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A PROSPECTIVE RANDOMISED CONTROL STUDY TO ASSESS THE EFFECT OF ORAL TIZANIDINE AS PREMEDICATION ON PROPOFOL REQUIREMENT FOR INDUCTION IN ENTROPY GUIDED GENERAL ANAESTHESIA

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ABSTRACT **Background:** Tizanidine is an α2-receptor agonist that has action in the central and peripheral sites of the autonomic nervous system, with sedative, analgesic and anxiolytic action. Hence we hypothesised its usefulness as an oral premedication to decrease the induction dose of propofol.

Objectives: This study evaluates the effects of oral Tizanidine on the requirement of induction dose of propofol while maintaining entropy between 40-60.

Materials And Methods: A randomised double-blind parallel study was performed on 60 ASA 1 and 2 patients posted for elective surgery under general anaesthesia. 30 patients (Group T) were given 4 mg of oral Tizanidine, another 30 (Group C) were given oral placebo (sugar pellet) 90 minutes before induction of anaesthesia. Propofol requirement based on entropy was assessed during induction. Vitals were monitored in the perioperative period. Sedation with Ramsay sedation scale (RSS) and anxiety with Hamilton anxiety rating scale (HAS) was assessed in pre and post-operative period. Post-operative pain was assessed with visual analogue scale (VAS).

Results: The demographic variables were comparable between the 2 groups. There was significant difference between the mean propofol dose for induction in group T and group C i.e 80.000±14.855 mg and 96.333±17.116 mg respectively with p value <0.001. Haemodynamic stability was maintained in the perioperative period in group T. There were lower scores of preoperative and postoperative RSS and HAS in group T.

Conclusion: Oral Tizanidine premedication reduces induction dose of Propofol, allays anxiety, improves postoperative sedation and VAS score.

KEYWORDS : Tizanidine, placebo, VAS score, Propofol, RSS, HAS.

INTRODUCTION

Tizanidine is an α2 adrenergic agonist with sedative, anxiolytic, analgesic properties. The site for sedative action is in the locus ceruleus of the brain stem acting on α2. A receptors whereas the site of analgesic action is probably the spinal cord. It inhibits neurotransmitter release from the presynaptic excitatory motor neurons in spinal and supraspinal sites producing agonistic activity at the noradrenergic α2 receptors. There is concomitant inhibition of facilitatory spinal pathways that enhance muscle movements.[1] Tizanidine is structurally similar to clonidine but with a shorter duration of action with lower incidence of bradycardia and hypotension. In the heart, the dominant α2 agonist action causes vagomimetic decrease in heart rate and may also be due to presynaptic mediated reduction of noradrenaline release.[2]

Currently, Tizanidine is FDA approved for management of increased muscle tone associated with spasticity resulting from CNS disorders such as multiple sclerosis or spinal cord Injury because of its centrally acting muscle relaxant properties.[3] We hypothesised that tizanidine maybe a useful, oral premedication owing to its central sedative, anxiolytic action. We anticipated a decrease in propofol induction dose thereby limiting the cardiovascular depressant effect of propofol with stable hemodynamics during induction.[4,5] Studies have positively reported reduced MAC of sevoflurane and isoflurane intraoperatively with reduced analgesic requirementsand reduced post operative shivering.

MATERIALS AND METHODS

A randomized double blind parallel study, the sample size was calculated based on pilot study involving 10 patients. The average consumption of propofol for induction was found to be 1.5 mg ±0.5 mg/kg. We hypothesized that, tizanidine would reduce Propofol consumption, assuming SD of 0.75 mg and reduction of 33% in Propofol consumption, a minimum of 26 patients was required in each group to attain a power of 80% at α error of 0.05, we included 30 patients in each group to compensate for possible dropouts.

After obtaining institutional ethical committee clearance, 60 ASA I and II patients aged 18-60 years of either sex, who are willing to give informed consent and scheduled for elective surgery lasting for 90-120 mins under general anaesthesia were included in the study.

