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A prospective randomized controlled study comparing intravenous dexmedetomidine plus ketamine combination with intravenous dexmedetomidine alone for awake fibreoptic nasotracheal intubation

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Abstract

Background: The purpose of this study was to compare the efficacy and safety of dexmedetomidine versus dexmedetomidine and ketamine for sedation during awake fibreoptic intubation (FOI) in patients posted for elective surgeries. Ninety-eight American Society of Anesthesiologists Physical Status (ASA-PS) I–II patients with difficult airway and scheduled for elective surgeries were enrolled in this study after institutional ethics committee approval. Patients were randomly allocated into 2 groups, i.e. 49 patients in each group. Group D patients received 1 μg/kg dexmedetomidine IV over 10 min in 100-mL normal saline followed by a continuous infusion at 0.5 μg/kg/h till FOI and 5-mL normal saline followed by saline infusion. Group DK patients received 1 μg/kg dexmedetomidine IV over 10 min in 100-mL normal saline. Further, they received IV ketamine 15 mg as a bolus of 5 mL, followed by continuous infusion of ketamine at 20 mg/h until the end of intubation. The primary objective was to compare the efficacy of the combination of IV dexmedetomidine and ketamine with IV dexmedetomidine alone as sedation for FOI. Vocal cord movement, sedation, coughing, facial grimace score, recall of procedure, and haemodynamics were also compared in both groups.

Results: Demographic data, vocal cord movement, cough score, facial grimace score, total drugs used, hoarseness, sore throat and level of recall were comparable in both groups. Haemodynamics were significantly better in group DK at 2, 3, 4 and 5 min compared to group D.

Conclusions: Addition of ketamine to dexmedetomidine did not improve intubating conditions, reduce cough or improve recall of FOI. However, patients remain sedated when ketamine was used with dexmedetomidine. The study was not registered prospectively in any clinical trial registry.

Keywords: Fibreoptic, Intubation, Dexmedetomidine, Ketamine, Sedation

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Background

Airway management is an important skill set learnt during training, and tracheal intubation is frequently required to ensure adequate airway management, while providing optimal operating conditions. However, in the presence of certain anatomical variants or airway pathology, visualization of the glottis by direct laryngoscopy can be difficult or impossible (Cook & MacDougall-Davis, 2012). Problems with tracheal intubation could be failure, difficulty, delay and cannot intubate cannot ventilate situation leading to aspiration and hypoxia which is undesirable. The principal adverse outcomes associated with the difficult airway include but are not limited to death, brain injury, cardiopulmonary arrest, unnecessary tracheostomy, airway trauma and damage to teeth (Cook et al., 2011a; Cook et al., 2011b). A fibreoptic intubation (FOI) plays a special role in securing the airway when tracheal intubation is difficult, when the airway is compromised, when the neck extension is to be avoided and in the presence of lower airway pathology (Wong et al., 2019; Collins & Blank, 2014). Nasal FOI is easier for securing the airway rather than an oral technique for anatomical reasons. Oral and facial surgeries can only be performed under nasotracheal intubation. However, it involves the risk of nasal bleeding (Hall & Shutt, 2003).

Currently, benzodiazepines, opioids and propofol are used alone or in combination for this purpose. Midazolam produces amnesia and makes the patient comfortable. Propofol has rapid onset and offset of action with profound amnesia. Opioids such as fentanyl suppresses respiratory centre and produces chest wall rigidity, and there is a risk of hypoxia and desaturation (Johnston & Rai, 2013; Liu et al., 2016).

