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Effect of Ketamine and Dexmedetomidine as Adjuvant to Total Intravenous Anesthesia on Intraoperative Cranial Nerve Monitoring in the Patients Undergoing Posterior Fossa Craniotomies—A Randomized Quadruple Blind Placebo-Controlled Study

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Abstract

Objectives Total intravenous anesthesia (TIVA) is used during surgery with intraoperative neurophysiological monitoring. Addition of adjuvant may minimize suppression of potentials by reducing doses of propofol. We studied the effect of addition of ketamine or dexmedetomidine to propofol–fentanyl-based TIVA on corticobulbar motor evoked potential (CoMEP) in patients undergoing posterior fossa surgeries.

Materials and Methods Forty-two patients were assigned to three groups ($n = 14$ each), Group S—saline, Group D—dexmedetomidine (0.25 µg/kg/h), and Group K—ketamine (0.25 mg/kg/h). Patients received propofol and fentanyl infusions along with study drugs. CoMEPs were recorded from muscles innervated by cranial nerves bilaterally at predefined intervals ($T_{baseline}$, T_2, T_3, T_4, and T_5). Effect on amplitude and latency of CoMEPs was assessed.

Results A significant fall in CoMEP amplitude was observed across all analyzed muscles at time T_4 and T_5 in saline and dexmedetomidine group as compared with ketamine group, p-value less than 0.05. A significant increase in latency was observed at T4 and T5 among groups (p-value, D vs. K = 0.239, D vs. S = 0.123, and K vs. S = 0.001).

Keyword
Dexmedetomidine
- intraoperative neurophysiological monitoring
- motor evoked potential
- MEP amplitude
- MEP
- latency ketamine

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Conclusion Both ketamine and dexmedetomidine provide and allow effective recording of CoMEPs. Ketamine emerges as a better agent especially when prolonged surgical duration is expected as even propofol–fentanyl-based TIVA adversely affects CoMEPs when used for long duration.

Introduction

Intraoperative neurophysiological monitoring (IONM) has reduced the incidence of neural deficits significantly.[1] Corticobulbar motor evoked potentials (CoMEPs) are being extensively used to monitor the functional integrity of corticobulbar tracts from the cortex through the cranial motor nuclei and to the muscle innervated by the cranial nerves.[2]

Anesthetic agents alter the neural function by causing a dose-dependent depression in synaptic activity, leading to inconsistent recordings.[3] Research has established propofol and opioid-based total intravenous anesthesia (TIVA) as the anesthetic technique of choice when IONM is employed during surgery.[4–6] However, larger doses and prolonged use of propofol can also have adverse effect on the CoMEPs.[6–9] They are also associated with side effects such as delayed awakening, propofol infusion syndrome, and postoperative respiratory depression.[8] Addition of adjuvants such as dexmedetomidine and ketamine during transcranial motor evoked potential (MEP) monitoring in spinal surgeries has proven effective in improving patient outcome. It has also helped in reducing the total dose of propofol and opioid required.[4,10] To the best of our knowledge, no study has evaluated the effects of addition of ketamine or dexmedetomidine on CoMEPs during intracranial surgeries.

The purpose of our study was to determine the effect produced on CoMEP recordings by addition of subanesthetic doses of ketamine (0.25 mg/kg/h) and dexmedetomidine (0.25 µg/kg/h) to propofol–opioid-based TIVA in patients undergoing elective posterior fossa surgeries.

Materials and Methods

This prospective, randomized, quadruple-blind placebo-controlled study was conducted at a tertiary care hospital in India, over a period of 18 months (September 2019–February 2021). The study was approved by the institutional ethics committee (ECR/736/Inst/UK/2015/RR-18) and was registered with Clinical Trials Registry India (CTRI/2019/08/020817) before patient enrollment. This study was conducted according to ethical principles of the Declaration of Helsinki (2013) and followed good clinical practice guidelines.

Patients aged 18 to 60 years, American Society of Anesthesiologists I to III with Glasgow coma scale (GCS) 13 to 15, planned for elective posterior fossa surgery with neuromonitoring were included for study. Patients who refused consent, had preoperative cranial nerve involvement in the form of paresis or palsy (except seventh and eighth nerves), presence of significant cardiovascular, pulmonary, renal or hepatic disease, and with known allergy to study drugs were excluded from the study. A total of 47 patients were evaluated and 42 were eventually included in the study (►**Fig. 1**). Written informed consent was obtained from all participants or from the next of kin if patient's GCS was less than 15.

Participating patients were randomly allocated to one of three study groups by using computer-generated random sequence: one receiving dexmedetomidine infusion (4 µg/mL) 0.25 µg/kg/h (Group D), one receiving ketamine infusion (4 mg/mL) 0.25 mg/kg/h (Group K), and one receiving saline infusion 0.05 mL/kg/h or equivalent infusion rate (Group S).

