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COMPARATIVE EVALUATION OF ORAL PREMEDICATION WITH CLONIDINE AND METOPROLOL ON SURGICAL FIELD CONDITIONS AND INTRAOPERATIVE HAEMODYNAMIC DURING FUNCTIONAL ENDOSCOPIC SINUS SURGERY

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Annotation:

Background and aims: Bloodless surgical field duringfunctional endoscopic sinus surgery (FESS) is essential part. Oral clonidine and metoprolol were found effective in producing intraoperative hypotension which led to bloodless surgical field. There is paucity of studies regarding to comparison of oral clonidine versus oral metoprolol for improvement of surgical field in FESS which emphasized the need to conduct present study.

Materials and Methods: Sixty-eight patients of American Society of Anesthesiologists (ASA) physical status (PS) I and II aged 18-60 years, of both genders, scheduled for FESS under general anaesthesia were randomly allocated in two groups. Group C(n=34) received oral clonidine 300µg and Group M(n=34) received oral metoprolol 50mg, 2 hours before surgery. Primary outcome measured was surgical field visualization by average category scale(ACS) and secondary outcomes measured were haemodynamic parameters, sevoflurane requirement and side effects. Categorical, continuous and ordinal data compared using chi-square test, t-test and mannwhitney test respectively. P< 0.05 was considered as statistically significant.

Result: ACS was significantly less in group C as compared to group M, upto 60min ($p<0.05$). Controlled hypotension was achieved in both groups. On intergroup comparison, SBP, DBP and MAP were significantly less in group C as compared to group M at all time intervals ($p<0.05$). Intraoperative sevoflurane requirement (vol %) was significantly less in group C (1.21±0.42) as compared to group M(1.68±0.53), p=0.000. Bradycardia was comparable between both the groups.

Conclusion: Premedication with oral clonidine is better than oral metoprolol for providing bloodless surgical field during FESS with much efficient controlled hypotension and anesthetic sparing effect.

Introduction

Functional endoscopic sinus surgery (FESS) is mainstay for treatment of sinus pathology. Establishing bloodless surgical field during FESS is essential because minor bleeding can severely reduce endoscopic vision that may increase duration of surgery and risk of complications.[1]

Anaesthesia for FESS aims to provide controlled hypotension using an easy method which is safe and effective in improving surgical field without delaying the recovery.There are many previous studies which have used vasodilators, beta blockers, calcium channel blockers, alpha 2 agonistsintravenously to provide

controlled hypotension and bloodless surgical field.[2, 3, 4] However intravenous administration needs infusion pumps to titrate the doses and intense hemodynamic monitoring to prevent complication. Hence oral drugs always draw interest which seems to be easy and safe.

Oral clonidine[4] and oral metoprolol[5]were found effective in producing intraoperative hypotension but have different mechanism of action. Clonidine is a centrally acting alpha 2 agonist, which has antihypertensive property by decreasing central sympathetic outflow causing decrease in blood pressure and heart rate. Metoprolol is a selective beta-1 adrenergic blocker and its haemodynamic effects are attributed to negative chronotropism and inotropism without significant vascular resistance changes.[5]

There is paucity of studies[5-7] which have compared oral clonidine versus oral metoprolol for improvement of surgical field in otorhinolaryngologicalsurgeries and their results were contradictory which emphasized the need to conduct further studies.

Hence, present study was aimed to comparethe effect of oral clonidineand oral metoprololpremedicationregarding surgical field visualization as primary objective and intraoperative haemodynamics, sevoflurane requirement and adverse effects as secondary objectivesin patients undergoing FESS under general anaesthesia.

Material and methods

This prospective randomized double blind comprative study was conducted after approval from the institution ethical committee (RNT/Stat./IEC/2021/854) and registration in clinical trials registry of India (CTRI/2022/10/046238) from November 2022 to April 2023 and codes laid by Helsinki declaration were followed.

