Effectiveness of nebulized dexmedetomidine as a premedication in flexible bronchoscopy in Indian patients -a prospective, randomized, double blinded study

Thomas Antony (t.antony5@gmail.com)
Kasturba Medical College Mangalore
Preetam Rajgopal Acharya
Kasturba Medical College Mangalore
Vishak Acharya
Kasturba Medical College Mangalore

Research Article

Keywords: Bronchoscopy, Nebulized Dexmedetomidine, Saline nebulization, Non-Invasive sedation

Posted Date: April 8th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1448717/v1

Title

Effectiveness of nebulized dexmedetomidine as a premedication in flexible bronchoscopy in Indian patients -a prospective, randomized, double blinded study

Names protocol contributors

Thomas Antony, Preetam Rajgopal Acharya, Vishak Acharya

Abstract

- **Background**: Studies have proven the efficacy of intravenous dexmedetomidine in patient comfort during flexible bronchoscopy without causing any respiratory depression. Intravenous administration of sedative agents requires expertise and presence of an anaesthetist. This adds to the cost of the bronchoscopy. Inhalational administration of sedative agents can improve the safety profile due to its local action, with similar efficacy. There are only limited studies which have looked at the effects of nebulized dexmedetomidine in bronchoscopy. Dexmedetomidine in nebulized form is an easy non-invasive method of sedation, in situations where manpower is not trained in intravenous sedation. It alleviates the need of an anesthetist, Shortens the duration of the procedure and hospital stay and thus reduces the overall procedural cost to the patient, without any adverse events
- **Methods**: The study is prospective, randomized, double blinded. Patients who requires bronchoscopy and is meeting the inclusion criteria is randomized to receive either dexmedetomidine nebulization or saline (0.9%) nebulization after recording the baseline vital parameters. The study parameters are assessed and recorded using a proforma. Patients are assessed both objectively and subjectively using a proforma at specific time periods. Data collected is analyzed using SPSS software
- **Discussion**: Commonly used agents for sedation in bronchoscopy including midazolam, fentanyl and dexmedetomidine. However, side effects with intravenous sedative agents like respiratory depression and bradycardia are seen. Dexmedetomidine, a relatively newer drug is proven to be effective agent for sedation compared to the other standard agents used. However nebulized form of dexmedetomidine, being locally acting is comparatively safer with lesser incidence of hemodynamic instability while being as effective as the intravenous form.

Trial registration: The study is submitted for registration with the Central Trial Registry – India

(CTRI) Reg No: **REF/2022/02/051720**

Keywords

Bronchoscopy, Nebulized Dexmedetomidine, Saline nebulization, Non-Invasive sedation

Administrative information

Trials guidance: please include this text in your protocol just above the Administrative information table:

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	Effectiveness of nebulized dexmedetomidine as a premedication in flexible bronchoscopy in Indian patients -a prospective, randomized, double blinded study.
Trial registration {2a and 2b}.	The trial is registered with the Central Trial Registry – India (CTRI). Reg No: **REF/2022/02/051720**
Protocol version {3}	N/A
Funding {4}	Financial and material support is given by the Directorate of Research, Manipal Academy of Higher education as an academic funding.
Author details {5a}	Thomas Antony- Senior Resident, Department of Respiratory Medicine, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, Karnataka, India. -Led the proposal and protocol development, Prepared study protocol, Data collection Preetam Rajgopal Acharya – Professor and Head, Department of Respiratory Medicine, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, Karnataka, India -Edited and contributed to the protocol, performs bronchoscopy

	Vishak Acharya – Professor and unit head, Department of Respiratory Medicine, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, Karnataka, India. -Proof reading the protocol, lead trial methodologist, performs bronchoscopy
Name and contact information for the trial sponsor {5b}	Directorate of Research, Manipal Academy of Higher Education, Manipal, Udupi, Karnataka.
Role of sponsor {5c}	There is no further role of study sponsor, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities. The fund is given for the study as a part of academic program from the university

