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ORIGINAL RESEARCH

Safety and effectiveness of deep sedation in pediatric patients undergoing flexible fibroscopy in spontaneous breathing

Federica Tosi[1], Giorgio Conti[2], Rossano Festa[1], Aldo Mancino[2], Marco Rossi[1], Antonio Chiaretti[3], Lavinia Capossela[3], Antonio Gatto[4,*]

[1]Department of Anesthesia and Pain Therapy, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy
[2]Pediatric Intensive Care Unit, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy
[3]Institute of Pediatrics, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS - Università Cattolica Sacro Cuore, Rome, Italy
[4]Institute of Pediatrics, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy

***Correspondence**
antonio.gatto@policlinicogemelli.it
(Antonio Gatto)

Abstract

Invasive diagnostics and minor surgical procedures with deep sedation on pediatric patients, such as fibroscopic examination, have increased over the past decade. The aim of this study was to evaluate the usefulness and safety of an anesthesiological technique, based on the use of midazolam and ketamine, conducted in spontaneous breathing on a population of pediatric patients with suspected tracheobronchial pathologies. Pediatric patients from birth to 18 years old who underwent sedation diagnostic fibroscopy between April 2018 and March 2019, were enrolled. The anesthesiological technique provided was the intravenous administration of midazolam 0.2 mg/kg and ketamine 2 mg/kg in spontaneous breathing using a face mask with support of O2 and air. Vital signs such as Heart rate (HR), Systolic and Diastolic blood pressure (PAS and PAD) and Arterial oxygen saturation were recorded at the beginning of the procedure, 10 minutes and 30 minutes from the start. Other parameter evaluated were patient's level of consciousness, quality of the procedure, major and minor complications, adequate recovery of the waking state. Sixteen patients were enrolled, 12 males and 4 females aged between 2 days of life and 7 years. Laryngomalacia tracheomalacia, tracheoesophageal fistula, and congenital airway malformations were the most frequent diseases. As for vital signs: the HR has gone from an average value of 133.4 $\pm$ 16.26 bpm at T0 to an average value of 129.3 $\pm$ 16.55 bpm at T10 and 133.7 $\pm$ 17.35 bpm at T30; PAS and PAD had not significant variations. Among drugs available for the fibroscopic examinations, the combined use of intravenous midazolam 0.2 mg/kg and ketamine 2 mg/kg is safe and well tolerated, reducing the anxiety associated with the examination, without major complications. The current literature is lacking in studies that have included such small and low weight patients. It would be interesting to make a comparison between various sedation techniques in order to identify the safest for the pediatric population.

Keywords

Sedation; Deep; Pediatric; Bronchoscopy

1. Introduction

Invasive diagnostics and minor surgical procedures on pediatric patients outside the traditional operating room have increased over the past decade [1–3]. This important change and the increased attention to ensuring analgesia and anxiolysis have led the improperly defined minor procedures to increase exponentially. Sedation in pediatric patients is one of the most important factors in a fibroscopic examination [4]. Although there are standardized guidelines in this regard such as those published by the American Academy of Pediatrics (AAP) and the American Society of Anesthesiologists (ASA), their effective application is not so immediate. The purpose of correct sedation is to ensure patient safety and well-being, reduce physical pain and anxiety and maximize the potential for amnesia.

Deep sedation is a drug-induced decrease in consciousness from which patients cannot be easily awakened but respond to repeated or painful stimuli; the ability to independently maintain ventilatory function may be impaired. Patients may need assistance to maintain airway patency and spontaneous ventilation may be inadequate and cardiovascular function is generally maintained [5].

Sedation of pediatric patients presents serious associated risks, such as hypoventilation, apnea, airway obstruction, laryngospasm and cardiopulmonary insufficiency [6, 7].

Hence the need to find, where possible, a method of sedation that can guarantee a good result in terms of quality of the procedure and safety for the patient.

The five classes of procedural sedation and analgesia drugs

are sedative-hypnotics, analgesics, dissociative sedatives, inhalational agents, and antagonists. The most widely used are sedative-hypnotics, including benzodiazepines (eg, midazolam, diazepam), barbiturates (eg, pentobarbital, methohexital), and several drugs in their own pharmacological class (eg, chloral hydrate, etomidate, propofol). Propofol, etomidate, methohexital, and thiopental are referred to as ultra-short acting agents because of their extremely rapid onset and brief duration of action that can increase when additional doses are given. Sedative-hypnotics lack specific analgesic properties and are frequently supplemented with opioids [8–10].

