DOI: 10.7860/JCDR/2017/24002.9235

Original Article

Anaesthesia Section

Use of Dexmedetomidine in Patients Undergoing Craniotomies

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ABSTRACT

Introduction: The neuroanaesthesia ensures stable perioperative cerebral haemodynamics, avoids sudden rise in intracranial pressure and prevents acute brain swelling. The clinical characteristics of dexmeditomidine make this intravenous agent a potentially attractive adjunct for neuroanaesthesia and in the neurological intensive care unit.

Aim: This study aimed to assess the effect of dexmedetomidine on intraoperative haemodynamic stability and to assess the intraoperative requirements of analgesic and other anaesthetic agents, and also to assess postoperative sedation, respiratory depression and any other side effects of dexmedetomidine as compared to placebo.

Materials and Methods: This prospective randomized study was done in 60 patients of either sex, age between 18 to 60 years and American Society of Anaesthesiologist (ASA) Grade I and II undergoing elective craniotomies under General Anaesthesia (GA) for intracranial Space Occupying Lesion (SOL). These 60 patients underwent thorough history, clinical examination and laboratory investigations. They were randomly divided into two groups, Group D (received Inj. Dexmedetomidine) and Group P (received Inj. Placebo). During bolus and infusion Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), Peripheral oxygen saturation (SPO_2) was recorded at every five minutes interval for first 20 minute.

Results: The mean age in Group D was 39.5 years and in Group P was 40 years. The sex distribution in two groups was in Group D, 12 patients (40%) were females and 18 (60%) patients were males. While in Group P 10 (33.3%) were females and 20 (66.7%) patients were males. The two groups were comparable with respect to diagnosis and type of surgery of patients and difference was not statistically significant. The mean HR, the mean DBP and the mean MAP was lower in Group D as compared to Group P and the difference was statistically significant.

Conclusion: Dexmedetomidine provided intraoperative haemodynamic stability. It attenuates the haemodynamic responses to laryngoscopy, intubation, at pin fixation and the emergence from anaesthesia.

Keywords: Analgesia, Haemodynamic stability, Neuroanesthesia

INTRODUCTION

The goals of neuroanaesthesia are to ensure stable perioperative cerebral haemodynamics and avoid sudden rise in intracranial pressure to prevent acute brain swelling [1]. The intense surgical stimuli associated with craniotomy frequently cause sympathetic activation which results in marked changes in systemic arterial pressure and Cerebral Blood Flow (CBF). These cerebrovascular responses may result in elevated Intracranial Pressure (ICP) and reduction in cerebral perfusion pressure which can lead to cerebral ischemia, especially in patients with impaired auto regulation and compromised cerebral compliance. Thus, the prevention and control of the haemodynamic response to nociceptive stimuli are of utmost importance to preserve stable cerebral homeostasis which is also important for neurosurgical patients for rapid and smooth recovery from anaesthesia which is often preferred to allow immediate neurological evaluation [1]. The haemodynamic stability may become more challenging in hypertensive patients undergoing neurosurgical procedures.

There are several drugs which have been used to maintain cerebral haemodynamics such as opioids, propofol, α-2 agonists and beta blockers. Opioid analgesic prevents haemodynamic responses intraoperatively but if given in excess may result in respiratory depression with carbon dioxide retention, with subsequent increase in the intracranial pressure during recovery. The α-2 agonists like clonidine blunt hypertensive response to intubation or during pin head-holder application, but may cause hypotension especially in elderly.

There are several concerns which must be addressed when a new drug is introduced into neuroanaesthesia practice. Principal considerations include the ability of a drug to allow a haemodynamically stable perioperative course and preservation of intracranial homeostasis, to be compatible with neurophysiological monitoring and to ensure rapid emergence to a level of consciousness permitting neurological assessment in the operating room. Furthermore, cerebral blood volume reduction, an optimization of the cerebral oxygen supply and demand relationship and neuroprotection add to these considerations [2].

Dexmedetomidine is a highly selective α-2 adrenoreceptor agonist recently introduced to anaesthesia practice [3,4]. It produces dose-dependent sedation, anxiolysis and analgesia (involving spinal and supraspinal sites) without respiratory depression. Dexmedetomidine has shown analgesic effects without significant respiratory depression. It provides good intraoperative haemodynamic stability with decreased intraoperative opioid requirements and other beneficial effects in terms of neural protection as suggested by animal studies.

This study aimed to assess effect of dexmedetomidine on intraoperative haemodynamic stability and to assess the intraoperative requirements of analgesic and other anaesthetic agents and also to assess postoperative sedation, respiratory depression and any other side effects of dexmedetomidine as compared to placebo.

MATERIALS AND METHODS

After institutional ethical committee approval, this prospective randomized study was done in 60 patients of either sex, age between 18 to 60 years and ASA Grade I and II undergoing elective craniotomies under GA for intracranial SOL from March 2010 to March 2013.

Variables	Group D				Group P				Mann-Whitney Test		
	Mean	SD (±)	Median	IQR	Mean	SD (±)	Median	IQR	z-value	p-value	Difference is-
Age (yrs) ^	38.87	16.53	39.50	36.25	41.57	13.3	40.00	24.25	-0.602	0.547	Not significant
Weight (Kg) ^	53.87	7.58	52.0	11.25	56.70	6.58	57.50	10.75	-1.606	0.108	Not significant
Duration of surgery (min) ^	290.0	23.08	300	15.00	293.5	21.46	300.0	15.00	-0.091	0.927	Not significant

[Table/Fig-1]: Comparison of age, weight and duration of surgery in Group D and Group P.
^ Mann-Whitney test applied as data failed 'Normality' test.