Introduction

Background and rationale {6a}

With the evolving medical practice, more and more diagnostic and therapeutic modalities are being introduced in clinical practice. The duration of procedures like flexible bronchoscopy is increased depending on the additional tests used, like biopsy, transbronchial needle aspiration or transbronchial lung biopsy. It is important for the respiratory physicians, not only to arrive at a diagnosis but also to provide a safe and comfortable experience to the patient while undergoing the flexible bronchoscopy. Hence the British Thoracic society (BTS) guidelines and Indian guidelines recommend the use of sedation in bronchoscopy. Dexmedetomidine along with other sedative agents like midazolam and fentanyl are being used as conventional agents for sedation in flexible bronchoscopy. These are effective in improving patient comfort during flexible bronchoscopy. Dexmedetomidine is an effective sedative agent and is a preferred agent by the bronchoscopists as it does not cause respiratory depression compared to the other agents used. However it may cause hemodynamic changes like hypotension and bradycardia. Hence the use of inhalational dexmedetomidine may reduce the adverse events as it is locally acting. The bronchodilator property of the inhalational dexmedetomidine gives an additional ease in the bronchoscopy procedure.

However, there are only limited studies with nebulized dexmedetomidine in flexible bronchoscopy. Dexmedetomidine, in its nebulized form has an additional advantage of relieving bronchospasm. Its use is known to attenuate the sympathetic stress of bronchoscopy on the hemodynamic parameters of the patient.

Objectives {7}

To study the patient comfort, tolerance and safety with nebulized dexmedetomidine during flexible bronchoscopy

Trial design {8}

Prospective, Randomized, double blinded, placebo controlled study, allocated to both groups at 1:1 ratio. It is a superiority trial.

Methods: Participants, interventions and outcomes

Study setting {9}

The study is being done in a tertiary care teaching hospital. Data collection is done only in India. Details of the sites of recruitment can be obtained from the CTRI website.

Eligibility criteria {10}

Inclusion criteria: All patients in the age group 18 to 65 years undergoing flexible bronchoscopy in the Department of Respiratory Medicine

Exclusion criteria*:*

a. Patients with known or suspected allergy to lignocaine or Dexmedetomidine

b. Patients with nasal infection or complete obstruction

c. Patients with renal or hepatic insufficiency

d. Patients with seizure disorder

e. COPD patients with FEV1 <50%

f. Patients with psychiatric disorder

g. Hemodynamically unstable patients including cardiac failure

h. Heart rate <50 beats per min or second or third degree heart block

i. Patients with body weight more than 70kg.

j. Pregnancy and lactation

k. Patients posted for bronchoscopy but not consenting to be a study participant.

The study will be performed by pulmonologists

Who will take informed consent? {26a}

Observer C in the study, who will be a junior faculty in the department, assess the patient, explains the study methodology, and takes the informed written consent.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable.

Interventions

Explanation for the choice of comparators {6b}

The comparator used in the study is normal saline in the form of nebulization, which is used as a placebo in the study. Patients undergoing the study will receive lignocaine local anaesthesia in addition to saline nebulization.

Intervention description {11a}

The study will begin with administration of either dexmedetomidine nebulization (group **A**) at 1mcg/Kg dose, diluted with normal saline to make up to 5 ml *or* saline nebulization (group **B**) (5ml of 0.9% solution) via nebulizer apparatus, 15 minutes prior to the procedure after recording the baseline characteristics and hemodynamic parameters. Patients in both groups **A** & **B** will receive two ml of **2 %** lignocaine jelly instilled into the patent nostril. Three sprays of **1%** lignocaine are used at the oropharynx. Two ml of 1% lignocaine is used as "spray-as-you-go" technique at the level of vocal cords, over trachea, and over each bronchus.

