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"Hemodynamic and recovery profile with Dexmedetomidine and Fentanyl in intracranial supratentorial surgeries: A comparative study"

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Abstract: Background: Dexmedetomidine (DEX) has shown analgesic effects without significant respiratory depression. As Dexmedetomidine (DEX) provides good perioperative hemodynamic stability with decreased intraoperative opioid requirements, and neural protection, it might be a suitable anaesthetic adjuvant to neurosurgical anaesthesia. Fentanyl is a synthetic opioid with analgesic potency 50-100 times more than that of morphine and can be a valuable component of neuroanesthesia but can cause respiratory depression.

Aims and objectives: The aim of this study is to compare hemodynamics and recovery profile with dexmedetomidine and fentanyl in supratentorial intracranial surgeries at a tertiary care hospital in central India.

Patients and methods: In this randomized, prospective and comparative group study, the recruited patients were randomly allocated in two groups, Fentanyl group received an intravenous bolus of 2 μg/ kg fentanyl with maintenance of 1g/kg/hour of fentanyl and Dexmedetomidine group received a loading dose of 1 μg/kg of dexmedetomidine followed by maintenance of 0.4-0.6 μg/kg/hour till completion of surgery. Hemodynamic parameters, recovery profile and postoperative complications are monitored and assessed in both the groups.

Results: Patients receiving Dexmedetomidine (group D) showed not only significantly a longer time to regain spontaneous ventilation (5 ± 1 vs. 4 ± 1, $P = 0.001$) but also of extubation (11 ± 2 vs. 8 ± 2, $P = 0.001$) than patients receiving Fentanyl group F. Better Post operative analgesia was observed in the patients receiving Dexmedetomidine (group D) than as compared with the patients receiving Fentanyl (group F).

Conclusion: In the present study, the hemodynamic control was better reported with the Dexmedetomidine group as compared to Fentanyl. In our study, the patients in the DEX group higher number of patients (37/50) reported a good quality extubation than patients in the Fentanyl group (26/50).

Keywords: *Dexmedetomidine, Fentanyl, Neuroanesthesia, Hemodynamics*

I. INTRODUCTION

The goals of neuroanesthesia are to provide good operating conditions and to ensure stable cerebral hemodynamics without sudden increases in intracranial pressure or acute brain swelling. Furthermore, fast recovery from anaesthesia is often preferred to allow immediate neurological evaluation. During recovery, abrupt increases in arterial blood pressure can pose a risk for postoperative hematoma. Adrenergic agonists have been introduced to clinical anaesthesia for their sympatholytic, sedative, anaesthetic sparing and hemodynamic stabilizing properties. Dexmedetomidine (DEX) has shown analgesic effects without significant respiratory depression. As Dexmedetomidine (DEX) provides good perioperative hemodynamic stability with decreased intraoperative opioid requirements, and neural protection, it might be a suitable anaesthetic adjuvant to neurosurgical anaesthesia. Opioid analgesia prevents hemodynamic responses to awakening and extubation but may result in respiratory depression and high carbon dioxide tension with subsequent increase in the intracranial pressure. Fentanyl is a synthetic opioid with analgesic potency 50-100 times more than that of morphine and can be a valuable component of neuroanesthesia. Intravenous administration of Fentanyl causes a short-onset analgesic effect lasting for about 30-60 min and its metabolism is not associated with the production of active metabolites. The intracranial pressure (ICP) effects of Fentanyl are similar to those of other opioids, and allows preservation of cerebral blood flow reactivity to arterial carbon dioxide concentration. For this reason, the relative dose of opioid can be increased in response to painful stimuli, allowing the possibility for a more reliable and rapid emergence from anesthesia. A randomized, multi-institutional, double-blinded, prospective trial found Fentanyl to be a useful analgesic during elective supratentorial craniotomy for space-occupying lesions. There are limited reports on the comparison of the hemodynamics and recovery profile with Dexmedetomidine and Fentanyl in anaesthesia and none for intracranial surgeries. We planned a prospective

comparative study on the hemodynamics and recovery profile with dexmedetomidine and fentanyl in intracranial surgeries at a tertiary care hospital in central India. We also tested perioperative hemodynamic variability and intraoperative anaesthetic requirements with these two agents.

