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A study on comparison of extubation quality scale between fentanyl and dexmedetomidine

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Abstract
Dexmedetomidine does not appear to have any direct effects on the heart. A biphasic cardiovascular response has been described after the application of dexmedetomidine. The administration of a bolus of 1μg/kg dexmedetomidine initially results in a transient increase of the blood pressure and a reflex decrease in heart rate, especially in younger, healthy patients. The initial reaction can be explained by the peripheral α_{2B}-adrenoceptor stimulation of vascular smooth muscle and can be attenuated by a slow infusion over 10 or more minutes. Patients were randomly allotted to each of study group, based on a computer generated random number table using Microsoft excel. 150 patients with 50 in each group of ASA (American Society of Anaesthesiologists) physical status I & II patients aged between 18-55 years undergoing elective surgical procedures, lasting between 1 and ½ hour to 4 hour, under general anesthesia requiring endotracheal intubation were enrolled for study. There was statistically significant (p<0.001) differences among group A, B & C with respect to extubation quality scale and also there was clinically significant difference among the three groups. Extubation quality was superior in decreasing order in group C (Dexmedetomidine); group B (Fentanyl) and group a (control group). Group C had best extubation quality, while group A had relatively poor extubation quality.

Keywords: Extubation quality scale, fentanyl, dexmedetomidine

Introduction
Fentanyl decreases cerebral drive of respiration. Upper airway, trachea and the lower respiratory reflexes are blunted. It blunts pulmonary vasoconstriction in response to tracheobronchial stimulation. It also inhibits pontine and medullary respiratory centers regulating respiratory rhythmicity resulting in increased respiratory pause, delayed expiration, irregular and or periodic breathing. Tidal volume, inspiratory flow and occlusion pressures are decreased. There may be secondary peak and respiratory depression**.** Fentanyl should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration [1].
Fentanyl brings haemodynamic stability during perioperative period by its action on the cardiovascular and autonomic regulatory areas. It decreases sympathetic tone and increase parasympathetic tone. There is no change in myocardial contractility. AV node conduction is slowed with prolongation of RR interval, AV node refractory period and action potential of purkinje fibers. There is no effect on coronary circulation. Fentanyl should be used with caution in patients with cardiac bradyarrhythmias [2].
Dexmedetomidine, an imidazole compound, is the pharmacologically active dextroisomer of medetomidine that displays specific and selective α_2-adrenoceptor agonism. Activation of the receptors in the brain and spinal cord inhibits neuronal firing, causing hypotension, bradycardia, sedation, and analgesia. The responses to activation of the receptors in other areas include decreased salivation, decreased secretion, and decreased bowel motility in the gastrointestinal tract; contraction of vascular and other smooth muscle; inhibition of renin release, increased glomerular filtration, and increased secretion of sodium and water in the kidney; decreased intraocular pressure; and decreased insulin release from the pancreas [3].
In general, presynaptic activation of the α_2.adrenoceptor inhibits the release of norepinephrine, terminating the propagation of pain signals. Postsynaptic activation of α_2 adrenoceptors in the central nervous system (CNS) inhibits sympathetic activity and thus can decrease blood pressure and heart rate. Combined, these effects can produce analgesia, sedation, and anxiolysis.

