RESEARCH PAPER

Propofol *versus* Fentanyl for Sedation in Pediatric Bronchoscopy: *A Randomized Controlled Trial*

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Objectives: To compare propofol and fentanyl to induce conscious sedation in children undergoing flexible bronchoscopy.

Study design: Randomized controlled trial.

Setting: Pediatric Pulmonology division at a tertiary care center in Delhi, India.

Participants: Children aged 3-15 years who underwent flexible bronchoscopy.

Intervention: Children received either intravenous propofol 1 mg/kg administered as a slow bolus over 1 minute followed by 2 mg/kg/hour infusion, or intravenous Fentanyl 2 µg/kg administered as a slow bolus over one minute.

Outcomes: Primary outcome was time to achieve conscious sedation (Ramsay score 3). Secondary outcomes were need for adjuvant midazolam, physician satisfaction, level of cough, recovery features, and side-effects in the groups.

Results: 53 children (propofol 27, fentanyl 26) were enrolled in the study. The mean (SD) time taken to achieve Ramsay score 03 was lower in propofol than fentanyl [15.7 (4.4) s *vs* 206 (55) s, *P*<0.001]. Propofol arm had significantly higher physician satisfaction, less requirement of adjuvant midazolam, less coughing and faster regain of full consciousness. There was no difference in drug side-effects between the groups.

Conclusion: Propofol has a shorter sedation induction time, less coughing during procedure, less recovery time, and better physician satisfaction compared to fentanyl for flexible bronchoscopy in children.

Keywords: *Conscious sedation, Endoscopy, Ramsay score, Visual analog scale*.

Trial registration: CTRI/2016/09/007307

Flexible video bronchoscopy with its ancillary procedures (broncho-alveolar lavage, transbronchial biopsy, bronchial washings, bronchial brushing and transbronchial needle aspiration) are well established diagnostic techniques, while endoscopic bronchial ultrasound and auto fluorescence bronchoscopy allow advanced evaluation of mediastinal, endobronchial and parenchymal lesions [1]. General anaesthesia was the preferred mode of anaesthesia for bronchoscopy in pediatric practice; however, according to modern practice, conscious sedation is the most routine anaesthetic measure utilized by pediatric bronchoscopists [2]. It is safer and economical than deep sedation or general anaesthesia [3].

Chloral hydrate, benzodiazepines such as midazolam and opioids such as fentanyl are the most common sedative medications used in pediatric procedure room [4]. In pediatric bronchoscopy, fentanyl is utilized widely, alone or in combination with other medications [5]. Propofol is being used increasingly in pediatric bronchoscopy procedures in recent times [6,7]. In addition, procedural sedation administration is done inside procedure room by physicians instead of anaesthetist, in many centers [8].

Propofol has been used in combination with fentanyl in pediatric bronchoscopy as a sedative strategy and it has been shown to be better than volatile agents [9]. Propofol and fentanyl have been used in isolation with good outcomes [5,7]. While multiple combinations have been compared in different studies [6,9], propofol and fentanyl have not been compared with each other. There is a need to establish a safe and effective sedation regimen for paediatric bronchoscopy and close a gap in the knowledge. Therefore, in this study, we compared the time required to induce the level of conscious sedation to achieve Ramsay score 3 [10] after administration of sedative medication (propofol or fentanyl) in children undergoing fibreoptic bronchoscopy.

METHODS

All children, 3 to 15 years of age, admitted to a tertiary-care hospital in northern India for flexible bronchoscopy in the division of Pediatric Pulmonology between 1st November, 2016 and 1st May, 2017 were screened for

eligibility for the study. Children with any of the following were excluded: previous untoward reaction for medications used for sedation, children with history of lipid allergy, cardiovascular instability (needing inotropic support), oxygen dependency at the time of enrolment, oxygen saturation <90% at the time of enrolment, encephalopathy or impaired consciousness, evidence of acute or chronic liver disease, children who are already on any sedative medication including antiepileptic drugs, or any intervention which would interfere with outcome, and contraindications to use these medications. Children were enrolled after written informed consent was obtained from parents or legally authorized representative. The trial was approved by the Institutional Ethics Committee.

As there is a lack of pediatric data to compare time to achieve conscious sedation with propofol and fentanyl, we did an interim analysis after 30 patients to calculate sample size. Mean time to achieve Ramsay score 3 in fentanyl group was 194.8 (62.12) seconds. We assumed that propofol would decrease this time by 25%. To detect this difference with 95% confidence and 80% power, the calculated sample size was 52 children (26 per group).

