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Evaluation of effect of intravenous dexmedetomidine infusion on intra-operative hemodynamic and recovery profile in patients undergoing intracranial surgery under general anaesthesia

Harindranath S Kumar[1*], **Anjali Modak**[2], **Neeta Verma**[2], **Sheetal Madavi**[3], **Nikhil Bhalerao**[4]

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Authors' Affiliation:
[1]Junior Resident, Department of Anaesthesiology, Jawaharlal Nehru Medical College, Sawangi, Wardha, Maharashtra, India; Email:harindranathskumar@gmail.com
[2]Professor, Department of Anaesthesiology, Jawaharlal Nehru Medical College, Sawangi, Wardha, Maharashtra, India
[3]Associate Professor, Department of Anaesthesiology, Jawaharlal Nehru Medical College, Sawangi, Wardha, Maharashtra, India
[4]Assistant Professor, Department of Anaesthesiology, Jawaharlal Nehru Medical College, Sawangi, Wardha, Maharashtra, India

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ABSTRACT

Background: The brain is critically dependent on uninterrupted blood flow for the supply of nutrients and clearance of metabolites. Both an increase and decrease in the blood flow are harmful to the brain. *Aim*: This study aimed to evaluate the effectiveness of Dexmedetomidine (in comparison to normal saline) in maintaining haemodynamic parameters during laryngoscopy among patients undergoing elective intracranial surgery. *Material and methods*: This was a single centre, parallel-group, 1:1, and single-blind, placebo-controlled, randomised control study. 60 patients undergoing elective neurosurgery were randomised to intravenous dexmedetomidine (0.4mcg/kg/hr) or a similar volume of normal saline. Following outcomes were measured: heart rate, mean arterial pressure (MAP), the dose of thiopentone, time to extubation, and level of sedation. *Results:* The time for extubation in the Group D group was 5.23 minutes and in the Group C group, it was 8.6 minutes ($p<0.0001$). At endline, the sedation score among participants in group D was less in comparison to participants in group C. The mean dose of thiopentone required in group D participants was significantly less than those required by participants in group C ($p<0.0001$). Dexmedetomidine effectively blunted the increase in heart rate and mean arterial pressure both at intubation and extubation. There was a difference of 21% point between the MAP values between group D and group C participants at intubation. *Conclusion:* Dexmedetomidine has an anaesthetic sparing effect, and it reduced the time of recovery among patients undergoing neurosurgery.

Keywords: Laryngoscopy, Intubation, Dexmedetomidine, Neurosurgery

1. INTRODUCTION

Modern neurosurgery arose secondary to three great advances in the 19th century viz., anaesthesia, bacteriology, and cerebral localisation (Nikova and Birbilis, 2017). The founding pillars of neurasthenia are smooth induction, hemodynamic stability, and best operative conditions (Spielman, 2005; Dinsmore, 2007). The physiological processes are challenged to a great extent during any neurosurgical procedure secondary to several stimuli acting in synergy (Spielman, 2005; Chivukula et al., 2014). The rise in blood pressure during neurosurgery can result in increased bleeding or oedema in the operative field (Dinsmore, 2007). Similarly, hypertension during the postoperative period can also cause a hematoma. Moreover, cerebrovascular responses may increase intracranial pressure and reduce cerebral perfusion pressure thus, worsening ischemic damage (Dinsmore, 2007).

In addition, it is desirable to rapidly reverse the effects of anaesthesia to facilitate the immediate evaluation of the neurological status of patients. Thus, anaesthetic techniques that improve pre-, intra-, and postoperative hemodynamics thereby, allowing quicker evaluation of patients but not causing any additional adverse effects are needed during neurosurgery. For all these reasons, general anaesthesia is a preferred choice for neurosurgical interventions (Dinsmore, 2007). For an exceedingly long time now, airway management during general anaesthesia are known to induce clinical changes in hemodynamic variables. King et al., (1951) were first to describe the cardiovascular reaction to Laryngoscopy and Endotracheal Intubation (LETI). They concluded that the highest increase in blood pressure is encountered during laryngoscopy while the highest increase in heart rate is seen during and after endotracheal intubation. Although the 'pressor' response is of shorter duration, it nevertheless, put significant detrimental effects on the coronary and cerebral circulation.

