Original Research Paper

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A COMPARATIVE STUDY TO EVALUATE EFFICACY OF CONTINUOUS PERI-OPERATIVE INFUSION OF DEXMEDETOMIDINE FOR SMOOTH EMERGENCE FROM GENERAL ANAESTHESIA IN LAPAROSCOPIC SURGERIES: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT Smooth extubation requires absence of coughing, shivering, agitation with hemodynamic stability. Dexmedetomidine is a drug which helps in smooth emergence from general anaesthesia if used judiciously. Its use as a bolus dose is associated with hypotension and braycardia.1 Hence, Dexmedetomidine used as an infusion intra-operatively was continued till the reversal of neuromuscular blockade to see its effect on extubation. **Aims:** To observe the effect of continuous IV Dexmedetomidine infusion till the reversal of neuromuscular blockade, on smooth emergence from general anaesthesia. **Settings and Design:** This randomized, single blinded study was conducted on patients aged 18-65 years, ASA grade I-II-III undergoing laparoscopic surgeries, at tertiary care centre. **Methods and Material:** Patients were assigned to Group D(Dexmedetomidine) and Group C(control group). In group C, Dexmedetomidine infusion was stopped at deflation of pneumoperitoneum while in group D, was continued till reversal of the neuromuscular blockade. Parameters noted were: Coughing, shivering, sedation/agitation and hemodynamic parameters. **Statistical analysis used:** Chi-square test was used to contrast incidence of coughing, shivering and sedation level. Fischer extract test was used to contrast hemodynamic parameters. **Results:** Incidence of coughing was less in group D compared to group C, which was statistically significant at 5, 10 and 15 minutes. Incidence of shivering was less in group D, but it was not statistically significant. Sedation/agitation were quite similar across groups, but group D patients tend to remain sedated slightly more than group C. Almost all patients remained hemodynamically stable in both the groups. **Conclusions:** Use of Inj.Dexmedetomidine infusion was effective in suppressing coughing and shivering during extubation without undue agitation/sedation, maintaining stable hemodynamics.

KEYWORDS : Dexmedetomidine, Extubation, Laparoscopic Surgery, General Anaesthesia

Introduction:

Emergence from general anaesthesia may be associated with coughing, agitation, hypertension, tachycardia and shivering.[1] Coughing is an aerosol generating event.[2] COVID-19 pandemic has sensitized us with the importance of developing techniques effective in reducing such events and achieving a smooth emergence. Dexmedetomidine is an α2 agonist, which can blunt hemodynamic responses to extubation, has sympatholytic, sedative, analgesic and anti-shivering properties without respiratory depression.[3]

In literature, researchers have tried it in various regimes to blunt the sympathetic response to extubation.[1] Our aim was to extend the infusions of Dexmedetomedine used during maintainence, till the reversal of neuromuscular blockade to see whether this helps in smooth extubation.

Subjects and Methods:

This prospective, randomized controlled study was approved by institutional ethics committee (IEC/HMPCMCE/120/Faculty/15/211/20) and registered under the clinical trial registry of India (CTRI/2020/12/029517). After obtaining written and informed consent from 100 patients aged between 18-65 years and ASA Grade I/II/III physical status, undergoing elective laparoscopic surgeries under general anaesthesia with estimated duration of 1-4 hours were included in the study. Patients who were allergic to Dexmedetomidine, obesity with BMI>35 kg/m^2, having febrile illness, pregnant women and patients whose pre-operative heart rate <60/min were excluded from the study.