Parameter	Group				Total		Chi-square test (p-value)
	Group D		Group P				
	No.	%	No.	%	No.	%	
Sex							
Female	12	40.0	10	33.3	22	36.7	0.592 (Not significant)
Male	18	60.0	20	66.7	38	63.3	
ASA Grade							
I	20	66.7	21	70.0	41	68.3	0.781(Not significant)
II	10	33.3	9	30.0	19	31.7	

[Table/Fig-2]: Comparison of sex and ASA Grade in Group D and Group P.

Diagnosis	Group				Total		Chi-square tests (p-value)
	Group D		Group P				
	No.	%	No.	%	No.	%	
Frontal Sol	3	10.0%	3	10.0%	6	10.0%	0.288 Not Significant
Sphenoidal Meningioma	5	16.7%	1	3.3%	6	10.0%	
Craniopharyngioma	5	16.7%	1	3.3%	6	10.0%	
Parietal Sol	1	3.3%	4	13.3%	5	8.3%	
Corpus Callosal Glioma ^	0	0.0%	4	13.3%	4	6.7%	
Frontal Glioma ^	3	10.0%	0	0.0%	3	5.0%	
Frontoparietal Sol ^	2	6.7%	1	3.3%	3	5.0%	
Frontotemporal Sol ^	0	0.0%	1	3.3%	1	1.7%	
Insular Glioma ^	1	3.3%	0	0.0%	1	1.7%	
Parasagital Meningioma ^	1	3.3%	0	0.0%	1	1.7%	
Parietal Meningioma ^	1	3.3%	0	0.0%	1	1.7%	
Pituitary Adenoma ^	0	0.0%	1	3.3%	1	1.7%	
Suprasellar Cystic Tumour ^	0	0.0%	2	6.7%	2	3.3%	
Suprasellar Epidermoid ^	0	0.0%	1	3.3%	1	1.7%	
Temporal Glioma ^	0	0.0%	4	13.3%	4	6.7%	
Temporal Meningioma ^	0	0.0%	1	3.3%	1	1.7%	
Temporal Sol ^	3	10.0%	0	0.0%	3	5.0%	
Temporoparietal Glioma ^	4	13.3%	0	0.0%	4	6.7%	
Temporoparietal Sol ^	0	0.0%	4	13.3%	4	6.7%	
Thalamic Glioma ^	0	0.0%	2	6.7%	2	3.3%	
Thalamic Sol ^	1	3.3%	0	0.0%	1	1.7%	
Total	30	100.0%	30	100.0%	60	100.0%	

[Table/Fig-3]: Comparison of diagnosis in Group D and Group P.
^ Mann-Whitney test applied as data failed 'Normality' test

Inclusion Criteria: All patients with age between 18 to 60 years, Glasgow coma scale 15, patients given consent for study drug administration and surgery and patients with no history of any drug or substance allergy were included in the study.

Exclusion Criteria: Patients on anti-hypertensive medication with alpha methyldopa, clonidine or other α-2 adrenergic agonists, patients with preoperative heart rate less than 45 or any heart block, pregnant women, patients with morbid obesity and patients with history of any drug or substance allergy were excluded from the study.

All the 60 patients were evaluated with detail history, general and systemic examination, airway examination and laboratory investigations such as complete blood count, liver function tests, renal function tests, random blood sugar, serum electrolytes, chest radiograph, ECG, HIV, HBsAg, HCV. Then after written informed consent they were randomly divided into two groups by simple random sampling method.

1) Group D received: Inj. Dexmedetomidine (Bolus + infusion).

2) Group P received: Inj. Placebo (Bolus + infusion).

On arrival in the operation theatre patient's identity and Nil by Mouth (NBM) status, consent was confirmed. Standard intraoperative monitoring of HR, SBP, DBP, MAP and SPO_2 was initiated. Baseline preoperative values of these parameters were recorded.

An 18 G intravenous (IV) catheter was inserted for drug and continuous fluid administration. IV infusion of normal saline was started at the rate of 5 to 10 ml/kg/hr. A left radial artery was cannulated for invasive arterial BP under LA taking all aseptic precautions.

In Group D, patients received IV bolus dose of Dexmedetomidine 1 μgm/kg which was diluted to make it of 20 cc volume given over 10 minutes followed by IV infusion of 0.5 μgm/kg/hr through infusion pump till skin closure.

In Group P, patients received bolus dose of IV placebo i.e., normal saline of 20 cc volume over 10 minute followed by IV infusion of normal saline 0.5 ml/kg/hr, through infusion pump till skin closure.

During bolus and infusion HR, SBP, DBP, MAP, SPO_2 was recorded at every five minutes interval for first 20 minutes.

After completion of bolus drugs and 10 minutes after initiation of infusion in both the groups, patients were preoxygenated for 5 minutes and simultaneously premedicated through a separate IV line with

1) Inj. Glycopyrrolate 0.004 mg/kg IV

2) Inj. Ondansetron 0.08 mg/kg IV

3) Inj. Fentanyl 2 μgm/kg IV

Induction was done after three minutes of premedication with propofol in incremental doses till the loss of eye lash reflex then neuromuscular block was achieved with Inj. Rocuronium 1mg/kg. Induction dose of propofol recorded. Patients were ventilated for three minute. Laryngoscopy and intubation was performed with adequate size of armored tube and proper size Ryle's tube was inserted. Throat was packed with wet roller gauge, bite block was inserted, air entry on both sides checked and endotracheal tube was secured properly with adhesive tape.