For most patients, the pressor reflex is easily tolerated by most patients (Kovac, 1996). However, among a subgroup with a history of cardiac ailments including atherosclerosis, hypertension, myocardial infarction, and cerebrovascular diseases including aneurysms and tumours, are at tremendous risk of adverse outcomes (Slogoff and Keats, 1985; Kovac, 1996). Furthermore, geriatric patients make up an increasingly substantial percentage of the inpatient population (Khan and Mahboobi, 2004). These patients have abnormal cardiovascular parameters (most importantly elevated blood pressure), placing them at increased risk of MI, stroke, congestive heart failure (CHF), or unfortunately sudden death (Slogoff and Keats, 1985; Kovac, 1996). Thus, it only seems logical and desirable that minimizing these physiologic challenges before, during, and after the surgery is in the best interest of the patient.

Studies support the hypothesis that controlling perioperative stress, including that due to LETI, improves outcomes, particularly among high-risk patients (Kovac, 1996). Several classes of pharmacological agents have been evaluated to blunt the cardiovascular reaction LETI. Drugs from various classes e.g., anticholinergic, antihypertensives, sedatives, adrenoreceptor agonists, deepening of anaesthesia, muscle relaxant, and local anaesthetics have been tried with various degrees of success. Specifically, clinical researchers have evaluated dexmedetomidine's role as an adjuvant to general anaesthesia, its effectiveness in reducing postoperative pain, and maintaining hemodynamic parameters during the perioperative period (Hall *et al.*, 2000; Lobo and Wagemakers, 2016).

We, therefore, conducted this trial to evaluate the clinical effectiveness of dexmedetomidine for attenuating the changes in hemodynamic parameters viz. heart rate and blood pressure during laryngoscopy and endotracheal intubation (and extubation) among patients undergoing intracranial surgery under general anaesthesia.

2 MATERIAL AND METHODS

Study Design

This was a single centre, parallel-group, 1:1, single-blind, placebo-controlled, randomised control study (Moher *et al.*, 2010).

Study Setting

Department of Anaesthesiology, Jawaharlal Nehru Medical College, affiliated with Datta Meghe Institute of Medical Sciences, Sawangi, Wardha. It is a tertiary care institute. This trial was approved by the Institute's Ethical Committee on Human Research.

Study Duration

24 months from October 2019 to October 2021.

Study Outcomes

Heart Rate
Mean Arterial Pressure
Dose of Thiopentone
Time to Extubation

Sedation

The intensity (and duration) of sedation was measured using the Ramsay sedation scale (Tandon and Goyal, 2015).

Study groups

The participants were divided into the following study groups using block randomization:

Group D (Intervention): Participants in the intervention group were given intravenous Dexmedetomidine at the rate of 0.4mcg/kg/hr as a continuous infusion during surgery.

Group C (control): Participants in the control group were given normal saline alone.

Participants' recruitment

The participants were recruited after verifying that they fulfilled the following selection criteria.

Inclusion Criteria

Patients between 20 and 65 years of age

Patients of all genders

Patients who were categorised as belonging to American Society of Anaesthesiologists (ASA) Class I & II

Patients who gave written informed consent to take part in the study

Exclusion Criteria

Patients with the following systemic disorders: hypertension, renal disease, cardiovascular, or hepatic disease.

Patients who were on any type of antihypertensive medications

Patients with a preoperative heart rate of <60 bpm

Sample Size Calculation

The minimum sample size for the study, we employed the formula recommended by Zhong, (2009) for a randomised control trial. Using the formula for randomised control trial, the minimum required sample size for the study was calculated as 60 (30 participants in each group).

Informed Consent

A tri-lingual (Marathi, Hindi, & English) consent form was drafted following the prescribed guidelines for research on human participants. The consent form was given to all the participants to read. Thereafter, the contents were explained to all the prospective participants. All the questions from participants about the study, drug, procedure, risk, and data privacy were answered. The participants were informed and explained that they have the right to withdraw at any point in time. Thereafter, willing participants were asked to sign the consent form.

Randomization and Allocation Concealment

A statistician (no involvement in the study) used statistical software Stata version 15.1 to generate random numbers. The allotment of the participants to either the normal saline or the dexmedetomidine group was achieved using a computer-generated programme based on a permuted block design (n=6). The details of the allocated groups were concealed from the principal investigator and research team by supplying random numbers in opaque and sealed envelopes.