Patients were randomly assigned into two groups Group C (Control) and Group D (Dexmedetomidine) using computer generated random numbers. In pre-operative room, baseline heart rate and blood pressure were recorded. Injection Dexmedetomidine infusion was started at loading dose (1mcg/kg over 15 minutes) prior to surgery. In the operating room, routine monitors were applied viz. BP cuff, electrocardiogram leads, Pulse oximeter probe, capnography (after intubation), peripheral nerve stimulator (Train of four-TOF). In all patients Inj dexmedetomidine infusion, was continued at maintainance dose at the rate of 0.2-0.7 mcg/kg/hour titrated keeping the hemodynamics within 20%of baseline values. This was done with increments or decrements of 0.1μg/kg/hour every 5 minutes, as required. Anaesthesia was induced using IV Glycopyrrolate 0.04mg/kg mg, IV Fentanyl 2 μg/kg, IV Xylocard 1.5 mg/kg, IV Propofol 1.5-2 mg/kg, Vecuronium 0.1 mg/kg or Succinylcholine 2 mg/kg depending on the plan of airway management. After orotracheal intubation, anaesthesia was maintained using O2+ air and Sevoflurane 1%-2% , using low flows in close circuit with volume controlled ventilation (tidal volume 7ml/kg and respiratory rate in order to maintain the ETCO2 between 30-35 mmHg with FIO2 of 50%). Intermittent doses of Inj Fentanyl (1/3 rd of loading) was given every hour and Inj. Vecuronium was titrated according to TOF monitoring i.e. was repeated on appearance of three twitches. After deflation of pneumoperitoneum by the surgeon, concealed envelope containing the group of patient was opened and thereby the participant was randomly allocated to group C or group D. In Group C, Injection Dexmedetomidine infusion was stopped at deflation of pneumoperitoneum. In group D, Injection Dexmedetomidine infusion was continued at maintainance dose. In all patients, at the end of surgery (when skin suturing completed), Sevoflurane was stopped (Defined as time zero or baseline of emergence process), fresh gas flow was increased to 4-6 lit/min, and Ondansetron 4 mg IV was given. On appearance of all four twitches of equal amplitude on TOF stimulation, reversal of neuromuscular blockade (Neostigmine 0.05 mg/kg+ Glycopyrollate 0.01 mg/kg) was initiated. At the same time, injection Dexmedetomidine infusion was stopped in Group D. Patient was extubated when he/she was responding to verbal commands with adequate tidal volume on spontaneous respiration. Cough scores, number of coughing episodes, shivering ,sedation/agitation, systolic BP, diastolic BP , heart rate, oxygen saturation and requirement of supplemental oxygen were recorded every 5 minutes for a period of 30mins after extubation. Time to extubation was also recorded which was defined as time from switching 'off' the Sevoflurane to removal of the endotracheal tube.

Chi-square test was used to contrast incidence of coughing, shivering and sedation level. Fisher-extract test was used to contrast hemodynamic parameters.

Results:

***Table 1. Comaparison of incidence of Cough during Extubation at different time points among both groups**

COUGH	PRESENT/ ABSENT	STUDY GROUP D		CONTROL GROUP C		P VALUE
		Frequency	%	Frequency	%	
5 MINUTES	ABSENT	45	91.8%	29	58.0 %	P=0.002
	PRESENT	4	8.2%	21	42.0 %	
10 MINUTES	ABSENT	44	89.8%	25	50.0 %	P< 0.001
	PRESENT	5	10.2%	25	50.0 %	

15 MINUTES	ABSENT	48	98%	40	80%	P=0.02
	PRESENT	1	2%	10	20%	
20 MINUTES	ABSENT	48	98%	50	100	P=0.31
	PRESENT	1	2%	0	0%	
25 MINUTES	ABSENT	48	98%	50	100	P=0.31
	PRESENT	1	2%	0	0%	
30 MINUTES	ABSENT	48	98%	50	100	P=0.31
	PRESENT	1	2%	0	0%	

***Table 2. Comaparison of incidence of Shivering during Extubation at different time points among both groups**

SHIVERING	PRESENT / ABSENT	STUDY GROUP D		CONTROL GROUP C		P VALUE
		Frequency	%	Frequency	%	
5 MINUTES	ABSENT	45	91.8%	38	76.0%	P=0.08
	PRESENT	4	8.2%	12	24.0%	
10 MINUTES	ABSENT	45	91.8%	39	78.0%	P=0.1
	PRESENT	4	8.2%	11	22.0%	
15 MINUTES	ABSENT	43	87.8%	45	90%	P=0.34
	PRESENT	6	12.2%	5	10%	
20 MINUTES	ABSENT	47	95.9%	49	98%	P=0.55
	PRESENT	2	4.1%	1	2%	
25 MINUTES	ABSENT	47	95.9%	49	98%	P=0.55
	PRESENT	2	4.1%	1	2%	
30 MINUTES	ABSENT	49	100%	49	98%	P=0.32
	PRESENT	0	0%	1	2%	