Anaesthesia was maintained with Nitrous oxide (N_2O) and Oxygen (O_2) (60%+40%), Isoflurane was initiated to achieve end tidal concentration of 0.5% and end tidal isoflurane concentration was monitored throughout the intraoperative period. For muscle relaxation Inj. Rocuronium was started at the rate of 0.5 mg/kg/hr. The intraoperative depth of anaesthesia and analgesia was adjusted as per haemodynamic status.

Monitoring of HR, SBP, DBP, MAP and SPO_2 was done at the following intervals: Preoperative; 5 min after bolus (5 min AB); 10 min after bolus (10 min AB); 5 min after infusion (5 min AI); 10 min after infusion (10 min AI); After premedication (A premed); After induction (AInd); After laryngoscopy (AL); At intubation (AInt); 5 min after intubation; At pin insertion (At PI); Then 15 min interval

Surgery	Group				Total		Chi-square test p-value
	Group D		Group P				
	No.	%	No.	%	No.	%	
Frontoparietal Craniotomy	10	33.3%	11	36.7%	21	35.0%	0.137 Not significant
Temporoparietal Craniotomy	6	20.0%	6	20.0%	12	20.0%	
Frontal Craniotomy ^	5	16.7%	2	6.7%	7	11.7%	
Pterional Craniotomy ^	1	3.3%	5	16.7%	6	10.0%	
Temporal Craniotomy ^	3	10.0%	1	3.3%	4	6.7%	
Bifrontal Craniotomy ^	2	6.7%	1	3.3%	3	5.0%	
Subfrontal Craniotomy ^	3	10.0%	0	0.0%	3	5.0%	
Parietal Craniotomy ^	0	0.0%	2	6.7%	2	3.3%	
Parieto-occipital Craniotomy ^	0	0.0%	2	6.7%	2	3.3%	
Total	30	100.0%	30	100.0%	60	100.0%	

[Table/Fig-4]: Comparison of types of surgery in Group D and Group P.

Heart Rate (beats/ min)	Group D				Group P				Unpaired t-test applied	
	Mean	SD (±)	Median	IQR	Mean	SD (±)	Median	IQR	t-value	p-value
Preop	82.47	8.74	80.50	10.25	83.47	8.45	80.00	14.50	2.128	0.078
5 min AB	78.23	7.62	78.00	10.50	82.33	9.32	82.00	15.25	-1.866	0.067
10 min AB	73.70	7.76	74.50	10.00	80.67	8.66	81.00	14.25	-3.282	0.00175*
5 min AI ^	69.00	6.37	70.00	6.25	77.30	9.11	77.00	14.50	-3.318	0.00091*
10 min AI^	65.30	6.27	66.50	3.50	76.60	8.40	75.50	13.50	-4.918	8.72E-07*
A Premed	61.83	5.99	61.00	5.50	71.63	8.28	70.00	14.00	-5.254	2.23E-06*
A Indu ^	59.63	6.83	59.00	6.75	70.40	7.94	70.00	12.50	-5.032	4.85E-07*
A Scopy ^	79.80	5.51	80.00	6.00	108.97	3.81	109.00	5.25	-6.669	2.57E-11*
A Intub	80.50	5.13	80.50	6.25	109.10	3.84	110.00	5.25	-24.45	3.08E-32*
5 minAInt ^	67.67	5.16	68.00	6.00	76.03	6.96	75.00	10.50	-4.556	5.22E-06*
At P I	80.00	5.10	80.00	6.25	108.98	3.89	111.00	5.25	-5.033	3.07E-31*
Then every 15 min										
15 min ^	81.70	15.23	77.00	28.00	92.47	23.49	80.00	47.75	-1.739	0.08203
30 min ^	88.70	10.68	89.00	20.00	101.70	19.29	105.00	38.25	-2.415	0.01574*
45 min ^	77.07	11.14	77.50	13.50	81.20	5.80	80.00	10.25	-1.803	0.077
60 min	68.13	5.44	68.50	7.00	78.27	4.53	78.00	6.00	-7.840	1.14E-10*
75 min	66.67	4.82	66.50	8.25	77.97	5.30	77.50	6.25	-8.642	5.20E-12*
90 min	65.33	5.54	66.50	7.50	78.23	6.28	77.50	7.25	-8.437	1.14E-11*
105 min	65.13	5.82	65.00	8.25	77.60	5.23	76.00	7.00	-8.724	3.80E-12*
120 min	65.03	5.99	66.00	6.25	77.73	5.44	78.00	7.75	-8.601	6.07E-12*
135 min ^	64.47	6.21	64.50	8.75	79.70	5.76	80.00	3.25	-6.345	2.23E-10*
150 min	64.57	5.45	64.00	6.75	80.43	3.99	80.00	3.00	-12.86	1.22E-18*
165 min ^	64.13	5.76	64.00	5.50	80.10	4.35	79.50	3.00	-6.593	4.30E-11*
180 min ^	64.17	5.69	64.00	7.25	80.13	4.93	80.00	5.25	-6.410	1.46E-10*
195 min ^	63.87	4.91	64.00	5.75	91.10	15.22	87.50	32.00	-6.614	3.73E-11*
210 min ^	63.90	5.14	64.00	7.00	93.48	14.51	90.00	28.00	-6.591	4.36E-11*
225 min ^	63.80	6.05	64.00	6.25	82.48	12.17	78.00	8.00	-6.262	3.81E-10*
240 min ^	63.70	5.72	63.50	7.25	79.90	3.50	80.00	2.00	-6.580	4.72E-11*
255 min ^	65.38	4.96	65.00	6.00	82.24	6.86	80.00	8.00	-6.327	2.50E-10*
270 min ^	65.28	4.56	65.00	7.00	80.31	3.32	80.00	3.50	-6.299	3.00E-10*
285 min	66.33	4.18	67.00	5.00	79.18	3.01	78.50	3.75	-12.85	1.82E-17*
300 min ^	66.27	4.50	65.50	4.50	78.00	2.20	78.00	2.75	-5.506	3.66E-08*
315 min ^	69.00	7.55	70.00	15.00	79.75	2.36	79.00	4.25	-2.141	0.03231*
At ext^	94.93	4.75	98.00	9.00	108.00	5.56	109.00	9.25	-6.504	7.84E-11*
Then every 30 min for 4 hrs										
30 min ^	71.23	5.20	72.00	6.25	77.93	9.69	78.00	16.50	-2.549	0.0108*