Blinding

This was a single-blind study; the participants were blinded by the study group. Both, the intervention, and the placebo were supplied by the manufacturer in an identical packet, moreover, the colour, smell, volumes etc., of the drugs were matched. An operation theatre nurse independent of the study prepared and gave the drug to the participants.

Data Collection

The data were collected in a paper-based questionnaire. The questionnaire had 4 parts as follows: (i) Demographic details, (ii) Pre-anaesthetic check-up details, (iii) Pre- and Intra-operative details and (iv) post-operative details.

End Point of Study

The study was terminated if: (i) Withdrawal of consent, (ii) Participants suffered any adverse/life-threatening event (due to any reason), (iii) after completion of the surgery.

Statistical Analysis

The chief outcome of the study was the change in vital parameters at various time points from the baseline values. Secondary outcomes were the dose of thiopentone, time for extubation, and level of sedation among the participants in the two groups. We tested whether data supplied evidence of the superiority of Dexmedetomidine to placebo for all outcomes.

3. RESULTS

While recruiting participants for the present study, we screened a total of 105 participants. Out of 105, 45 (42.8%) were excluded: 35 did not fulfil selection criteria and 10 participants refused to participate (Figure 1).

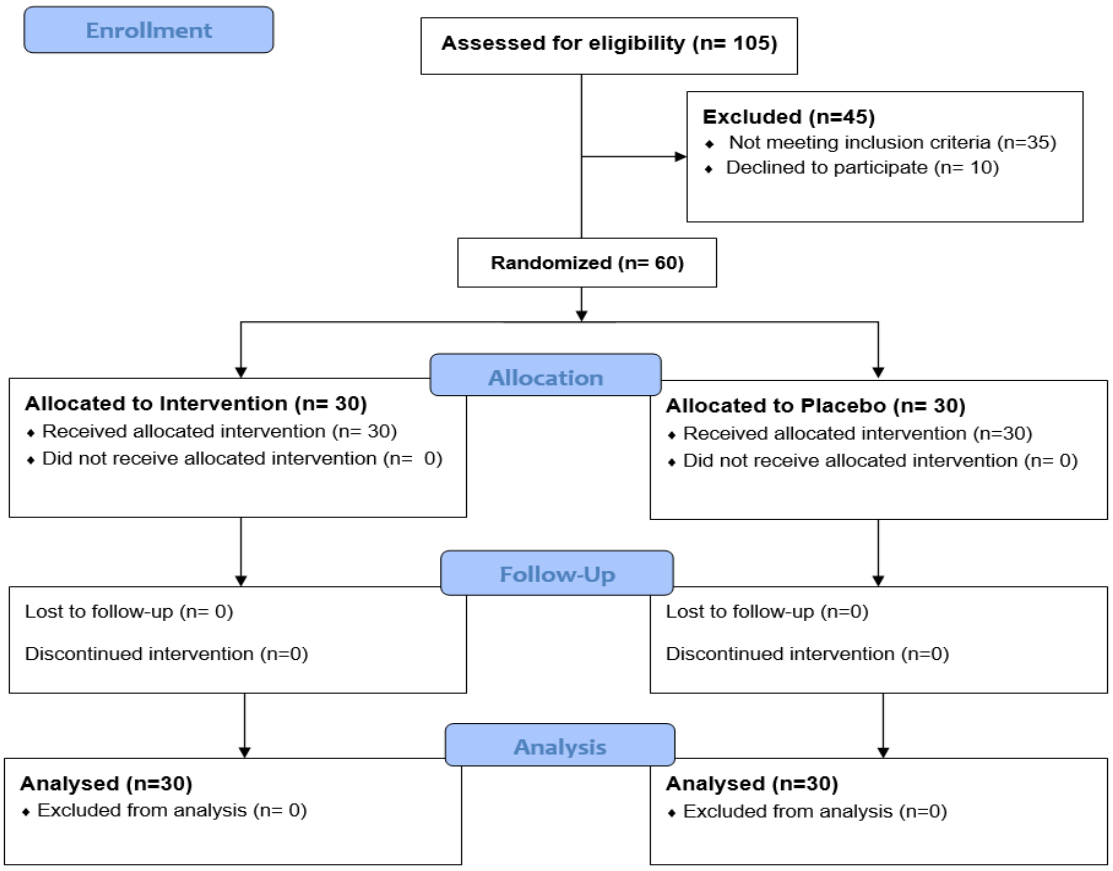

Figure 1 CONSORT Diagram

The mean and median age of participants in group D was 49.1 and 51.5 years, respectively (Table 1). The mean and median ages of participants in group C were 44.2 and 46 years, respectively. Overall, there were slightly more (53.3%) female participants. Individually in both groups, there were 16 (53.3%) and 14 (46.7%), female and male participants, respectively (p = 1.00). The mean and median weight of participants in the Group D group was 64.8 Kg and 61.5 Kg, respectively. Comparatively, the mean and median weight of the participants in the NS group was 61.5 Kg and 62 Kg. Overall, 53.3% and 46.7% of the participants belonged to ASA grade II and grade I, respectively. Individually, in group D, each of the 50.0% of participants had ASA Grade I and II, respectively. In comparison, 43.3% and 56.7% of the participants given normal saline had ASA Grade I and II, respectively (P-value = 0.6048).

