

ORAL CLONIDINE IN CHILDREN: EFFICACY AS PREMEDICANT AND EFFECT ON POSTOPERATIVE RECOVERY. (COMPARISON OF TWO DIFFERENT DOSES 3µg/kg AND 4µg/kg)

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ABSTRACT: BACKGROUND: This study was conducted to see the efficacy of two different doses of oral clonidine as a premedication in pediatric patients. **MATERIAL AND METHOD:** In a prospective randomized study of 60 cases of 4-12 year old children receiving oral clonidine either 3µg/kg (group C₃) or 4µg/kg (group C₄) as a premedication 90 minutes prior to surgeries. Preoperatively, the level of sedation, response to parental separation, mask acceptance, intravenous cannulation and response to intubation as well as hemodynamic were noted. Postoperative recovery was assessed using Alderate recovery room score. **RESULTS:** Clonidine 4µg/kg group had higher sedation score compared to clonidine 3µg/kg. At 90 minutes, almost 90% children in C₄ group were asleep but arousable on calling and in C₃ group 33% were asleep, 60% were drowsy and rest 7% children were calm. Parental separation and mask acceptance scores were also higher with clonidine 4µg/kg group. The response to intubation was better attenuated in clonidine 4µg/kg group. There was no respiratory depression or oxygen desaturation at any point of time in our study perioperatively and no delay in postoperative recovery as well as no significant difference in the incidence of post operative nausea and vomiting in both the groups. **CONCLUSION:** Oral clonidine 4 µg/kg provided better sedation than clonidine 3µg/kg without prolonging the postoperative recovery.

KEYWORDS: Oral clonidine, Premedication, Pediatric

INTRODUCTION: Planning and carrying out a smooth transition from child's awake normal state to condition of surgical anaesthesia is one of anesthesiologist's greatest challenges. The anesthesiologist should always consider the child's emotional needs and create an environment that will minimize or abolish fear and distress. Therefore, the anesthetic practice in this age group demands a continuous search for an ideal premedicant that can be administered by convenient route to the pediatric patient.

Clonidine, the α₂ agonist has the property of good anxiolysis and sedation without causing respiratory depression. It has antisialogogue and analgesic action. It also prevents the hemodynamic response to intubation, decreases the doses and minimum alveolar concentration (MAC) value of anesthetic agent and prevents post operative nausea and vomiting. ^(1,2,3,4,5,6,7,8) Along with its rapid and smooth postoperative recovery profile and low cost makes it a good premedication of choice. ^(3,4,5,6.) Considering all, we planned the study to compare two different

doses of clonidine 3µg/kg and 4µg/kg, to identify its efficacy and its other advantage and disadvantage.

AIMS OF STUDY:

We compared following parameters.

- (1) Level of sedation.
- (2) Anxiolysis e.g. response to parental separation, intravenous cannulation, face mask application.
- (3) Hemodynamic response to clonidine e.g. pulse rate, blood pressure changes in preoperative period and during laryngoscopy and intubation.
- (4) Changes in Respiratory rate and Oxygen saturation
- (5) Antisialagogue effect
- (6) Postoperative recovery
- (8) Postoperative nausea and vomiting.

MATERIALS & METHOD: This was a prospective randomized, single blind, comparative clinical study comprised of 60 pediatric patients of comparable weight & either sex, aged 4 to 12 years of ASA grade I and II undergoing elective surgeries like Otolaryngeal, Plastic, Orthopedic, General and Ophthalmic surgeries.

The following patients were excluded from study.

1. History of recent URTI.
2. Any congenital anomaly of heart, kidney and gastro intestinal tract.
3. If they are judged to have very difficult intravenous access.
4. Known to have any drug allergy.

Thorough preoperative assessment was done. Specific Consideration included.

1. Vital parameters
2. Haemogram, Random blood sugar
3. Urine Albumin and Sugar
4. Airway assessment.

All parents were explained details about the procedure. A written and informed consent was taken. All patients were kept nil by mouth for 6 hours for solid and non clear liquid and 2-3 hours for clear fluid and they were divided randomly into two groups, 30 patients in each group.

Group C₃ - Oral Clonidine 3µg /kg + inj. Atropine 0.03 mg/kg

Group C₄.. Oral Clonidine 4µg /kg + inj. Atropine 0.03 mg/kg

The clonidine tablet (Arkamine) 100µg was dissolved in 5ml of 25% dextrose to make it more palatable and appropriate dose according to weight. Then Injection Atropine taken at a dose 0.03µg/kg into same syringe and given to child to be taken orally 90 minute before surgery in the preparation room. The children were kept in bed along with parents.