After cough subsides, the bronchoscope will be advanced further to examine the entire bronchial tree and the planned sampling procedure will be completed. Additional 1% lignocaine aliquots will be sprayed if the patient develops recurrent cough. A composite scoring will be done by observer C (junior faculty in the department) at the level of nasopharynx, during passage through trachea and when crossing the carina. Heart rate, Non-invasive blood pressure (NIBP), respiratory rate, and pulse oximetry saturation will be recorded before the start of bronchoscopy (t1), at 5 minutes (t2), 10 minutes into the procedure (t3), monitored continuously during the procedure till its completion (t4) and 10 minutes post procedure (t5). At the end of the procedure, the senior faculty (observer B) who does the flexible bronchoscopy procedure marks the ease of bronchoscopy based on his experience. Patient is further assessed after 2 hours (tx) and asked to give their opinion on the procedure, the quality of sedation, discomfort, any adjustment needed in the dose of sedation and willingness for a repeat procedure if required and is documented in a proforma. The patient will be monitored by both Observer B and Observer C during the procedure and post procedure by Observer C.

Criteria for discontinuing or modifying allocated interventions {11b}

The participant will be discontinued from the trial and the code is broken by the observer A (a junior faculty from the department) in case of any serious adverse events or death or if the knowledge of the administered drug is essential in management of an untoward event that arise during the study period

Strategies to improve adherence to interventions {11c}

Not applicable

Relevant concomitant care permitted or prohibited during the trial {11d}

Patients who develop intolerable cough, distress or pain will be given an additional 1 ml of 1% lignocaine aliquot. Patient will be continuously monitored, keeping records of the vital parameters. Oxygen will be administered if the patient develops desaturation (change in spO2 measurement by atleast 4% from baseline). Hypotension (systolic blood pressure < 90 mmHg) will be managed by intravenous crystalloids. Bradycardia (Heart rate<50 beats per minute will managed by intravenous atropine (0.01mg/Kg).

Provisions for post-trial care {30}

Post trial, patient will be monitored for 24 hours, any adverse events will be managed, and those events which are directly related to the study will be managed free of cost.

Outcomes {12}

- ***Primary outcome measures:***

    1. Composite score during the bronchoscopy procedure. The composite score assess the patient comfort, tolerance during the procedure. It is assessed both before and after passing the bronchoscope through the vocal cords.
    2. Numerical Rating Scale (NRS) for pain intensity and distress. Measures the pain and distress faced by the patient during the procedure. It is assessed both during and post procedure both objectively and subjectively.
    3. Visual Analogue Scale (VAS) for cough. VAS score is used to assess the severity of cough during the bronchoscopy and two hours after the procedure.
    4. Ramsay sedation score (RSS). To assess the level of sedation.
    5. Ease of bronchoscopy procedure as assessed by Observer B during the procedure.

- ***Secondary Outcome measures:***
    1. Willingness for repeatability of the procedure as felt by patient.
    2. Variations in heart rate (HR), blood pressure (BP), oxygen saturation (SpO2). Vital parameters are monitored non-invasively at baseline, 5 minutes, 10 minutes, at the end of scopy and 10 minutes post procedure.

3. Duration of bronchoscopy procedure
4. Procedures underwent during bronchoscopy (Bronchial washing, broncho-alveolar lavage (BAL), bronchial brushing, endobronchial biopsy, transbronchial needle aspiration (TBNA), or transbronchial lung biopsy (TBLB)

Participant timeline {13}

Figure. schedule of enrolment, interventions, and assessment.

		STUDY PERIOD						
	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT**	$-t_1$	0	t_1	t_2	t_3	t_4	t_5	t_x
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
[List other procedures]	-							
Allocation		X						
INTERVENTIONS:								
[Intervention A]			←	—	—	→		
[Intervention B]			←	—	—	→		
[List other study groups]								
ASSESSMENTS:								
[List baseline variables]	X	X						
[List outcome variables]			X	X	X	X	X	X
[List other data variables]								

-t1: Where the patient is screened whether the patient meets the inclusion. Patient is explained regarding the study methodology and informed consent is taken.
0: Patient is randomized into either of the two groups based on computer generated randomization table using Microsoft Excel software.
t1 : At the start of bronchoscopy, vital parameters and primary outcome measures are assessed.
t2 : At 5 minutes into the procedure, vital parameters are assessed
t3 : 10 minutes into the procedure, vital parameters are assessed

t4 : At the end of bronchoscopy, vital parameters are assessed
t5 : 10 minutes after the procedure, vital parameters are documented
tx : Two hours after the procedure, secondary outcome variables and vital parameters are assessed

Intervention is done from t1 to t4; primary outcomes variables are assessed during the intervention period (t1-t4).

