have overall good outcome. Oral clonidine when used at a dose of 3mcg/kg as an oral premedication has good opioid sparing effect, decreases the stress response caused due to laryngoscopy, prolongs the duration of analgesia, decreases total analgesic requirement for first 24 hours with minimal side effects like bradycardia.

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