II. PATIENTS AND METHODS

This study was done as per tenets of Helsinki. The study was approved by the institutional Ethical' Committee and a written informed consent were obtained before enrolling the patient in the study. In this randomized, prospective and comparative group study, we compared hemodynamics and recovery profile with Dexmedetomidine and Fentanyl in intracranial `surgeries. All the consecutive patient aged 20–65 yr, with Glasgow Coma Scale score 14 or 15 and scheduled for elective intracranial supratentorial surgery under general anaesthesia, were considered eligible for the study. The sample size was calculated on the basis of the assumption of a difference of 10 mmHg in SBP between the two study groups and a SD within 10% difference and 95% confidence limit calculated sample size for each group was 42 patients. Total of 50 patients were recruited to compensate for possible dropouts.

The exclusion criteria were as follows: pregnant or nursing woman, morbid obesity; preoperative heart rate (HR) <45 beats min^{-1}; second or third degree AV block; antihypertensive medication with a-methyldopa, clonidine or other a2-adrenergic agonist; participation in another drug study during the preceding 1 month period. Intracranial vascular procedures were excluded because of the possible requirement for induced hypotension/hypertension and neuro-protective procedures that might have complicated emergence from anesthesia.

III. THE RECRUITED PATIENTS WERE RANDOMLY ALLOCATED IN TWO GROUPS

Group F: The Fentanyl group received an intravenous bolus of 2μg/kg Fentanyl immediately before the induction of anesthesia, followed by an infusion of 1 μg/kg/h until the completion of surgery.

Group D: The Dexmedetomidine group received a loading dose of 1 μg/kg intravenous infusion over 10 min before the induction of anesthesia. 2μg/kg of fentanyl was given just before induction. Intraoperatively, the dexmedetomidine intravenous infusion was continued at a rate of 0.4-.6 μg/kg/h until the completion of surgery. 50 μg bolus doses of fentanyl was given in both the groups for pain when required as at the time of skin incision and pin insertion.

IV. PERIOPERATIVE MANAGEMENT

Baseline values for HR, systolic and diastolic blood pressure (SBP and DBP) were recorded at least 8 h before the induction of anaesthesia. Routine medications were continued as clinically indicated. The state of consciousness was assessed on BIS score immediately before premedication, and subjective sedation was assessed on a Sedation agitation scale (SAS) from 0 (not tired at all) to 10 (very tired, almost impossible to stay awake). Upon arrival in the operating room, a large bore i.v. catheter was inserted for drug and continuous fluid administration (Normal Saline). A radial or femoral artery was cannulated for arterial pressure monitoring and obtaining blood samples. After the assessment of the state of consciousness and subjective sedation, and recordings of SBP, DBP, HR, SpO_2 and obtaining samples for blood gas analysis, the study drug infusion was commenced approximately 20 min before the induction of anaesthesia. During the infusion, SBP, DBP, HR and SpO_2 were recorded at 5 min intervals. Before the induction of anaesthesia, the state of consciousness and subjective sedation were assessed, and samples for blood gas analysis were obtained.

All patients received general anesthesia after preoxygenation for 5 min, and rapid-sequence induction was performed with thiopental 3-5 mg/kg. Cricoid pressure was applied, laryngoscopy was performed, and tracheal intubation was performed. Anesthesia was maintained with 0.5-1 MAC of isoflurane in 50% O2 and 50 % air. Rocuronium 0.5 mg/kg was given for muscle relaxation. Patients were ventilated to maintain an $EtCO_2$ of 30-35 mmHg. The Dexmedetomidine or Fentanyl infusion was stopped just before completion of surgery. At the end of the surgery, isoflurane was discontinued and residual neuromuscular block was antagonized with neostigmine 50μg/kg and atropine 20μg/kg, and then the trachea was extubated. Intracranial surgeries were performed using established techniques. During these periods, SBP, DBP, HR and SpO_2 were at 5 min intervals. Arterial samples for blood gas analyses were obtained at 60 min intervals during surgery. The exact times of anaesthetic induction, the dose of thiopental and the time of intubation were recorded. The number of interventions occurring when hemodynamic variables were outside the predetermined window was recorded