The children were monitored at 0, (basal) 30, 40, 50, 60, 70, 80 and 90 minutes with following parameters.

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- Pulse Rate
- Systolic Blood Pressure
- Respiratory rate
- SPO₂
- Level of Sedation with following score ⁽⁹⁾
 - 0- Agitated, crying, clinging to parents.
 - 1- Alert, awake but not cling to parent
 - 2- calm, sitting or lying comfortable with eyes spontaneously opening
 - 3- drowsy, lying comfortably with eyes closed but responds to minor stimuli
 - 4- asleep, eyes closed and not responds to minor stimuli.
- Response to parental separation as ⁽¹⁰⁾
 - 0- poor (anxious, combative).
 - 1- good (anxious but easily reassured)
 - 2- excellent (calm, drowsy)

Then the child was taken to operation theater. The response to intra venous cannulation with appropriate cannula (1-crying, 2-calm) and response to facemask application noted with 5 point rating scale. (1- agitated, 2-alert, initially refuse then accept mask, 3-calm and accept mask, 4-Drowsy, accept mask, 5-Asleep, accept mask) ⁽¹¹⁾

After preoxygenation with 100% oxygen for 3minutes, all patients were induced with Injection Pentothal sodium (4-7 mg/kg) intravenously till loss of eye lash reflex. Then injection Succinylcholine 2mg/kg was given intravenously. Oral endotracheal intubation was done with appropriate sized cuffed or plain tube. During Intubation the following parameters were monitored to identify the response to intubation at 1, 3 and 5 minutes.

- (a) Pulse rate
- (b) Systolic blood pressure
- (c) Secretion as
 - 0 - None
 - 1 - Mild
 - 2 - Moderate
 - 3 - Copious

Anesthesia was maintained with O₂ and N₂O (50:50%) with Isoflurane and Injection Vecuronium Bromide. At the end of surgery, residual motor block was antagonized by Injection Neostigmine 0.05mg/kg and Injection Glycopyrrolate 0.01 mg/kg intravenously. Once response to verbal command, intact airway protective reflex and other extubation criteria fulfilled, children were extubated and shifted to recovery room. All children were monitored for 6 hours post operatively in the recovery room. Alderate recovery room score were recorded at 10 minute interval for 30 minutes, then every 30 minutes for 2 hours and then every hourly for 6 hours. Patients must score greater than 9 for safe discharge from the recovery room. Children were given paracetamol syrup 10mg/kg if they complained for pain at the surgical site. The incidence and time of occurrence of vomiting were recorded within 6 hours of operation. Any other side effect like hypotension systolic blood pressure (<70mm of Hg) rebound hypertension (systolic blood pressure > 140mm of Hg), bradycardia (Heart rate < 60 beats/minute) and hypoxia (SPO₂ < 90%) noted during post

operative period. The demographic variables and vitals were compared using Student 't' test. The sedation and anxiolysis scores were compared using the Mann-Whitney test and Chi-Square test. A P value ≤ 0.05 considered as significant.

OBSERVATION & RESULTS: As shown in table 1, the two groups were comparable in respect to age, sex, height, weight and ASA grading. However, unintentional male predominance found in both groups.

Table 2 suggests that the baseline sedation score was comparable between two groups. In both groups there was increase in sedation score as time elapsed. The rise in mean sedation score was statistically significant after 30 minutes where the score was higher in C₄ group compared to C₃ group.

The graph 1 shows that 76.67% in group C₃ and in 94% children in group C₄ were separated easily. The graph 2 shows that less children were crying on intravenous cannulation in group C₄ (66.6% in group C₃ v/s 40% in group C₄).

Responses to face mask application inside Operation Theater were as shown in graph 3. In C₃ group 53.26% children were calm and accepted mask easily. 10% children refused mask & 36.6% child accepted mask after persuasion. But in Group C₄ 93.2% children had excellent mask acceptance and only 6.6% children accepted mask after persuasion.

As shown in graph 4, the base line pulse rate (122.00 ± 7.97) in group C₃ and (122.66 ± 4.37) in group C₄ was comparable. There was significant difference in pulse rate at 60 and 70 minutes between two groups and the difference became highly significant at 80 and 90 minutes.