Sixty-eight patients of American Society of Anesthesiologists (ASA) physical status (PS) I and II aged between 18 to 60 years,of bothgenders, scheduled for FESS under general endotracheal anaesthesia were enrolled. Patients, having allergy to study drug, obese difficult airway, coexisting medical illness, preexisting hypotension (systolic blood pressure < 100 mm Hg) and bradycardia (HR< 60bpm) were excluded.

Based on previous study[5] with the assumption of that 40% more proportion of subjects in clonidine group had surgical field grading as ‘good’ (average category scale 0 or 1) than in metoprolol Group, with the power of 80%, alpha error 5% and superiority trial, parallel design, equal allocation, A sample size of 24 in each Group was required. To remain in compliance with central limit theorem which states ‘minimum sample size of 30 patients in each group was adequate for randomized control trial for normal sampling distribution’ and considering 10 % dropout rate the calculated sample size was34 patients in each Group.

Patients were randomly allocated in two groups using block randomization generator and concealment was done using opaque sealed envelopes as depicted in figure-1. Group C patients received oral clonidine 300 µg(two tablets of 150 µg clonidine, Tab Arkapres 150 byRivpra formulations Pvt Ltd). Group Mpatients received oral metoprolol 50 mg (two tablets of 25 mg metoprolol, TabMetolar-25, Cipla Ltd), both 2 hours before surgery.

To ensure double blinding, administration of study drugs was done by one anaesthesiologist as per group allocation who was not further involved in the study. Another anaesthesiologist who administered general anaesthesia and recordeddata, and the surgeon who assessed surgical field condition for bleeding were unaware of group allocation. The patients were also kept unaware of group allocation by keeping both oral drugs identical looking.

All patients were subjected to a detailed pre-anesthetic examination and investigations were carried out accordingly for evaluation. A written informed consent was taken from all patients after explaining about

the anesthetic procedure. On the day of surgery, in preoperative area baseline parameters including heart rate(HR), non-invasive blood pressure(NIBP), electrocardiogram(ECG) and peripheral oxygen saturation(SpO_2) were recorded. After confirming nil by mouth status, a peripheral intravenous cannula 18G was taken and ringer lactate infusion 500ml was started. Then patients were premedicated orally with either 300 µg clonidine or 50 mg metoprolol 2 hours before surgery according to groupallocation.

After 2 hours of oral premedication, patients were shifted to operation theatrea multipara monitoring involving NIBP, ECG, SpO_2 and Bispectral index (BIS) was applied.'Preinduction' vital parameters were recorded.

Preanaesthetic medication was given with inj midazolam 0.02mg/kg, glycopyrrolate 0.2mg, ondansetron 4mg and fentanyl 2µg/kg intravenously (IV) After pre oxygenation, induction was done with inj propofol 2mg/kg and vecuronium 0.1mg/kg IV and after 3 minutes of mask ventilation, tracheal intubation was done with appropriate size of cuffed endotracheal tube. Maintenance of anaesthesia was done using intermittent positive pressure ventilation with 50% O_2 in 50% Nitrous oxide with closed circuit and to maintain end tidal carbon dioxide (EtCO2) between 30-40 mmHg. Sevoflurane (volume %) was titrated to maintain BIS 40-60 and intermittent inj. vecuronium 0.02 mg/kg IV was given for muscle relaxation. All patients received Ringer lactate solution as per standard guidelines, blood and colloids were also given if excess bleeding or hypotension occurred as per need of patient. Urinary catheterization was done in all patients to monitor urine output. Target MAP was kept between 65-75 mm Hgintraoperatively to provide controlled hypotension and it was achieved by increasing sevoflurane.

Haemodynamic parameters like SBP, DBP, MAP and HR were recorded immediately after intubation (0 min) and thereafter every 15 min till the end of surgery or upto 120 min whichever is later. Surgery was done by standard technique by same ENT surgeon's team. Intra operatively surgeon was asked about quality of surgical field every 15 min till the end of surgery and graded it according to the six-point Average Category Scale (ACS 0-5)by Fromme and Boezzart [8]as follows

0 No bleeding (cadaveric conditions)

1 Slight bleeding, no suctioning required.

2 Slight bleeding, occasional suctioning required.

3 Slight bleeding, frequent suctioning required; bleeding threatens surgical field a few seconds after suction is removed.