The literature shows an overview of the current reality in the field of pediatric bronchoscopy and although multiple therapeutic strategies have been used in the field of sedative drugs, some of these have presented serious complications. Hence the need to identify an optimal anesthesiological strategy for the correct execution of the examination in compliance with the most accurate patient safety standards that the scientific community shows us today [11].

2. Material and methods

2.1 Study design and setting

This study was a monocentric prospective study conducted in the Sedation Room of the Pediatric Intensive Care Unit of Fondazione Policlinico Universitario Agostino Gemelli, IRCCS in Rome, in the period between April 2018 and March 2019.

2.2 Selection of participants

Pediatric patients from birth to 18 years old who underwent sedation diagnostic fibroscopy procedures were enrolled in the study.

The inclusion criteria were pediatric patients from birth to 18 years old with suspected tracheobronchial pathologies who needed sedation diagnostic fibroscopy procedures.

The exclusion criteria were previous demonstrated adverse reactions to drugs administered for the procedure.

2.3 Intervention

The anesthesiological technique provided was the intravenous administration of midazolam 0.2 mg/kg and ketamine 2 mg/kg, after monitoring the vital signs and maintenance of spontaneous breathing using a face mask with support of O2 and air. The procedure was carried out using a trans nasal approach with an Olympus BFXP160F bronchoscope with an external diameter of 2.8 mm.

2.4 Methods and measurements

The following vital signs were recorded at the beginning of the procedure (T0), 10 minutes from the start (T10) and 30 minutes from the start (T30):

- Heart rate (HR) bpm/min
- Systolic Blood Pressure (PAS) mm/Hg
- Diastolic blood pressure (PAD) mm/Hg
- Arterial oxygen saturation (SaO2) % using cardiopulmonary monitoring

Other parameter evaluated by the operators were:

- patient's level of consciousness and reactivity (Comfort B scale).
- quality of the procedure: easy progress of the instrument along the airways and through the chordal plane.
- major and minor complications.
- adequate recovery of the waking state.

We evaluated as major complications: pneumothorax, persistent desaturation $< 90\%$ (not managed by retracting the bronchoscope regain the baseline saturation and eventually accompanied by bradycardia or hypotension), bronchospasm and laryngospasm associated with severe desaturation. Minor complications considered were epistaxis, transient episodes of desaturation (transient drop in SpO2 below 90%) All cases of desaturation were transient and were managed by retracting the bronchoscope for a limited time to regain the baseline saturation and then resuming the procedure. These episodes were not accompanied by bradycardia or hypotension), transient laryngospasm and cough.

2.5 Outcomes

The study's primary outcome was to evaluate the usefulness and safety of an anesthesiological technique based on the use of midazolam and ketamine carried out in spontaneous breathing on a population of pediatric patients with suspected tracheobronchial pathologies.

2.6 Statistical analysis

The data obtained were processed using Microsoft Excel version 16.24 calculation software for Mac and Prism statistical software version 8.0 for Mac. The HR, PAS and PAD values recorded in the 3 different times were analyzed, using Student's *t* test for paired data, comparing the different recording times of the parameters two by two:

- T0 vs T10
- T0 vs T30
- T10 vs T30

in order to seek any significance in the variations (Fig. 1).

The quality of the procedure, intended as easy progress of the instrument along the airways and through the chordal plane, major and minor complications and recovery of the waking state, were assessed exclusively on the basis of the qualitative data.

3. Results

During the period of study a total of 16 patients were enrolled, 12 males and 4 females aged between 2 days of life and 7 years (mean 9.68 ± 2256 months) who underwent sedation diagnostic fibroscopy procedures (Table 1). The average weight of the patients in this study was 5.6 ± 6.02. With regard to gestational age, 2 patients were premature, 8 were preterm, 6 were born at term.