Dexmedetomidine which is an α2-adrenoreceptor agonist is a valuable drug of use during fibreoptic intubation as it induces sedation and analgesia without depressing respiratory function (Chopra et al., 2016). In addition, xerostomia is commonly reported by patients. These two effects make dexmedetomidine highly desirable for awake, nasotracheal FOI. Unlike patients sedated with propofol, patients receiving dexmedetomidine are easily aroused to cooperate with medical procedures without expressing irritation. The relative sympatholysis achieved during dexmedetomidine infusions is an additional benefit in a procedure that may lead to elevations of heart rate and blood pressure (Cabrini et al., 2019). Ketamine, an NMDA antagonist, has been studied extensively as an adjunctive analgesic in the perioperative setting. At sub-anaesthetic doses, ketamine is well tolerated and has a low incidence of mild psychomimetic symptoms, nystagmus and double vision (Porter, 2019). While bradycardia and hypotension have been reported with dexmedetomidine, this is not observed in patients receiving a concurrent ketamine bolus injection. The undesirable feature of increasing airway secretions with ketamine administration is attenuated by the xerostomia induced by dexmedetomidine. Ketamine is selected to take advantage of its minimal impact on ventilator drive and analgesic properties. In addition, dexmedetomidine attenuates ketamine-induced cardiostimulatory effects and drug-induced delirium. Ketamine combined with dexmedetomidine provided excellent conditions for awake FOI including satisfactory sedation, patient cooperation and dry airway in randomized-controlled trials (Kumar et al., 2019; Sinha et al., 2014).

We hypothesized that sedation with dexmedetomidine plus ketamine combination for FOI could produce better intubating conditions when compared to using dexmedetomidine alone. The primary objective was to compare and study the efficacy of the combination of intravenous dexmedetomidine and ketamine with intravenous dexmedetomidine alone as sedation agents to facilitate awake, fibreoptic-guided nasal intubation with respect to intubation conditions (sedation score, vocal cord movement, cough score). Secondary outcomes were to compare the haemodynamic responses to intubation, incidence of desaturation, time taken for intubation, total dose of lignocaine/dexmedetomidine used, patient satisfaction score, level of recall and adverse events like sore throat and hoarseness.

Methods

This was a prospective, interventional, randomized controlled, double-blinded study which included patients between 18 and 60 years of either gender posted for elective surgeries (laparoscopic surgeries like appendicectomy, cholecystectomy, umbilical and epigastric hernioplasty, laparoscopic inguinal hernioplasty), belonging to ASA-PS I/II and with anticipated difficult intubation (Modified Mallampatti score III/IV). The study was approved by the Institutional Ethics Committee. Pregnant ladies, known alcoholics or drug abusers and those who have an allergy to the drugs involved in the study, bradycardia (baseline HR <40 beats/min), atrioventricular block, heart failure, significant neurological, hepatic, renal and pulmonary disease, emergency surgeries and any contraindication for nasal intubation like thrombocytopenia or coagulopathies were excluded from this study.

All the patients underwent a thorough pre-anaesthetic evaluation including relevant investigations like complete blood picture, bleeding time, clotting time, blood urea, serum creatinine and blood sugar. All systems were examined including the airway, and the procedure to be carried out was explained to the patients. After confirming 6 h nil by mouth, patients were shifted to OR and appropriately sized intravenous (IV) access

was secured. After obtaining written informed consent, patients satisfying the inclusion criteria were randomized into 2 groups using a computer-generated random number list. All patients were premeditated with IV pantoprazole 40 mg, IV ramosetron 0.3 mg and IV glycopyrrolate 0.2 mg as an institutional protocol for awake FOI. Standard monitoring using Philips Intellivue MP20 (pulse oximetry, non-invasive blood pressure monitors on the upper limb, respiratory rate, electrocardiography with lead 2, 3) was used for all patients. Oxygen at 2 L/min was administered through a nasal cannula.

Group D (dexmedetomidine) patients received a bolus dose of dexmedetomidine at 1 μg/kg over 10 min in 100-mL normal saline followed by a continuous infusion at 0.5 μg/kg/h using an infusion pump (Smiths Medical, Graseby™ 2000 syringe pump). Further, they received 5-mL normal saline, followed by plain normal saline infusion until the end of intubation. Group DK (dexmedetomidine plus ketamine) patients received a bolus dose of dexmedetomidine at 1 μg/kg over 10 min in 100-mL normal saline followed by a continuous infusion of dexmedetomidine at 0.5 μg/kg/h using an infusion pump. Further, they received IV ketamine 15 mg as a bolus of 5 mL, followed by a continuous infusion of ketamine at 20 mg/h until the end of intubation.

Any decrease in heart rate below 50/min was considered as bradycardia and was treated with 0.6 mg of atropine injection. Similarly, any fall of the mean blood pressure of more than 20% of baseline was considered as hypotension and was treated with fluid boluses and 6 mg of mephentermine injection boluses 6 mg IV. Any drop in saturation of oxygen below 90% was considered desaturation and was treated by stopping of study drug infusions and intubating the patient. Both groups had two infusion pumps.