Table 1 Distribution of key variable among the participants (n = 60)

Variable	Study Group		P-Value
	D	C	
AGE			
Mean (SD)	49.1 (12.7)	44.2 (14.1)	0.1669
Median (IQR)	51.5 (40-55)	46 (30-55)	
Range	27-76	21-73	
WEIGHT			
Mean (SD)	64.8 (10.8)	61.5 (6.3)	0.1643
Median (IQR)	61.5 (57-75)	62(58-65)	
Range	48-88	45-72	
ASA GRADE			
I	15 (50.0)	13 (43.3)	0.6048
II	15 (50.0)	17 (56.6)	
GENDER			
FEMALE	16 (53.33)	16 (53.33)	1.000
MALE	14 (46.67)	14 (46.67)	
SD- Standard Deviation IQR- Inter Quartile Range			

The mean and median 'time for extubation' in the Group D group was 5.23 and 5.25 minutes, respectively (Table 2). None of the participants in group D had duration of extubation longer than 8 minutes. In comparison, the mean and median duration of extubation in the Group C group was 8.6 and 8.5 minutes, respectively. None of the participants in group C had duration of extubation of fewer than 4 minutes. After 30 minutes of intubation, participants in Dex group were less sedated than participants in group C. The mean dose of thiopentone required in group D and Group C was 273 mg and 340.5 mg. The median dose of thiopentone required in group D and Group C was 260 mg and 350 mg (Table 2). We measured the sedation score at extubation and 30 minutes after extubation. At extubation, the median sedation scores were less in group D in comparison to group C participants. Thus, at extubation, participants in group D were less sedated in comparison to participants in group C (Table 2).

Table 2 Secondary outcomes among study participants of both groups (n=60)

Outcome	Group		P-value
	D	C	
TIME FOR EXTUBATION			
Mean (SD)	5.23(1.4)	8.6(1.3)	<0.0001
Median (IQR)	5.25 (4-6)	8.5 (7.5-9.5)	
Range	3-8	6-11	
DOSE OF THIOPENTONE			
Mean (SD)	273(42.4)	340.5(32.5)	<0.0001
Median (IQR)	260 (250-300)	350 (305-360)	
Range	200- 360	300-400	
SEDATION SCORE (MEDIAN)			
At Extubation	3	4	
After 30 Minutes	1.5	2	-

Table 3 shows the trend for the heart rate among patients in the intervention and the control group. At baseline, the heart rate was greater among the participants in the intervention group (83 bpm) but the difference in HR in the two groups was statistically not significant (P-value= 0.24). The difference in HR between the intervention and the control group was statistically highly significant ($p<0.0001$) at all-time points during the period of observations (Table 3). None of the participants in our study had an episode of bradycardia.