4 Slight bleeding, frequent suctioning required, and bleeding threatens surgical field directly after suction is removed.

5 Severe bleeding, constant suctioning required; bleeding appears faster than can be removed by suction; surgical field severely threatened and surgery usually not possible.

Surgical field was graded as Good-ACS 0 or 1, Fair -ACS 2 or 3, Poor-ACS 4 or 5.

At the end of surgery, administration of anaesthetic agent was discontinued and reversal of neuromuscular blocking agent was done using inj. neostigmine 0.05 mg/kg, glycopyrrolate 0.008 mg/kg. Tracheal extubation was done after the return of adequate muscle power patient was shifted to post anaesthesia care unit.

Occurrence of side effects like hypotension, bradycardia, arrythmia were noted in pre medication room and intraoperative period. Hypotension was defined as 25% decrease in MAP as compared with baseline value and treated with fluid bolus and inj. mephentermine 6 mg. Bradycardia (heart rate less than 55/min or less than 25% of baseline)was treated by giving inj. atropine 0.6mg. Patients were also observed for other adverse effects like nausea, vomiting, dizziness, headache, sedation etc.

Primary outcome measured was surgical field visualization by Average Category Scaleand secondary outcomes measured were haemodynamic parameters (SBP, DBP, MAP and HR), sevoflurane requirement (end tidal volume %) and side effects.

Statistical analysis

Data were entered and analyzed using MS (Microsoft) Excel no. 10 and SPSS (Statistical Package of Social Sciences) version 16. Initially, the normal distribution of data was investigated using Skewness and Kurtosis test. Categorical (qualitative) data were presented as number (percentage) and compared using chi-square test. Continuous variables were presented as Mean ± SD and compared using student 't' test. Ordinal data as ACS were presented as Median (Interquartile Range) and compared using Mann Whitney test, $P < 0.05$ was considered as statistically significant.

Results

Total 78 patients were assessed for eligibility, 10 patients were excluded (three due to uncontrolled hypertension, two due to refusal for participation, two due to preexisting hypotension and three due to bradycardia) finally 68 patients were enrolled for the study. Both the groups were comparable with respect to age, weight, gender and ASA physical status ($p>0.05$)(Table-1).

Patient distributionaccording to ACS gradingis described in Table-2.In group C median (IQR) value of ACS was significantly less and higher proportion of patients had lower ACS scores ascompared to group M, at 15, 30, 45 and 60 min, thereafter ACS scores were comparable in both the groups at 75, 90 and 105min. 'Good' surgical field condition (ACS1) were achieved by significantly higher proportion of patients in group C as compared to group M during first 60 min thereafter they were comparable (Figure-2). However, all patients in both the groups had surgical field grading ACS 1, 2 or 3 at alltime intervals, none of the patients ever had ACS 4 or 5. It shows acceptable surgical condition were achieved in both the groups though they were significantly better in group C during first 60 min thereafter they were comparable.

Controlled hypotension was achieved in both groups because SBP, DBP, MAP and HR showed a significant fall from baseline, which was 10-20% and clinically acceptable, because none of the patient had hypotension. (Figure-3 and 4)

On intergroup comparison, SBP, DBP and MAP were significantly less in group C as comparedto group M at all time intervals, showing controlled hypotension was more effectively achieved in group C. However mean HR was significantly less in group M than in group C at all time intervals, showing metoprolol was more effective in reducing heart rate.

Intraoperative sevoflurane requirement in terms of mean value of end-tidal sevoflurane (vol %) was significantly less in group C (1.21±0.42) as compared to group M (1.68±0.53), p=0.000.Duration of surgery was also significantly less in group C (105±8.15) as compared to group M (115±10.20), p= 0.000.

Regarding side effects, bradycardia was observed in the study, which was comparable between both the groups. One patient (2.94%) in group C and five patients (14.7%) in group M had bradycardia (p=0.102) which was manageable.