Exclusion Criteria included patients with systemic disorders involving respiratory, cardiac, renal or hepatic system, patients with anticipated difficult airway, pregnant women, patients with psychiatric illness. The recruited patients were allocated to two different groups using www.randomizer.org :Group T– (received oral tizanidine 4 mg 90 min prior to surgery), Group C (received placebo (sugar pellet) orally 90 min prior to surgery).

After pre anaesthetic check up, all patients were kept fasting overnight. Patients were given Inj pantoprazole 40 mg intravenous (IV) and tab alprazolam 0.5mg on the previous night of surgery. Vitals were recorded and then the study drug was administered by senior anaesthesia consultant who was not further involved in the study. Electrocardiography (ECG), heart rate (HR), plethysmography (SpO_2), non-invasive blood pressure (NIBP), anxiety with Hamilton anxiety score (HAS) and sedation with Ramsay sedation scale (RSS) was noted at 0, 15, 30, 45, 60, 75 and 90th min. Side effects of tizanidine like bradycardia (heart rate <60/min) and hypotension (drop in Systolic blood pressure > 20% of baseline) were noted. Bradycardia was treated with Inj atropine 0.6 mg IV. Hypotension was treated with rapid bolus of IV fluids.

Basic monitoring was continued intraoperatively along with respiratory rate (RR), entropy, end tidal carbon-di-oxide ($EtCO_2$), Train of four (TOF). All patients were pre-medicated with Inj glycopyrrolate 0.005 mg/kg IV, Inj fentanyl 2µg/kg IV, Inj ondansetron 4 mg IV and Inj 2% preservative free lignocaine 2 ml IV and pre-oxygenated with 100% oxygen for 3 min. Then, Inj propofol in incremental doses was given IV till entropy value between 40-60 was achieved and dose noted. Inj vecuronium 0.1 mg/kg was then given and airway secured with appropriate sized cuffed endotracheal tube. Rescue doses of propofol were given IV if entropy increased above 60 during the 3 minutes of mask ventilation and noted. Anaesthesia was maintained with oxygen 33% and nitrous oxide 66%, isoflurane titrated to maintain entropy between 40-60. Inj vecuronium 0.02mg/kg at a TOF count of 2 was administered. At the end of surgery, patients were reversed with Inj glycopyrrolate 0.01 mg/kg and Inj neostigmine 0.05 mg/kg and extubated at TOF count of 4.

Post operatively, vitals along with visual analogue scale (VAS) , requirement for first analgesia and RSS every 15 mins for half an hour, every 30 mins for next 2 hr and hourly till 6th hour was noted. All data recording was done by junior anesthesia consultant blinded to the study drug.

Data was entered into micro soft excel sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions. Chi-square test was used as test of significance for parametric data. Independent t test and Mann Whitney U test were used as tests of significance for non parametric data. P value of <0.05was considered to be statistically significant.

RESULTS

There were no dropouts and demographic data were comparable in both the groups.

Table1: Demograhic Data Comparison Between The Groups

DEMOGRAPHIC DATA	GROUP T	GROUP C
Age (In Years)	41.17±12.32	42.56±10.56
Gender (M:F)	18:12	16:14
ASA (1:2)	22:8	21:9
Body Weight (Kg)	57.1±2.1	58.2±2.4
BMI	25.38±2.37	25.31±2.69

Dose of propofol required for induction was significantly reduced in group T, mean dose required being 80 mg (p = <0.001) compared to 96.33 mg in group C (table 2) and also rescue doses of propofol required was less in group T (table 3).

Table 2: Mean Dose Of Propofol Consumption Between The Groups.

Mean dose of propofol consumption (mg)				
Group T (30)		Group C (30)		p value
Mean	SD	Mean	SD	
80.00	14.85	96.33	17.12	0.001

Table 3: Requirement Of Rescue Doses Of Propofol Between The Group.