Table 3 Mean Heart Rate among study participants at various time points (n=60)

Time	Heart Rate (BPM)				P-value
	Group D		Group C		
	Mean	SD	Mean	SD	
BASELINE	83.46	10.2	80.07	12.3	0.2489
5 mins after Infusion	69.60	6.1	84.33	9.4	<0.0001
10 mins after Infusion	67.73	8.2	87.97	11.1	<0.0001
Intubation	77.33	7.8	100.90	13.3	<0.0001
3 minutes after Intubation	76.53	8.5	98.10	12.9	<0.0001
6 minutes after Intubation	73.67	7.3	93.03	11.2	<0.0001
9 minutes after Intubation	70.63	7.3	88.17	10.2	<0.0001
Suctioning	76.53	8.5	98.10	12.9	<0.0001
3 minutes after Suctioning	68.60	6.8	84.23	10.7	<0.0001
6 minutes after Suctioning	69.60	6.1	84.67	9.5	<0.0001
9 minutes after Suctioning	69.60	6.3	84.43	9.6	<0.0001

Figure 2 illustrates the change in the Heart Rate in terms of the percentage concerning baseline value. In group D, the highest decline (- 18.81%) from the baseline level was observed 10 minutes after the infusion. Furthermore, throughout the observation, the heart rate did not cross the baseline level i.e., the percentage change was always negative (Figure 2). In the NS group, the maximum change (increase) from the baseline value (80 bpm) was observed immediately following intubation (+26.7%). The heart rate in group C was higher than baseline values thorough out the period of observations. The heart rate in both groups D and C increased at extubation. However, the magnitude of increase in HR was lower (7%) among group D participants in comparison to group C participants (13%).

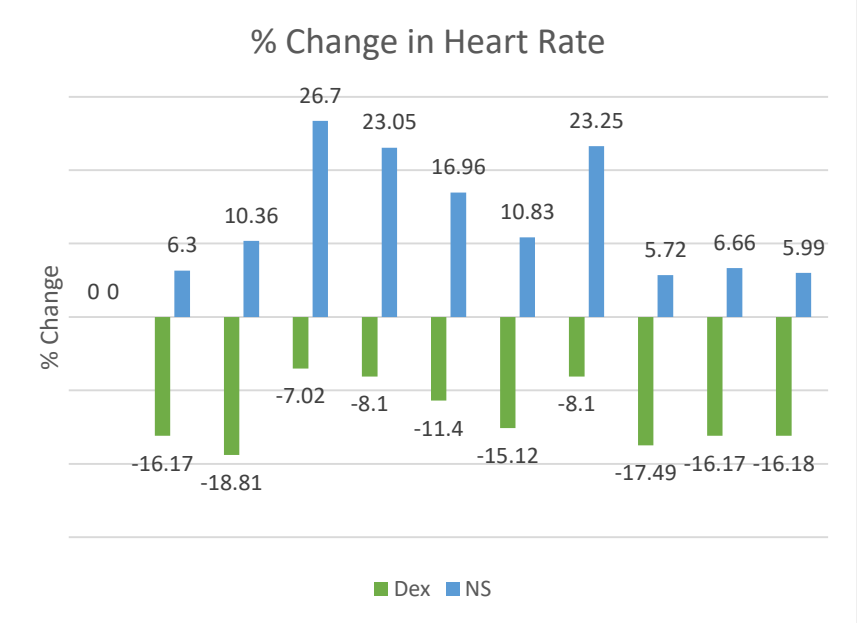

Figure 2 Percent Change in Heart Rate over time among study participants

Table 4 illustrates the trends in MAP among the patients in the intervention and the control group. Following the infusion of dexmedetomidine, in Group D participants, the mean MAP (mmHg) decreased from the baseline value of 97 mm Hg to a minimum value of 80 mm Hg ten minutes after infusion (Table 4). Throughout the observation, the MAP remained below the baseline level. Comparatively, among participants given normal saline, the mean arterial pressure declined to its minimum recorded value just ten minutes after infusion but increased sharply to reach its maximum value (108 mm Hg) immediately after intubation. At end line observations, the MAP was almost equal to the baseline value. During the study, the MAP was comparatively higher among participants in the control group (Table 4).