***Table 3. Comaparison of Sedation/Agitation during Extubation at different time points among both groups**

AGITATION-SEDATION SCALE	PRESENT/ ABSENT	STUDY GROUP D		CONTROL GROUP C		P VALUE
		FREQUENCY	%	FREQUENCY	%	
5 MINUTES	ALERT& CALM/ DROWSY	31	63.3 %	31	62%	P=0.90
	SEDATED/ AGITATED	18	36.7 %	19	38%	
10 MINUTES	ALERT& CALM/ DROWSY	42	85.7 %	41	82%	P=0.62
	SEDATED/ AGITATED	7	14.3 %	9	18%	
15 MINUTES	ALERT& CALM/ DROWSY	46	93.9 %	47	94%	P=0.98
	SEDATED/ AGITATED	3	6.1%	3	6%	
20 MINUTES	ALERT& CALM/ DROWSY	46	93.9 %	49	98%	P=0.30
	SEDATED/ AGITATED	3	6.1%	1	2%	
25 MINUTES	ALERT& CALM/ DROWSY	48	98%	49	98%	P=0.99
	SEDATED/ AGITATED	1	2%	1	2%	
30 MINUTES	ALERT& CALM/ DROWSY	48	98%	49	98%	P=0.99
	SEDATED/ AGITATED	1	2%	1	2%	

Hemodynamic parameters were remained within 20% of baseline in almost all patients of both the groups.

Discussion:

Extubation is a critical event during general anaesthesia, commonly associated with hemodynamic disturbances and airway reflexes which can cause hypertension, tachycardia, coughing , laryngospasm, arrhythmias and bronchospasm.[4]

Expectoration of secretions that become aerosolized during extubation could increase the risk of exposure to Covid 19 infection to the involved health care personnel.[5]

Various drugs like Remifentanyl[6], Esmolol[7], Lignocaine[8], Dexmedetomidine[9], have been introduced so far to reduce the sympathetic response during emergence. Dexmedetomidine is a selective α2-agonist which has analgesic, sedative, sympatholytic properties without any respiratory depression.[3] Hence, this drug is used in anaesthesia intraoperatively to maintain haemodynamics [10] and as a analgesic in a balanced anaesthesia technique[11] ,during extubation to prevent agitation[12] and give a smooth emergence. In our study, after loading dose of 1μg/kg over 15 minutes, we have continued the Dexmedetomidine infusion at maintainance dose of 0.2-0.7μg/kg/hr till reversal of neuromuscular blockade and tried to see its effect on emergence profile like coughing, shivering, agitation/sedation, hemodynamic parameters postoperatively.

Coughing and bucking frequently accompanies tracheal extubation.[13]. In our study, there was statistically significant lower incidence of coughing in study group with maintainace infusion at 0.2 to 0.7 μg/kg/hour, at 5,10 and 15 minutes after extubation.

Sneha Suresh et al. in 2020 found that Dexmedetomidine 0.75 μg/kg, 30 minutes prior to extubation didn't affect the severity of cough.[14] whereas in our study we had given a bolus dose followed by infusion till reversal of the neuromuscular blockade ,which gave us effective cough suppression at extubation.

Park, Jeong-soo MD, et al. in 2016 found that Remifentanyl target controlled infusion at 2.0 ng/ml reduces emergence cough more effectively than single dose administration of Dexmedetomidine 0.5 μg/kg , 10 minutes before extubation.[15] They had discontinued the Remifentanyl infusion in Dexmedetomidine group and gave the Dexmedetomidine 0.5 μg/kg dose 10 minutes before the end of surgery, while in Remifentanyl group, they continued the infusion till extubation, That could be the reason why they got more cough suppression in the Remifentanyl group.

