CLINICAL INVESTIGATION

ORAL CLONIDINE IN CHILDREN : EFFICACY AS PREMEDICANT AND POSTOPERATIVE ANALGESIC AS COMPARED TO DIAZEPAM

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SUMMARY

This study was carried out to assess sedative, anxiolytic and analgesic effect of oral clonidine (2 or 4 mgkg^{-1}) in children. In a prospective randomised double blind trial, 75 children of 2-12 years received either oral clonidine 2 (group 2C) or 4 mgkg^{-1} (group 4C) or diazepam 0.2 mgkg^{-1} (group D) 90 minutes prior to minor surgeries. Perioperatively the level of sedation, quality of parental separation, mask acceptance and haemodynamics were recorded. Postoperative pain was assessed using Objective Pain Scale (OPS). OPS > 6 demanded rescue analgesic. Clonidine 4 mgkg^{-1} group had higher sedation score (2.77±0.42), compared to clonidine 2 mgkg^{-1} group (2.39±0.63;p <0.05) and diazepam group (2.08±0.57; p <0.001). At 90 mins, sedation score of 3 was achieved 48%, 72% and 20% in 2C, 4C and D groups respectively. The difference of this proportion between 4C and D groups was 52% with confidence interval (CI) from 73% - 31% and the difference between 2C and D group was 28% with 95% CI of 53.6% to 2.4%. Parental separation and mask acceptance scores and number of patients with IV acceptance were higher with both clonidine groups compared to diazepam; there was no significant difference between two clonidine groups for the same. Rescue analgesics were required in 20% of clonidine group versus 96% of diazepam group patients; 52% of diazepam group required a repeat dose (p<0.001). The two clonidine groups showed a reduction in rescue analgesia requirement of 76% (96% in D and 20% each in 2C and 4C groups) with 95% CI of 93% and 59%.Incidence of postoperative hypotension was 8% with clonidine 4 mgkg^{-1}. A single oral dose of clonidine 2 mgkg^{-1} can provide good anxiolysis and postoperative analgesia with minimum side effects.

Keywords : Preanaesthetic medication, Clonidine, Alpha 2 agonists, Clonidine, Paediatric.

Introduction

Anxiety and pain are two factors causing considerable emotional stress in children. Recent advances on alpha 2 agonists focus on the possible use of clonidine as sedative and analgesic.[1,2] Further, it has an excellent bioavailability following oral administration. The prospect of sedation and analgesia provided by one drug in a single oral dose, not withstanding its other attractive features, prompted us to study its efficacy as a premedication in paediatric patients. Taking into consideration, the possibility of adverse effects like hypotension and bradycardia, we studied the effect of drug administered in two different doses for premedication (2 or 4 mgkg^{-1}) to find out the optimum dose.

Methods

In a prospective randomised double blind trial, 75 children of 2-12 years age and ASA grade I, undergoing reconstructive, orthopaedic, otological or ophthalmologic procedures were enrolled. Institutional approval and informed consent from parents were obtained. Patients were randomly assigned according to a computer generated random table, to receive one of the three groups viz. 2C, 4C and D groups who were to receive premedicant drugs clonidine 2 or 4 mgkg^{-1} or diazepam 0.2 mgkg^{-1} respectively along with atropine 0.03 mgkg^{-1}, orally 90 minutes prior to induction of anaesthesia.

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Clonidine and diazepam premedication were prepared by dissolving crushed tablets of clonidine 100 mg (Arkamine) and diazepam 5 mg (Calmpose) in 10 ml of 5% dextrose. Second anaesthesiologist, who was unaware of the premedicant administered, did the rest of the management, including the observations. Before and every 30 minutes after premedication, heart rate (HR), systolic BP (SBP), diastolic BP (DBP), and respiratory rate (RR) were recorded. Level of sedation was recorded according to three points scale [1= Tearful/combative, 2= Alert/aware, 3= Drowsy/sleepy]. Parental separation score i.e. behaviour of the child while entering the theatre was assessed using three points scale [1= Poor (anxious and combative), 2= Good (anxious but easily reassured), 3= Excellent (sleepy and calm)].