Dexmedetomidine combines all these effects, thus avoiding some of the side effects of multi-agent therapies.
The baroreceptor reflex is well preserved in patients who receive dexmedetomidine, and the reflex heart rate response to a pressor stimulus is augmented [4].
Dexmedetomidine does not appear to have any direct effects on the heart. A biphasic cardiovascular response has been described after the application of dexmedetomidine. The administration of a bolus of 1μg/kg dexmedetomidine initially results in a transient increase of the blood pressure and a reflex decrease in heart rate, especially in younger, healthy patients. The initial reaction can be explained by the peripheral α_{2B}-adrenoceptor stimulation of vascular smooth muscle and can be attenuated by a slow infusion over 10 or more minutes. Even at slower infusion rates, however, the increase in mean arterial pressure over the first 10 minutes was shown to be in the range of 7%, with a decrease in heart rate between 16% and 18%. The initial response lasts for 5 to 10 minutes and is followed by a decrease in blood pressure of approximately 10% to 20% below baseline and a stabilization of the heart rate, also below baseline values; both of these effects are caused by the inhibition of the central sympathetic outflow overriding the direct stimulating effects. Another possible explanation for the subsequent heart rate decrease is the stimulation of the presynaptic α2-adrenoceptor, leading to a decreased norepinephrine release [5].
Dexmedetomidine could result in cardiovascular depression, i.e., bradycardia and hypotension. The incidence of postoperative bradycardia has been reported as high as 40% in healthy surgical patients who received dexmedetomidine, especially high doses. Usually, these temporary effects were successfully treated with atropine or ephedrine and volume infusions.
At clinically effective doses, dexmedetomidine has been shown to cause much less respiratory depression than other sedatives. However, co administration of dexmedetomidine with anesthetic agents, sedatives, hypnotics, or opioids is likely to cause additive effects.
In clinical doses dexmedetomidine also exhibits decongestant, antisialagogue, antishivering, antiemetic effects**.** Other claimed advantages include minimal respiratory depression with cardioprotection, neuroprotection and renoprotection, thus making it useful at various situations including offsite procedures [6].

Methodology
In our study, we have calculated sample size with a significance level of $p<0.05$ corresponding to confidence level of 95% (α-error 1.96) and power of 90% to detect a difference of 15% between groups. The minimum number calculated was 29. However to compensate loss of data in some patients, we have taken total of 150 subjects, with 50 in each group.

Inclusion Criteria
Patients were randomly allotted to each of study group, based on a computer generated random number table using Microsoft excel. 150 patients with 50 in each group of ASA (American Society of Anaesthesiologists) physical status I & II patients aged between 18-55 years undergoing elective surgical procedures, lasting between 1 and ½ hour to 4 hour, under general anesthesia requiring endotracheal intubation were enrolled for study.

Exclusion Criteria
Patients with following condition were excluded from study. Pregnant women, patients with bronchial asthma, Chronic Obstructive Pulmonary Diseases (COPD), ischemic heart diseases, hypertension, chronic renal disease, and patient with deranged liver function, cirrhosis. Patients with difficult airway, obesity, psychiatric illness etc. Patients coming for Surgeries on neck, oral cavity were also excluded from the study.
All the patients undergoing planned elective surgery were assessed as per the routine preoperative protocol. Preoperative investigations like hemoglobin and complete blood count, blood sugar level, blood urea, serum creatinine level, Serum electrolytes, electrocardiogram (age >40 yrs) and Chest X-ray (in chronic smokers) were ordered depending on patient characteristics' and surgery planned
All the patients were kept NPO at least 6 hours before surgery. Patients were premedicated with Tab alprazolam 0.25mg at night and inj glycopyrrolate 0.2mg I.M before shifting to operation theatre.

All the patients were randomized in to 3 groups of 50 each, named as
Group A receiving 0.9% normal saline.
Group B receiving IV fentanyl.
Group C receiving IV dexmedetomidine.

On arrival to the operating the room, non-invasive monitors like Electrocardiogram (ECG), Non-invasive BP, pulse-oximetry was connected. Neuromuscular monitor (TOF-watch) was attached to assess adequacy of block and to know ideal time for extubation. Entropy monitors (GE Health care's sensors) was attached to monitor depth and awareness during surgical procedure and during extubation. Intravenous access was established with 18/20 G intravenous cannula and Lactated Ringer's solution (10ml/kg) was used for intravenous (IV) hydration. Baseline vital parameters like systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP), oxygen saturation, entropy were noted.
After pre-oxygenation for 3 to 5 minutes, all the patients in 3 groups were induced with lignocaine 1.5mg/kg IV, propofol 2mg/kg IV, fentanyl 2μg/kg IV. Muscle relaxation was achieved with atracurium 0.5mg/kg IV. Paracetamol 1 gm infusion was given in all the patients. After achieving TOF count of less than 4, gentle laryngoscopy with suitable size Macintosh blade and endotracheal intubation was performed with appropriate size endotracheal tube, cuff pressure was set to 30 cmH2O with air and fixed at appropriate level after confirming bilateral equal air entry.
A temperature probe was inserted in nasopharynx. Anaesthesia was maintained with isoflurane (0.8-1.5%) in oxygen and air. Muscle relaxation was achieved with atracurium 0.3mg/kg/hr IV infusion 30 minutes after intubation. Intra-operative analgesia was maintained by using fentanyl 0.5-1μg/kg/hr IV infusion depending on the type of surgery, for major surgical procedures it was 1μg/kg/hr IV infusion and for minor surgeries infusion was 0.5/kg/hr IV**.** Adequate intravenous fluids were infused to avoid changes in hemodynamic which may affect the study. Intra-operatively entropy was maintained between 40-60 by titrating isoflurane between 0.8-1.5% Intraoperative vital parameters were maintained within 20% of baseline values, with adequate anaesthetic depth, analgesia, hydration, and