The time from the discontinuation of inhalational anaesthesia to regaining spontaneous ventilation was recorded (ventilation time), the time from discontinuation of inhalational anaesthesia to extubation was recorded (extubation time), and the quality of extubation was observed. Postoperative pain was assessed using the pain SAS (0–10) 20 min, 1, and 4 h after extubation. Time for the first analgesic (analgesic rescue time) was recorded and the total analgesic requirements for each group were observed and recorded for the first 24 h postoperatively. Postoperative complications such as nausea and vomiting were recorded.

Assuming sufficient patient sedation and analgesia and adequate fluid balance, hemodynamic abnormalities were treated. All drugs and fluids administered and all clinical events during the first six postoperative hours were recorded.

V. STATISTICAL ANALYSIS

Continuous data were presented as mean ± SD and analyzed using the unpaired Student *t*-test and the Mann–Whitney *U*-test. Repeated measures (ABP, HR, etc.) were analyzed by two-way analysis of variance. Categorical data (incidence of complications, VAS, etc.) were presented as the number (frequency) and were analyzed using the χ^2 or the Fisher exact test when appropriate. Data were considered significant if the *P* value was less than 0.05. Data were analyzed using the SPSS statistical program (version 20, IBM, USA). A P-value <0.05 was considered statistically significant

VI. RESULTS

We did not observe difference between the two study groups with respect to their age, weight, duration of surgery, and baseline laboratory investigations as shown in table 1. As shown in table 2, the patients receiving Dexmedetomidine (group D) had a significantly lower HR , SBP and DBP and compared with the patients receiving Fentanyl (group F) during the course of anaesthesia (p=0.00-0.02). Patients receiving Dexmedetomidine (group D) showed a not only significantly a longer time to regain spontaneous ventilation (5 ± 1 vs. 4 ± 1, *P* = 0.001) but also of extubation (11 ± 2 vs. 8 ± 2, *P* = 0.001) than patients receiving Fentanyl group F . Better Post operative analgesia was observed in the patients receiving Dexmedetomidine (group D) than as compared with the patients receiving Fentanyl (group F). Not only the VAS was significantly lower in group D than in group F { 20 min [1 (1–2) vs. 3 (2–5), *P* = 0.01], after 1 h [3 (2–5) vs. 6 (5–8), *P* = 0.01], and after 4 h [2 (1–4) vs. 4 (3–6) *P* = 0.01] }, but also number of patients who requested for rescue postoperative analgesic and the analgesic rescue time was significantly lower in group D than in group F [23 (46%) patients vs. 50 (100%) *P* = 0.001]. The three patients receiving Dexmedetomidine (group D) suffered from headache where as vomiting after extubation was observed in four receiving fentanyl (group F) as compared with two patients in group D. Six patients of group F reported respiratory depression but none in group D.

Table1. Postoperative interventions upon hemodynamic changes

Hemodynamic abnormality		**Intervention**
Bradycardia	Heart rate < 40 beats per min	Atropine 0.5 mg increments
Hypotension	SBP< 90 mm Hg	Ephedrine 5 mg increment
Tachycardia	Heart rate > 100 beats per min	Esmolol 5 mg increments
Hypertension	SBP> 160 mm Hg	Dihydralazine 6.25 mg increments
Hypertension and tachycardia		Labetalol 10 mg increments

Table 2. DEMOGRAPHIC DATA

DEMOGRAHIC AND CLINICAL DETAILS OF STUDIES PATIENTS	DEX group Mean ±SD	F group Mean ±SD	*P value*
Age in years	56.4±6.7	52±9.6	1.33
Weight(Kg)	72.4±6.3	74.9±3.5	0.43
Duration of surgery (minutes)	149.2± 18.6	154.7± 28.3	0.41