Rescue Doses Of Propofol Required	Group	No Of Patients	Mean	P Value
	GROUP T	2	10.00	0.312
	GROUP C	4	15.00	

There was significant difference in mean heart rate after administration of tizanidine from 30th min (p=0.001) pre operatively, intraoperatively and postoperatively up to 5th hour. HR at these intervals was lower in tizanidine group than in placebo group, though no incidences of bradycardia was observed in either group. (fig 1)

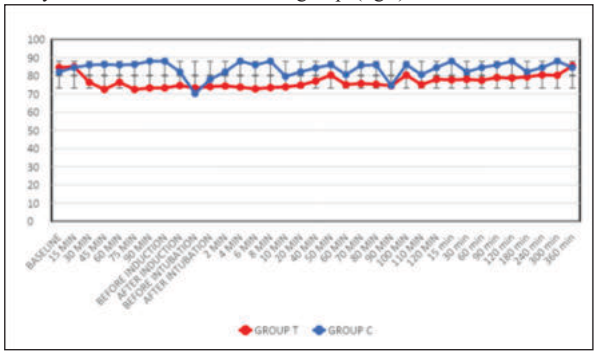

Fig 1: Heart Rate Variation Between The Groups.

There was significant difference in the SBP preoperatively starting from 45th min (p= 0.01) and was lower in tizanidine group till 5th hour post operatively. After laryngoscopy and intubation, tizanidine group had better hemodynamic stability (fig 2)

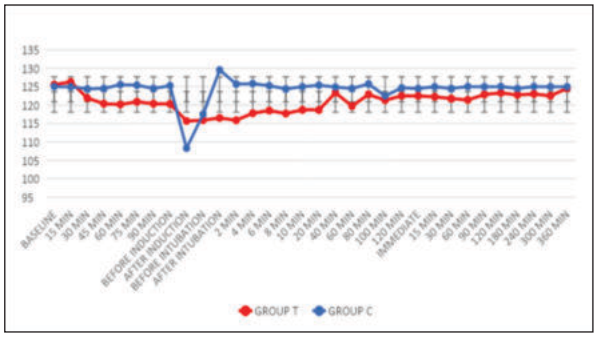

Fig 2: SBP comparison between the groups

The DBP was also found to be lower in the tizanidine group pre operatively from 45th min (p=0.002), intra operatively and post operatively (fig 3).

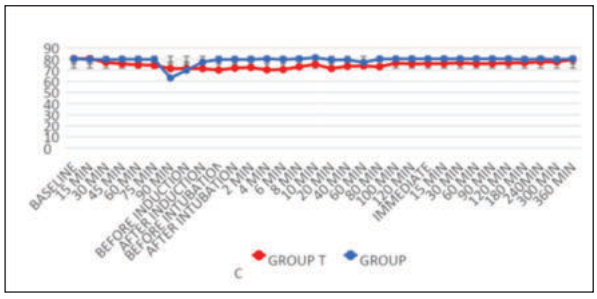

Fig 3: DBP Comparison Between The Groups

The MAP was lower pre operatively from 45th min (p = 0.002), intra operatively and post operatively for two hours in the tizanidine group. (fig 4). No incidence of hypotension was reported in either group.

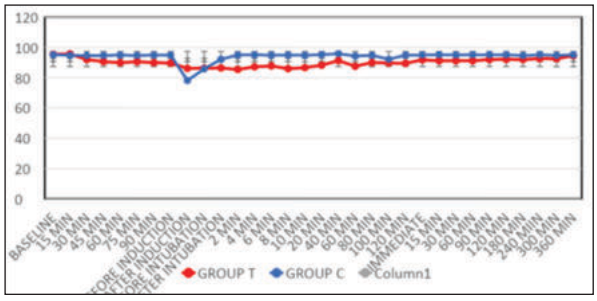

Fig 4: Comparison Of MAP Between The Groups

There was no significant difference in the entropy value intraoperatively between the groups.

There was significant difference in mean RSS score preoperatively from 45th min after drug administration with mean RSS score being 2.3 in group T (p <0.0001) as compared to mean RSS score of 2 in group C. Post operatively (till 6th hour), group T had higher RSS score, with mean RSS score of 2 compared to mean RSS of 1in group C at 6thhour (p=0.001).