Patients, principal investigator, surgeon, and the statistician were blinded to group allocation. Blinding was ensured by using opaque sealed envelopes which were opened on day of surgery by the anesthesiologist, who was not a part of the study. To achieve blinding during the surgery, drugs were prepared as infusate with normal saline in 50 mL syringe and labeled as study drug. Study drug infusion rates were calculated and started by an anesthesiologist who prepared the drugs and was not a part of the study.

Once the patient was shifted to operating room, standard monitors were attached, and a peripheral venous cannulation was established. Anesthesia was induced with intravenous (IV) fentanyl (2 µg/kg) and propofol titrated to loss of verbal response. Vecuronium (0.1 mg/kg) was given to facilitate tracheal intubation. Arterial line was inserted for continuous blood pressure monitoring and serial blood gas measurements. Bispectral index (BIS) electrodes and axillary surface temperature probe was placed for depth of anesthesia and temperature monitoring, respectively.

Mechanical ventilation was carried out at fresh gas flow of 1 L/min with 50% mixture of oxygen and air. End-tidal carbon dioxide was maintained between 30 and 35 mm Hg and partial pressure of carbon dioxide between 35 and 38 mm Hg. TIVA with target controlled infusion (TCI) of propofol 2 to 5 µg/mL (effect site concentration) and fentanyl (1–2 µg/kg/h) was initiated immediately after intubation. Study drug as per randomization was also started simultaneously with propofol and fentanyl. TIVA was titrated to achieve BIS values between 40 and 60 throughout the surgery. Neuromuscular blockade monitoring was done by train of four stimulation of the ulnar nerve at wrist. Once the train of four count reached 4, no further neuromuscular blockade was administered for the remaining duration of surgery.

NIM-Eclipse (Medtronic) neurophysiologic monitoring system was used. Sterile stimulating and recording electrodes were placed after induction. Recording electrodes were placed bilaterally in masseter, orbicularis oculi, mentalis, stylopharyngeus, trapezius, and tongue muscles as they reflect the motor components of cranial nerves V, VII, IX, XI, and XII, respectively. MEPs from bilateral abductor pollicis