Following the bolus doses, sedation score was assessed by an anaesthesiologist unaware of the regime used by modified observer assessment of alertness sedation (5 = respond readily to name spoken in a normal tone, 4 = lethargic response to name spoken in a normal tone, 3 = respond only after name spoken loudly or repeatedly, 2 = respond after mild prodding or shaking, 1 = does not respond to mild prodding or shaking). Xylometazoline nasal drops 0.1% (2 drops in each nostril), followed by 2 mL of 4% of lignocaine, were administered intranasally. Two puffs of 10% lignocaine spray were instilled in the same nostril immediately before inserting a nasal fiberscope. An endotracheal tube (ETT) of appropriate size (softened in warm water) was mounted over the fiberscope (Olympus BF Type PE2/TE2) and introduced through the selected nostril after 10 min of the start of study drugs. After visualization of the glottis and vocal cords, 2 mL of 4% lignocaine was injected through the epidural catheter passed through the working channel. Further aliquots were given if the vocal cords moved vigorously. A lubricated ETT was passed over it into the trachea and positioned 2–3 cm above the carina. The cuff was inflated, and the bronchoscope was withdrawn. General anaesthesia was administered using 2–2.5 mg propofol IV, and neuromuscular blockage was achieved using 0.5-mg/kg atracurium followed by discontinuation of study drugs.

The primary outcome was the comparison of intubation scores as assessed by vocal cord movement (1 = open, 2 = moving, 3 = closing, 4 = closed). Secondary outcomes were comparison of modified observer assessment of alertness/sedation (5 = respond readily to name spoken in a normal tone, 4 = lethargic response to name spoken in a normal tone, 3 = respond only after name is spoken loudly or repeatedly, 2 = respond after mild prodding or shaking, 1 = does not respond to mild prodding or shaking), coughing (1 = none, 2 = one gag or cough only, 3 ≥ 1 gag or cough, acceptable conditions, 4 = unacceptable conditions) and patient tolerance as assessed by facial grimace score (1 = no grimace, 2 = minimal grimace, 3 = mild grimace, 4 = moderate grimace, 5 = severe grimace, 6 = very severe grimace). Haemodynamics and oxygen saturation were monitored and noted at regular intervals (T1 = baseline, T2 = 2 min after sedation, T3 = at the beginning of fiberscope as it passes through the nostril, T4 = after advancing the ETT through the nasopharynx, T5 = 2 min after endotracheal intubation).

Other parameters compared were the time taken for intubation (time from the start of FOI to the correct placement of endotracheal tube), total dose of lignocaine and dexmedetomidine used, satisfaction score (1 = excellent, 2 = good, 3 = fair, and 4 = poor), level of recall (memory of pre-anaesthetic preparations, topical anaesthesia, endoscopy and intubation) and adverse events (sore throat, hoarseness). To achieve blinding, three anesthesiologists were required to conduct the study. One anesthesiologist prepared and controlled the drug infusions (who was not concerned with the patient management and data collection), the second one performed FOI and assessed the intubating conditions, and the third anesthesiologist documented the data and made postoperative visits the next day.

Statistical analysis

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements were presented as mean ± standard deviation, and results on categorical measurements are presented as number (%). Significance was assessed at 5% level of significance. The Student *t* test was used to find the significance of the study parameters on a continuous

scale between the two groups. The chi-square test was used to find the significance of the study parameters on a categorical scale between the two groups. Statistical analysis of the data collected was done using suitable statistical methods using GraphPad Prism 8. We referred to the study by Sinha et al. (Sinha et al., 2014) for sample size where authors enrolled 60 patients, i.e. 30 patients in each group. However, we included 49 patients in each group to compensate for possible exclusion due to adverse events on non-cooperation. Therefore, we decided to perform a post hoc analysis of power subsequently.