Heart Rate (beats/ min)	Group D				Group P				Unpaired t-test applied	
	Mean	SD (±)	Median	IQR	Mean	SD (±)	Median	IQR	t-value	p-value
60 min ^	74.67	5.47	76.00	8.00	85.83	12.00	85.50	24.25	-3.480	0.0005*
90 min	82.27	8.12	80.50	12.00	84.90	10.31	85.00	18.25	-1.099	0.276
120 min ^	87.37	6.76	90.00	11.00	89.73	8.42	77.50	11.50	-3.665	0.25
150 min ^	80.63	6.46	82.00	8.75	78.80	6.83	76.00	11.25	-1.104	0.27
180 min	81.07	5.74	82.00	8.50	79.57	6.25	78.50	10.50	0.968	0.337
210 min	81.20	5.43	82.00	6.00	80.00	5.59	79.00	10.00	0.844	0.402
240 min	81.53	5.18	82.50	6.25	80.73	5.34	80.00	7.25	0.589	0.558

[Table/Fig-5]: Comparison of HR at various time intervals between Group D and Group P.
^ Mann-Whitney test applied as data failed 'Normality' test, t-value replaced by Z-value
*- p-value significant (<0.05)

Systolic BP (mmHg)	Group D				Group P				Unpaired t-test applied	
	Mean	SD (±)	Median	IQR	Mean	SD (±)	Median	IQR	t-value	p-value
Preop	122.2	4.61	120.5	7.5	122.63	10.5	120	6.5	-1.116	0.264
5 min AB	122.27	18.42	118	6.25	123.63	9.26	120	7.75	-2.236	0.025*
10 min AB	115	16.62	110.5	9	122.8	9.14	120	8.75	-4.406	1.05E-05*
5 min AI ^	104.47	6.2	103	10	121.9	7.69	119.5	6.25	-6.57	5.02E-11*
10 min AI^	100.2	5.43	100	8.5	121.17	6.05	119.5	6.25	-6.662	2.71E-11*
A Premed	97.63	5.96	97	7.25	118.33	5.58	117	5	-6.595	4.26E-11*
A Indu ^	93.77	6.36	92	6.5	104.4	5.44	104	9.25	-5.606	2.07E-08*
ALaryng ^	130.8	4.11	130.5	6	140.23	3.65	140	4	-9.411	2.80E-13*
A Intub	131.37	5.07	132	9.5	139.5	3.58	140	3.5	-5.444	5.22E-08*
5 minAInt ^	101.1	6.13	100	11	110.4	4.55	110	6.5	-6.677	1.02E-08*
At P I	123.10	5.44	129.00	10.50	140.80	3.53	138.50	4.25	-5.434	2.79E-08*
Then every 15 min										
15 min ^	116.47	20.12	125	39.25	124.2	21.63	109.5	39.25	-2.13	0.033*
30 min ^	123.77	13.45	124	22.5	131.8	22.53	138.5	44.25	-1.221	0.222
45 min ^	108.63	13.48	104	22.25	109.27	4.98	108.5	6	-1.185	0.236
60 min	99.3	6.24	98.5	5.25	107.27	2.46	107	3.25	-5.067	4.04E-07*
75 min	98.23	5.51	97.5	5.5	107.17	2.45	107	4	-5.176	2.27E-07*
90 min	96.7	4.69	95.5	4.25	107.47	3.2	107.5	3.25	-5.969	2.38E-09*
105 min	97	4.64	96	4.25	107.03	2.66	107	2.5	-6.005	1.91E-09*
120 min	95.5	4.11	94	5.25	107.73	2.24	108	3.25	-6.517	7.17E-11*
135 min ^	96.33	4.85	94.5	5	108.5	2.5	109	3.25	-6.177	6.55E-10*
150 min	96.03	4.68	94	4.25	108.7	2.67	108.5	3	-6.366	1.94E-10*
165 min ^	95.2	4.33	94	4.25	109.03	2.7	109	2.25	-6.341	2.29E-10*
180 min ^	95.57	4.07	94	4	109.8	4.07	109	2	-6.335	2.37E-10*
195 min ^	95.67	4.51	94	4.25	121.17	15.56	116	33	-6.352	2.13E-10*
210 min ^	95.9	4.25	94	5	125.07	18.13	116	35	-6.441	1.19E-10*
225 min ^	95.97	3.69	95	5	111.48	12.46	107	4	-6.566	5.17E-11*
240 min ^	95.63	4.21	95	5.25	107.72	1.79	108	3	-6.309	2.82E-10*
255 min ^	96.77	3.98	96	4.25	108.97	7.18	108	2.5	-6.116	9.59E-10*
270 min ^	96.52	4.67	96	4.5	107.86	2.15	109	3	-5.766	8.11E-09*
285 min	96.58	4.04	96	5.5	106.21	1.75	107	2	-5.656	1.55E-08*
300 min ^	98.09	4.2	98	4.25	106.15	2.11	106	4	-7.74	1.79E-09*
315 min ^	98	4	98	8	107.25	2.06	107	3.75	-4.048	0.01*
At ext ^	119	3.48	130	3.5	129.67	3.88	129	3.25	-0.887	0.03751*
Then every 30 min for 4 hrs										