Discussion

In this study we found that oral clonidine 300mcg premedication 2 hrs before induction of anaesthesia was more effective as compared to oral metoprolol 50mg for providing bloodless surgical field during FESS with effective controlled hypotension which significantly decreased surgicaltime. Oral clonidine was also found more effective in decreasing sevoflurane requirement intraoperatively without significant side effects.

One important task of anaesthesiologist during FESS is to provide controlled hypotension to achieve bloodless surgical field even a minor bleeding hampers endoscopic view, which not only prolongs the

duration of surgery but increases risk of complications. Therefore, there is always search of drugs which are cheap, easy to administer, safe and effective in providing controlled hypotension and improvement in surgical field visualization. It has been postulated that reduction of MAP during general anesthesia can minimize intraoperative bleeding.[9] But regarding haemodynamic variables, not only MAP, but also HR, venous pressure and capillary blood flow account for the extent of surgical bleeding.

Oral clonidine and oral metoprolol premedication in FESS was found easy and effective method to improve surgical field condition, though their comparative studies and to find better drug are sparse.

In this study, clonidine was found better agent for providing bloodless surgical field, because bleeding score were significantly less in clonidine groupduring first 60min. Oral clonidine was also found more efficient in providing controlled hypotension because MAP remained significantly less in group C as compared to group M at all time interval. Moreover target MAP (65-75mmHg) was achieved at lower sevoflurane concentration (end tidal vol%) in group C (1.51±0.42%) than in group M (2.01±0.53%), p=0.000. It denotes clonidine is more effective in producing hypotension and has anesthetic spring effect also.

Similar findings were observed by PuttinVeetil et al [5] who compared oral clonidine with oral metoprolol in FESS and reported that majority of clonidine group patients had lower ACS score as compared to metoprolol group patients up to 60 min $p<0.05$, thereafter difference was comparable. Gohit et al[7]studied oral diazepam 10 mg with oral clonidine 300 µg and oral diazepam 10 mg with oral metoprolol 50 mg, 2 hours before inductionof anaesthesia in FESS and reported that bleeding severity score were significantly lower in clonidine group. Blood loss was also significantly less in clonidine group (156.9±33.71 ml) than in metoprolol group (179.3±33.63ml) $p<0.05$. We did not measure blood loss, though none of our patient needed blood or colloid due to excess bleeding.

Dose regimen used in these studies were also same as used in our study. However, both these studies found no significant difference in SBP, DBP and MAP in two groups. They did not measure anesthetic requirement and also not mentioned about target MAP during FESS.

On the contrary Katdare et al[6] reported that oral metoprolol 50mgwas more effective in providing controlled hypotension as compared to oral clonidine 150mcg, given 90 min before induction for microscopic ear surgery. MAP was significantly less in metoprolol group at 15, 30, and 60 min than in clonidine group. This could be because they used lower dose of clonidine than ours. This study did not assess surgical field condition, or anesthetic sparing effect.All above studies as well as ours found that HR was significantly less in metoprolol group than in clonidine group.

Difference in hemodynamic parameters observed in clonidine and metoprolol group can be attributed to different mechanism of action of two drugs. Fall in blood pressure with metoprolol is due to antagonistic effect on beta 1 receptors in heart which reduces contractility, heart rate and cardiac output resulting in reduction of SBP mainly[9] Improved surgical field during FESS with a beta blocker has been attributed to vasoconstriction of the mucous membrane arterioles and pre-capillary sphincters resulting from unopposed alpha-adrenergic effects of endogenous catecholamines in addition to its effect onreduction in MAP and HR.[10]

On the other hand,clonidine is an alpha 2 agonist which stimulates presynaptic α_2 receptors in vasomotor centre suppressing the release of norepinephrine, ATP and neuropeptide γ. It causes bradycardia by increasing signaling through vagus nerve. It also stimulates endothelial α_2 adrenoreceptors mediating release of endothelium derived relaxing factor (EDRF) producing vasodilatation. All above mentioned actions decrease blood pressure by decreasing peripheral vascular resistance, heart rate and cardiac output[11, 12, 13] Therefore, SBP, DBP, MAP all were significantly less in clonidine group as compared to metoprolol group in our study.