Results

A total of 98 patients completed the study, 49 in group D and 49 in group DK. Figure 1 shows the CONSORT flow diagram. Demographic data (age, gender, weight, ASA-PS) were comparable (Table 1). Sedation score and time for intubation (in minutes) was more in group D compared to group DK (p = 0.003 and p = 0.010, respectively) which was statistically significant (Table 1). Other variables like vocal cord movement, cough score, facial grimace score, total drugs used, hoarseness, sore throat and level of recall were comparable in both groups (Tables 2 and 3). The mean heart rate and MAP (at T2, T3, T4 and T5) were statistically significant in group DK than in group D (p value < 0.05) [Table 4]. Oxygen saturation was comparable between both groups at T1, T2, T3, T4 and T5 (Table 4). We performed a post hoc analysis of power mean ± standard deviation of primary outcomes and a type 1 error as 0.05 and found it to be 88%.

Discussion

Based on the analysis of our results, we found that although the addition of ketamine to dexmedetomidine did not improve intubating conditions, reduce cough or improve haemodynamic fluctuations, patients were more sedated compared to patients receiving dexmedetomidine alone. However, patients in the DK group were more satisfied.

Awake FOI is a stressful procedure, and thus, sedoanalgesia may be necessary to relieve anxiety, ease discomfort and reduce pain. A patient who undergoes FOI frequently experiences pain, cough and sensation of asphyxiation and might remember the procedure as a noxious experience. With the intention of alleviating apprehension before the procedure, providing amnesia and patient comfort, sedation is frequently used (Knudsen et al., 2016; Ramkumar, 2011). Propofol, ketamine, benzodiazepines, opiates and dexmedetomidine are the most commonly used, alone or in combination for sedation (Zhou et al., 2016; Yousuf et al., 2017). But deeply