The composite score in the primary outcome is measured at two different levels, i.e., before vocal cords and then after when the bronchoscope passes the vocal cord

Sample size {14}

Anticipating a SD of 3.39 and a minimum clinically significant difference of 3 in composite score for a power of 90% at 95% confidence level, a minimum of 30 in each group need to be recruited.

Recruitment {15}

Patients who are admitted in the hospital and is requiring bronchoscopy for either therapeutic or diagnostic purpose will be included in the study, provided they meet the inclusion criteria.

Assignment of interventions: allocation

Sequence generation {16a}

Patients are randomized based on a computer generated randomization table, using Microsoft excel software. Patients who meet the inclusion criteria is randomized as per pre-generated randomization table

Concealment mechanism {16b}

The randomization is done by Observer A in the study (a junior resident in the department). Observer A keeps the pre-generated randomization table until the end of the study and allocates patients to the two groups without the knowledge of any other observers or patients involved in the study. Observer A is not further involved in the study

Implementation {16c}

The randomization is done by Observer A in the study (a junior resident doctor in the department). Observer A keeps the pre-generated randomization table until the end of the study and allocates patients to the two groups without the knowledge of any of the observers or patients involved in the study. Observer A is not further involved in the study

Assignment of interventions: Blinding

Who will be blinded {17a}

Outcome assessors and patients will be blinded to the study. The randomization and patient

allocation is done by Observer A in the study (a junior resident in the department). Other observers and patients are not aware of the study drugs used. Observer A is not involved in the further part of the study.

Procedure for unblinding if needed {17b}

In the event of any serious adverse events or death of the patient or in certain situations where management of the complications require the knowledge of the study drug, it will be revealed by the Observer A.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Patients who are posted for bronchoscopy in the department for various indications are initially screened for eligibility and baseline vital parameters like non-invasive blood pressure, pulse rate, peripheral oxygen saturation (spO2) are recorded (-t1). After allocating into one of the two groups, vital parameters are recorded at the start of bronchoscopy (t1). Patient vitals are continuously monitored and recorded at 5 minutes (t2), 10 min (t3), at the end of the scopy (t4), 10 minutes post procedure (t5). Primary outcome variable used for assessing patient comfort and tolerance to bronchoscopy procedure is the composite score, which is assessed before and after crossing the vocal cord. It is assessed during the bronchoscopy. Other primary outcome variables that are assessed include the numerical rating scale (NRS) for pain intensity and distress. The NRS is a numerical scale, in which 0-3 is mild, 3-6 is moderate and more than 6 is severe pain or distress. NRS is assessed during bronchoscopy. Visual analogue scale (VAS) for cough is a scale which is marked from 0-10 where 0 is the least and 10 marks the worst cough. It is assessed by the observer C during bronchoscopy and is further marked by the patient based on his experience two hours after the procedure (tx). Ramsay sedation score (RSS) is assessed during bronchoscopy by the observer C. Ease of bronchoscopy is assessed by the observer B, who does the bronchoscopy based on his experience, and is marked either easy, slightly difficult or very difficult. Vital parameters are recorded at baseline (-t1), at the start of bronchoscopy (t1), 5 minutes (t2), 10 minutes (t3), at the end of scopy (t4), 10 minutes post bronchpscopy (t5). Patient is further asked to mark his experience with the procedure in a preformed questionnaire, 2 hours after the procedure including willingness to repeat the study if required and whether sedation was adequate.

Plans to promote participant retention and complete follow-up {18b}

NA

Data management {19}

Data entry will be done by a junior faculty in SPSS software version 27 (2020) on weekly basis. The administered drugs will be entered at the end of the study at the time of analysis. The data will be stored in external storage device as well as in cloud storage. After data entry the values will be checked by the junior faculty and cross checked for any errors by a senior faculty.