As shown in graph 5, the baseline systolic blood pressure between two groups (114.33 ± 3.28 in C₃) and (115.06 ± 3.81 in C₄) was comparable. The systolic blood pressure decreased in both groups but there was significant decrease in systolic blood pressure in Group C₄ at 40 minutes and the decrease was highly significant after 50 minutes in C₄ as compared to C₃ group.

The table 3A and 3B show the pulse rate and blood pressure between two groups during intubation which were compared at 1, 3, 5 minutes in both groups. There was rise in both from the 90 minutes value in both groups but the rise was highly significant in C₃ group compared to C₄ group at all intervals. 85% in group C₄ and 83.3% in group C₃ had no secretion and 16.6% in group C₃ & 15% in group C₄ showed mild secretion.

During postoperative period there was no respiratory depression and oxygen desaturation seen in both the groups. But children in group C₄ were more sedated compared to group C₃. By 120 minutes, all children in group C₃ were fully awake and by 240 minutes, all children in group C₄ were fully awake. At no point of time recovery score was below 7.

9.9% children in C₃ group and 6.6% children in C₄ group had postoperative nausea and vomiting (PONV). Comparing both groups, incidences of PONV were statistically insignificant.

DISCUSSION; The anaesthetic management in pediatric age group is a challenge, as they are aware of strange hospital environment and parental separation in contrast to adult who are usually concerned about the prospect of surgery and health; children were principally worried about pain and separation from parents so sedation and anxiolysis are the essential components of pediatric anaesthesia.

We prefer oral route for administration of drugs in our study because it avoids fear of needle prick and is most convenient route for administration. We made drug more palatable and sweet by administering it with 25% dextrose. The clonidine has 95% oral bioavailability

via oral route and absorption is complete ^(1,2). In our study we added Atropine simultaneously at a dose 0.03mg/kg to add the antisialogogue effect of clonidine and also Atropine can act as an effective antidote for bradycardia and hypotension which reported by Mikawa et al with the use of clonidine 5µg /kg ⁽⁴⁾. Also, it has good oral bioavailability.

Clonidine orally used with dose schedule from 1-5µg/kg but appropriate dosing is still under investigation. Clonidine 2µg/kg used by Mikawa et al & Malde et al causing no benefit ^(3,9). Clonidine 3µg/kg used by Ramesh et al showed sedation effect comparable to diazepam ⁽¹⁰⁾. Clonidine 4µg/kg used by Mikawa et al, Remier et al, Batra et al and Malde et al ^(3,5,8,10,13,14). They found that clonidine 4µg/kg had better sedation, anxiolysis and attenuation of haemodynamic response than diazepam. So we tried the dosing schedule 3µg/kg & 4µg/kg for getting maximum benefit without adverse effect.

In both the groups there was a significant rise in sedation score from the baseline value. The peak sedation was seen at 90 minutes where the sedation score in C₃ group was 3.26 and C₄ group was 3.90 i.e. at 90 minute almost 90% children in C₄ group were asleep but arousable on calling and in C₃ group 33% were asleep, 60% were drowsy and rest 7% children were calm. Our results were comparable to Y K Batra et al, Ramesh et al, Mikawa et al, Fazi et al and Malde et al ^(3,10,12,14,15,16,17).

The sedation in clonidine is mainly due to stimulation of α₂ receptor in the locus cerulus in the brainstem. Activation of α₂ receptor suppresses the spontaneous firing rate of locus coeruleus. This results in an increasing activity of inhibitory interneuron's such as GABAergic pathways to produce CNS depression. ⁽¹²⁾. At the point of maximum anxiolysis i.e. when children were sleepy, drowsy or calm, they were shifted to the operation theater which was 90 minutes after giving premedication in our study. Clonidine 4 µg/kg is more effective for preinduction sedation than oral diazepam 0.4 mg/kg if it is administered at least 90 minutes before induction ⁽¹²⁾.

The response to parental separation was graded as excellent, good and crying. As shown in graph 3, in group C₃ 76.6% children were easily separable and 23% were crying but in group C₄ 94 % children were easily separated, only 6% were anxious of parental separation. Mikawa et al reported clonidine 4µg /kg has better parental separation than clonidine 2µg/kg or oral diazepam ⁽³⁾. Malde et al showed there was no difference between two doses of clonidine 4µg/kg or 2µg/kg but in our study group C₄ had significantly better parental separation than group C₃ ⁽¹⁰⁾. Mithani et al 1984 in a study of effect of α₂ agonist and antagonist in maze exploration model of fear motivated behavior study showed that clonidine also causes anxiolysis independent of sedation.