Children were randomized using computer-generated block randomization with variable block sizes, performed by a person not involved in the study. The respective randomization lists were kept in sequentially numbered, sealed, opaque envelopes for allocation concealment. All the envelopes were kept inside the bronchoscopy room in a locker and envelopes were taken out according to the serial number and were opened by bronchoscopy nurse-in-charge and the arm was documented against the serial number in a separate paper. Selected intervention was given by resident in-charge of the bronchoscopy room. Due to the apparent difference in the colour of the medications in this study, the investigator and residents were not blinded to the study arm. However, the assignment was not disclosed to the patient or the bronchoscopist.

For children randomized to arm 1, intravenous propofol 1 mg/kg (maximum of 50 mg) was administered as a slow bolus over 1 minute followed by 2 mg/kg/hour infusion for maximum of 15 minutes or till end of the procedure, whichever occurred earlier. One percent propofol (10 mg/mL) was used for slow bolus and propofol was diluted with 5% dextrose to make dilution of 2 mg/mL for infusion. For children randomized to arm 2, intravenous Fentanyl 2 µg/kg (maximum of 100 µg) was administered as a slow bolus over one minute. Fentanyl was diluted with normal saline to make it 10 µg/mL.

The child's oxygen saturation, pulse rate and respiratory rate were documented and monitored during the procedure and thereafter, by a designated health worker, till recovery from sedation. Free flow oxygen at flow rate of 10 L/min was administered through a tube (from the nostril other than the one used for inserting the bronchoscope). Standard resuscitation facilities were available during the procedure and till recovery from sedation. IV propofol or fentanyl was administered according to the selected arm and a digital stop watch was started at the end of administration of the respective bolus medication. The stop watch reading was documented in seconds with the achievement of spontaneous closure of eyes (Ramsay Score 3), by the principal investigator [10].

If Ramsay score of 3 could not be achieved at end of 180 seconds of end of IV propofol/fentanyl bolus, a dose of IV midazolam 0.1 mg/kg (maximum dose of 5 mg) was administered and child observed for 1 minute; in case of failure, second dose (0.1 mg/kg) was administered and child observed for another 1 minute. At the end of 5 minutes, if sedation had been not achieved, it was considered as sedation failure. In addition, midazolam was administered at a dose of 0.1 mg/kg (maximum dose of 5 mg) bolus at a time up to maximum of two doses, for those who had inadequate sedation to continue procedure irrespective of the arm. Number of midazolam boluses was documented.

The video recording of bronchoscopy was started at the beginning of procedure and stopped once procedure was over. The cough score, secretion score, and physician satisfaction score were decided separately by the bronchoscopist and an independent observer as soon as the procedure was over, using the 100 mm visual analogue score [11-13]. The best possible response was taken as 100 and the worse possible finding was scored as 0. Scores were documented independently and the average was taken as the final score.

Pauses in respiration, maximum drop of pulse rate and maximum rise of pulse rate were also documented. Recovery time was documented as time to regain full consciousness (in minutes) after the end of bronchoscopy procedure. The stop watch readings was documented once Ramsay score 01 was achieved. Monitoring and administration of sedation were done by two residents, assisted by pediatric respiratory nurse. The bronchoscopies were performed by experienced pediatricians.

Statistical analysis: Data were collected using a pre-tested data collection sheet by principal investigator and data were managed using Microsoft Excel. STATA 13 (Stata Corp., College Station, TX, USA) was used for

analysis. Time to achieve Ramsay score 3, visual analogue scores (physician satisfaction, cough, secretion), additional doses of midazolam, and time to achieve full recovery in two groups were calculated and expressed as mean (SD). Differences were compared using independent t test. In addition, Fisher's exact test was used to compare categorical variables. Intention-to-treat analysis was used. Statistical significance was taken as *P* value less than 0.05.

RESULTS

One hundred and twelve children were screened for eligibility for the study over a duration of approximately six months. After excluding 59 children, a total of 53 children were randomized; 27 in propofol arm and 26 in fentanyl arm (***Fig.* 1**). Fifty two children completed the study and one patient who was in fentanyl group, sedation was not administered according to the protocol (***Fig.* 1**). ***Table* I** shows the baseline characteristics of the enrolled children. There were no significant differences between the two groups.

The mean (SD) time taken to achieve Ramsay score 3 was lower in the propofol arm than in the fentanyl arm [15.7 (4.4) s *vs* 206 (55) s]; the mean difference (95% CI) was 190.3 (168.9, 211.6) s and it was statistically significant *(P*<0.001) (***Fig.* 2**).