Laryngomalacia, tracheomalacia, tracheoesophageal fistula and congenital airway malformations were the most frequent diseases for which patients underwent fibroscopy procedures. In particular, tracheomalacia occurred in 6 patients, tracheoesophageal fistulas occurred in 2 patients, congenital airway

TABLE 1. Characteristics of the study population

PATIENTS	AGE (months)	WEIGHT (kg)	SEX	GESTATIONAL AGE	DISEASE
BN	4.6	3.5	M	36	FISTULA
CM	87	25	M	40	TRACHEOMALACIA
KA	1.27	4.2	F	39.85	TRACHEOMALACIA
MA	1	3.7	F	38	MALFORMATIVE SYNDROME
SF	3.6	2.4	M	26.57	STRIDOR
PL	38	15	M	35.57	INFECTION
SATM	3.7	5.3	M	40	TRACHEOMALACIA
FCL	2.6	4.7	F	40	MALFORMATIVE SYNDROME
CA	0.26	2	M	36	STRIDOR
MS	0.06	3,3	M	40.42	LARYNGOMALACIA
ABJI	7.2	3.7	M	24.57	LARYNGOMALACIA
BN	0.1	2.5	M	36	FISTULA
CV	0.66	2.9	M	38.57	STRIDOR
IC	2.1	3.2	M	34.71	TRACHEOMALACIA
IC	2.1	3.2	M	34.71	TRACHEOMALACIA
KG	0.7	2.8	F	39.28	TRACHEOMALACIA
MEDIA ± DS	**9.68 ± 22.56**	**5.46 ± 6.02**	-	**36.28 ± 4.82**	-
			M = 12	PREMATURE: 2	TRACHEOMALACIA: 6
			F = 4	PRETERM.: 8	FISTULA: 2
				TERM: 6	MALFORMATIVE SYNDROME: 2
					STRIDOR: 3
					LARYNGOMALACIA: 2
					INFECTION: 1

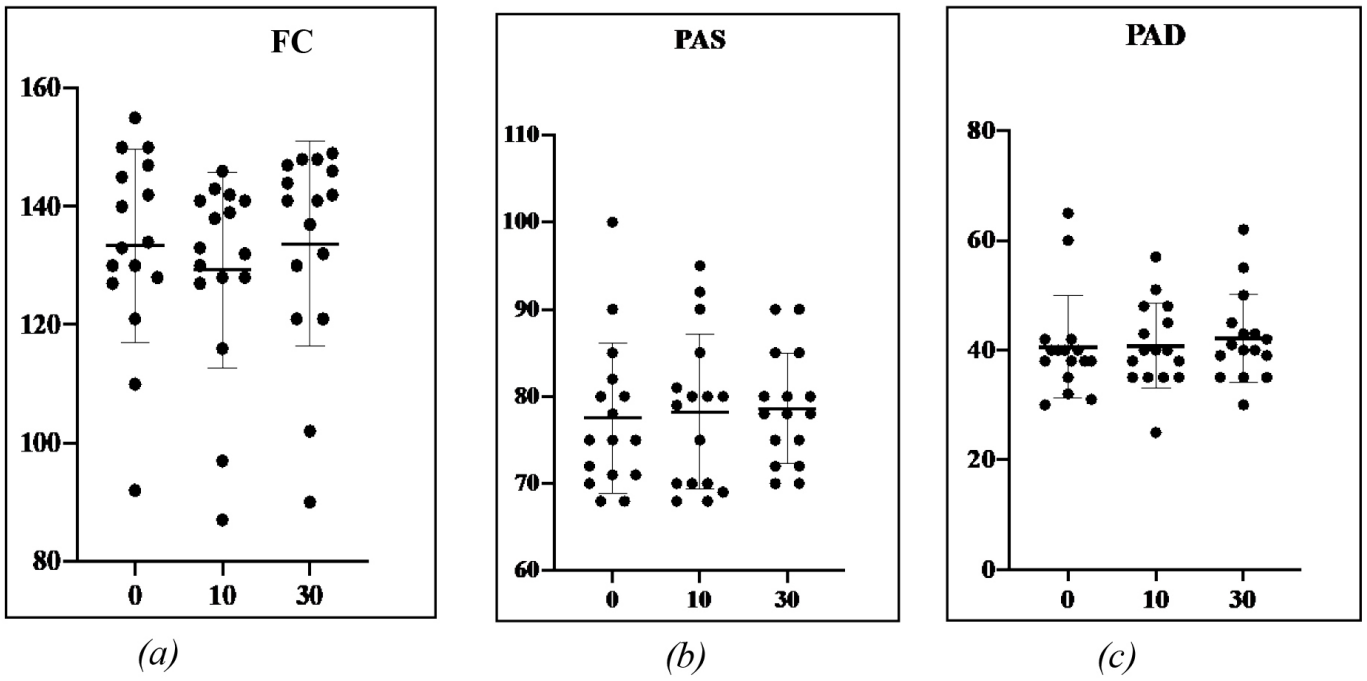

FIGURE 1. Trend of vital parameters at T0, T10 and T30.
(a) Heart Rate (bpm); (b) Systolic blood pressure (mm/Hg); (c) Diastolic blood pressure (mm/Hg).

malformations in 2 patients, laryngomalacia occurred in 2 patients and infection occurred in 1 patient.