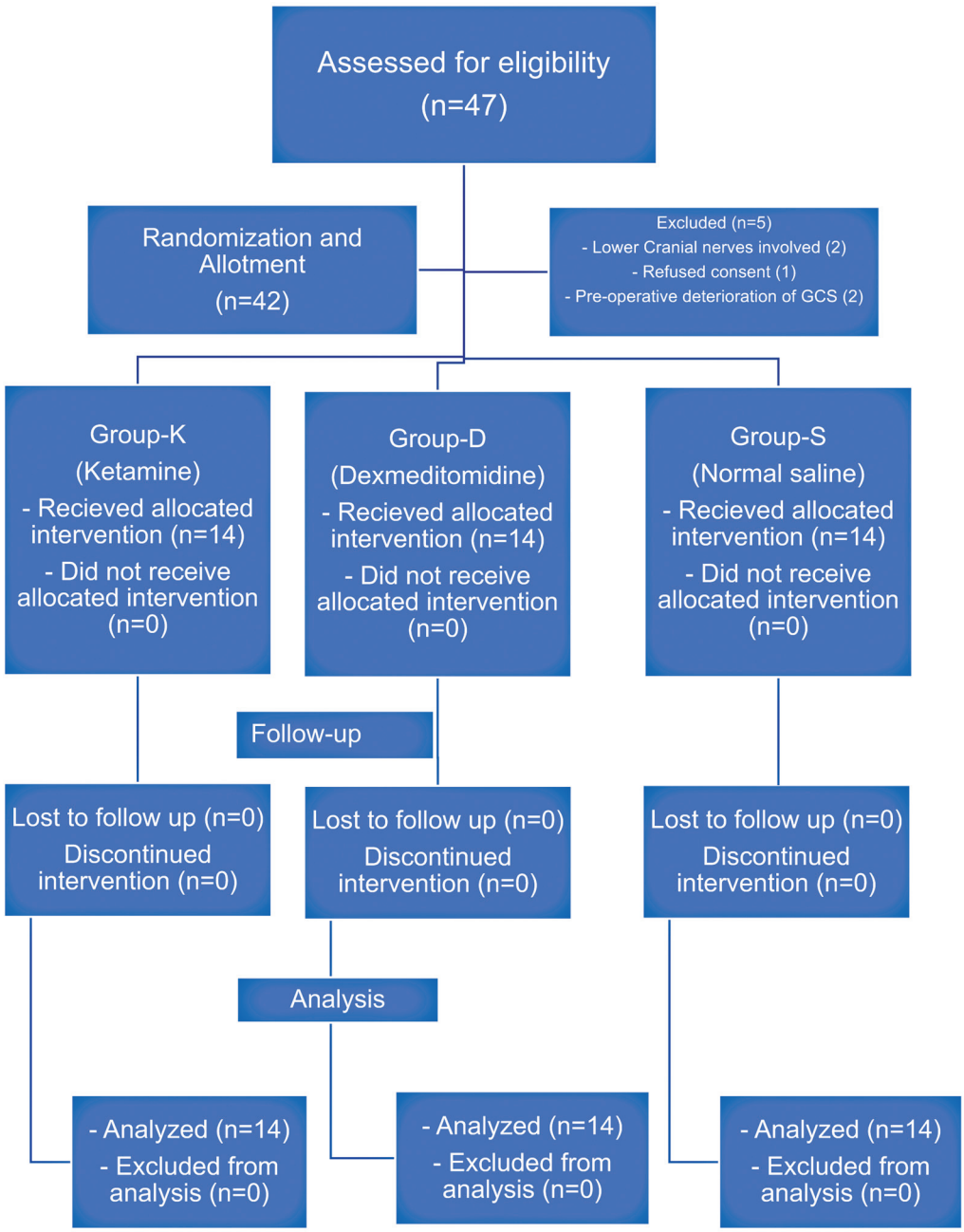

Fig. 1 CONSORT flow diagram .

brevis and tibialis anterior muscles acted as controls. Stimulating "corkscrew" electrodes were inserted at C3 and C4 sites (international 10–20 system). Stimulation parameters used included: a short train consisting of one to three stimuli each with duration of 0.5 milliseconds, separated by an interstimulus interval of 2 milliseconds, and with a train repetition rate of 2 Hz and intensity typically ranging between 200 and 300 V. Free running electromyographies (EMGs) were recorded continuously throughout the procedure. Triggered EMGs were recorded by sterile handheld stimulating mono- or bipolar electrode used by the surgeon during tumor dissection.

Once TOF count reached 4, baseline recording of CoMEP was done ($T_{baseline}$). The latency (defined as the measure of time taken for intracortical processing, corticofugal conduction, spinal processing, and neuromuscular transmission) was measured by the NIM-Eclipse monitoring system 100 milliseconds before the stimulus artifact. The amplitude (defined as the distance from a negative peak to a positive peak in the waveform) was calculated as the voltage difference between the maximum positive and maximum negative peak and expressed in millivolt.[11] Subsequent readings were taken at 15 minutes interval for next 60 minutes, and their average was defined as time T_2. Next set of reading was obtained once the tumor dissection began and recorded for every 15 minutes over next 120 minutes and averaged as time T_3. Two more readings were taken namely at hemostasis (T_4) and dural closure (T_5). Stimulation was started with

lower voltage and increased till appropriate response was acquired but never increased beyond 300 V.

Once dura was opened, surgeon was asked to comment upon the brain relaxation and, graded as 1—perfectly relaxed, 2—satisfactorily relaxed, 3—firm brain, and 4—bulging brain.[12] As soon as dural closure was started, study drug infusion was stopped. Decision to extubate the patient at the end of surgery depended on preoperative condition of patient and intraoperative events, and it was at discretion of the attending anesthesiologist. If extubation was planned, remaining infusions were also stopped at the time of skin closure. Total amount of propofol and fentanyl consumed throughout the procedure was recorded. If the patient was extubated immediately postsurgery, then time taken for eye opening, extubation, following of verbal commands, and postoperative pain was also assessed. The presence of any emergence reaction was documented. The complications including hemodynamic instabilities (such as bradycardia—heart rate < 45 beats/min managed with inj. atropine 0.6 mg IV, hypotension—mean arterial pressure (MAP) less than 60 mm Hg managed with inj. mephentermine 3 mg IV bolus and hypertension MAP more than 100 mm Hg managed with inj. labetalol 5 mg IV bolus) and respiratory compromise were noted. Postoperative examination of patients was done to assess the development of new deficit or worsening of preexisting deficit of cranial nerves.