Systolic BP (mmHg)	Group D				Group P				Unpaired t-test applied	
	Mean	SD (±)	Median	IQR	Mean	SD (±)	Median	IQR	t-value	p-value
30 min ^	109.27	3.19	109	2	121.63	6.94	119	5	-6.411	1.45E-10*
60 min ^	112.27	4.19	112	5.25	126.4	6.51	128.5	10.25	-6.195	5.85E-10*
90 min ^	117.47	7.44	117	11.25	124.67	6.52	123.5	10.75	-3.643	0.0003*
120 min	125.07	4.93	127.5	9.25	122	4.93	121	4	2.411	0.01911*
150 min^	118.83	4.96	120	5.25	121.23	2.37	121	2	-2.404	0.0162*
180 min^	117.77	4.9	119	6.25	122.03	2.14	122	2.25	-4.003	6.25E-05*
210 min^	117.77	4.75	120	7.5	121.37	1.75	121.5	2	-3.477	0.0005*
240 min^	119.2	4.79	120	4.5	121.63	1.96	121	3	-2.273	0.023*

[Table/Fig-6]: Comparison of SBP between Group D and Group P.
^ Mann-Whitney test applied as data failed 'Normality' test, t-value replaced by Z-value
*- p-value significant (<0.05)

Diastolic BP (mmHg)	Group D				Group P				Unpaired t-test applied	
	Mean	SD (±)	Median	IQR	Mean	SD (±)	Median	IQR	t-value	p-value
Preop	81.90	2.12	83.00	4.00	83.00	4.49	83.50	7.25	-1.214	0.230
5 min AB	79.83	7.48	78.50	2.25	83.37	4.17	84.00	6.25	-3.822	0.000*
10 min AB	75.83	8.01	74.00	8.00	83.20	3.65	83.50	6.00	-5.100	3.40E-07*
5 min AI ^	69.43	4.83	68.50	4.25	83.07	3.45	83.00	3.25	-6.440	1.19E-10*
10 min AI^	65.97	5.30	65.50	7.00	82.07	3.44	83.00	4.00	-6.561	5.35E-11*
A Premed	63.30	4.44	62.00	4.50	79.17	3.64	79.50	4.50	-6.521	6.97E-11*
A Indu ^	61.53	3.88	61.00	4.25	68.03	4.26	68.00	4.25	-6.180	6.87E-08*
ALaryng ^	78.23	6.31	80.00	9.50	87.17	1.97	87.00	2.25	-7.401	6.21E-10*
A Intub	79.23	5.61	80.00	7.25	87.60	1.96	87.00	2.25	-6.104	1.04E-09*
5 minAInt ^	66.13	6.31	67.00	8.00	72.40	4.46	73.00	6.75	-4.441	4.09E-05*
At P I	80.20	5.59	80.50	7.50	86.90	1.98	86.50	2.25	-6.103	1.03E-09*
Then every 15 min										
15 min ^	75.23	11.58	80.00	22.25	80.13	12.89	76.00	23.75	-1.643	0.10043
30 min ^	80.20	8.27	83.50	9.00	84.53	10.15	87.50	18.00	-1.920	0.0548
45 min ^	69.27	9.97	68.00	20.00	77.47	5.69	79.00	10.00	-3.147	0.00165*
60 min	63.13	7.06	62.00	9.25	77.20	5.62	78.00	7.25	-8.544	7.56E-12*
75 min	60.30	5.80	60.50	7.25	76.90	5.30	76.50	7.00	-11.570	1.06E-16*
90 min	59.77	5.61	60.50	7.00	77.57	5.11	78.00	4.75	-12.845	1.32E-18*
105 min	59.73	5.08	59.00	6.00	77.73	5.38	77.00	7.25	-13.333	2.60E-19*
120 min	59.17	4.31	59.00	8.00	79.00	3.68	79.50	5.25	-19.181	8.67E-27*
135 min ^	58.67	4.57	58.00	8.00	80.03	4.29	80.00	3.25	-18.685	3.22E-26*
150 min	59.43	5.03	59.50	7.50	79.77	2.32	80.00	2.25	-6.674	2.49E-11*
165 min ^	59.50	4.90	59.50	7.50	80.43	2.58	80.00	3.00	-6.670	2.56E-11*
180 min ^	59.33	5.89	60.00	7.50	80.70	3.21	80.00	5.00	-6.652	2.89E-11*
195 min ^	57.33	4.37	58.00	5.00	82.83	5.87	82.50	11.00	-6.664	2.67E-11*
210 min ^	58.07	5.17	58.50	6.50	84.10	5.02	87.00	10.00	-6.604	3.99E-11*
225 min ^	56.73	4.93	57.00	7.00	80.45	4.21	80.00	4.50	-6.610	3.85E-11*
240 min ^	57.37	5.57	58.50	7.00	79.90	2.40	80.00	3.00	-6.613	3.77E-11*
255 min ^	57.50	4.23	58.00	7.00	80.07	3.13	80.00	2.50	-6.375	1.83E-10*
270 min ^	56.76	3.91	57.00	6.50	79.97	2.68	80.00	3.00	-6.307	2.84E-10*
285 min	57.63	4.18	58.50	7.25	79.14	2.46	79.00	3.50	-6.183	6.31E-10*
300 min ^	57.23	4.09	57.50	6.50	78.85	2.37	79.00	3.00	-5.550	2.86E-08*
315 min ^	59.33	1.16	60.00	2.00	79.75	0.50	80.00	0.75	-2.223	0.02622*
At ext ^	84.13	4.02	84.00	5.25	88.20	2.75	88.50	3.25	-4.579	2.52E-05*
Then every 30 min for 4 hrs										