The results obtained were expressed in the form of mean ± SD where required and are summarized in Table 2.

TABLE 2. Comparison between vital parameters at T0, T10 and T30 (*f* T0 vs T10; § T10 vs T30)

PARAMETERS	T0	T10	T30	*P*
FC (bpm)	133.4 ± 16.26	129.3 ± 16.55	133.7 ± 17.35	*0.016 f 0.0032 §*
PAS (mmHg)	77.50 ± 8.65	78.25 ± 8.87	78.63 ± 6.38	*ns*
PAD (mmHg)	40.56 ± 9.36	40.81 ± 7.72	42.13 ± 8.01	*ns*

As for vital signs: the HR has gone from an average value of 133.4 ± 16.26 bpm at T0 to an average value of 129.3 ± 16.55 bpm at T10 and 133.7 ± 17.35 bpm at T30, Student's *t* test showed significance ($P = 0.016$) in the comparison T0 vs T10 and in the comparison T10 vs T30 ($P = 0.0032$); PAS showed average values of 77.50 ± 8.65 mm/Hg at T0, 78.25 ± 8.87 mm/Hg at T10 and 78.63 ± 6.38 at T30, without significant variations; finally PAD went from the average values of 40.56 ± 9.36 mm/Hg of T0, to 40.81 ± 7.72 mm/Hg of T10 to 42.13 ± 8.01 of T30, without showing significant variations.

During the execution of the fibroscopy, the evaluation of the patient's pain and distress was obtained by means of Comfort B scales [8], which remained so as to guarantee a good execution of the procedure: all patients reported values between 12 and 17; the introduction of the instrument through the airways and the chordal plane was easy, except for one patient who subsequently reported severe desaturation (major complication). None of our patients reported minor complications.

4. Discussion

The number of diagnostic and minor surgery procedures performed on pediatric patients outside the traditional operating room has increased in recent decades. At the same time, the need for sedation has grown.

Sedation in the pediatric field is different than in adults. The ability of a child to control his emotional state behavior to collaborate on a procedure depends both on his chronological age and on cognitive/emotional development. Many short and painless procedures can be performed by distraction and guided imagery techniques, together with the use of local anesthetics. Often, the medical act itself places the child in front of so much anxiety that it makes the awakening procedure difficult or impossible.

Complications related to sedation can be avoided through a careful preoperative anesthesiological examination, bearing in mind that multiple pathological conditions can have a decisive influence on the success of a procedure [12, 13].

In this context, bronchoscopy with flexible fiberscope, an endoscopic technique that allows to directly visualize the patient's airways for diagnostic and treatment purposes, fits perfectly [14].

Since bronchoscopy allows the assessment of the static and dynamic anatomy of the respiratory system, it finds multiple indications, as indeed this work has also highlighted. In fact, children with anatomical anomalies such as tracheo-esophageal fistulas, stridor, laryngus or tracheomalacia, suspected granulomas, pleuropneumonia or patients suffering from real genetic syndromes have been included [15].

Apart from the visualization of the parts of the airway tree and their structure as well as patency, it can also be used to take tissue biopsy specimens, collect secretions from the airways and bronchoalveolar lavage which can also get cellular elements from the distal alveoli. In recent decades, more and more instruments have been used to expand the utility of the flexible bronchoscope for interventions ranging from bronchial toilet, foreign body removal, airway stenting, and lasers or cryotherapy for airway injuries. The wide applications of this instrument make it very relevant for pulmonary and therapeutic investigations [16].

The delicacy of the structures that make up the airways, combined with their reduced caliber, certainly requires particular attention from the operator.

In their work published in 2018, Mondal and Dalal [17] compared moderate sedation and general anesthesia during bronchoscopy, observing which of the two techniques had more complications, and underlining how, in the pediatric field, the data present in the literature are missing and often unclear, proposing a wide range of drug combinations.

An interesting study conducted by Abulebda *et al.* [18] in 2017 compared propofol only with ketamine prior to propofol to evaluate the safety and efficacy of sedating pediatric patients for outpatient flexible bronchoscopy, concluding that children can be effectively sedated for outpatient flexible bronchoscopy with high rate of success.