Statistical Analysis

Sample size was calculated using G power version 3.1.9.2 based on a pilot study conducted by us, which showed that mean and standard deviation (SD) of CoMEP with ketamine was 969.4 ± 18.03 µV, dexmedetomidine was 943.81 ± 24.73 µV, and that for saline group was 950.2 ± 12.55 µV. Thus, a total of 14 patients per group were required to demonstrate a difference between ketamine, dexmedetomidine, and saline with a statistical power of 0.8 and type 1 error rate of 0.05 (adjusted for comparison of three groups). Data were analyzed with SPSS software version 21.0. Categorical variables were presented as number and percentage, and quantitative data with normal distribution were presented as the means $\pm$ SD and the data with nonnormal distribution as median with 25th and 75th percentiles (interquartile range). Kolmogorov–Smirnov's test was used to check data normality. The variables which were quantitative and not normally distributed in nature were analyzed using Mann–Whitney's test (for two groups) and Kruskal–Wallis' test (for more than two groups), and variables which were quantitative and normally distributed in nature were analyzed using analysis of variance. To check homogeneity of variance, Levene's test was used. To check the robustness of homogeneity of variance, Brown–Forsythe's test was used if p-value for Levene's test was less than 0.05 and post hoc comparison was done using Bonferroni correction. Paired t test was used for comparison across follow-up. Independent t test was used for comparison between the two groups. Comparison of the variables which were qualitative in nature were analyzed using chi-square test. If any cell had an expected value of less than 5, then Fisher's exact test was used. A p-value of less than 0.05 was considered statistically significant.

Results

During the study period, a total of 42 patients were randomly assigned using computer-generated random number table to one of the three study groups. All 42 patients completed the study and were analyzed at study completion (►**Fig. 1**).

Study patients had comparable demographic variables and baseline parameters (►**Table 1**). Various tumors included in our study were cerebellopontine angle tumors ($n = 23$), fourth ventricular tumor ($n = 7$), brain stem cavernoma ($n = 1$), foramen magnum meningioma ($n = 3$), pineal region tumor ($n = 6$), and petroclival meningioma ($n = 2$). Mean propofol and fentanyl consumption was significantly higher in Group S as compared with Groups K and D ($p = 0.012$), while it was comparable between Groups K and D (►**Table 1**).

CoMEP Amplitude and Latency

The latencies for all the muscle groups increased significantly in the patients of Group S as compared with Groups K and D. The difference was statistically insignificant between Groups D and K ($p = 0.239$) and Groups D and S ($p = 0.123$), while it was statistically significant for Groups K and S ($p = 0.001$). Latencies started increasing from time T_3 onward in the saline group. ►**Table 2** represents the latencies of all the muscle groups.

The amplitudes taken at Tbaseline were comparable across all muscles among three groups (►**Table 3**). Significant fall in amplitude was seen in Groups D and S across all muscle groups at time T_4 and T_5 ($p < 0.05$), while it remained close to the baseline in Group K. Groups D and S patients had significant fall in amplitude from time T_3 onward in masseter, stylopharyngeus, and trapezius muscle group. ►**Table 3** also represents the post hoc analysis which revealed significant fall in amplitude across all muscles in Group S as compared with Group K ($p < 0.05$) at times T_4 and T_5. Among Groups D and K, a greater fall is seen in Group D and the effect is statistically significant for five out of eight muscles (►**Table 3**). Among Groups D and S, greater fall is seen in Group S, and the result is statistically significant for four muscles.

Baseline values of heart rate, MAP, and BIS were comparable among the groups. After 40 minutes of starting of TIVA, heart rates were found to be significantly lower in patients receiving dexmedetomidine as the study drug ($p = 0.021$). New-onset deficit was found in 1 out of 14 patients in Group K, 3 out of 14 in Group D, and 7 out of 14 in Group S ($p = 0.045$). In Group K, one patient developed sixth and seventh nerve palsies, while in Group D, two patients developed ninth nerve paresis, one had ninth nerve palsy, and in Group S, three patients developed ninth nerve paresis, two patients developed seventh nerve paresis, and one patient developed complete seventh nerve palsy. Post hoc analysis revealed a significant difference between Groups K and S ($p = 0.033$), while there was no significant difference between Groups D and S ($p = 0.236$) and Groups D and K ($p = 0.596$).

Table 1 Comparison of sociodemographic, baseline characteristics, and surgical and anesthetic variables between ketamine, dexmedetomidine, and saline