Confidentiality {27}

The study data does not include any personal information related to the patient. Patient details which is included in the patient consent form will be kept in separate folder for future references if any need arise.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

NA

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

To compare composite score, between the two groups, independent t-test or Mann-Whitney U test will be used. Continuous variables like age, height, weight etc. will be compared between the two groups using independent t test, whereas categorical variables like gender, Ramsay sedation score etc. will be compared between the two groups using chi-square test/ Fishers exact test.

Interim analyses {21b}

NA

Methods for additional analyses (e.g. subgroup analyses) {20b}

NA

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

NA

Plans to give access to the full protocol, participant level-data and statistical code {31c}

NA

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The trial is a single center trial conducted in Kasturba medical college hospital, Mangalore. The trial is run on individual basis by the principal investigators and supervised by the senior faculty in the department. The trial will be overseen by the departmental scientific committee on a weekly basis or as when need arise, in case of any adverse events. The institutional ethics committee will oversee the overall conductance of the trial and inspection will be done by the ethics committee as and when required. A detailed report shall be submitted to the ethics committee at the end of six

months. In addition, if any adverse events arise, at any point of time which is directly related to the study, it will be reported to the ethics committee.

Composition of the data monitoring committee, its role and reporting structure {21a}

DMC is not needed for the study as the study involves small group of patients and is in a single center. Further, data will be stored in SPSS software and kept in local storage as well as in cloud storage. The data does not contain any personal information of the patients.

Adverse event reporting and harms {22}

Adverse events if any, which is directly related to the study drug will be monitored, assessed by both senior and junior faculty involved in the study. Patient will be on continuous monitoring of vital parameters. If any such adverse events arise during the study, will be reported to the departmental scientific committee, institutional ethics committee, and pharmacovigilance committee in the hospital. Any such events will be managed by the treating physician and the cost for the same will be covered under the departmental trial fund.

Frequency and plans for auditing trial conduct {23}

The overall conduct of the study will be overseen by the departmental scientific committee on a weekly basis, which is constituted by the senior faculty members in the department. The study will be further observed by the institutional ethics committee and can ask for a detailed report as and when instructed by the committee in addition to mandatory six-monthly report. This will be independent from the investigators.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Any change in the conductance of the study made in the protocol will be informed in the specified format to the Institutional ethics committee and the CTRI. As the study does not have follow up, patients who have already completed the study are not informed about any change in the protocol.

Dissemination plans {31a}

The result of the study will be shared with the public or participants or health care professionals via publication in suitable journal. There are no publication restrictions.

Discussion

The ease of bronchoscopy is assessed by observer B. As there are two senior consultants involved in the study, we anticipate some observer-to-observer variation in the assessment.

Patient-to-patient variation is may be seen as each patient has different perception of pain or

distress.

Trial status

Recruitment started 10/04/2022

Trial will take approximately one year or when the study sample size is attained.

Abbreviations

CTRI- Central Trial Registry of India

IEC- Institutional Ethics Committee

Declarations

Trials guidance: All manuscripts must contain the following subheadings:

- Acknowledgements
- Authors' contributions
- Funding
- Availability of data and material
- Ethics approval and consent to participate
- Consent for publication
- Competing interests
- Authors' information (optional)

Acknowledgements

Not applicable

Authors' contributions {31b}

TA is the Chief Investigator; he conceived the study, led the proposal and protocol development. PA contributed to study design and to development of the proposal. VA was the lead trial methodologist. All authors read and approved the final manuscript.

Funding {4}

The financial and material support will be provided the Directorate of research, Manipal academy of higher education, under which the institution belongs. The fund was allocated as a part of academic development program. The funding source have no further role in the research

Availability of data and materials {29}

The data will be entered and stored in external storage device and cloud storage by a junior faculty. Analysis will be done by statistician who is not involved in the study. Investigators will not have access to the data until the study is over. There is no contractual agreements that limit access for investigators.

Ethics approval and consent to participate {24}

Prior approval for the study is taken from Institutional Ethics Committee (IEC), Kasturbe Medical College Hospital, Mangalore (Ref No: IEC KMC MLR 10/2021/310). Written informed consent will be taken from all the study participants

Consent for publication {32}

Not applicable.