Children were allowed to breath 50% N_2O and 0.5 to 3% halothane in oxygen through a mask. Quality of mask acceptance was graded with a four points scale [1= Poor (combative and angry), 2= Fair (fearful and not easily

calmed), 3= Good (fearful but easily calmed), 4= Excellent (unafraid and cooperative)]. If the child was cooperative an IV access was established. If not, the inhalational induction was continued till the child allowed IV access to be secured. Thiopentone followed by vecuronium was administered and trachea was intubated after three minutes. Anaesthesia was maintained with 66% N_2O and 0.5 to 3% halothane in oxygen with controlled ventilation. No other sedative or analgesic was administered.

Postoperatively, all children were observed in recovery room for six hours. Pain score as per Objective Pain Scale (OPS, 0-10), Alderate recovery score and postoperative level of sedation were recorded every ½ hourly for first two hours and then every hourly interval for six hours. Postoperatively level of sedation was assessed by a four points scale [0=Awake and crying; 1=Awake and settled; 2=Drowsy but aroused by gentle stimulation; 3=Unarousable].

Incidence of adverse effects i.e. hypotension (SBP < 70 mmHg), hypertension (SBP > 140 mmHg), bradycardia (HR < 60/min), respiratory depression (RR < 12/min), desaturation (SpO_2 < 90% for 15 seconds), postoperative nausea and vomiting (PONV) and shivering if occurred were noted. Bradycardia was treated with atropine. Hypotension was corrected using IV fluids; atropine was administered, if it was accompanied by bradycardia; if persistent and severe, an infusion of dopamine was planned.

In recovery room, if OPS exceeded six, rescue analgesic in the form of pentazocine 0.3 $mgkg^{-1}$ with promethazine 0.2 $mgkg^{-1}$ was administered. However, before providing rescue analgesic, a time period of 15-30 minutes was allowed to observe if the patient responded to parental reassurance and sympathy. After six hours, children were transferred to the ward. In the ward, if OPS exceeded six, syrup Ibugesic (Ibuprofen and paracetamol) was administered. The highest OPS within first six hours were recorded for each patient. This was used for calculating mean highest OPS for each group and for finding out the percentage of patients falling into various severity of pain groups i.e. pain free (OPS 0-3), mild pain (OPS 4-6) and severe pain (OPS 7-10).

Statistical analysis

Analysis of variance (ANOVA), followed by Student Newman Keuls test were used for comparison of demographic data, mean sedation and pain scores. Intragroup comparison of haemodynamic data was done by repeated measures ANOVA. Differences in parental separation scores and quality of mask acceptance were analysed using Kruskal Wallis test. $P < 0.05$ was considered statistically significant.

The sample size required in this study (n=25 in each group) was based on four assumptions: a) an incidence of severe pain in control group of 50%; b) clonidine would reduce the incidence by 50%; c) a type I (a) error of 5%; d) a type II (b) error of 20%.

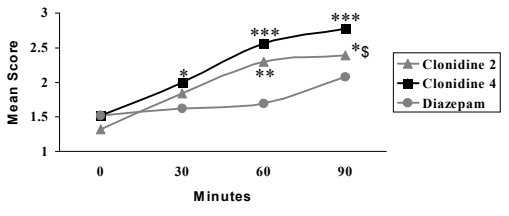
Results

Demographic characteristics were comparable in all the three groups (Table - 1). 4C, 2C and D groups had significant sedative effect starting at 30, 60 and 90 minutes onwards respectively; maximum being at 90 minutes in all three groups (Fig. 1). Patients of group 4C (2.77±0.42, P <0.001) and group 2C (2.39±0.63; P <0.05) had better sedative effect compared to group D (2.08 ± 0.57). Among two clonidine groups, group 4C gave better sedative effect ($P < 0.05$). At 90 minutes, sedation score of 3 was achieved in 48%, 72% and 20% of 2C, 4C and D group respectively (Fig. 2).

The difference of this proportion between 4C and D groups was 52% with 95% confidence interval (CI) from 73% to 31% and the difference between 2C and D groups was 28% with 95% CI of 53.6% to 2.4%.