Group T showed significant lower HAM-A score preoperatively from 45th mins after study drug administration with mean HAM-A being 18in group T compared to 25 (p<0.0001) in group C. Post operatively group T had lower HAM-A score of 22 in group T compared to HAM-A score of 26 (p=<0.0001) in group C recorded till 6th.

In group T incidence of side effects were slightly higher compared to group C (Fig 5). 4 out of 30 patients developed dizziness in group T compared to no such complaints in group C. Another 4developed asthenia in group T compared to 1in30 in group C. Patients with asthenia and dizziness were reassured as it was not severe requiring treatment and self limiting. Complaints did not last more than 7th hour post operatively. Nausea and vomiting were complained by6 out of 30 patients in group T compared to 4 patients out of 30 in group C. Inj dexamethasone 8 mg was given for PONV in postoperative period as a rescue antiemetic.

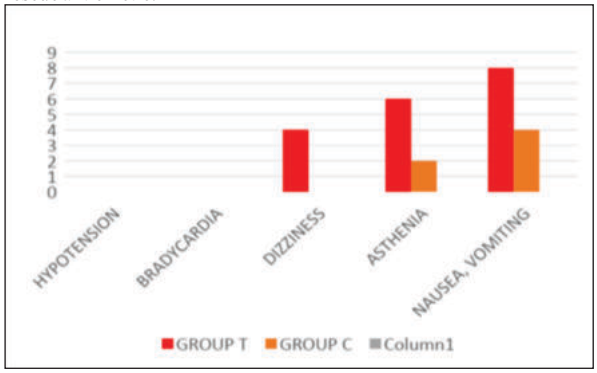

Fig 5: Incidence of side effects

DISCUSSION

α adrenergic agonists have been evaluated as adjuncts to anaesthesia owing to their sedative, analgesic and anxiolytic effects. Studies have proven that these drugs reduce the requirement of volatile anaesthetics[4,5], benzodiazepines[8], opioids and post op analgesics[9]. Anxiolysis effect of α 2 adrenergic agonists is comparable to that produced by benzodiazepines[10].Also they yield haemodynamic stability in the perioperative period.

Miettinen and his co workers (1996) studied 3 different doses of tizanidine 4, 8 and 12 mg and compared them to 150g of clonidine and found that the incidence of hypotension was significantly higher with tizanidine 8mg and 12 mg than with tizanidine 4mg. Hence in our study we chose 4mg.

Takaneka and his colleagues (1996) found that tizanidine given as a premedication attenuated the perioperative hemodynamic response significantly and the sedative and hypnotic effects were stronger.[8] Our study also found positive sedative and anxiolytic effects with oral tizanidine premedication.

Oguz et al in their study on premedication with orally administered tizanidine found that the dose requirement of propofol for loss eyelash reflex were significantly less in patients who had received tizanidine 4 mg preoperatively, Our study also found mean propofol requirement at induction with entropy guidance to be less in group T.

Sane et al (2016), in their study on evaluation on the effect of preoperative oral tizanidine on the rate of anaesthetic consumption and hemodynamic changes in TIVA concluded that using oral tizanidine as a premedication decreased BIS level and diminished induction time of anaesthesia, decreased requirement of propofol and remifentanil and yielded stability in MAP and HR during surgery. We also observed stable hemodynamics in the tizanidine group as compared to the control group.

Tabari and his associates (2013), in their study on evaluation of oral tizanidine effects on hemodynamic response during direct laryngoscopy under general anaesthesia found that using oral tizanidine as a premedication yielded stability in BP and HR during surgery and decreased required propofol consumption and considering its short duration of action they recommended tizanidine to be used as a premedication for sedation and stabilization of hemodynamic responses during surgery. In our study also we found tizanidine to have a short duration of action with post operative RSS being same at 6th hour between intervention and control groups.[10]

Limitations:

Effects of tizanidine on isoflurane consumption and on muscle relaxants were not assessed.

CONCLUSION

Oral tizanidine given as premedication reduced propofol requirement during induction, blunts hemodynamic stress response at the time of laryngoscopy and during surgery, also provides anxiolysis and sedation.

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