Mean±SD, No significant difference was found between the two groups regarding the demographic data

Table 3. Shows haemodynamic parameters of studied patients

Haemodynamic parameters		**Group D**	**Group F**	***P* value**
		Mean ±SD	**Mean ±SD**	
Heart rate(Beats/Minute)	HR (induction)	103.3 ± 8.6	105.8 ± 9.6	0.01
	HR (intubation)	100.2 ± 9.2	107.9 ± 10.7	0.00
	HR (skin incision)	107± 10.4	116.8± 13.8	0.00
	HR (during surgery)	90.4 ± 10.8	98.7 ± 11.5	0.00
	HR (extubation)	98.2 ± 8.2	111.8 ± 11 .6	0.00
Systolic blood				

pressure (mm Hg)				
	SBP (induction)	134.5± 8.6	128± 9.6	0.0006
	SBP (intubation)	136.6 ± 9.2	144.7± 6.5	0.0001
	SBP (skin incision)	137.5 ± 6.4	145.1± 12.4	0.0002
	SBP (during surgery)	130 ± 11.1	139.7±15.6	0.0005
	SBP (extubation)	139.5 ±8.2	146.3± 11.9	0.0012
Diastolic blood pressure(mm Hg)				
	DBP (induction)	82.3± 7.9	86.2± 8	0.02
	DBP (intubation)	85.1± 6.2	90.8 ± 5.2	0.001
	DBP (skin incision)	83.6± 7.2	88.1 ± 8.7	0.02
	DBP (during surgery)	75.3 ± 12.7	74.4 ± 10.8	0.5
	DBP (extubation)	808±75	86.2 ± 8.9	0.02

Table 4: Post operative observations in studied patients

		Group D	Group F	*P* value
Sedation agitation score				
Mean(range)	SAS 1 (20 min)	1 (1–2)	3 (2–5)	0.01
Mean(range)	SAS 2 (1 h)	3 (2–5)	6 (5–8)	0.01
Mean(range)	SAS 2 (4 h)	2 (1–4)	4 (3–6)	0.01
Postoperative analgesia	Total number of patients	N=50	N=50	
Number	Analgesic requests	23	50	0.001
	Analgesic rescue time (min)	189 ± 94	55 ± 24	0.001
Number	NSAID after 1 h	23	50	0.001
Number	Opioids after 4 h	10	22	0.02
Postoperative measurements	Total number of patients	N=50	N=50	
Number	Extubation quality (good quality)	37	29	0.0017
Number	Complication: nausea vomiting	2	4	0.72
	Respiratory depression	0	6	0.01
	Hypotension	3	0	0.2
Number	Bradycardia	2	0	0.5

Data are presented VAS, visual analogue score; median (range); number (frequency); Group D, dexmedetomidine group; group F, fentanyl group; Significance in comparison with the F group.

VII. DISCUSSION

The concept of neuro-anaesthesia includes several principles, the hemodynamic stability perioperatively being one of utmost importance. Low arterial pressures predispose the patients to cerebral ischemia, because autoregulation of the cerebral blood flow (CBF) is often impaired near tumours or traumatized areas. In some earlier reports, oral clonidine (the archeotypical alpha2-agent) premedication provided attenuation of the hypertensive response to laryngoscopy and intubation and head holder application in patients undergoing supratentorial surgery. In patients undergoing general or gynaecological surgery, numerous studies

have shown that Dexmedetomidine blunts the cardiovascular responses to intubation,' In the present study, the patients receiving Dexmedetomidine (group D) had a significantly lower HR , SBP and DBP and compared with the patients receiving Fentanyl (group F) during the course of anaesthesia(p 0.00-0.02) In addition to this theoretically beneficial property of alpha2-agonists, they have also been reported to increase the risk of hypotension and bradycardia. These effects have most often been seen in young healthy volunteers or after rapid bolus administration. In our study , patients receiving DEX (group D) , 2 had bradycardia and 3 had hypotension but none of the patients in the receiving Fentanyl (group F) group(p 0.01-0.03) .