The anaesthesia sparing effect of clonidine that was observed in our study as well as by others[4,14] is attributed to inhibition of adenylate cyclase in pontine locus ceruleus which contains high density of alpha 2 receptors resulting in changes in transmembrane ion conductance and hyperpolarization of excitable neural cells, thus producing sedation and analgesia[11,12].Studies on metoprolol versus placebo have also shown comparatively lesser anaesthetic consumption with metoprolol, because it lowers BP and HR and provides haemodynamic stability itself. Whereas in control groups anaesthetic concentration need to be increased to reduce intraoperative surgical blood pressure and heart rate that occur due to stress related physiological responses[15]. But by itself metoprolol has no sedative effect, while clonidine has sedative and analgesia effect by action on locus ceuleus.[11,12]

Negligible side effects were observed after single oral dose of clonidine and metoprolol as found in our study as well as others. [6,7,16]

There were few limitations of studies such as firstly invasive blood pressure monitoring could have compared controlled hypotension more precisely.Secondly blood loss measurement could be an additional objective parameter,becauseassessment of surgical field bleeding score using ACS can contribute to subjective error though surgeon in all cases was same.Moreover our study was in ASA I, II patients so our results cannot be extrapolated on patients with coexisting medical illness. Further studies can be planned in future considering above factors.

Conclusion

Premedication with oral clonidine 300mcg is better than oralmetoprolol50mg for providing bloodless surgical field during FESS with much efficient controlled hypotension and anesthetic sparing effect.

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Table 1 Comparison of demographic profile between two groups

Parameters	Group C (n=30)	Group I (n=30)	p value
Age (years)	33.8±12.7	35.38±11.2	0.596
Weight (kg)	64.8 ± 10.4	65.6 ± 10.9	0.744
Gender (Male/Female)	24/21	10/13	0.609
ASA(I/II)	28/30	6/4	0.493
Mean duration of surgery (min)	105±8.15	115±10.20	0.000

Table 2 Comparison of patient distribution according to Average Category Scale (ACS)

Time interval		Group C(n=34)			Group M(n=34)			P value
		ACS1	ACS2	ACS3	ACS1	ACS2	ACS3	
15 min	n (%)	24 (70.58)	09 (26.47)	01 (2.94)	10 (29.41)	16 (47.05)	08 (23.52)	**0.001**
	Median (IQR)	1(1-2)			2(1-2)			**0.000**
30 min	n (%)	20 (58.82)	10 (29.41)	04 (11.76)	07 (20.58)	17 (50)	10 (29.41)	**0.005**
	Median (IQR)	1(1-2)			2(2-3)			**0.002**
45 min	n (%)	21 (61.76)	09 (26.47)	04 (11.76)	08 (23.52)	16 (47.05)	10 (29.41)	**0.006**
	Median (IQR)	1(1-2)			2(1.75-3)			**0.002**
60 min	n (%)	19 (55.88)	11 (32.35)	05 (14.40)	08 (23.52)	17 (50)	08 (23.52)	**0.034**
	Median (IQR)	1(1-2)			2(1-2.25)			**0.041**
75min	n (%)	15 (44.11)	17 (47.05)	03 (8.82)	10 (29.41)	17 (50)	07 (20.58)	0.364
	Median (IQR)	2(1-2)			2(1-2)			0.510
90min	n (%)	14 (41.17)	16 (50)	3 (50)	13 (38.23)	15 (44.11)	06 (17.64)	0.303
	Median (IQR)	2(1-2)			2(1-2)			0.886
105 min	n (%)	19 (41.17)	15 (55.88)	0 (2.94)	20 (32.35)	14 (61.76)	0 (5.88)	0.673
	Median (IQR)	1(1-2)			1(1-2)			0.398

Data are presented as number(n), percentage (%) and median (interquartile range) and compared with chi-square test and Mann Whitney test respectively