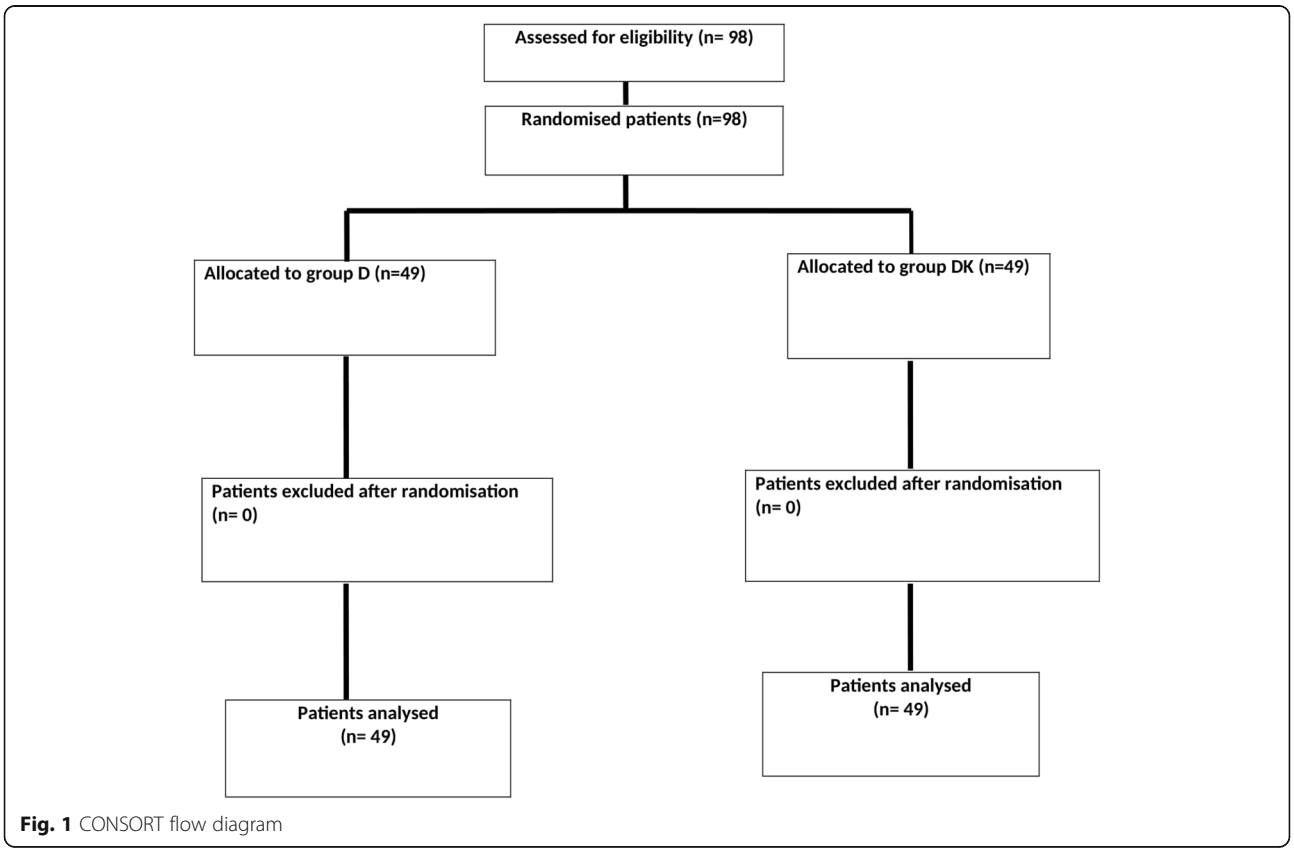

Fig. 1 CONSORT flow diagram

Table 1 Comparison of demographic data

Variables	Group D (n = 49)	Group DK (n = 49)	p value
Age (years)	43.86 ± 9.914	44.55 ± 8.92	0.716
Weight (kg)	63.04 ± 10.37	62.90 ± 10.06	0.945
Gender (male/female)	31/18 (63/37)	23/26 (46/54)	0.104
ASA-PS (I/II)	21/28 (43/57)	30/19 (61/39)	0.068

sedated patient may be unable to follow commands, like protrusion of the tongue and swallowing. Even worse, excessively sedated patient might aspirate and might even compromise airway and ventilation (Gonzalez et al., 2003).

The primary goals for sedation during awake FOI are maintenance of spontaneous respiration, adequate oxygenation, and sufficient ventilation. The patient's ability to inspire deeply on command facilitates ventilation and oxygenation (Kar Kurt et al., 2015). Secondary goals also include amnesia and the ability to cooperate with instructions to take deep breaths or protrude the tongue. Amnesia of potentially uncomfortable procedures is desirable for the patient's psychologic outlook towards repeat awake fibreoptic intubation and other medical care (Wahidi et al., 2011). No single agent provides amnesia, anxiolysis and analgesia, so a combination of drugs is necessary (Johnston & Rai, 2013). The sedation regimen should be simple and the degree of sedation kept to the minimum required for patient comfort.

Sedation induced by dexmedetomidine has unique properties, which is well documented in intubated and ventilated ICU patients (Sharma et al., 2017; Dhasmana, 2014; Hoy & Keating, 2011). It produces an unusually cooperative form of sedation in which the patient is calm and easily roused from sleep to wakefulness to allow task performance and excellent communication and cooperation while intubated and ventilated and then quickly back to sleep when not stimulated. The primary site of action of α2-adrenoceptor agonists is the locus ceruleus (nucleus in the pons) and not the cerebral cortex, as would be the case with GABA-mimetic drugs (Reel & Maani, 2020). This should be the reason why this class of drugs produces a different type of sedation when compared to propofol and benzodiazepines.

While bradycardia and hypotension have been reported with dexmedetomidine, this is not observed in patients receiving a concurrent ketamine bolus injection. It has been suggested that low-dose ketamine infusion (4 μg/kg/min) effectively lowers postoperative narcotic requirements without significant effect on mood, perception and cognition (Kumar et al., 2019; El Sharkawy, 2019). The undesirable feature of increasing airway secretions with ketamine administration was attenuated by the xerostomia induced by dexmedetomidine. In addition, dexmedetomidine attenuated ketamine-induced cardio stimulatory effects and drug-induced delirium. The combination of dexmedetomidine and ketamine may have resulted in higher sedation level in group DK patients, which was statistically significant ($p < 0.003$). The sedative effects of the combination of ketamine and dexmedetomidine were found to be additive at the endpoints of hypnosis and anaesthesia. Synergism has been found between agents with known functional links in the central nervous system.