The hemodynamic responses to intracranial surgery are most often elicited at the beginning or the end of the procedure. Similarly, the manipulation of certain structures within the brain may produce cardiovascular changes. In the present study, the need to treat hypertension or tachycardia was similar in all groups. DEX has been widely studied as an anaesthetic adjuvant, and its anaesthetic sparing effects are well known. In numerous studies, it has been shown to reduce the isoflurane requirements dose-dependently up to 90%. It has also been shown that DEX potentiates analgesia caused by Fentanyl in animals' and reduces its dose requirements in humans during surgery. In the present study, not only the SAS was significantly lower in patients receiving Dexmedetomidine than Fentanyl {20 min [1 (1–2) vs. 3 (2–5)], $P = 0.01$} but very few patients receiving Dexmedetomidine (23 [46%) patients] requested for rescue postoperative analgesic [vs. 50 (100%)] ($P = 0.001$). It became apparent in our results, that Dexmedetomidine not only provide superior analgesic effect but also maintains better hemodynamic stability than Fentanyl in neurosurgical patients.

The hemodynamic responses to emergence from anaesthesia and extubation are blunted with DEX, ' and the centrally mediated sympatholytic effect has continued well into the postoperative period. Also, in our study, only 2 out of 50 patients receiving Dexmedetomidine (group D) suffered from bradycardia which showed that Dexmedetomidine not only attenuated cardiovascular responses to the emergence from anaesthesia and this advantageous effect extended in to the recovery period as well.

'The golden standard' of neuroanesthesia includes maintenance of anaesthesia with isoflurane or propofol with fentanyl. In the present study, we administered isoflurane in concentrations less than 1 MAC, and also moderate hyperventilation was used. In spite of this three out of 50 patients receiving Dexmedetomidine (group D) suffered from headache. In the present study, we demonstrated that intraoperative Dexmedetomidine infusion decreased hemodynamic responses to various noxious stimuli and attenuated the emergence from anaesthesia both by decreasing the immediate hemodynamic response and the time to removal of the tracheal tube as compared to intraoperative Fentanyl infusion.

In the present study, Fentanyl was given to one group of study patients to compare its effect on CBF regulation with that on Dexmedetomidine. The Fentanyl group received an intravenous bolus of 2μg/kg F immediately before the induction of anesthesia, followed by an infusion of 1 μg/kg/h until the completion of surgery. In these doses only 6 out of 50 patients were reported to have respiratory depression. The incidence of respiratory depression is reported to be higher with the use of larger doses of Fentanyl. Remifentanil, on the other hand, is reported to be rapidly metabolized and is compatible with quick awakening, but the abrupt termination of Remifentanil analgesia may cause hypertension at emergence from anaesthesia and during the immediate postoperative period. In the present study, the hemodynamic control was better reported with the Dexmedetomidine group as compared to Fentanyl.

DEX has been shown to have minimal effects on respiration and ventilatory weaning and tracheal extubation has been successfully carried out in critically ill patients under continuing DEX sedation. In our study, the patients in the DEX groups higher number of patients (37/50) reported a good quality extubation in than patients in the Fentanyl group (29/50). It may, however, reflect the lack of respiratory depression of Dexmedetomidine. Indeed, fewer patients in the Dexmedetomidine groups needed rescue analgesia as compared to Fentanyl group.

VIII. CONCLUSION

In the study, we have concluded that patients who had received dexmedetomidine had a more stable hemodynamic parameters than patients received fentanyl during and after the course of anesthesia. Ventilation time and extubation time was found higher in patients received dexmedetomidine, analgesia was also found better with dexmedetomidine group. Hypotension and bradycardia were more common with dexmedetomidine while nausea, vomiting and respiratory depression were more common with fentanyl.

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