Diastolic BP (mmHg)	Group D				Group P				Unpaired t-test applied	
	Mean	SD (±)	Median	IQR	Mean	SD (±)	Median	IQR	t-value	p-value
30 min ^	71.77	3.82	71.00	3.25	82.80	3.12	83.50	5.00	-12.247	1.01E-17*
60 min ^	75.03	5.73	76.00	4.50	83.67	2.41	84.00	2.25	-5.953	2.64E-09*
90 min ^	77.50	7.71	80.00	3.25	84.27	2.29	85.00	3.00	-5.177	2.25E-07*
120 min	81.87	2.89	82.00	3.25	83.60	2.54	84.00	4.50	-2.469	0.017*
150 min^	79.20	5.08	80.00	4.50	83.90	2.66	84.50	5.00	-4.501	6.76E-06*
180 min^	77.20	6.75	80.00	4.25	83.97	3.01	84.50	6.00	-5.011	5.42E-07*
210 min^	77.10	7.48	80.00	2.25	83.63	2.79	84.00	5.25	-4.892	9.98E-07*
240 min^	78.50	8.03	80.00	2.25	84.10	2.44	85.00	4.00	-4.755	1.99E-06*

[Table/Fig-7]: Comparison of DBP at various time intervals between Group D and Group P.
^ Mann-Whitney test applied as data failed 'Normality' test, t-value replaced by Z-value
*- p-value significant (<0.05)

MAP	Group D				Group P				Unpaired t-test applied	
	Mean	SD (±)	Median	IQR	Mean	SD (±)	Median	IQR	t-value	p-value
Preop ^	95.33	2.63	95.83	4.42	96.21	5.65	94.33	5.42	-0.045	0.964
5 min AB ^	93.98	10.03	91.83	3.50	96.79	5.12	95.17	7.33	-3.553	0.000382*
10 min AB ^	88.89	10.57	86.33	6.17	96.40	4.73	94.67	7.17	-5.051	4.41E-07*
5 min AI ^	81.11	4.60	80.67	7.00	96.01	4.09	95.67	4.00	-6.610	3.84E-11*
10 min AI ^	77.38	4.88	76.33	6.17	95.10	3.49	94.83	4.50	-6.618	3.64E-11*
A Premed ^	74.74	4.16	74.00	5.33	92.22	3.69	91.83	3.58	-6.654	2.85E-11*
AInd ^	72.28	4.23	71.67	3.25	80.16	3.84	80.17	5.50	-5.753	8.76E-09*
AL ^	95.76	4.73	96.83	7.42	104.86	1.74	104.67	2.08	-6.465	1.02E-10*
AInt ^	96.61	4.53	97.50	6.17	104.90	1.75	104.83	2.08	-6.413	1.42E-10*
5 min AInt ^	77.79	5.61	78.00	8.25	85.07	3.50	84.67	5.50	-4.954	7.26E-07*
At P I	96.59	4.50	97.50	6.18	105.00	1.73	105.70	2.07	-6.403	1.43E-09*
Then every 15 min										
15 min ^	88.98	14.15	95.83	26.58	94.82	15.59	86.00	30.00	-1.885	0.059414
30 min ^	94.72	9.63	96.83	14.0	100.29	13.88	104.0	26.17	-1.760	0.07834
45 min ^	82.39	10.69	79.17	18.0	88.07	4.75	88.50	9.83	-2.448	0.01435*
60 min	75.19	6.02	73.83	7.42	87.22	4.13	87.33	5.50	-9.028	1.19E-12*
75 min	72.94	4.38	72.33	4.50	86.99	3.80	86.83	5.59	-13.28	3.09E-19*
90 min	72.08	4.42	72.33	6.92	87.53	3.96	87.67	4.92	-14.27	1.22E-20*
105 min ^	72.16	4.25	71.17	6.08	87.84	5.27	87.00	4.17	-6.613	3.77E-11*
120 min ^	71.28	3.50	71.00	5.42	88.58	2.69	88.83	3.92	-6.655	2.83E-11*
135 min ^	71.22	3.58	71.00	6.09	89.81	4.38	89.67	2.50	-6.656	2.81E-11*
150 min ^	71.63	4.39	71.67	6.42	89.41	2.11	89.00	2.08	-6.657	2.80E-11*
165 min ^	71.40	4.02	71.67	5.66	89.97	2.07	89.67	2.50	-6.658	2.77E-11*
180 min ^	71.41	4.45	71.33	5.84	90.40	2.46	89.83	4.00	-6.655	2.82E-11*
195 min ^	70.11	3.61	69.67	5.75	95.61	8.67	93.00	17.83	-6.655	2.83E-11*
210 min ^	70.68	4.18	70.50	6.08	97.76	9.11	94.67	18.33	-6.598	4.17E-11*
225 min ^	69.81	3.74	70.00	4.67	90.79	6.69	88.67	2.66	-6.598	4.18E-11*
240 min ^	70.12	4.54	70.67	6.42	89.17	1.84	89.00	2.50	-6.599	4.14E-11*
255 min ^	70.59	3.52	71.00	4.58	89.70	4.04	88.67	2.17	-6.359	2.03E-10*
270 min ^	70.01	3.26	69.33	5.33	89.26	2.15	89.00	2.17	-6.292	3.14E-10*
285 min ^	70.61	3.61	71.00	5.58	88.17	2.06	88.00	3.00	-6.172	6.75E-10*
300 min ^	70.85	3.50	70.33	4.42	87.95	2.19	88.67	3.58	-5.542	2.99E-08*
315 min	72.22	1.54	71.33	2.67	88.92	0.96	89.00	1.75	-17.858	1.01E-05*
A ext ^	99.42	3.33	99	5.33	102.02	2.59	101.67	4.08	-2.952	0.00316*
Then every 30 min for 4 hrs										