Sedation produced by dexmedetomidine is unique when compared to propofol and other narcotics because of its mechanism of action in the locus ceruleus (nucleus in the pons) which is involved in the physiological response to stress and anxiety. The fact that patients maintain spontaneous breathing with dexmedetomidine while attempts are made to secure their airway, makes it an ideal agent for use in elective and critical intubation (Gao et al., 2017; Hassan & Mahran, 2017; He et al.,

Table 2 Comparison of sedation, cough and grimace score, time for intubation, adverse events and total drug used

Parameter	Group D (n = 49)	Group DK (n = 49)	p value
Sedation score	3.82 ± 0.635	3.469 ± 0.504	0.003
Vocal cord movement	1.57 ± 0.58	1.49 ± 0.50	0.46
Cough score	1.57 ± 0.61	1.40 ± 0.497	0.15
Facial grimace score	1.59 ± 0.497	1.49 ± 0.50	0.32
Time for intubation (min)	7.10 ± 0.898	6.655 ± 0.77	0.010
Total lidocaine used (mg)	279.32 ± 59.06	254.36 ± 65.92	0.051
Total dexmedetomidine used (μg)	66.77 ± 11.05	66.40 ± 10.51	0.863
Hoarseness (Y/N)	6/43	2/47	0.14
Sore throat (Y/N)	13/36	4/45	0.16

Table 3 Comparison of level recall for various events

Level of recall	Group D (n = 49)	Group DK (n = 49)	p value
Pre-anaesthetic preparation	100%	100%	–
Topical anaesthesia (Y/N)	45/4	44/5	0.726
Endoscopy/intubation (Y/N)	42/7	38/11	0.296

2014). Our study showed similar results to Sinha et al. providing similar sedation and patient satisfaction (Sinha et al., 2014). Dexmedetomidine blocks the sympathetic supply of the upper airway and produces xerostomia, while ketamine attenuated the xerostomia by producing increased airway secretions. In addition, the use of glycopyrrolate in both groups effectively decreased airway secretions. We used the 'spray as you go' technique which involves instillation of a topical agent through the advancing bronchoscope (Xue et al., 2009). Lidocaine jelly was used to lubricate the flexible FOI prior to nasal insertion.

Our study was similar to that performed by Sinha et al. in terms of methodology. However, our sample size was more (60 patients in the previous study versus 98 patients in our study). We also performed a post hoc analysis of power which was 88%.

One of the limitations of the study was the small sample size. We suggest further randomized controlled trials before extrapolating the results of this study in clinical practice.

Table 4 Comparison of haemodynamic parameters

Parameter	Group D (n = 49)	Group DK (n = 49)	p value
Heart rate (per min)			
T1	88.83 ± 9.01	83.32 ± 8.99	0.4083
T2	87.04 ± 13.62	80.14 ± 8.8	0.0037
T3	89.12 ± 11.12	84.18 ± 10.09	0.0234
T4	89.25 ± 10.07	82.67 ± 9.99	0.0016
T5	94 ± 8.70	87.42 ± 11.77	0.0022
MAP (mmHg)			
T1	95.22 ± 10.65	88.59 ± 10.01	0.6411
T2	89.53 ± 9.89	84.94 ± 7.24	0.0102
T3	94.34 ± 9.46	88.67 ± 8.24	0.002
T4	85.94 ± 9.98	89.96 ± 8.99	0.038
T5	91.75 ± 10.20	83.39 ± 10.64	0.001
SpO_2 (%)			
T1	99.63 ± 0.9	99.61 ± 0.77	0.90
T2	98.59 ± 0.78	98.53 ± 0.81	0.70
T3	98.51 ± 0.89	98.42 ± 0.83	0.605
T4	99.02 ± 0.90	99.12 ± 0.88	0.579
T5	99.75 ± 1.1	99.75 ± 0.99	1

Conclusion

To conclude, the addition of ketamine to dexmedetomidine does not improve intubating conditions, reduce cough or improve recall of FOI. Rather, patients are more likely to be sedated compared to patients receiving dexmedetomidine alone.

Abbreviations

FOI: Fibreoptic intubation; ASA-PS: American Society of Anesthesiologists Physical Status; D: Dexmedetomidine; DK: Dexmedetomidine ketamine; GABA: Gamma amino butyric acid; ETT: Endotracheal tube; IV: Intravenous

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Ethical approval and consent to participate

The study was approved by the Ethics Committee of Yashoda Hospitals, Secunderabad, Telangana State, India. Written informed consent was obtained from all patients. Reference number not available.

Authors' contributions

DJ: literature review, manuscript preparation, and followed the patients. GF: manuscript review, data analysis, and followed the patients. SD: concepts and design. BV: concepts and design. AN: literature review, manuscript editing, final draft, and data analysis. All authors read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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