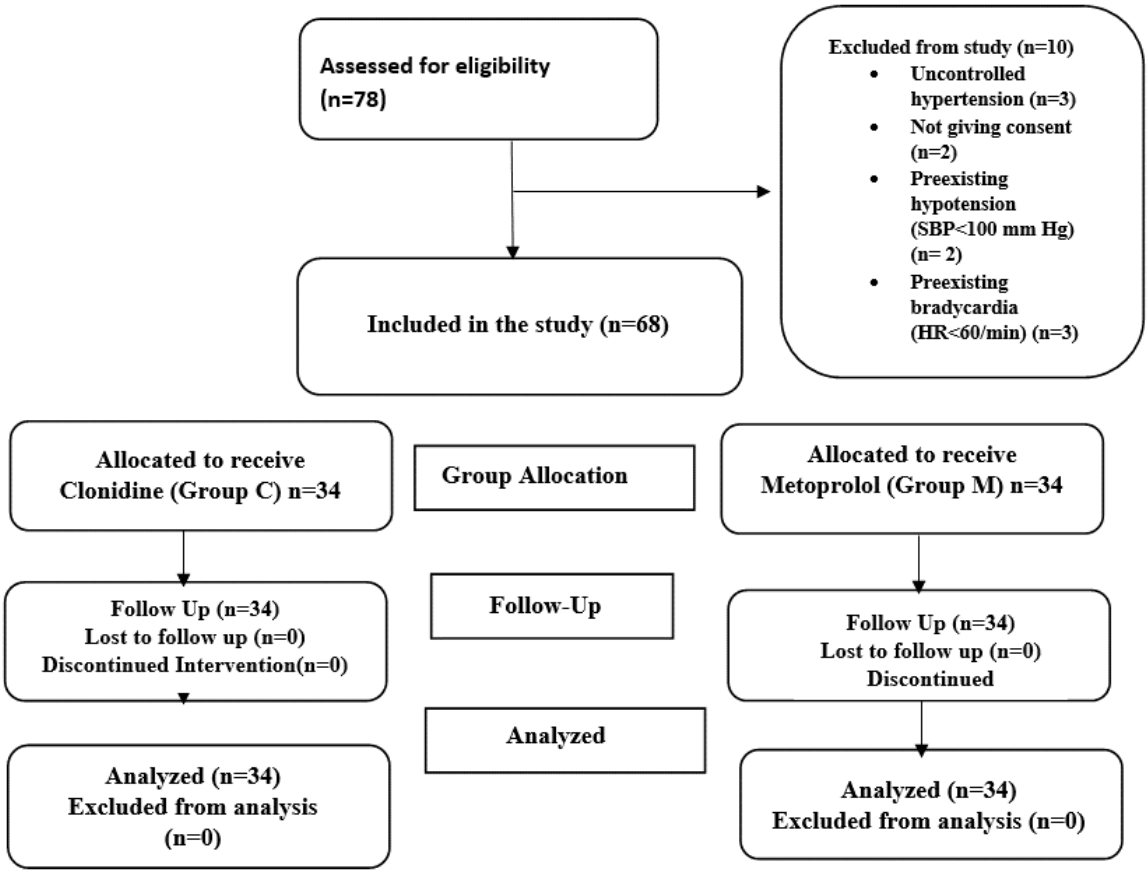

Figure:1 CONSORT flow chart

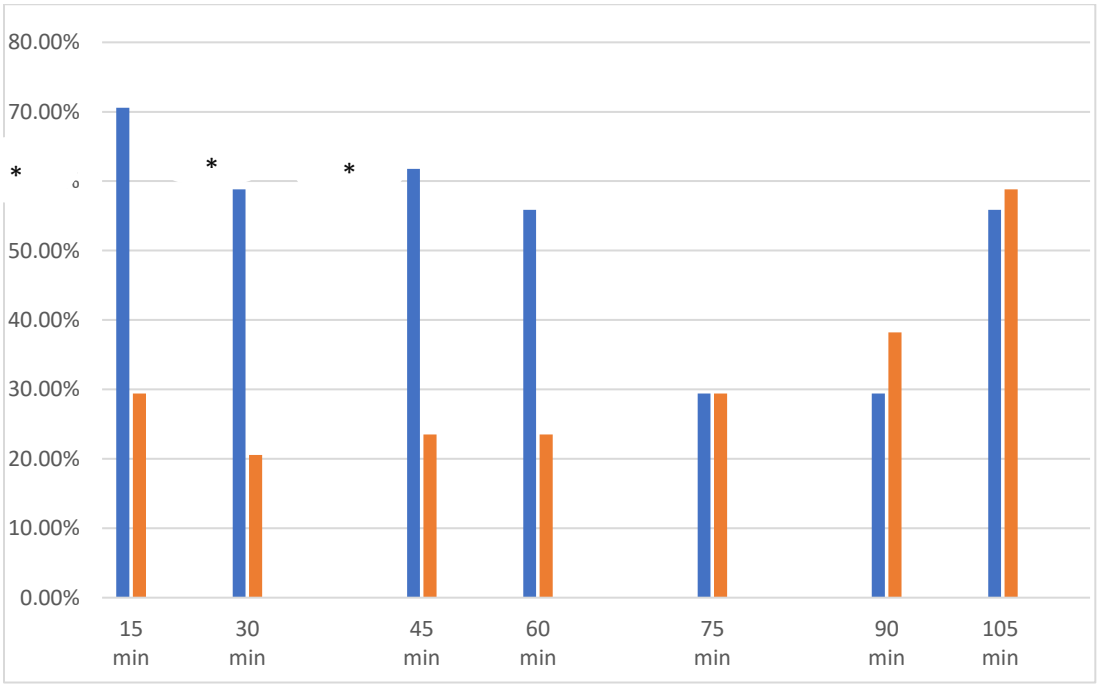

Figure: 2 Comparison of proportion of patients having 'good' surgical field condition (ACS1) in two groups