Jae Hwan Kim et al. in 2019 found that single dose (0.5μg/kg) of Dexmedetomidine combined with low dose of Remifentanyl infusion at 1 ng/ml during emergence was not inferior to high dose of Remifentanyl infusion at 2 ng/ml infusion alone, for cough suppression in thyroidectomy.[6] Dexmedetomidine and Remifentanyl both delay awakening and prolongs extubation. Hence, addition of Dexmedetomidine to low dose of Remifentanyl resulted in effective cough suppression than high dose of Remifentanyl alone.

Jeong Soo Lee et al. in 2014 found that in addition to infusion of low dose target controlled Remifentanyl infusion , infusion of Dexmedetomidine 0.5 μg/kg over 10 minutes at the end of surgery was effective in suppressing cough incidence and severity.[9] Combination of a single dose of Dexmedetomidine and Remifentanyl infusion might have induced a deeper level of sedation and more delay in awakening, Hence resulted in suppression of incidence and severity of cough.

As seen in above studies, Remifentanyl as an infusion, was quite effective in suppression of cough during extubation. As Remifentanyl is not freely available in india, we used Dexmedetomidine infusion instead of bolus dose to get similar effects without any side effects.

Varun Jain et al. in 2019 found that intra-operative use of Dexmedetomidine at 0.2 μg/kg/hour in adults undergoing anterior cervical discectomy and fusion surgery showed no difference in incidence of coughing among both groups.[13] They used lowest recommended dose of 0.2 μg/kg/hr, whereas in our study we used titrated infusion (at 0.2 to 0.7 μg/kg/hour) to maintain cardiovascular stability till reversal which gave us the desired effect without side effects.

Qin Ye, et al. in 2021 found that administration of 0.6 μg/kg and 0.8 μg/kg Dexmedetomidine infusion, 10 minutes before induction can decrease the incidence of cough during emergence compared to 0.4 μg/kg, in patients undergoing laparoscopic cholecystectomy.[16] Instead of giving bolus doses perioperatively , we titrated the infusion of

Dexmedetomedine in our study as we had participants who were hypertensive on anti-hypertensive medications and/or beta-blockers which could have caused synergistic effects on haemodynamic parameters .We found similar results in terms of cough suppression especially in the first 15 mins after extubation .

Marie T. Aouad, et al. in 2019 found that Dexmedetomidine 1 µg/kg dose before extubation was effective in providing best quality of emergence in terms of suppression of cough, shivering, agitation and hemodynamic stability, but caused hypotension. While, 0.5 µg/kg dose was also effective in providing hemodynamic stability and in suppression of shivering and agitation but less effective in cough suppression.[1] Instead of giving bolus dose, we have continued the infusion at 0.2-0.7 µg/kg/hour till the reversal of neuromuscular blockade and found statistically significant cough suppression.

Post-operative shivering is a physiological response to hypothermia and body's second heat preservation mechanism after peripheral vasoconstriction.[17]

A lot of research has been done so far to attenuate the post-operative shivering after spinal anaesthesia; but not many have done the research to suppress the shivering after general anaesthesia. Various drugs have been tried to suppress post-operative shivering. In our study, shivering was observed to be less in Dexmedetomidine group than control group, however the difference was not statistically significant.

Taku Nakagawa et al. in 2017 found that the incidences of post anaesthetic shivering was significantly decreased in patients in whom intravenous Tramadol given at induction of anaesthesia.[18]

Sneha suresh et al. in 2020 found that effect of single dose of Dexmedetomidine 0.75 µg/kg, 30 minutes prior to end of surgery, as an infusion over 10 minutes, did not cause any significant difference in suppression of shivering.[14]

Xianhui Kang et al. in 2019 in the retrospective cohort study in patients of lung surgeries found that intraoperative Dexmedetomidine infusion resulted in less incidence of shivering.[19] In our study, we did not find any statistical significant effect on postoperative shivering after continuous infusion of Dexmedetomedine intraoperatively .