Response to intravenous cannulation was graded as calm or crying. As shown in graph 4, 66.6% children in group C₃ and 40% children in group C₄ were crying during intravenous cannulation. Our results coincide with Malde et al ⁽¹⁰⁾. Higher percentage of children responded to intravenous cannulation compared to Mikawa et al in 1993 because they have used O₂ and N₂O inhalation via face mask during intravenous cannulation to decrease pain of needle prick. In a study by American dental society of anesthesiology 2006, oral clonidine pretreatment prior to intravenous cannulation in adult showed that clonidine increases the acceptance of intravenous cannulation by decreasing discomfort and pain and clonidine also increase cutaneous blood flow enable easier intravenous access ⁽¹⁸⁾. As shown in graph 5, in group C₄, more number of children were calm and accepted mask easily than in group C₃ and similar to the study done by Mikawa et al and Malde et al ^(3,10).

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Comparing both the groups, the decrease in pulse rate was statistically insignificant. Comparing base line value in each group, there was highly significant decrease in pulse rate at all time interval but we did not encounter a single case of troublesome bradycardia. Similarly, Ramesh et al and Mikawa et al also showed significant decrease in pulse rate with clonidine but in no case bradycardia occurred ^(8,12).

Following premedication in both the groups, there was fall in systolic blood pressure significantly. The decrease in systolic blood pressure started from 30 minutes onwards. The fall in systolic blood pressure was statistically highly significant when compared with basal level in both the groups. Our results were similar to Mikawa et al , Fazi et al and Malde et al ^(3,10,15). The peak effect was seen at 90 minutes corresponded to peak plasma concentration of clonidine. The cardiac action of clonidine was due to imidazoline specific receptor in nucleus reticularis lateralis of brain stem and thus decreases in central sympathetic output. (Teberica et al 1991). Clonidine also acts by decreasing sympathetic tone and lowers set point around which arterial blood pressure regulated (Badoen et al 1983) ^(1,2). Based on observation, Rozen 1988 concluded that, a preoperative pharmacological sympathectomy with clonidine in oral doses $\leq 5\mu\text{g}/\text{kg}$ appears to be safe and useful stabilizer of both heart rate and blood pressure as well as myocardial performance ^(3,8).

As shown in table 3A and 3B, there was rise in pulse rate and blood pressure from the 90 minutes value in both groups but it was highly significant in C₃ group compared to C₄ group at all intervals. The stress response was maximally attenuated in C₄ group. Our results tally with study by Mikawa et al, Ramesh et al , Malde et al and Raval DL et al ^(3,8,10,12,19). Clonidine may successfully attenuate hemodynamic changes following intubation in children and may be suitable than opioids because of less respiratory depressive effect ⁽⁸⁾. The heart rate decreased after 90 minutes of clonidine administration and the difference between two groups was maintained before induction, after induction and after intubation. So it appears that the decreased in tachycardic response to intubation with clonidine was due to generalized reduction in heart rate even prior to induction. Mikawa et al also demonstrated that clonidine inhibits central sympathetic flow with resultant suppression of catecholamines ⁽⁸⁾.

There was no significant change in respiratory rate and Spo₂ in either group at any interval. The small decrease in respiratory rate from basal level was due to reduction of anxiety and due to sedation. Mikawa et al, Ramesh et al and Fazi et al also observed the same. ^(3,12,15,16,17)

We observed for any secretion in oral cavity during intubation and only 16.6% children in group C₃ and 15% children in group C₄ had mild oral secretion. Clonidine decreases salivary secretion by inhibiting Acetylcholine release (Watkins et al 1980) and as we had also taken oral Atropine simultaneously which added to antisialogogue effect ⁽¹⁰⁾.

After tracheal extubation all children transferred to recovery room. A modified Alderate score of at least 9 out of 10 indicates readiness for discharge. We observe all children for 6 hours postoperatively. In our study postanesthetic recovery was not delayed or not affected by clonidine. Our results were comparable with Mikawa et al, Ramesh et al, Batra et al and Malde et al ^(3,10,12,14). In study of psychomotor function and sedation following clonidine premedication by Batra et al showed that clonidine 4mcg/kg produce good sedation and least effect on psychomotor function ⁽¹⁴⁾. Nausea and vomiting in post operative period causes significant distress to any patient and delay the discharge. In our study only 9.9% children in group C₃ and 6.6% children in group C₄ had nausea and vomiting. There was no statistically significant difference between two groups. Mikawa et al and Malde et al also reported the same in their study ^(3,10).