Sociodemographic and baseline characteristics	Group K (ketamine) ($n = 14$)	Group D (dexmedetomidine) ($n = 14$)	Group S (saline) ($n = 14$)	*p*-Value
Age (y)				
≤ 20	2 (14.29%)	3 (21.43%)	1 (7.14%)	0.522 K vs. D: 0.670 K vs. S: 0.670 D vs. S: 0.305
21–30	2 (14.29%)	5 (35.71%)	5 (35.71%)	
31–40	6 (42.86%)	4 (28.57%)	3 (21.43%)	
41–50	3 (21.43%)	1 (7.14%)	1 (7.14%)	
> 50	1 (7.14%)	1 (7.14%)	4 (28.57%)	
Gender				
Female	8 (57.14%)	5 (35.71%)	7 (50%)	0.513 K vs. D: 0.256 K vs. S: 0.445 D vs. S: 0.705
Male	6 (42.86%)	9 (64.29%)	7 (50%)	
Preoperative Glasgow coma scale				
13	1 (7.14%)	1 (7.14%)	0 (0%)	1 K vs. D: 1 K vs. S: 1 D vs. S: 1
14	1 (7.14%)	0 (0%)	1 (7.14%)	
15	12 (85.71%)	13 (92.86%)	13 (92.86%)	
Preoperative cranial nerve deficit (in form of paresis or palsy)				
Absent	4 (28.57%)	8 (57.14%)	4 (28.57%)	0.199 K vs. D: 0.252 K vs. S: 0.252 D vs. S: 1
Present	10 (71.43%)	6 (42.86%)	10 (71.43%)	
American Society of Anesthesiologists status				
I	12 (85.71%)	12 (85.71%)	9 (64.29%)	0.446 K vs. D: 1 K vs. S: 0.385 D vs. S: 0.385
II	2 (14.29%)	2 (14.29%)	5 (35.71%)	
Surgery duration (h)				
Mean $\pm$ SD	7.24 ± 2.32	7.01 ± 2.83	7.97 ± 2.22	0.564 K vs. D: 1 K vs. S: 0.924 D vs. S: 1
Anesthesia duration (h)				
Mean $\pm$ SD	8.75 ± 2.45	8.33 ± 3.03	9.38 ± 2.29	0.564 K vs. D: 1 K vs. S: 0.924 D vs. S: 1
Intraoperative drug consumption (mean $\pm$ SD)				
Propofol (mg)	$3,814.29 \pm 1,237.15$	$3,907.14 \pm 1,099.28$	$5,178.57 \pm 1,482.29$	0.012 K vs. D: 1 K vs. S: 0.023 D vs. S: 0.037
Fentanyl (μg)	553.93 ± 202.01	543.57 ± 241.87	875 ± 275.09	0.0008 K vs. D: 1 K vs. S: 0.002 D vs. S: 0.003

Abbreviation: SD, standard deviation.

Table 2 Comparison of mean latencies of muscle groups

Latency (ms)	Time	Group K (ketamine) ($n = 14$)	Group D (dexmedetomidine) ($n = 14$)	Group S (saline) ($n = 14$)	*p*-Value[a]
Right masseter	$T_{baseline}$	13.17 ± 0.66	13.28 ± 0.93	12.69 ± 0.88	0.145
	T_2	13.34 ± 0.74	13.28 ± 0.89	13.01 ± 0.66	0.491
	T_3	13.26 ± 1	13.36 ± 0.87	14.04 ± 0.77	0.051
	T_4	13.04 ± 1.08	13.65 ± 0.83	14.37 ± 0.77	0.001
	T_5	12.94 ± 1.23	13.71 ± 0.82	14.38 ± 0.77	0.001
Left masseter	$T_{baseline}$	12.94 ± 0.5	12.91 ± 0.65	12.46 ± 0.9	0.147
	T_2	12.73 ± 0.63	13.02 ± 0.65	12.88 ± 0.64	0.505
	T_3	12.88 ± 0.66	13.38 ± 0.65	13.84 ± 0.92	0.006
	T_4	13.01 ± 0.73	13.72 ± 0.62	14.24 ± 1.06	0.001
	T_5	13 ± 0.72	13.72 ± 0.68	14.17 ± 1.07	0.002
Left oculi	$T_{baseline}$	13.28 ± 0.84	13.22 ± 0.91	13.43 ± 0.93	0.818
	T_2	13.05 ± 0.81	13.37 ± 0.94	13.67 ± 0.91	0.196
	T_3	13.17 ± 0.86	13.55 ± 0.95	14.49 ± 0.99	0.001
	T_4	13.09 ± 0.82	13.66 ± 0.95	15.15 ± 0.99	< 0.0001
	T_5	13.22 ± 0.9	13.81 ± 1.01	15.2 ± 0.95	< 0.0001
Left mentalis	$T_{baseline}$	13.4 ± 0.8	13.3 ± 0.98	13.61 ± 0.99	0.658
	T_2	13.1 ± 0.83	13.38 ± 0.96	13.87 ± 1.05	0.103
	T_3	13.2 ± 0.86	13.57 ± 0.94	14.54 ± 1.05	0.001
	T_4	13.11 ± 0.91	13.59 ± 1.03	14.64 ± 1.13	0.001
	T_5	13.14 ± 0.89	13.66 ± 0.95	14.76 ± 1.11	0.0003
Right soft palate	$T_{baseline}$	13.84 ± 0.79	13.81 ± 0.84	13.82 ± 0.64	0.85
	T_2	14.8 ± 0.78	13.86 ± 0.87	14.05 ± 0.87	0.012
	T_3	14.9 ± 0.83	14 ± 0.87	14.9 ± 1.04	0.018
	T_4	14.94 ± 0.91	14.12 ± 0.89	15.2 ± 1.13	0.016
	T_5	15.01 ± 0.87	14.14 ± 0.9	15.26 ± 1.1	0.009
Left soft palate	$T_{baseline}$	14.01 ± 0.81	13.69 ± 0.88	13.91 ± 0.59	0.579
	T_2	14.8 ± 0.8	13.83 ± 0.87	14.27 ± 0.98	0.021
	T_3	14.92 ± 0.88	13.98 ± 0.9	15.15 ± 1.25	0.010
	T_4	14.92 ± 0.91	13.99 ± 0.92	15.5 ± 1.29	0.002
	T_5	15.01 ± 0.86	14.02 ± 0.84	15.46 ± 1.38	0.002
Right trapezius	$T_{baseline}$	14.85 ± 0.72	15.09 ± 0.59	14.57 ± 0.55	0.78
	T_2	15.83 ± 0.65	15.13 ± 0.59	15.37 ± 0.8	0.030
	T_3	15.84 ± 0.69	15.27 ± 0.54	16.99 ± 1.17	< 0.0001
	T_4	15.9 ± 0.73	15.28 ± 0.64	17.3 ± 1.23	< 0.0001
	T_5	15.92 ± 0.68	15.38 ± 0.49	17.35 ± 1.23	< 0.0001
Left trapezius	$T_{baseline}$	15.08 ± 0.64	15.07 ± 0.55	14.41 ± 0.46	0.12
	T_2	15.81 ± 0.65	15.12 ± 0.58	15.25 ± 0.82	0.026
	T_3	15.83 ± 0.68	15.26 ± 0.55	17.04 ± 1.1	< 0.0001
	T_4	15.89 ± 0.73	15.46 ± 0.56	17.4 ± 1.2	< 0.0001
	T_5	15.93 ± 0.73	15.34 ± 0.53	17.53 ± 1.06	< 0.0001