Table 4 Mean Arterial Pressure among study participants at various time points (n=60)

TIMEPOINTS	MAP (mm Hg)				P-value
	Group D		Group C		
	Mean	SD	Mean	SD	
BASELINE	97.6	6.2	97.19	5.8	0.7957
5 mins after Infusion	86.82	4.8	98.80	5.1	<0.0001
10 mins after Infusion	80.26	3.9	93.32	4.7	<0.0001
Intubation	87.26	4.6	108.4	5.2	<0.0001
3 minutes after Intubation	87.35	4.6	104.30	5.0	<0.0001
6 minutes after Intubation	87.31	4.5	101.76	3.8	<0.0001
9 minutes after Intubation	87.55	4.8	99.46	4.7	<0.0001
Suctioning	87.35	4.6	104.3	5.0	<0.0001
3 minutes after Suctioning	87.50	4.6	97.20	4.3	<0.0001
6 minutes after Suctioning	86.82	4.8	97.94	3.4	<0.0001
9 minutes after Suctioning	87.81	5.3	97.40	4.3	<0.0001

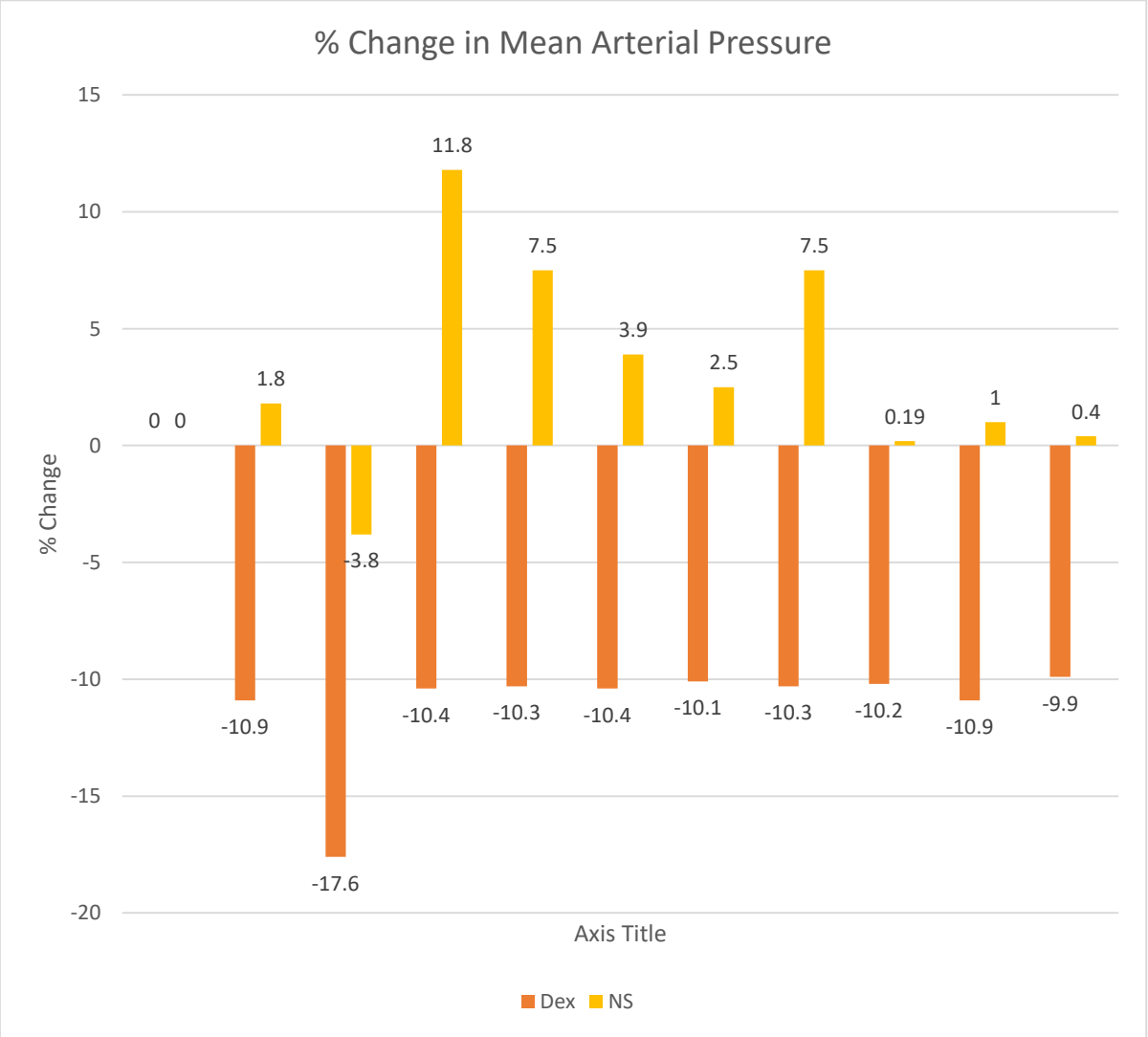

Figure 3 Percentage change in the Mean Arterial Pressure

As seen from figure 3 before intubation the MAP declined in both groups. However, in group D, the MAP was 10 % below the baseline value immediately after the following intubation. The corresponding value in group C participants after intubation was 11% more than the baseline value. Therefore, the total difference in MAP value at intubation between the two groups was about 20%. The total difference in MAP at extubation was a 17% difference in MAP values (Figure 3). The difference in the change in MAP from baseline among study participants in groups D and C were statistically highly significant at all time points (p-value <0.0001). The MAP in group D participants was 10% lower than the baseline value at the endline. Comparatively, in group C the MAP was either more or equal to the baseline value throughout the study (Figure 3).

4. DISCUSSION

Managing hemodynamic vital parameters during any type of surgical intervention including neurosurgical procedures is of paramount importance to ensure the optimal outcome. Clinical studies conducted in past have concluded that even the deeper level of anaesthesia does not reliably ablate the haemodynamic response to surgical intervention (King et al., 1951). In susceptible patients, uncontrolled variation in cardiovascular parameters during and following surgical interventions may compromise blood flow to various organs including the brain. Laryngoscopy and endotracheal intubation (LETI) are associated with pressor response mediated by the sympathetic system causing a sudden spike in MAP and HR (King et al., 1951). An increase in blood pressure can cause haemorrhage and vasogenic oedema while low blood pressure can cause cerebral ischemia (Ormond and Hadjipanayis, 2014). Additionally, an increase in blood pressure at the time of emergence from anaesthesia can also cause intracranial haemorrhage and cerebral oedema (Forbes and Dally, 1970).