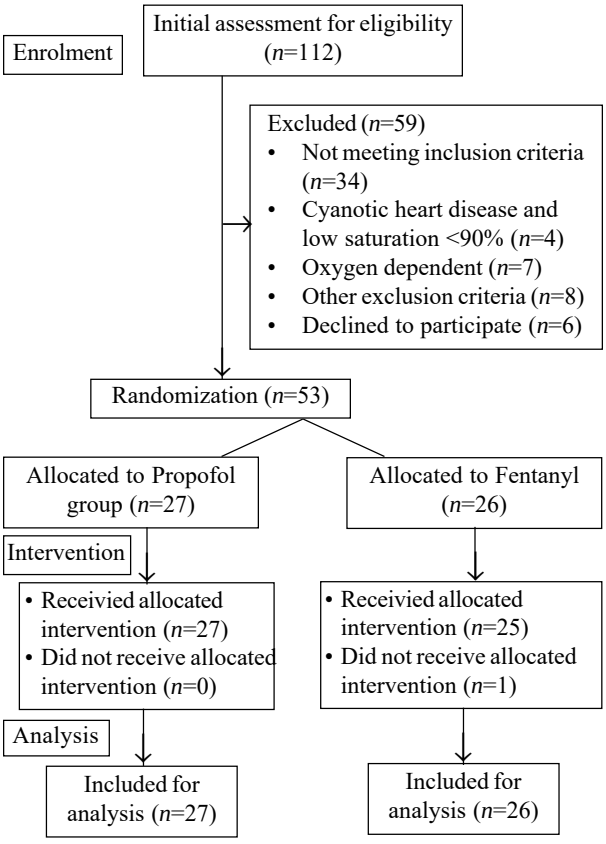

FIG. 1 *Study flow diagram.*

TABLE I BASELINE CHARACTERISTICS OF STUDY PARTICIPANTS

	Propofol arm n= 27	*Fentanyl arm n= 26*
Male: Female	11: 16	17: 9
Age, y	9.6 (3.4)	8.9 (3.5)
At baseline		
Oxygen saturation, %	99.1 (1.5)	99.1 (1.4)
Pulse rate, per min	94.7 (7.7)	98.3 (7.2)
Respiratory rate, per min	20.9 (2.9)	21.4 (2.6)
Ramsay score	1	1

All values are mean (SD), unless specified.

The assessment of procedure related characteristics (physician satisfaction score, cough score, and secretion score, need of additional midazolam and number of additional midazolam) were significantly better in propofol group (***Table* II**). Safety parameters were comparable between arms. The recovery time was significantly quicker in propofol group (***Table* II**).

Two children from fentanyl group and one child from propofol group had brief apneic episodes; however, they recovered with stimulation without further intervention. In addition, 10 out of 27 children in propofol group complained of mild self-limiting burning sensation at the site of administration but it was not observed at the time of recovery.

DISCUSSION

We performed this open label randomized controlled trial to compare two sedative medications for conscious