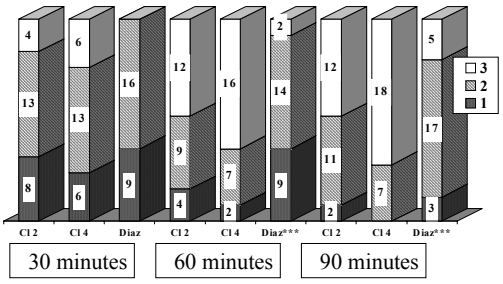
Table - 1 : Demographic characteristics

Parameters	Clonidine 2 $mgkg^{-1}$	Clonidine 4 $mgkg^{-1}$	Diazepam 0.2 $mgkg^{-1}$
Number	25	25	25
Age (years)	7.12±3.23	6.23±2.59	6.14±2.76
Sex (M : F)	20 : 5	17 : 8	15 : 10
Weight (Kg)	19.25± 6.16	17.68±6.70	17.08±4.92
Duration of surgery (min)	90.22±39.46	88.6±37.05	74.68±24.30
Duration of anaesthesia (min)	97.34±40.03	92.28±37.51	78.71± 27.63
Premedication time (min)	91.42±5.90	94.89±6.88	96.32±6.45



* P < 0.05 with respect to diazepam group
**P < 0.01 with respect to diazepam group
*** P < 0.001 with respect to diazepam group
$ P < 0.05 between clonidine 2 and 4 μ gm/kg groups

Fig. 1 : Preoperative sedation score



*** P < 0.001 compared to both clonidine groups

Cl2 -clonidine 2 μ gm/kg
Cl4 -clonidine 4 μ gm/kg
Diaz - diazepam

Fig. 2 : Sedation score

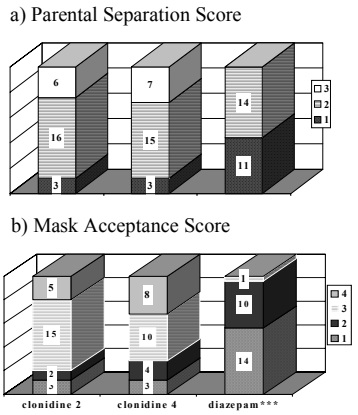
Without any significant intergroup difference both clonidine doses gave better parental separation and mask acceptance scores compared to diazepam ($P < 0.001$) (Table - 2). None of the diazepam group patient had excellent parental separation. Only 4% of diazepam group Vs 80% and 72% of 2C and 4C respectively had good / excellent quality of mask acceptance (Fig. 3). Intravenous induction was accepted in 68% and 64% of 2C and 4C Vs 36% of D group patients ($P < 0.05$). There was no significant change in respiratory rate in any of the groups.

Table - 2 : Main features.

Parameters	Clonidine 2 mgkg n = 25	Clonidine 4 mgkg^{-1} n = 25	Diazepam 0.2 mgkg^{-1} n = 25
Parental separation score Mean±SD	2.14±0.59	2.16±0.62	1.58±0.49 ***
Mask acceptance score Mean±SD	2.85±0.87	2.90 ± 1.04	1.47±0.65 ***
Highest OPS in 1st 6 hrs Mean±SD	4.93±1.53	4.82±1.89	7.45±1.23 **
Rescue analgesia 0 - 6 hours. Number (%) 6 – 4 hours. Number (%)	5 (20%) 0	5 (20%) 0	24 (96%)*** 13 (52%) ***

** $P < 0.01$ – Diazepam Vs both clonidine groups.
*** $P < 0.001$ – Diazepam Vs both clonidine groups.

Following premedication decrease in heart rate occurred in both the clonidine groups. However, degree of reduction was higher with group 4C ($P < 0.05$) and onset was earlier at 30 minutes Vs at 60 minutes with group 2C. A significant decrease in systolic BP was noted only in group 4C ($P < 0.01$). Troublesome hypotension or bradycardia by definition did not occur in any patient in the preoperative period. During intubation all three groups showed rise in heart rate and systolic BP; but, higher rise was noted in diazepam group ($P < 0.001$) and it persisted even at10 minutes (Fig. 4).