neuromuscular blockade.
Atracurium and fentanyl infusion were stopped 20-30 minutes before time of extubation. With closure of the skin or 10-20 minutes prior to extubation isoflurane was discontinued.
Study drug to be given was diluted and loaded in 20ml syringe. Before 10 minutes of extubation study drug was given by bolus infusion over a period of 10 minutes by infusion pump keeping flow rate at 120ml per hour.

Group A: Patients were given intravenous 20ml plain normal saline bolus infusion over period of 10 minutes, 10 minutes prior to extubation.

Group B: Patients were given intravenous fentanyl 1µg/kg (diluted in 20ml normal saline) bolus infusion over period of 10 minutes, 10 minutes prior to extubation.

Group C: Patients were given intravenous dexmedetomidine 1µg/kg (diluted in 20ml normal saline) bolus infusion over period of 10 minutes, 10min prior to extubation.

Results

Entropy parameter was used to monitor anaesthetic depth in our clinical study. Just prior to reversal entropy in group A was 47.96±7.81 was, in group B 52.72±12.07, and in group C it was 49.04±9.72. Even though there was statistically significant difference among 3 groups studied (P=0.048), it was of no clinical relevance. At extubation the entropy was 97.24±1.27 in group A, 96.30±1.83 in group B, and 96.66±1.70 in group C. There was statistically significant difference among the 3 groups as p value was 0.015. Control group (group A) entropy was higher (woke up early) than fentanyl (group B) and dexmedetomidine (group C) group. But there was no clinically significant difference in awakening among the 3 groups studied.

Table 1: Comparison of entropy in % of three groups studied

ENTROPY in %	Group A	Group B	Group C	P value
Pre-induction	98.54±1.20	98.44±1.33	98.30±1.20	0.626
Iso-stopped	40.34±4.42	40.88±6.07	41.04±4.76	0.775
prior to Rev.	47.96±7.81	52.72±12.07	49.04±9.72	0.048
Reversal	71.56±8.06	73.28±8.14	72.08±6.31	0.507
Extubation	97.24±1.27	96.30±1.83	96.66±1.70	0.015

P value <0.05 is statistically significant in comparison of entropy among the group's studies and has been shown in blue color.

Train of Four Ratio was used for neuromuscular monitoring during anesthesia and extubation. Intra-operatively TOF ratio was similar in groups A, B and C. TOF ratio at extubation in group A was 91.02±1.94%, in group B was 90.44±1.99% and in group C was 90.10±3.36%. There was no statistical significance difference between the groups studied (p=0.185).

Table 2: Comparison of TOF-ratio in of three groups studied

TOF-Ratio in %	Group A	Group B	Group C	P value
Isoflurane -stopped	5.60±4.59	5.40±4.81	5.56±4.55	0.974
Prior to Reversal	20.02±12.42	22.96±14.91	21.14±13.14	0.549
Reversal	70.66±3.74	68.90±7.75	67.88±10.52	0.204
Extubation	91.02±1.94	90.44±1.99	90.10±3.36	0.185