Competing interests {28}

The authors declare that they have no competing interests

Authors' information (optional)

1. Thomas Antony, Senior Resident, Department of Respiratory Medicine, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal.
2. Preetam Rajgopal Acharya, Senior Resident, Department of Respiratory Medicine, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal
3. Vishak Acharya, Senior Resident, Department of Respiratory Medicine, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal

References

1. Abdel-Ghaffar HS, Kamal SM, El Sherif FA, Mohamed SA. Comparison of nebulised dexmedetomidine, ketamine, or midazolam for premedication in preschool children undergoing bone marrow biopsy. Br J Anaesth [Internet]. 2018;121(2):445–52. Available from: https://doi.org/10.1016/j.bja.2018.03.039
2. Kumari P, Kumar A, Sinha C, Kumar A, Rai DK, Kumar R. Fentanyl vs dexmedetomidine nebulization as adjuvant to lignocaine: A comparative study during awake flexible fiberoptic bronchoscopy. Trends Anaesth Crit Care [Internet]. 2020;(xxxx). Available from: https://doi.org/10.1016/j.tacc.2020.09.009
3. Mikami M, Zhang Y, Kim B, Worgall TS, Groeben H, Emala CW. Dexmedetomidine's

inhibitory effects on acetylcholine release from cholinergic nerves in guinea pig trachea: A mechanism that accounts for its clinical benefit during airway irritation. BMC Anesthesiol. 2017;17(1):1–11.

4. Goneppanavar U, Magazine R, Janardhana BP, Achar SK. Intravenous Dexmedetomidine Provides Superior Patient Comfort and Tolerance Compared to Intravenous Midazolam in Patients Undergoing Flexible Bronchoscopy. 2015;2015.
5. Du Rand IA, Blaikley J, Booton R, Chaudhuri N, Gupta V, Khalid S, et al. British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults. Thorax. 2013;68(SUPPL. 1).
6. Anant Mohan, Karan Madan, Vijay Hadda, Pawan Tiwari, Saurabh Mittal, Randeep Guleria GK, SK Luhadia, RN Solanki, KB Gupta, Rajesh Swarnakar, SN Gaur, Pratibha Singhal IIA, Shweta Bansal, Prashu Ram Bista, Shiba Kalyan Biswal, Ashesh Dhungana, Sachin Doddamani DD, Avneet Garg, Tajamul Hussain, Hariharan Iyer, Venkatnarayan Kavitha, Umasankar Kalai RK, Swapnil Mehta, Vijay Noel Nongpiur, Loganathan N, Sryma PB, Raju Prasad Pangeni PS, Jugendra Singh, Tejas Suri, Sandip Agarwal, Ritesh Agarwal, Ashutosh Nath Aggarwal GA, et al. Guidelines for Diagnostic Flexible Bronchoscopy in Adults: Joint Indian Chest Society/National College of Chest Physicians (I)/Indian Association for Bronchology Recommendations. Lung India. 2019;36::S37-89.
7. Cruickshank M, Henderson L, MacLennan G, Fraser C, Campbell M, Blackwood B et al. Alpha-2 agonists for sedation of mechanically ventilated adults in intensive care units: a systematic review. Heal Technol Assess. 2016;20(25)(March):v–xx, 1–117.
8. Rahul Magazine, Shivaraj Kumar Venkatachala, Umesh Goneppanavar, Vyshak Uddur Surendra, Vasudeva Guddattu BC. Comparison of midazolam and low-dose dexmedetomidine in flexible bronchoscopy: A prospective, randomized, double-blinded study. Indian J Pharmacol. 2020;52(1)(Jan-Feb):23–30.
9. Ryu JH, Lee SW, Lee JH, Lee EH, Do SH, Kim CS. Randomized double-blind study of remifentanil and dexmedetomidine for flexible bronchoscopy. Br J Anaesth. 2012;108(3):503–11.
10. Gu W, Xu M, Lu H, Huang Q, Wu J. Nebulized dexmedetomidine-lidocaine inhalation as a premedication for flexible bronchoscopy: A randomized trial. J Thorac Dis. 2019;11(11):4663–70.
11. Ouchi K, Sugiyama K. Dexmedetomidine dose dependently enhances the local anesthetic action of lidocaine in inferior alveolar nerve block: A randomized double-blind study. Reg Anesth Pain Med. 2016;41(3):348–55.