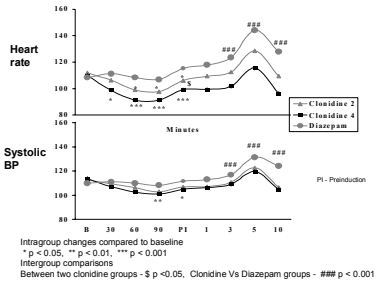
** p < 0.001 - Diazepam compared to both Clonidine groups

Fig. 3

Table - 3 : Postoperative sedation score.

Score	Clonidine 2 mgkg^{-1}	Clonidine 4 mgkg^{-1}	Diazepam 0.2 mgkg^{-1}
0	6 (24)	4 (16)	21 (84)
1	9 (36)	6 (24)	3 (12)
2	10 (40)	14 (56)	1 (4)
3	0 (0)	1(4)	0 (0)

Data is presented as number (%) of patients

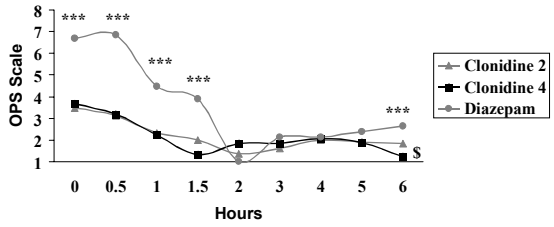


Intragroup changes compared to baseline
* p < 0.05, ** p < 0.01, *** p < 0.001
Intergroup comparisons
Between two clonidine groups - $ p <0.05, Clonidine Vs Diazepam groups - ### p < 0.001

Fig. 4 : Hemodynamic parameters

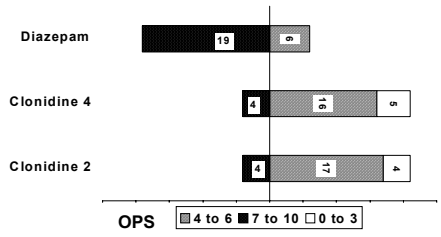
*** p < 0.001 - Diazepam Vs both Clonidine groups

Both clonidine treated groups had lower OPS scores in initial $1^1/_2$ hours and at six hours compared to D group ($P < 0.001$); 4C group had significantly lower ($P < 0.05$) OPS scale (1.23±1.12) compared to 2C group (1.83±0.85) at six hours (Fig. 5). None of D group Vs 16 and 20% of 2C and 4C group were pain free. In fact, 76% of D group had severe pain (Fig. 6). Significantly higher number of D group patients required rescue analgesia and even the repeat dose (Table - 2). The two clonidine groups showed reduction in rescue analgesia requirement of 76% (96% in D and 20% each in 2C and 4C groups) with 95% CI of 93% to 59%.



*** P < 0.001 diazepam Vs both clonidine groups
$ P < 0.05 between two clonidine groups

Fig. 5 : Objective pain scale



Data represented as number of patients
*** P < 0.001 Diazepam Vs both Clonidine groups

Fig. 6 : Comparison of highest OPS within first six hours

Postoperatively 84% of D group patients were crying (Table-3); two even developed hypertension associated with higher OPS scale. Two patients in 4C group had hypotension associated with vomiting and required fluid challenges. One patient in 2C group developed transient bradycardia and required atropine. No patient had respiratory depression. There was no significant difference in incidence of PONV with 2C(4%), 4C(8%) and D(16%). Incidence of shivering with D (72%) was higher compared to 2C(4%) and 4C(0%) ($P < 0.001$).

Discussion

In last few years, many reports have permeated the anaesthesia literature addressing the desirable properties of alpha 2 agonists in the perioperative period.[3,4] In adults 0.3 mg of oral clonidine produced sedation and anxiolysis.[5] Carabine et al[6] noted that higher doses had better sedative effect; 0.2 mg being effective for anxiolysis.

Initial animal experiments[7] and later human studies using neuraxial administration[8,9,10] of clonidine have shown significant analgesia. Oral clonidine is seldom used for analgesia.[11] Though it is less effective compared to neuraxial route, it has two distinct advantages; a) it can be used for upper dermatological surgeries; b) it is the simplest and most acceptable route for children. Mikawa et al[12] demonstrated lower pain scores, greater pain free period and less requirement of rescue analgesics in children premedicated with 4C compared to 2C and control groups.