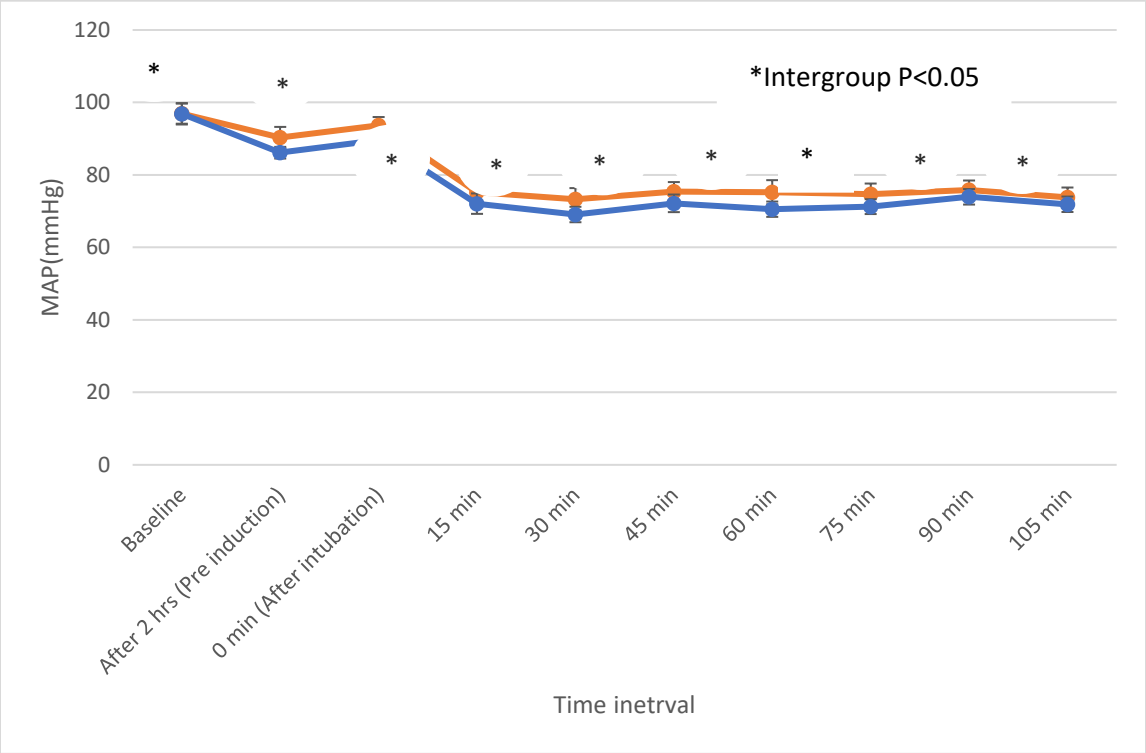

Figure: 3 Comparison of perioperative mean arterial blood pressure (mm Hg) between the two groups