Higher the extubation quality scale, poorer is the extubation quality. Scale of 3 and >3 are associated with poor extubation, more haemodynamic changes consequently more chances of clinical intervention.
The overall extubation quality in group A was 2.68±0.47, in group B it was 1.94±0.55, and in group C quality scale was 1.50±0.58
In group A, 16 out of 50 patients studied had extubation quality scale of 2 (32%), while 34 patients had extubation quality scale of 3 (68%).
In group B, 8 out of 50 patients studied had extubation quality scale of 1 (16%), 38 patients had extubation quality scale of 2 (76%), 3 had scale of 3(6%), while 1 patient had extubation quality scale of 4 (2%).
In group C, 27 out of 50 patients studied had extubation quality scale of 1 (54%), while 21 patients had extubation quality scale of 2 (42%), 2 patients had a scale of 3 (6%).

Table 3: Extubation quality scale of patients in three groups studied

Extubation Quality Scale	Group A		Group B		Group C	
	No	%	No	%	No	%
1	0	0.0	8	16.0	27	54.0
2	16	32.0	38	76.0	21	42.0
3	34	68.0	3	6.0	2	4.0
4	0	0.0	1	2.0	0	0.0
5	0	0.0	0	0.0	0	0.0
Total	50	100.0	50	100.0	50	100.0
Mean ±SD	2.68±0.47		1.94±0.55		1.50±0.58	

Over all P = <0.001
Group A-Group B: P <0.001
Group A-Group C: P <0.001
Group B-Group C: P <0.001.

There was statistical significant difference between group A & group B (P <0.001) as 76% of patient of group B had scale of 2 against 32% of group A. 16% of group B had scale of 1 against 0% of group A. Only 6% in group B had scale of 3 against 68% of group A. There was clinical significance as higher extubation quality scale in group A was associated with significant haemodynamic changes which required clinical intervention.
In group A & C, there was statistical significant difference (P<0.001) with respect to extubation quality scale, as 54% of patient in group C had extubation scale 1 against 0% in group A, 42% of patients in group C had a scale of 2 against 32% in group A, only 4% in group C had scale of 3 against 68% patients in group A. Extubation in Group A were associated with higher scale, so clinical interventions were more in group A when compared to group C.
Among group B & C, there was statistical significant difference between group B & group C (P <0.001) as 54% of patient in group C had extubation scale 1 against 16% in group B, 42% of patients in group C had a scale of 2 against 76% in group B, only 4% in group C had scale of 3 against 6% patients in group B. Since most of patients extubated in group B & C had quality scale of either 1 or 2, only few were in scale 3 and 4.So there were less clinical intervention in group B & C when compared to group A& B and A & C.
To summarize there was statistically significant (p<0.001) differences among group A, B & C with respect to extubation quality scale and also there was clinically significant difference among the three groups. Extubation quality was superior in decreasing order in group C (Dexmedetomidine); group B (Fentanyl) and group A

(control group). Group C had best extubation quality, while group A had relatively poor extubation quality.
Rescue drugs were used to control acute rise in HR, SBP or DBP after extubation which might have affected patient's clinical outcome.

Table 4: Showing use of rescue drugs in three groups

Use of Rescue Drugs.	Group A		Group B		Group C	
	No (n=50)	%	No (n=50)	%	No (n=50)	%
No	33	66.0	49	98.0	50	100.0
Yes	17	34.0	1	2.0	0	0.0
• Esmolol 30 iv	9	18.0	0	0.0	0	0.0
• Propofol given	0	0.0	1	2.0	0	0.0
• Xylocard 100mg	1	2.0	0	0.0	0	0.0
• Xylocard 50mg	3	6.0	0	0.0	0	0.0

Over all P = <0.001
Group A-Group B: P <0.001
Group A-Group C: P <0.001
Group B-Group C: P =1.000

In group A, 17 of 50 patients studied had acute haemodynamic changes which required use of rescue drugs (34%). In group B only one out of 50 patients studied required use of rescue drugs (2%). While in group C no patients had significant haemodynamic variability which required rescue drugs.
When group A and group B are compared with respect to use of rescue drug, there was statistically significant difference (p<0.001) as rescue drugs were most frequently used in group A (34%) than group B (2%).
Similarly there was significant statistical (p<0.001) and clinical difference among group A and C, as recue drugs were used 34% of patient in group A against 0% patients in group C.
There was no significant statistical (p=1.00) & clinical difference among group B and group C with respect to use of rescue drugs.