Dexmedetomidine causes central stimulation of parasympathetic outflow and inhibition of sympathetic outflow from locus ceruleous in the brainstem, thereby producing sedation.[20] In our study, we found that most of the patients were calm and alert or drowsy in both the groups. However, in the study group; patients tend to remain more sedated clinically as compared to the control group.

Dong Jun Kim et al. in 2015 found that intraoperative Dexmedetomidine infusion at 0.4 µg/kg/hour significantly decreases emergence agitation and resulted in calm state in postoperative period after orthopedic surgery in elderly patients.[21] We also observed similar findings in both groups but predominantly in the study group.

P. Rani et al. in 2016 in found that single dose of Dexmedetomidine(0.75 µg/kg), given 15 minutes before last surgical suture, was able to achieve better sedation score compared to Fentanyl.[20] Instead of giving single dose, we continued the Dexmedetomidine infusion and found that most of the patients were awake but drowsy during emergence, which also would have been beneficial in suppressing cough.

Laparoscopic surgeries are associated with significant alterations in hemodynamics due to sympathetic stimulation, which results in increase in heart rate, mean arterial pressure. Various drugs and methods have been studied so far to attenuate hemodynamic alterations like use of Propofol[3], Esmolol[7], Dexmedetomidine[10] etc. In our study, we found that, continuation of Dexmedetomidine infusion till reversal of neuromuscular blockade, resulted in stable hemodynamics (in terms of heart rate, systolic and diastolic blood pressure were maintained within 20% of baseline) across both the groups.

Nita Gosai et al. in 2015 proved that, Dexmedetomidine 0.5µg/kg was more effective than Lignocaine 1.5mg/kg, in attenuating hemodynamic response after extubation in intracranial surgery.[8] In this study, 20% of the patients developed hypotension following administration of Dexmedetomidine, which may be due to bolus dose.

In our study we continued the infusion at the maintenance rate (0.2-0.7µg/kg/h) and found hemodynamics within 20% of its baseline during emergence in majority of the patients.

Nirav Kotak et al. in 2018 demonstrated that patient in Dexmedetomidine group had lower heart rate, systolic-diastolic blood pressure and mean arterial pressure compared to Esmolol group during extubation in abdominal and lower limb surgeries.[7]. In this study, though both the drugs were able to attenuate stress response, Dexmedetomidine was better for the above purpose. Moreover, optimum dose of Esmolol and timing of its administration for hemodynamic stability during extubation is not defined yet.[7]

Vatika Bhardwaj et al. in 2020 demonstrated that Dexmedtomidine 0.75 µg/kg, and 1 µg/kg, as 10 ml infusion over 10 minutes, were able to attenuate increase in heart rate and mean arterial pressure .The 1 µg/kg dose was associated with hypotension. They proved that, 0.75 µg/kg was the optimal dose for maintaining hemodynamic stabilty during extubation and facilitated smooth extubation, without undue sedation.[22] They did their study in hypertensive patients and gave bolus doses over 10 minutes prior to extubation, while we have given infusion and found similar hemodynamics during emergence.

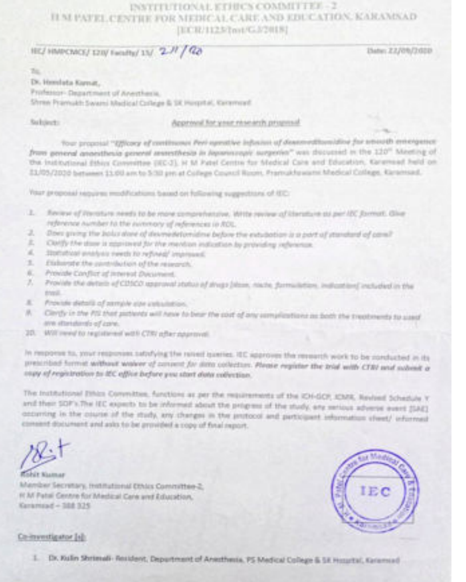
While, Kwon-Hui Seo et al. in 2014 also proved that intravenous infusion of 0.5 µg/kg Dexmedetomidine, 30 minutes before end of surgery, was effective in attenuation of cardiovascular response to emergence without prolonging extubation time. Doses more than 0.5 µg/kg did not have any additional advantage on cardiovascular response, but it prolonged the extubation time.[23] Though higher dose more than 0.5 µg/kg was effective in suppression of cough shivering etc during emergence, but they caused dose dependent hypotension and delayed extubation.