MAP	Group D				Group P				Unpaired t-test applied	
	Mean	SD (±)	Median	IQR	Mean	SD (±)	Median	IQR	t-value	p-value
30 min ^	84.27	2.91	83.67	3.41	95.74	3.71	95.33	3.84	-6.589	4.43E-11*
60 min ^	87.44	4.18	87.83	2.91	97.91	3.29	99.17	4.91	-6.418	1.38E-10*
90 min ^	90.82	6.48	91.33	7.5	97.73	3.02	97.17	4.08	-4.821	1.43E-06*
120 min ^	96.27	3.15	96.67	5.42	96.4	2.67	95.83	2.84	-0.451	0.651659
150 min ^	92.41	4.59	93.33	4.17	96.34	1.99	96.33	2.5	-4.284	1.84E-05*
180 min ^	90.72	5.46	93	4.17	96.66	2.2	97.33	3.17	-5.342	9.21E-08*
210 min ^	90.66	5.83	93.17	3.33	96.21	1.87	96.33	2.83	-5.335	9.57E-08*
240 min ^	92.07	6.52	93.33	1.83	96.61	1.88	97	2.67	-4.567	4.96E-06*

[Table/Fig-8]: Comparison of MAP between Group D and Group P.
^ Mann-Whitney test applied as data failed 'Normality' test, t-value replaced by Z-value
*- p-value significant (<0.05)

intraoperative; At extubation; 30 min. interval postoperatively for 4 hours; The incidents of haemodynamic changes which are outside the predetermined window were recorded.

RESULTS

The demographic data with respect to age, weight, duration of surgery and sex and ASA grade were comparable in both groups as shown in [Table/Fig-1,2] respectively.

The median (range) age in Group D was 39.5 (18-60) years and in Group P was 40 (18-60) years. By applying, Mann-Whitney test, (p =0.547): difference in the age was not significant.

The sex distribution in two groups was: in Group D out of 30 patients, 12 (40%) were females and 18 (60%) were males and in Group P out of 30 patients, 10 (33.3%) were females and 20 (66.7%) were males.

As shown in [Table/Fig-1], the median (range) duration of surgery in Group D was 300 minutes (240–315 min) and in Group P was 300 minutes (195-315 min). By applying, Mann-Whitney test, (p= 0.927): difference between duration of surgery was not significant. Thus, the two groups were comparable with respect to duration of surgery. [Table/Fig-2] shows the comparison of sex and ASA Grade between the groups, which was not significant.

The two groups were comparable with respect to diagnosis of patients as shown in [Table/Fig-3] and the difference was not significant by applying Pearson chi-square test (p=0.288).

Similarly, [Table/Fig-4] shows that the two groups were comparable with respect to type of surgery of patients and difference was not significant by applying Fishers-Exact test (p=0.137). The various haemodynamic parameters recorded were HR, SBP, DBP and MAP. These parameters were recorded preoperatively and then at five minutes interval during bolus (10 minute period) and first 10 minutes of infusion, after premedication, after induction, after laryngoscopy, at intubation, five minutes after intubation and at pin insertion. After that the parameters were recorded at 15 minutes interval during intraoperative period, at extubation and then at 30 minutes interval postoperatively for four hours.

As shown in [Table/Fig-5], at the time of pin insertion mean HR in Group D and in Group P was 80.00±5.10 bpm and 108.98±3.89 bpm, respectively. The mean HR was lower in Group D as compared to Group P and the difference was statistically significant (p-value=3.07E-31). Thus, the sympathetic response at the time of pin insertion was obtunded by dexmedetomidine as compared to placebo. Thus, the difference between the mean HR in Group D and Group P at various events viz., premedication, induction, laryngoscopy, intubation and pin insertion was statistically significant.

[Table/Fig-6] shows that the mean SBP at the time of pin insertion in Group D and in Group P was 123.10±5.44 mmHg and 140.80±3.53 mmHg respectively. The mean SBP was lower in Group D as compared to Group P and the difference was statistically significant (p-value = 2.79E-08). Thus, the sympathetic response at the time of pin insertion was obtunded by dexmedetomidine as compared to placebo. Thus, difference between the mean SBP in Group D and Group P at various events viz., premedication, induction, laryngoscopy, intubation and pin insertion was statistically significant. After extubation the mean SBP was noted at 30 minute intervals for four hours and it was significantly lower in Group D as compare to Group P throughout the postoperative period.

[Table/Fig-7] shows that after laryngoscopy the mean DBP in Group D and in Group P was 78.23±6.31 mmHg and 87.17±1.97 mmHg respectively. The mean DBP was lower in Group D as compared to Group P and the difference was statistically significant (p=6.21E-10). After extubation the mean DBP was noted at 30 minute intervals for four hours and it was significantly lower in Group D as compare to Group P throughout the postoperative period.