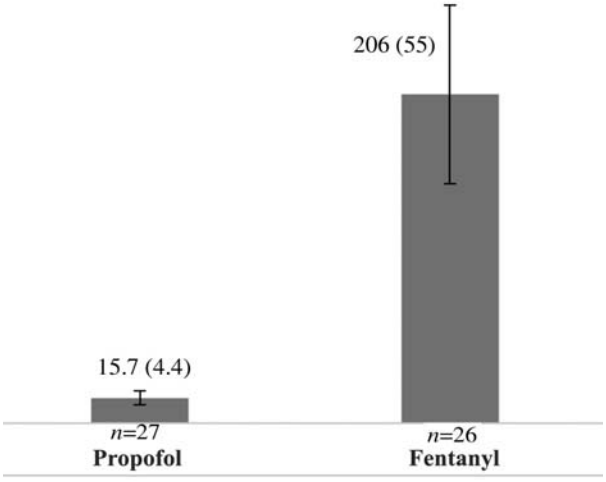

FIG. 2 *Mean (SD) time (s) taken to achieve Ramsay score 3 in both arms.*

TABLE II SECONDARY OUTCOMES IN CHILDREN UNDERGOING BRONCHOSCOPY

	Propofol arm n= 27	*Fentanyl arm n= 26*	*Mean (95% CI) difference*	*P value*
Additional midazolam doses needed, no.	11	25	Not applicable	<0.001
Number of additional midazolam doses per patient, mean (SD)	0.41 (0.5)	1.96 (0.2)	1.55 (1.33, 1.76)	<0.001
Physician satisfaction: Visual analogue score, mean (SD)	87 (12)	54 (22)	33.0 (23.2, 42.7)	<0.001
Cough score: Visual analogue score, mean (SD)	85 (10)	56 (17)	29.0 (21.3, 36.6)	<0.001
Secretion score: Visual analogue score, mean (SD)	89 (6)	80 (11)	9.0 (4.1, 13.8)	0.001
Any pause in breathing, no.	1	2	Not applicable	0.507
Time taken to regain full consciousness, (min), mean (SD)	7.7 (5.6)	67 (27)	59.3 (48.6, 69.9)	<0.001

sedation in paediatric bronchoscopy. Propofol had significantly faster sedation induction time, less recovery time, less coughing, better physician satisfaction and no differences in adverse effects as compared to fentanyl.

Propofol slow bolus with or without infusion has been previously studied and it was well tolerated in children [11,12]. The drug has been approved for utilization in children [13]. However, hypotension, bradycardia and apnoea were demonstrated in propofol anaesthesia [12,14,15]. Similarly, fentanyl has been a well-established medication in pediatric practice, especially for short procedures. It has been used as bolus and infusions with minimal adverse effects though post administration bradypnea and cardiovascular instability have been reported [16]. Nevertheless, conscious sedation is effective and safer than general anaesthesia for flexible bronchoscopy and level of sedation can be monitored with Ramsay score [17].

Propofol and fentanyl have not been compared for sedation for paediatric bronchoscopy in a trial. Lower induction time for propofol in children was described by Rashed, *et al.* [7] in a prospective study without comparative group. However, the induction time was much higher than that of this study. Probably because deeper level of anaesthesia was targeted [7]. Although sedation induction is not well defined in children, fentanyl has quick action to achieve procedural sedation [18]. In the field of paediatric gastroenterology, non-anesthesiologists administer sedation commonly [19].

Physician satisfaction, level of cough, and level of airway secretions are major parameters in assessing effectiveness of sedation for bronchoscopy in many settings as a primary research tool [9,20]. Physician satisfaction has been reported to be higher with combinations of propofol/opioids and propofol/benzodiazepines than propofol or volatile agents [9]. Cough response is much lower with opioid-driven sedation than propofol [21-23]. We observed that propofol arm performed better than fentanyl on these parameters.

Bradycardia and respiratory depression have been reported with propofol, however, it is comparatively higher with combination of sedatives [21,24,25]. Despite sedation, opioids may be associated with higher pulse rate and respiratory depression [10,21,24]. Similar findings were observed in our study although none of the children had significant adverse event. Mild self-limiting burning sensation at injection site is a known untoward effect of propofol [26].

Recovery time is one of the determinants of duration of hospital stay and duration of post procedure monitoring. Therefore, it influences the utilization of resources and manpower in the institution. Lower recovery time would improve cost effectiveness and patient safety [17,22]. In our study, children receiving propofol had faster recovery and shorter time of drowsiness, confirming observations of earlier studies [7,12,21]. Fentanyl is considered to have a quicker recovery time in comparison with other opioids [17].

In this experimental study, target level of anaesthesia was lower. Therefore, induction time could have been shorter. In addition, utilization of medication dose and top-up doses could have been lower; all these could be reasons for lower adverse effects and shorter recovery. Moreover, utilisation of solitary medication in propofol arm could have led to better outcome.

A limitation of the study was its open-label design. As propofol and fentanyl can easily be distinguished with external appearance and having a subsequent infusion, therefore double dummy technique could have been used to overcome the situation. The strength of this study was a randomized control design with adequate sample size. Our study suggest that propofol can be used safely and effectively by well-trained pediatrician for flexible bronchoscopy in children. It provides one more option of

WHAT IS ALREADY KNOWN?

- Conscious sedation is increasingly being utilized for flexible bronchoscopy in children.
- Combination of propofol and fentanyl is better than volatile agents for pediatric bronchoscopy.

WHAT THIS STUDY ADDS?

- Propofol has shorter sedation induction time, better procedure related satisfaction and quicker recovery as compared to fentanyl in pediatric flexible bronchoscopy.
- Propofol is an effective and safe modality for conscious sedation in pediatric bronchoscopy.

conscious sedation in practice of flexible bronchoscopy in children.

To conclude, propofol may have shorter sedation induction time, better procedure related satisfaction and quicker recovery when used for conscious sedation in pediatric bronchoscopy.

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