Thus, clonidine 3µg/kg and 4µg/kg with Atropine 0.03 mg/kg can be used as an oral premedication before 90 minute of induction of general anaesthesia in children to produce good sedation, anxiolysis, no respiratory depression and attenuation of hemodynamic response to intubation without causing any delay in the post operative recovery and with less incidence of PONV but clonidine 4µg/kg gives better results than 3µg/kg.

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Table 1. DEMOGRAPHIC DATA

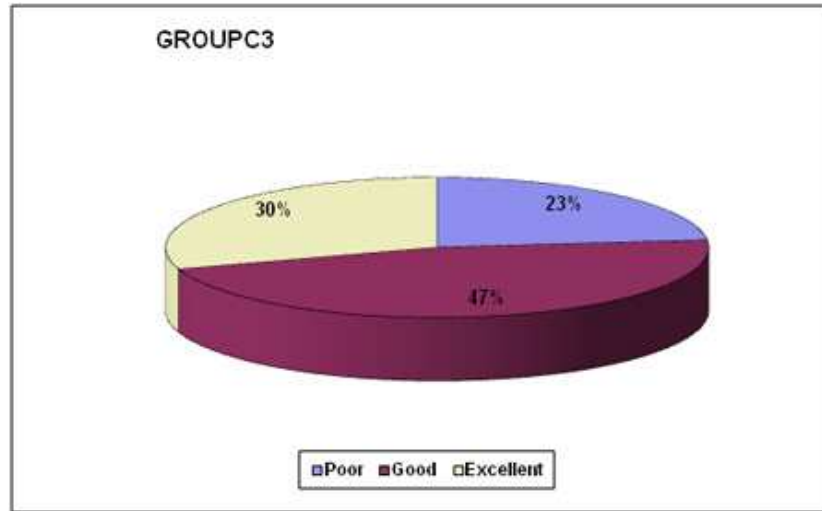
	Group C ₃	Group C ₄	P. Value
AGE (YEAR)	8 ± 2.43	8.41 ± 3.42	P > 0.05
WEIGHT(KG)	20.033 ± 5.63	20.36 ± 4.86	P > 0.05
SEX MALE/ FEMALE	17 /13	20/10	
ASA GRADING			
ASAI	20(66.66%)	18(60%)	P>0.05
ASA II	10(33.33%)	12(40%)	P>.0.05
DURATION OF SURGERY(MIN)	129.137±15.64	128.33±17.38	P>.0.05

TABLE 2 - SEDATION SCORE

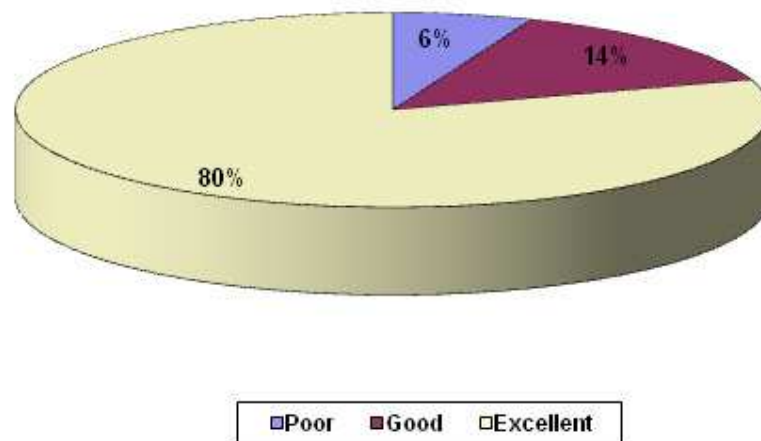
TIME	C ₃ GROUP						C ₄ GROUP						P.VALUE
	0	1	2	3	4	MEAN	0	1	2	3	4	MEAN	
0	26	4	0	0	0	0.133	25	5	0	0	0	0.166	P>0.05
30	0	25	5	0	0	1.16	0	20	10	0	0	1.33	P<0.05
40	0	10	17	3	0	1.93	0	2	20	8	0	2.2	P<0.05
50	0	0	24	4	2	2.26	0	0	5	18	7	3.06	P<0.001
60	0	0	14	13	3	2.63	0	0	2	11	17	3.5	P<0.001
70	0	0	9	14	7	2.93	0	0	1	9	20	3.63	P<0.001
80	0	0	5	16	9	3.13	0	0	0	5	25	3.83	P<0.001
90	0	0	2	18	10	3.26	0	0	0	3	27	3.9	P<0.001