12. Hetta DF, Kamal EE, Mahran AM, Ahmed DG, Elawamy A, Abdelraouf AMS. Efficacy of local dexmedetomidine add-on for spermatic cord block anesthesia in patients undergoing intrascrotal surgeries: Randomized controlled multicenter clinical trial. J Pain Res. 2017;10:2621–8.
13. Zanaty OM, El Metainy SA. A comparative evaluation of nebulized dexmedetomidine, nebulized ketamine, and their combination as premedication for outpatient pediatric dental surgery. Anesth Analg. 2015;121(1):167–71.
14. Anupriya J, Kurhekar P. Randomised comparison between the efficacy of two doses of nebulised dexmedetomidine for premedication in paediatric patients. Turkish J Anaesthesiol Reanim. 2020;48(4):314–20.
15. Bonagua DM, Crisostomo HC, Hernandez AGC, Brodit SE. The effect of dexmedetomidine nebulization as a premedication prior to peripheral intravenous access in pediatric patients and its effect on separation anxiety score and acceptance to intrave- nous cannulation score. 2020;8(2):120–8.
16. Misra S, Behera BK, Mitra JK, Sahoo AK, Jena SS, Srinivasan A. Effect of preoperative dexmedetomidine nebulization on the hemodynamic response to laryngoscopy and intubation: A randomized control trial. Korean J Anesthesiol. 2021;74(2):150–7.
17. Nimmagadda R R Kumar, Nirmala Jonnavithula, Shibani Padhy VS, Naik VV. Evaluation of nebulised dexmedetomidine in blunting haemodynamic response to intubation: A prospective randomised study. Indian J Anaesth [Internet]. 2020;(october). Available from: https://journals.lww.com/ijaweb/Fulltext/2020/64100/Evaluation_of_nebulised_dexmedetomidine_in.8.aspx
18. Saikat Niyogi, Asit Biswas, Indrani Chakraborty SC, Acharjee A. Attenuation of haemodynamic responses to laryngoscopy and endotracheal intubation with dexmedetomidine: A comparison between intravenous and intranasal route. Indian J Anaesth [Internet]. 2019;(november). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6868674/pdf/IJA-63-915.pdf
19. Oriby ME. Comparison of intranasal dexmedetomidine and oral ketamine versus intranasal midazolam premedication for children undergoing dental rehabilitation. Anesthesiol Pain Med. 2019;9(1):1–6.
20. Mumtaz Hussain, Nidhi Arun, Sanjeev Kumar, Arvind Kumar, Rajnish Kumar SS. Effect of Dexmedetomidine Nebulization on Attenuation of Haemodynamic Responses to Laryngoscopy: Randomized Controlled Study. Indian J Anesth Analg. 2019;6(4).
21. Shafa A, Habibzadeh M, Shetabi H, Aghil A. Comparing the hemodynamic effects of

nebulized dexmedetomidine and nebulized lidocaine in children undergoing fiberoptic bronchoscopy. J Adv Med Biomed Res. 2019;27(120):14–9.

22. Ahmad Sabry MH, El Gamal N, Elhelw N, Ammar R. Comparison of the use of nebulized dexmedetomidine, ketamine, and a mixture thereof as premedication in pediatric patients undergoing tonsillectomy: a double-blind randomized study. Res Opin Anesth Intensive Care. 2020;7(1):70.

23. Breivik H, Borchgrevink PC, Allen SM, Hals EKB, Kvarstein G, Stubhaug A. Assessment of pain. Br J Anaesth. 2008;101(1):P17-24.

24. Ramsay MAE, Savege TM, Simpson BRJ GR. Controlled Sedation with Alphaxalone-Alphadolone. Br Med J. 2(5920)(656–9.).