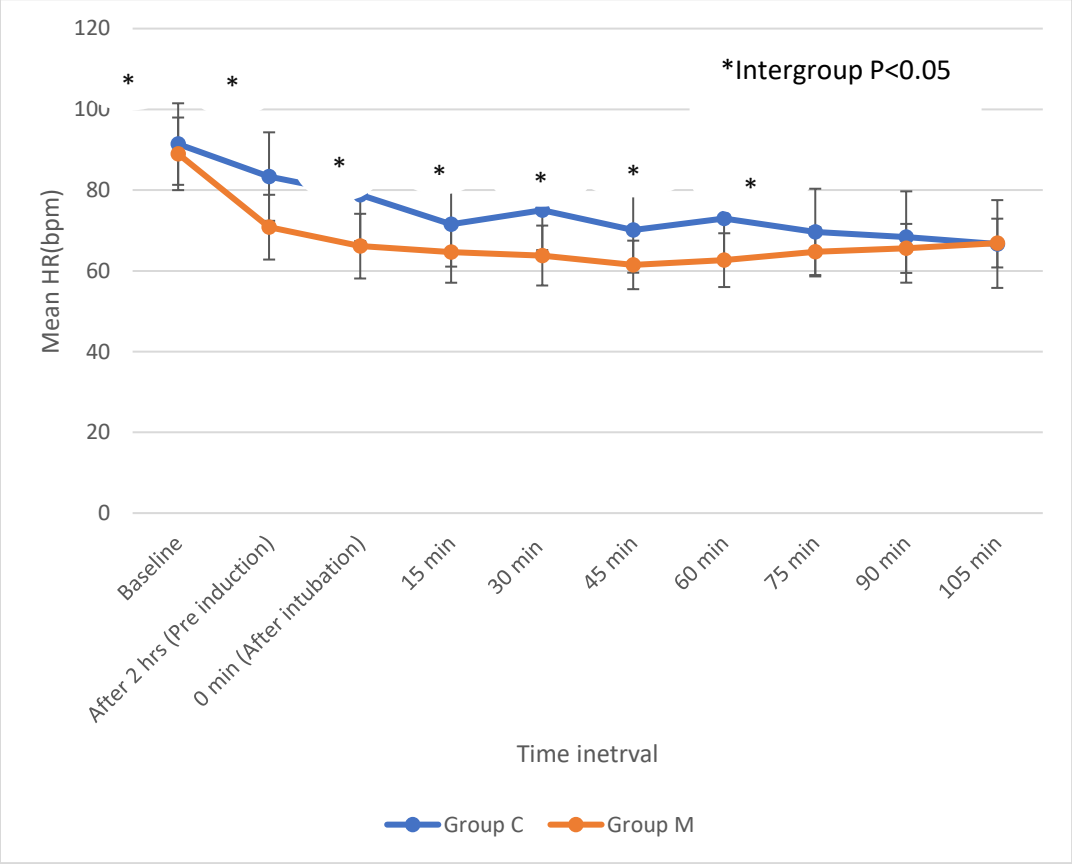

Figure: 4 Comparison of perioperative heart rate (beats/min) between the two groups