We conducted a study to assess the efficacy of clonidine premedication in a single oral dose as sedative, anxiolytic and for attenuation of postoperative pain. Opioids were not included in this study as we aimed to produce a calm and cooperative child but not at the cost of respiratory depression, nausea, vomiting and pruritus and further to avoid painful pricks. The study was limited to the children older than two years as cardiac output in younger ones depend on heart rate and clonidine is known to give rise to bradycardia.

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. Mikawa et al[13] found better parental separation and mask acceptance with 4C. In our study, without significant intergroup difference, both clonidine groups had better parental separation and mask acceptance and allowed an easy and relatively fight free induction. Higher number of clonidine treated patients accepted IV induction. Considering that the groups are comparable with respect to age and weight, it stands to reason that the children in clonidine premedicated groups were calm and sedated enough to allow IV access.

Comparable to previous study,[14] 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.

Various studies have reported a significant reduction in HR, BP and cardiovascular response to intubation.[15,16,17] We noted significant reduction in HR in both clonidine treated groups; however significant reduction in systolic BP occurred only with group 4C. Attenuation of haemodynamic response to intubation occurred in our study also. But, this attenuation is not so important in children, where in fact, we would prefer increase in HR and systolic BP and avoid the frequently seen vagally induced bradycardia in response to airway instrumentation. This attenuation would be beneficial in children at risk of cerebrovascular accidents and dysrhythmias, or children with renal hypertension or cardiac insufficiency. In our study troublesome hypotension or bradycardia did not occur in preoperative period or during surgery; perhaps this could be because of atropine premedication.

Various authors[16,18] have noted a decrease in anaesthetic requirement in clonidine treated patients. We could not reliably measure halothane requirement, as there was a lack of uniformity in halothane delivery apparatus and because of lack of availability of measurement of end tidal halothane concentration.

In our study, clonidine treated patients had lower pain score for first 90 minutes and then at six hours

compared to D group. At the end of 90 minutes, 96% of D group patients received pentazocine as rescue analgesia resulting in nearly similar pain scores till five hours. At the sixth hour, perhaps because of wearing off of pentazocine's action, D group showed higher pain scores. Only 16% of clonidine treated group had severe pain; 16 and 20% of patients of 2C and 4C group were pain free in spite of absence of prior administration of analgesics; majority had only mild pain. This indicates that clonidine has significant analgesic property. Though patients can localize pain, there is significant attenuation of response to pain. Contrary to earlier findings, in our study group 4C did not result in superior analgesia compared to group 2C. None of the clonidine treated groups required rescue analgesic six hours later, a finding not of surprise, considering the elimination half-life of 12 hours of clonidine.

Majority of children, in clonidine groups were calm or settled compared to D group, wherein most were tearful and wide-awake. Pain also could be the contributing factor for this. Only one child in 4C group was unarousable, otherwise majority were not excessively sedated to cause problems. Jorris et al[19] demonstrated the efficacy of IV clonidine to prevent postoperative shivering. Clonidine treated patients had less shivering in our study. Oral clonidine achieves peak plasma concentration at 90 minutes and has long half-life, so plasma levels after minor surgeries remain adequate to attenuate shivering.

One of the most important side effects of clonidine is hypotension and bradycardia.[20] 8% incidence of hypotension with group 4C and 4% incidence of bradycardia with group 2C suggest the need of careful postoperative vigilance. It may also preclude one from using the drug for ambulatory surgery. Two patients in D group had an episode of hypertension associated with higher OPS, which subsided with pain relief.

Thus group 2C or 4C resulted in calm, cooperative child without undue drowsiness, excellent anxiolysis, easy separation from parents, good mask acceptance, easier IV access, excellent pain relief, less requisition of analgesics and no respiratory depression. But 4C did produce an 8% incidence of hypotension, which is not acceptable for minor surgeries. 2C gave similar advantage, with fewer complications. Hence, 2C will be more suitable for minor surgeries; however it does not exclude the necessity of vigilant postoperative monitoring.

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