[a]Data are represented as mean ± standard deviation, *p*-values were calculated using analysis of variance.

Table 3 Comparison of CoMEP amplitude(μV) of various muscle groups

Amplitude (μV)	Time	Group K (ketamine) ($n = 14$)	Group D (dexmedetomidine) ($n = 14$)	Group S (saline) ($n = 14$)	*p*-Value[a]
Right masseter	$T_{baseline}$	948.07 ± 41.60	961.61 ± 61.42	961.5 ± 44.56	0.723
	T_2	952.35 ± 41.88	955.71 ± 59.13	962.28 ± 40.84	0.857
	T_3	954.42 ± 44.43	946.92 ± 61.69	931.5 ± 51.45	0.512
	T_4	960.92 ± 14.61	929 ± 61.16	898.78 ± 48.208	0.0037 K vs. D: 0.16 K vs. S: 0.0025 D vs. S: 0.2008
	T_5	963.35 ± 14.09	928 ± 62.32	893 ± 57.66	0.002 K vs. D: 0.15 K vs. S: 0.0016 D vs. S: 0.162
Left masseter	$T_{baseline}$	959.86 ± 18.6	970.86 ± 16.31	982.21 ± 32.08	0.51
	T_2	958.73 ± 17.33	963.89 ± 12.18	981.2 ± 26.44	0.011 K vs. D: 1 K vs. S: 0.013 D vs. S: 0.073
	T_3	962.23 ± 15.57	953.09 ± 13.36	918.09 ± 34.97	0.0001 K vs. D: 0.924 K vs. S: < 0.0001 D vs. S: 0.001
	T_4	957.71 ± 19.05	951.29 ± 16.48	913.57 ± 37.11	0.0001 K vs. D: 1 K vs. S: 0.0002 D vs. S: 0.001
	T_5	957.86 ± 18.63	950.93 ± 14.74	914.5 ± 33.69	0.0001 K vs. D: 1 K vs. S: 0.0001 D vs. S: 0.001
Right oculi	$T_{baseline}$	952.92 ± 23.29	938.14 ± 52.31	950.07 ± 43.98	0.61
	T_2	949.28 ± 25.51	933.5 ± 50.402	945.14 ± 47.68	0.601
	T_3	950.42 ± 25.36	933.28 ± 56.48	918.21 ± 48.81	0.186
	T_4	952.5 ± 27.205	929.5 ± 52.54	881.5 ± 48.17	0.0004 K vs. D: 0.36 K vs. S: 0.0003 D vs. S: 0.017
	T_5	949.5 ± 27.49	928 ± 55.22	881.5 ± 48.12	0.001 K vs. D: 0.42 K vs. S: 0.00083 D vs. S: 0.025
Left occuli	$T_{baseline}$	964.42 ± 16.51	962.57 ± 35.34	954 ± 33.79	0.617
	T_2	959.5 ± 16.78	955 ± 32.27	955.5 ± 32.24	0.902
	T_3	962.57 ± 13.44	949.35 ± 34.60	942.64 ± 31.24	0.173
	T_4	969.35 ± 10.13	939.78 ± 33	918 ± 34.46	0.0001 K vs. D: 0.02 K vs. S: 0.00006 D vs. S: 0.11
	T_5	974 ± 12.01	938.71 ± 43.92	917 ± 36.39	0.0002 K vs. D: 0.02 K vs. S: 0.00018 D vs. S: 0.21
Right soft palate	$T_{baseline}$	991.07 ± 23.65	980.14 ± 23.08	963.21 ± 44.45	0.08
	T_2	984 ± 20.29	974.92 ± 21.43	965.42 ± 45.51	0.303
	T_3	992.92 ± 20.28	970.07 ± 13.72	941.5 ± 53.53	