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GRAPH 1: RESPONSE TO PARENTAL SEPARATION



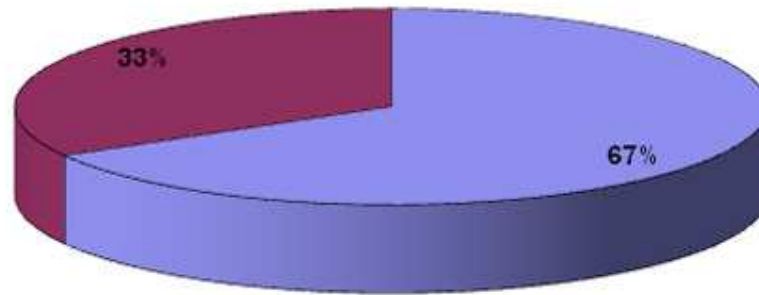
GROUP C4



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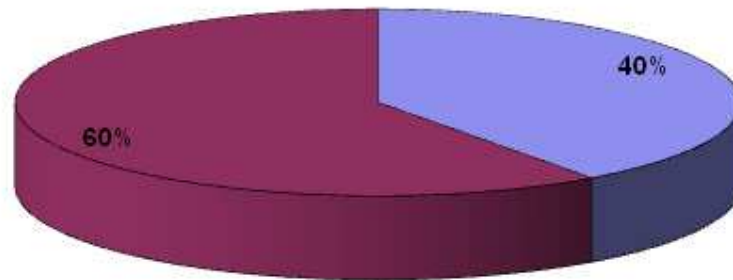
GRAPH 2: RESPONSE TO INTRA VENOUS CANNULATION

GROUP C3



■ Crying ■ Calm

GROUP C4

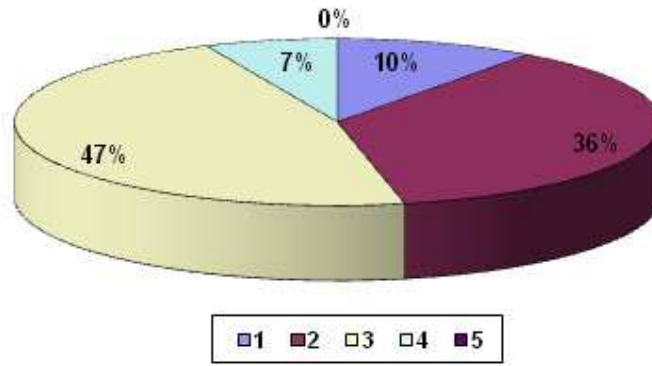


■ Crying ■ Calm

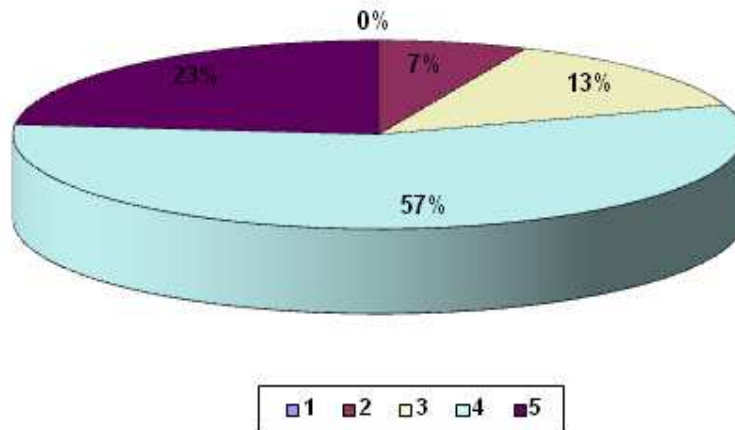
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GRAPH 3: RESPONSE TO FACE MASK APPLICATION