On the other hand, a randomized trial designed by Gunathilaka *et al.* [19] compared Propofol versus Fentanyl for sedation in pediatric bronchoscopy coming to the conclusions that 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.

Furthermore, Berkenbosch *et al.* [20] studied that a remifentanil/propofol mixture provided effective sedation and rapid recovery in pediatric patients undergoing fiberoptic bronchoscopy.

A significant retrospective trial by Zhang *et al.* [21] showed that there were significant differences between sedation with dexmedetomidine-remifentanil (DEX-RF) and dexmedetomidine-propofol (DEX-P) in children undergoing flexible bronchoscopy in terms of the overall incidence of hypertension, tachycardia, and hypoxemia. Although underwent longer recovery time and more incidence of rescue scheme, DEX-RF resulted in more stable hemodynamic profiles and bronchoscopist-satisfaction scores, lesser patient movements, and can hence be more effectively used in children undergoing flexible bronchoscopy than dexmedetomidine-propofol.

Among all the drugs available for the execution of fibroscopic examinations, most of which on infants, the combined

use of intravenous midazolam 0.2 mg/kg and ketamine 2 mg/kg was chosen for this work.

Safety of ketamine and midazolam sedation has been evaluated in previous studies, and it has already been assessed that infant flexible fiberoptic bronchoscopy can be safely and effectively performed using ketamine sedation [22].

Furthermore, our study also revealed that deep sedation fibroscopy in the child represents a safe and well tolerated examination, reducing the anxiety associated with the examination and without major complications. In fact, most adverse events are due to drug overdose, monitoring and inadequate sedation [23].

In our study, in fact, only one case of major complication such as severe desaturation was reported and none of our patients reported minor complications.

In a study conducted by Brown L. *et al*. in 2008, the authors assessed that when adjunctive atropine is omitted during ketamine sedation in children, excessive salivation is uncommon, and associated airway complications are rare, thus anticholinergic prophylaxis is not routinely necessary in this setting. In our study, the increasing mucosal secretion as a side effect of ketamine did not occur, due to the small number of patients enrolled [24].

Other study about complications of flexible bronchoscopy in children pointed up that flexible bronchoscopy is a safe procedure with $<$ 2% major complications. Minor complications included moderate and transient episodes of desaturation, isolated excessive coughing, excessive nausea reflex with coughing, transient laryngospasm and epistaxis; major complications included persistent oxygen desaturation to $<$ 90%, either isolated or associated with laryngospasm coughing, bronchospasm and pneumothorax. Major complications involving oxygen desaturation were associated with age $<$ 2 years and laryngotracheal abnormalities. The overall frequency of complications was similar between conscious but sedated patients and patients under deep sedation. However, the frequency of transient desaturation was significantly higher in children undergoing fibroscopy under deep sedation [25].

In other cases, instead, the examination allowed an optimal visualization of the child's airways, with stable vital parameters, without complications during the procedure and with a valid recovery of the awakening state.

Therefore, deep sedation fibroscopy can be safely used for diagnostic and therapeutic purposes in children; compared to general anesthesia, it reduce both the "scope time" (the time in which the instrument is inside the airways) and the post-procedural recovery time for the lowest level of sedation achieved.

Furthermore, this sedation technique reduced the anxiety and discomfort associated with the procedure, not interfering with exam success [26], allowing it to be carried out with maximum safety without serious complications and allowing the use of deep sedation in spontaneous breathing, already used for some time in adults, even in children [27–29].

5. Conclusions

In this study a pediatric population of 16 patients were enrolled, some of which were extremely small (average weight about 5 kg). The current literature is lacking in studies that have included such small patients, certainly giving this one a privileged position. Almost all, there were limits that would be interesting to investigate in the future: first of all, the sample treated was extremely small. Secondly, a case control study between deep sedation in spontaneous breathing with midazolam 0.2 mg/kg and ketamine 2 mg/kg versus other sedation modality has not been carried out, thus comparing the safety of the two. In addition to this, it was a monocentric study.

It would be interesting, in the future, to make a comparison between various sedation techniques in order to identify the safest for the pediatric population, going to involve also other centers to further expand the sample under examination and identify and address these issues more conclusive.

AUTHOR CONTRIBUTIONS

FT and GC designed the research study. FT, AM, and MR performed the research. MR and RF analyzed the data. AG, LC and AC wrote the manuscript.

All authors contributed to editorial changes in the manuscript.

All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent: Informed consent was obtained for all individual participants included in the study.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

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