Discussion

Though studies have shown the efficacy of individual drugs, there are very few studies that have compared fentanyl, dexmedetomidine with placebo under ideal anaesthetic condition by using anesthesia depth monitors (entropy) and neuromuscular monitors (TOF Ratio). The two drugs chosen in our study were different pharmacologically, with respect to mechanism of action and duration of action, hence comparing the efficacy of these drugs in attenuation of stress response during emergence.
In our study we have enrolled 163 patients in total. In group A 55 patients were included out of which 5 patients were excluded as 2 of the patients' surgery was cancelled, intra-operatively induced hypotension was maintained in 3 patients as per surgeons' request. In group B, 53 patients' were included; procedure was cancelled on the day of surgery in 3 patients. In group C total 55 patients were included, one patient was found to have hypertension on table, and for 4 patients induced hypotension was given.
There are studies where fentanyl is used in different dosages to attenuate extubation stress response. Nishina *et al* [7] showed that fentanyl 2µg/kg attenuated the increase in HR, SBP and DBP more effectively than 1µg/kg without prolonging the recovery. Habib Bostana & Ahmet Eroglu [8] carried out a clinical trial to compare clinical efficacies of fentanyl1µg kg-1, esmolol 1mg kg-1 and lidocaine 1mg kg-1 in preventing the hemodynamic responses to endotracheal intubation and extubation. Study drug was administered before intubation and extubation. They concluded three drugs were effective in suppressing the hemodynamic response to laryngoscopy, intubation and extubation. In our study, patients received IV fentanyl 1µg/kg.
Esra Sagiroglu A *et al*. [9] conducted a study to find out different doses of dexmedetomidine to attenuate haemodynamic stress response to endotracheal intubation. Group I patients received 1.0µg.kg-1 in 10 min and group II patients received 0.5µg.kg-1 dexmedetomidine in 5min respectively. They concluded that dexmedetomidine 1µg.kg^{-1} was found more effective than dexmedetomidine 0.5µg.kg^{-1} in controlling haemodynamic responses to tracheal intubation. Wang BS, *et al*. [10] conducted a clinical study to observe the effect of 0.5µg.kg-1 dexmedetomidine hydrochloride given at the end of surgery, on stress responses during extubation in patients undergoing uvulo-palato-pharyngoplasty (UPPP). They concluded that dexmedetomidine hydrochloride could efficiently restrain the stress response around tracheal extubation, reduce postoperative complications in patients undergoing UPPP. In our study, we chose to use 1.0µg.kg-1 dexmedetomidine 10 min before extubation.
Onset of action of IV fentanyl is almost immediate and its action lasts for 0.5 to 1hour. Whereas IV dexmedetomidine action starts after 5 to 10mins following bolus infusion and lasts for 1 to 2hours. Therefore, in our study, we started the study drug bolus 10 minutes before extubation. In a previous study, fentanyl has been administered at the time of peritoneal closure intraoperatively. In our study; patients were administered fentanyl for analgesia at induction and during maintenance of anaesthesia and stopped 20-30 minutes before extubation. To attenuate the stress response to extubation, fentanyl was re-administered as a bolus infusion of 1µg/kg diluted in 20ml normal saline, 10min before extubation.
G. Turan *et al* conducted a clinical study to evaluate advantageous effects of dexmedetomidine on haemodynamic and recovery responses during extubation by administering it intravenously (over 60 seconds) five minutes before conclusion of surgery. They concluded that without interfering in recovery time, dexmedetomidine stabilizes haemodynamics, allows easy extubation, and provides a more comfortable recovery and early neurological examination following intracranial operations in comparison to control group (0.9% Nacl). Other studies like Barkha Bindu *et al* and D Jain *et al*. also found that

dexmedetomidine 0.75 mcg/kg to 1µg/kg administered 10 to 15 minutes before extubation, stabilizes haemodynamics and facilitates smooth extubation.

Conclusion

Extubation quality is superior with dexmedetomidine than with placebo

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