In our study, instead of bolus dose, we have given infusions of Dexmedetomidine at a maintainance rate and seen similar results.

Avneesh Khare et al. in 2017 gave loading dose of Dexmedetomidine followed by infusion at 0.6 µg/kg in the laparoscopic surgeries and found that mean arterial pressure and heart rate were significantly reduced after intubation at various time points.[10] They found stable hemodynamics intraoperatively with maintainance rate at 0.6 µg/kg. We continued the Dexmedetomidine infusion at 0.2-0.7 µg/kg till reversal and found similar results.

Limitations of our study: We have done this study in surgeries lasting for 2-3 hours, hence in prolonged surgeries, use of Dexmedetomidine infusion might lead to more sedation and/or hemodynamic instability and needs to be evaluated for the same .

Conclusion: We conclude that, continuation of Dexmedetomidine infusion till reversal of neuromuscular blockade, was able to suppress cough and shivering during emergence with stable hemodynamics without agitation or undue sedation.


INSTITUTIONAL ETHICS COMMITTEE - 2
H M PATEL CENTRE FOR MEDICAL CARE AND EDUCATION, KARAMSAD
[ECR/1123/Inst/GJ/2018]

IEC/ HMPCMCE/ 120/ Faculty/ 15/ 2/1/20   Date: 22/09/2020

To,
Dr. Hemlata Kamat,
Professor- Department of Anesthesia,
Shree Pramukh Swami Medical College & SK Hospital, Karamsad

Subject: Approval for your research proposal

Your proposal "*Efficacy of continuous Peri operative infusion of dexmedetomidine for smooth emergence from general anaesthesia general anaesthesia in laparoscopic surgeries*" was discussed in the 120th Meeting of the Institutional Ethics Committee (IEC-2), H M Patel Centre for Medical Care and Education, Karamsad held on 21/05/2020 between 11:00 am to 5:30 pm at College Council Room, Pramukhswami Medical College, Karamsad.

Your proposal requires modifications based on following suggestions of IEC:

1. *Review of literature needs to be more comprehensive. Write review of literature as per IEC format. Give reference number to the summary of references in ROL.*
2. *Does giving the bolus dose of dexmedetomidine before the extubation is a part of standard of care?*
3. *Clarify the dose is approved for the mention indication by providing reference.*
4. *Statistical analysis needs to refined/ improved.*
5. *Elaborate the contribution of the research.*
6. *Provide Conflict of interest Document.*
7. *Provide the details of CDSCO approval status of drugs [dose, route, formulation, indication] included in the trail.*
8. *Provide details of sample size calculation.*
9. *Clarify in the PIS that patients will have to bear the cost of any complications as both the treatments to used are standards of care.*
10. *Will need to registered with CTRI after approval.*

In response to, your responses satisfying the raised queries. IEC approves the research work to be conducted in its prescribed format **without waiver** *of consent for data collection.* ***Please register the trial with CTRI and submit a copy of registration to IEC office before you start data collection.***

The Institutional Ethics Committee, functions as per the requirements of the ICH-GCP, ICMR, Revised Schedule Y and their SOP's.The IEC expects to be informed about the progress of the study, any serious adverse event [SAE] occurring in the course of the study, any changes in the protocol and participant information sheet/ informed consent document and asks to be provided a copy of final report.

Rohit Kumar
Member Secretary, Institutional Ethics Committee-2,
H M Patel Centre for Medical Care and Education,
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IEC

Co-investigator [s]:

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