[Table/Fig-8] shows that, after five minute of intubation the mean MAP in Group D and in Group P was 77.79±5.61 mmHg and 85.07±3.50 mmHg. The mean MAP was lower in Group D as compared to Group P and the difference was statistically significant (p-value = 7.26E- 07). At extubation although there was rise in mean HR, SBP, DBP and MAP in both groups, the difference between the changes in these parameters at extubation was statistically significant. Thus the pressor response at extubation was also attenuated in Group D. On comparing the changes in mean HR, SBP, DBP and MAP between the two groups at various intervals the haemodynamic stability was observed in Group D.

DISCUSSION

Perioperative haemodynamic stability is one of the most important concepts of neuroanaesthesia [1]. During surgery, low arterial pressure predisposes patient to cerebral ischaemia, as auto regulation of the cerebral blood flow is often impaired near tumours and traumatized areas. On the other hand, abrupt rise in arterial pressure may cause cerebral oedema or bleeding in the operating field [3,4]. Haemodynamic stability is also, important for rapid and smooth recovery which is preferred for immediate neurological evaluation [2]. Talke P et al., studied, the haemodynamic and ad-renergic effects of perioperative dexmedetomidine infusion after vascular surgery [5]. They found that during emergence from anaesthesia, heart rate was slower with dexmedetomidine (73±11 bpm) than placebo (83±20 bpm) (p=0.006) and the percentage of time the heart rate was within the predetermined haemodynamic limits was more frequent with dexmedetomidine (p<0.05). So, they conclude that dexmedetomidine attenuates increases in heart rate during emergence from anaesthesia. In the present study at the time of extubation the mean HR in Group D and in Group P was 94.93±4.75 bpm and 108±5.56 bpm, respectively. The HR in Group

D was significantly lower as compared to Group P (p-value = 7.8E-11). Thus, observation in present study was in concurrence with above study. Tanskanen PE et al., studied 54 patients undergoing intracranial tumour surgery randomized to receive in a double-blind manner a continuous dexmedetomidine infusion (plasma target concentration 0.2 or 0.4 ng/ml) or placebo, beginning 20 minutes before anaesthesia and continuing until the start of skin closure [1]. They found that, the median percentage of time points when systolic blood pressure was within more or less than 20% of the intraoperative mean was 72, 77 and 85 in placebo, DEX-0.2 and DEX-0.4 groups, respectively ($p<0.01$), DEX-0.4 groups differed significantly from the other groups. Tachycardiac response to intubation is blunted with DEX ($p< 0.01$) as well as the hypertensive response to extubation ($p< 0.01$). The heart rate variability in DEX-0.4 group from placebo (93 vs. 82%, $p<0.01$) was statistically significant. So, they concluded, dexmedetomidine increased perioperative haemodynamic stability in patients undergoing brain tumour surgery. In the present study unlike above study dexmedetomidine blunted both tachycardia and hypertensive response to intubation and extubation as compared to placebo.

Bakhamees HS et al., studied 80 morbidly obese patients undergoing laparoscopic gastric bypass who were randomly assigned to one of two study groups [6]; Group D (40 patients) received dexmedetomidine (0.8 µg/kg bolus, then as infusion 0.4 µg/kg/hr) and Group P (40 patients) received normal saline (placebo) in the same volume and rate. dexmedetomidine showed significant decrease of intraoperative and postoperative mean blood pressure, heart rate. They concluded that, dexmedetomidine offers better control of intraoperative and postoperative haemodynamics. As in above study, in the present study there was significant decrease in MAP and HR in Dexmedetomidine group as compared to placebo. dexmedetomidine also offered better control of intraoperative and postoperative haemodynamics. Thus, results of present study are in concurrence with this study.

Bekker A et al., studied the effect of dexmedetomidine on perioperative haemodynamics in patients undergoing craniotomy [3]. In this study, 72 patients scheduled for elective craniotomy were randomly assigned to receive either sevoflurane-opioid or sevoflurane-opioid-dexmedetomidine anaesthesia. They concluded that intraoperative dexmedetomidine infusion was effective for blunting the increases in SBP perioperatively. In the present study dexmedetomidine obtunded the rise in SBP at the time of intubation, laryngoscopy, pin insertion and extubation as compared to placebo. Thus the observations in present study were in concurrence with above study.

Keniya VM et al., studied 60 patients scheduled for elective surgery of more than three hours into two groups [7]; one is the control group which received isoflurane-opioid and the other is study group which received isoflurane-opioid-dexmedetomidine anaesthesia. After tracheal intubation, maximal average increase was 8% in systolic and 11% in diastolic blood pressure in dexmedetomidine group, as compared to 40% and 25%, respectively, in the control group. Also, the average increase in heart rate was 7% and 21% in the dexmedetomidine and control groups, respectively. Hence they concluded that dexmedetomidine is effective in attenuating sympathoadrenal response to tracheal intubation. In the present study at the time of intubation the HR, SBP, DBP was significantly lower in dexmedetomidine group as compared to placebo. Thus, dexmedetomidine obtunded the haemodynamic response to intubation. Thus, observations in present study were in concurrence with above study.

Our study is limited by small sample size and lack of comparative data in humans.

CONCLUSION

Dexmedetomidine provided intraoperative haemodynamic stability. It attenuated the haemodynamic responses to laryngoscopy, intubation, at pin fixation and the emergence from anaesthesia. It has significant opioid and anaesthetic sparing effect. There was significantly faster recovery after extubation with dexmedetomidine. There were fewer incidences of hypotension and bradycardia observed with dexmedetomidine.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Sep 07, 2016**
Date of Peer Review: **Oct 10, 2016**
Date of Acceptance: **Nov 03, 2016**
Date of Publishing: **Jan 01, 2017**