(*Continued*)

Table 3 (*Continued*)

Amplitude (μV)	Time	Group K (ketamine) ($n = 14$)	Group D (dexmedetomidine) ($n = 14$)	Group S (saline) ($n = 14$)	*p*-Value[a]
					0.0011 K vs. D: 0.18 K vs. S: 0.00078 D vs. S: 0.07
	T_4	990.92 ± 17.49	959.07 ± 14.20	917 ± 54.001	< 0.0001 K vs. D: 0.04 K vs. S: 0.00001 D vs. S: 0.005
	T_5	990.42 ± 19.13	957.78 ± 15.68	914 ± 48.31	< 0.00001 K vs. D: 0.02 K vs. S: 0.00001 D vs. S: 0.001
Left soft palate	$T_{baseline}$	985.78 ± 16.95	978.64 ± 15.33	1002 ± 43.21	0.093
	T_2	979.92 ± 17.45	972.78 ± 13.52	996.42 ± 39.32	0.059
	T_3	991.92 ± 19.44	966 ± 15.66	966.1 ± 35.72	0.01 K vs. D: 0.02 K vs. S: 0.02 D vs. S: 0.99
	T_4	986.14 ± 15.44	958.78 ± 13.68	942.21 ± 24.18	< 0.00001 K vs. D: 0.0009 K vs. S: < 0.000001 D vs. S: 0.056
	T_5	987.85 ± 14.75	952.42 ± 15.28	936.07 ± 21.93	< 0.00001 K vs. D: 0.00001 K vs. S: < 0.000001 D vs. S: 0.04
Right trapezius	$T_{baseline}$	1,173.36 ± 100.58	1,194.64 ± 139.02	1,270.14 ± 130.57	0.11
	T_2	1,168.86 ± 99.69	1,121.84 ± 133.47	1,222.46 ± 126.2	0.10
	T_3	1,166.94 ± 100.41	1,085.42 ± 99.16	1,009.07 ± 75.36	0.0003 K vs. D: 0.074 K vs. S: 0.0002 D vs. S: 0.104
	T_4	1,165.64 ± 103.23	1,081.14 ± 117.82	978.57 ± 54.29	< 0.0001 K vs. D: 0.074 K vs. S: < 0.0001 D vs. S: 0.022
	T_5	1,164.57 ± 103.14	1,078.64 ± 66.01	973.86 ± 43.71	< 0.0001 K vs. D: 0.013 K vs. S: < 0.0001 D vs. S: 0.002
Left trapezius	$T_{baseline}$	1,166.93 ± 95.48	1,186.71 ± 117.78	1,249 ± 128.97	0.156
	T_2	1,169.73 ± 97.06	1,120.59 ± 128.48	1,183.45 ± 111.52	0.313
	T_3	1,168.82 ± 98.62	1,087.19 ± 100.3	1,004.64 ± 77.83	0.0002 K vs. D: 0.076 K vs. S: 0.0001 D vs. S: 0.071
	T_4	1,168.93 ± 99.73	1,074.93 ± 84.81	987.57 ± 84.03	< 0.0001 K vs. D: 0.026 K vs. S: < 0.0001 D vs. S: 0.042
	T_5	1,166.29 ± 98.43	1,073.93 ± 105.21	987.57 ± 80.89	0.0001 K vs. D: 0.043 K vs. S: < 0.0001 D vs. S: 0.065

Abbreviation: CoMEP, corticobulbar motor evoked potential.
[a]Data are represented as mean ± standard deviation, *p*-values were calculated using analysis of variance.