In the present study, despite the heart rate being higher among participants given dexmedetomidine at baseline, the heart rate was lower in Dex group participants in comparison to the control group for the remaining period of observation, (p<0.0001) at all time points. Among participants given dexmedetomidine, the highest change (-18.81%) from the baseline value was noted 10 minutes after the infusion of dexmedetomidine. The heart rate in group C was higher than baseline values thorough out the period of observations. Like our findings, Batra et al., (2017) observed a progressive decline in heart rate among participants given dexmedetomidine. However, among the NS participants, there was a 20% rise in the HR. Tanskanen et al., (2006) also reported that the increase in HR after laryngoscopy and intubation was attenuated by dexmedetomidine. Uyar et al., (2008) reported that heart rate was almost similar to the baseline level immediately after the application of the skull pin. In comparison, skull pin attachment significantly increased heart rate among the participants given isotonic saline both in comparison to the baseline value and the dexmedetomidine group. Rashwan et al., (2015) reported that the heart rate was statistically significantly lower in Dex group than group P at all-time points. Bekker *et al*., (2008) observed that the intra-operative dexmedetomidine was effective for maintaining haemodynamic responses during the perioperative period.

In the present study following the infusion of dexmedetomidine, the mean MAP decreased from the baseline value of 97 mm Hg to a minimum value of 80 mm Hg ten minutes after infusion and then increased gradually to reach a maximum value of 87 mm Hg at the end of observation. Throughout the observation, the MAP remained below the baseline level. Comparatively in group C, the mean arterial pressure declined to its minimum recorded value just ten minutes after infusion but increased sharply to reach its maximum value (108 mm Hg) immediately after intubation. Similar to our findings, Batra et al., (2017) also reported that following infusion of Dexmedetomidine, the MAP decreased. They further reported that the MAP remained lower than the baseline value throughout the observation. Uyar et al., (2008) reported that MAP values reduced significantly in comparison to baseline values following the infusion of dexmedetomidine. They also note that there was a slight increase in MAP, but it was lower than the baseline level. Yacout et al., (2012) reported that dexmedetomidine given to patients under general anaesthesia was associated with lower MAP in comparison to NS.