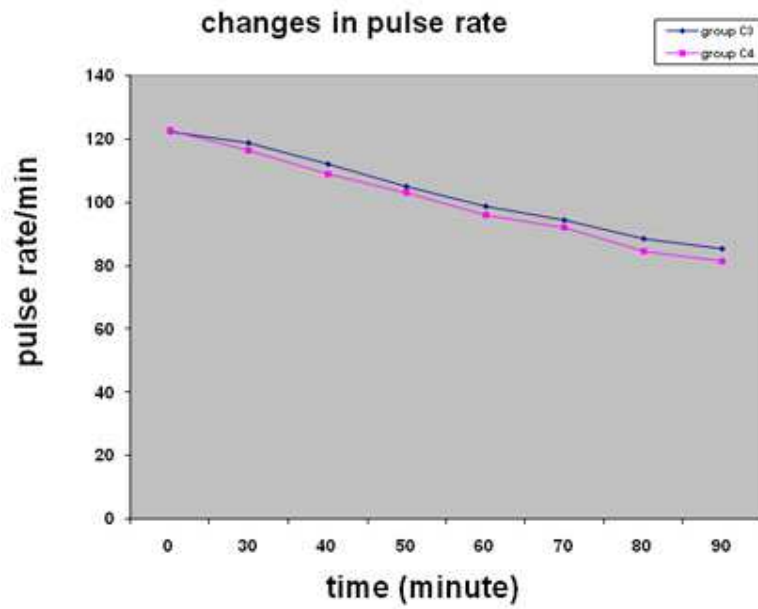
GROUP C3



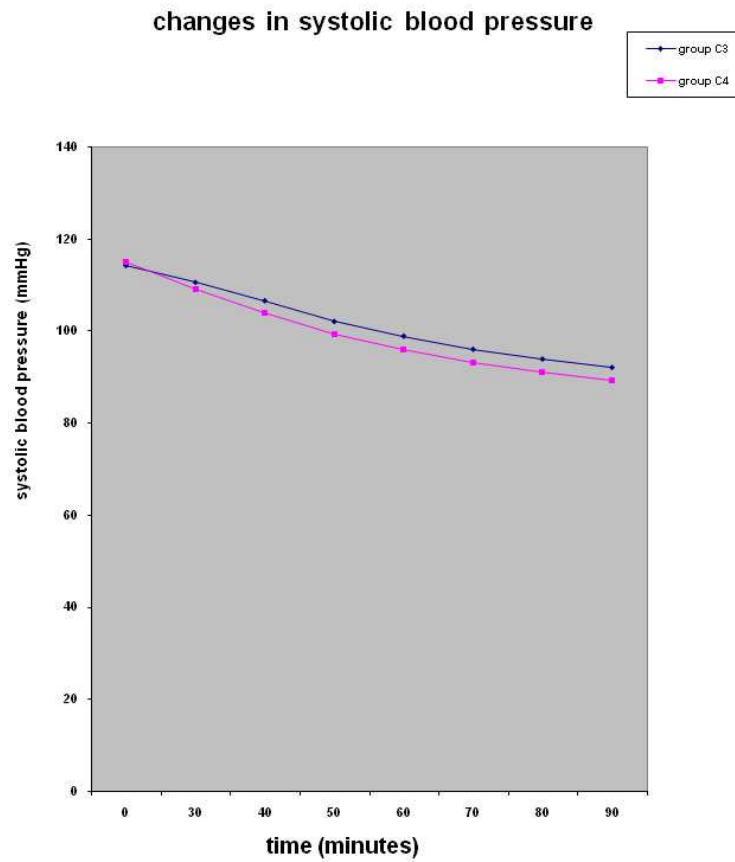
GROUP C4



GRAPH 4



GRAPH 5



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Table No. 3A : RESPONSE TO INTUBATION

PULSE RATE/ MINUTE

TIME/ MINUTE	GROUP C₃ Mean±SD	GROUP C₄ Mean±SD	P VALUE
1.	115.26±3.30	103.33±2.69	P<0.001
3.	125.26±3.91	114.80±2.44	P<0.001
5	103.80±3.37	92.26±2.76	P<0.001

Table No. 3B: SYSTOLIC BLOOD PRESSURE (mm Hg)

TIME/ MINUTE	GROUP C₃ Mean±SD	GROUP C₄ Mean±SD	P VALUE
1.	108.93±3.13	101.26±2.69	P<0.001
3.	121.06±3.51	114.88±1.89	P<0.001
5	101.7±3.79	91.46±1.47	P<0.001