Discussion

We were able to obtain sustained and reliable MEPs in all three groups in our study. Amplitudes and latency were largely maintained close to baseline in Group K, while amplitude decreased, and latency increased significantly in Groups S and D. The decrease in amplitude and increase in latency was more profound in Group S as compared with Group D. Anesthetic agents have been reported to affect evoked potentials in variable manner. Since MEPs are generated through a polysynaptic pathway, they are very sensitive to the effect of anesthesia and muscle relaxant.

Lam et al reported no significant difference in repeated amplitude measurement during spinal surgery between ketamine (0.5 mg/kg loading followed by 0.2–0.5 mg/kg/h infusion) and dexmedetomidine (0.1–0.4 µg/k/h infusion) in their retrospective analysis on 35 adult patients.[13] In our study, intragroup analysis revealed that amplitude values for Groups D and S decreased significantly from baseline. In Group K, MEP amplitudes were maintained more or less similar to the baseline values. This difference in effect may be attributed to use of subanesthetic dose of ketamine in our study (0.25 mg/kg/h) as opposed to higher doses used by Lam et al.

Rozet et al found consistent and reliable recording of MEPs with 0.6 µg/kg/h dexmedetomidine.[14] Li et al evaluated the effect of the addition of dexmedetomidine (0.5 µg/kg over 10 minutes followed by 0.5 µg/kg/h) to the propofol–remifentanil target-controlled infusion regime on MEPs and found no significant changes in the amplitude and latency on intergroup and intragroup analyses.[15] In contrast, our study revealed that the MEPs decreased in both Groups S and D, but the decrease in Group S was more than Group D (►**Table 3**). Difference in outcome can be explained by the fact that our patients had longer surgical and anesthetic duration, we used a lower rate of infusion of dexmedetomidine, and no loading dose was given.

On post hoc analysis, we observed that the amplitudes decreased slightly in ketamine group as well. In contrast, available literature which reports increase in amplitude with ketamine. This finding was explained when we performed intergroup analysis between Groups S and K and realized that the amplitude decrease in Group S was significantly more than that in Group K. Propofol infusion is stated as a reason for the dose-dependent decrease in amplitude by several researchers, especially when used for longer duration.[7,9,15] This is very clearly evident from our study as well. The effect of propofol on amplitude was decreased by the amplitude augmenting effect of ketamine in Group K and thus explains the huge difference in amplitudes among the three groups. Ubags et al have documented similar nonsignificant improvement in amplitude after 0.5 mg/kg IV bolus dose of ketamine during etomidate/opioid/N_2O/partial neuromuscular blockade-based anesthesia.[16] Sihle-Wissel et al in their study concluded that ketamine (1 mg/kg/h) diminishes the depressing effect of propofol on MEPs.[17]

A significant number of patients from Group S ($n = 7$) developed either a new deficit or worsening of preoperative deficit. This can be attributed to the higher requirements of propofol and fentanyl in this group which may have confounded the effect of surgery on intraoperative MEP recordings, though in no muscle group was the recorded potential less than 50% of baseline at any time point during monitoring.

Our study had a few limitations including lack of use of TCI for fentanyl infusion, and it was not targeted by any pain index. In our study, we only assessed effect on MEP, and this result cannot be generalized on other modalities of neuromonitoring.

Conclusion

In conclusion, intraoperative infusion of subanesthetic doses of ketamine and dexmedetomidine as adjunct to propofol–fentanyl-based TIVA provides good conditions for intraoperative neuromonitoring. Ketamine attenuates the dose depressant effect of propofol on CoMEPs and provides recordings comparable to baseline. Though dexmedetomidine also produces depressant effect on CoMEP, depression of amplitude is significantly less than that produced by use of propofol alone. Even though ketamine produces good conditions for IONM, its effect on brain relaxation and postoperative delirium/disorientation cannot be disregarded and a further study to determine the optimal dose is necessitated.

Ethical Approval

This study was approved by the university's ethical review committee under the ID: ECR/736/Inst/UK/2015/RR-18, 09/08/2019. The Clinical Trials Registry India ID is CTRI/2019/08/020817

Note

This paper was presented orally at SNACC-2021 (Virtual mode). The study confirms to the Declaration of Helsinki .

Authors' contribution

S.P. and P.G. have given substantial contributions to the conception and the design of the manuscript. S.P. has worked toward acquisition, analysis and interpretation of the data. All authors have participated to drafting the manuscript, P.G. revised it critically. A.K. and K.B. have provided critical input to the drafting of manuscript. All the authors have read and approved the final version of the manuscript.

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Conflict of Interest

None declared.

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