We observed that the extent of sedation was measured on two occasions: at extubation and 30 minutes after extubation. The author observed that at extubation, most participants in Dex group were less sedated in comparison to participants in group C. Further, even 30 minutes after the extubation, participants in group D were still less sedated than participants in group C. The difference in the sedation score in two groups was statistically significant both at extubation and thirty minutes after extubation. Very similar to our findings, Batra et al., (2017) also reported that the sedation score of Group D was lower than the control group both at extubation and 30 min thereafter. They concluded that the difference in sedation scores among participants of the two groups was significant (Batra *et al.*, 2017).

In contrast to our findings, Madhusudan et al., (2016) reported that both at extubation and 30 minutes later, patients in Group D had higher sedation scores compared to Group S. A study conducted by Upadhyay et al., (2018) also reported that the median sedation score was higher among subjects belonging to the dexmedetomidine group. Such a contrast in findings of the sedation

score could be attributed to how the dexmedetomidine was given to participants. Both in the present study and Batra et al., (2017) gave dexmedetomidine as a continuous infusion; however, other researchers gave the drug in a bolus. Therefore, further studies including a systematic review are recommended to identify the difference in effectiveness and side effects profile by comparing bolus dosage with continuous infusion of Dexmedetomidine.

As mentioned earlier, dexmedetomidine has many desirable properties from an anaesthesiologist's perspective. One such property is its ability to reduce the dependency on anaesthetics. We noted that the amount of thiopentone required in group D and Group C was 273 mg and 340.5 mg (p-value <0.0001). Batra et al., (2017) reported that the total dose of thiopentone needed for inducing anaesthesia was significantly greater in the control group (337.0 mg) in comparison to the dexmedetomidine Group (280.0 mg) ($P < 0.001$)(Batra *et al.*, 2017). Similarly, Altan et al., (2005) also noted that dexmedetomidine results in low requirements for both analgesia and anaesthetics. Tanskanen et al., (2006) reported that the total dose of thiopentone for inducing anaesthesia was 294 and 315 mg in the Dexmedetomidine and the control group.

We noted that the mean 'time for extubation' in the Group D group and group C was 5.23 and 8.5 minutes, respectively (p<0.0001). Quite similar to our findings, Batra et al., (2017) also observed that the meantime to extubation was higher among the participants given normal saline (8.60 minutes) when compared to participants given dexmedetomidine (5.32 min) ($P < 0.001$). Tanskanen et al., (2006) also noted that among patients given dexmedetomidine, the time (4 minutes) for extubation was shorter than the placebo group (6 minutes) (p=0.041). Uyar et al., (2008) also noted that the meantime to extubation was significantly higher in the normal saline group (7.2 minutes) as compared to Group D (4.90 minutes) (P=0.031). Kang et al., (2020) in their respective studies, observed significantly reduced extubation time among participants given dexmedetomidine.

5. CONCLUSION

The dexmedetomidine exhibited several desirable properties from an anaesthesiologist's perspective. The dexmedetomidine has an anaesthetic sparing effect. The dexmedetomidine quickened the recovery because the mean 'time for extubation' was longer among the participants given isotonic normal saline. The dexmedetomidine provided haemodynamic stability during the perioperative period. Throughout the study after the infusion of the test drugs, the heart rate was lower among participants in the intervention group. Further, dexmedetomidine effectively blunted the increase in heart rate intubation and extubation. Further, dexmedetomidine effectively blunted a rise in mean arterial pressure at intubation and extubation.

Author Contributions

Dr Harindranath S Kumar: Proposal writing, Review of Literature, Questionnaire design, Data collection, Data analysis, Paper writing, Revisions
Dr Anjali Modak: Proposal writing, Questionnaire design, Data analysis, Paper writing, Revisions
Dr Neeta Verma: Proposal writing, Data analysis, Paper writing, Revisions
Dr Sheetal Madavi: Proposal writing, Paper writing, Revisions
Dr Nikhil Bhalerao: Proposal writing, Paper writing, Revisions

Ethical approval

The study was approved by the Medical Ethics Committee of Datta Meghe Institute of Medical Sciences, Sawangi, Wardha. Ethical approval code:-DMIMS (DU)/IEC/Sept-2019/8376.

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Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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