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Ketamine for Sedation During Bronchoscopy Procedures: A Review of Clinical Effectiveness, Safety, and Guidelines

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Abbreviations

EBUS-TBNA	endobronchial ultrasonography – transbronchial needle aspiration
F	fentanyl
FPM	fentanyl + propofol + midazolam
K	ketamine
KP	ketamine + propofol
KPM	ketamine + propofol + midazolam
M	midazolam
MP	midazolam + propofol
P	propofol
RCT	randomized controlled trial

Context and Policy Issues

Bronchoscopy is the insertion of an endoscope in the airways and is generally used for the diagnosis and management of a variety of lung conditions and respiratory disorders.[1-3] The two main types of bronchoscopy include rigid bronchoscopy and flexible bronchoscopy.[1] Sedation is used during bronchoscopy procedures to facilitate examination of the airways, decrease patient movement, and improve patient safety and comfort. Sedation can be induced with drugs such as benzodiazepines (e.g., midazolam), opioids (e.g., fentanyl), propofol, and ketamine.[2]

Ketamine is a N-methyl-D aspartate receptor antagonist that produces a dissociative state, in which normally perceived sensory input (sight, hearing, touch) is blocked from reaching consciousness.[2] There is growing interest regarding the use for ketamine and how it compares with other agents for bronchoscopy procedures.

The purpose of this report is to review the clinical effectiveness, and safety of ketamine use for bronchoscopy, and to review the evidence-based guidelines regarding the use of ketamine during bronchoscopy.

Research Questions

1. What is the clinical effectiveness and safety of ketamine for sedation during bronchoscopy procedures?
2. What are the evidence-based guidelines for the use of ketamine for sedation during bronchoscopy procedures?

Key Findings

Six relevant publications were identified. These comprised one systematic review, two randomized controlled trials and three non-randomized studies (one prospective single-arm

study, and two retrospective studies). Various drugs, including ketamine, propofol, midazolam, fentanyl, and/or their combinations, were used for sedation for the bronchoscopy procedures.

There were no significant differences in recovery time, or in the proportion of patients experiencing hypoxia, for adult or pediatric patients between sedative drug combinations that included ketamine and alternative procedural drugs.

Sedative drug combinations including ketamine were associated with statistically significantly higher mean arterial pressure and a higher proportion of patients experiencing high blood pressure compared with alternate sedative combinations in adults undergoing bronchoscopy. Also, the number of pediatric patients requiring mask ventilation was statistically significantly greater in the group receiving a sedative drug combination including ketamine compared with an alternate sedative combination. The proportion of pediatric patients experiencing bronchospasm and emergence agitation was numerically higher with ketamine compared with propofol.

Findings regarding hypotension and desaturation were inconsistent.

Findings need to be interpreted with caution considering there is limited number of studies evaluating specific sedation procedures with ketamine for patients undergoing bronchoscopy and overall low quality of the body of evidence.

No evidence-based guideline was identified hence no summary could be provided.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were ketamine and bronchoscopy. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and June 29, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult and pediatric patients with suspected lung disease (e.g., persistent cough, lung infection, bleeding) or suspected lung obstruction (e.g., removal of a foreign body)
Intervention	Bronchoscopy performed with sedation using ketamine
Comparator	Q1: Bronchoscopy performed with sedation using

	standard procedural drugs (e.g. short-acting benzodiazepines alone or in combination with opioid analgesic). No comparator (safety outcomes only) Q2: Not applicable
Outcomes	Q1. Clinical effectiveness and safety (e.g., adequate sedation during the procedure, time to recovery, hypotension, hypoxia, respiratory depression, agitation, need for additional sedation if patient wakes up, emergence delirium, need for intubation) Q2. Recommendations regarding the use of ketamine for sedation during bronchoscopy (e.g., contraindications for use, type of monitoring required, post-operative procedures)
Study Designs	Systematic reviews, randomized controlled trials, non-randomized studies, and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2010. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by one reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[4] for systematic reviews, and the Downs and Black checklist[5] for randomized and non-randomized studies. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 37 citations were identified in the literature search. Following screening of titles and abstracts, 25 citations were excluded and 12 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 12 potentially relevant articles, six publications were excluded for various reasons, and six publications met the inclusion criteria and were included in this report. These comprised one systematic review,[6] two RCTs,[2,7] and three non-randomized studies.[3,8,9] No evidence-based guidelines were identified. Appendix 1 presents the PRISMA[10] flowchart of the study selection.

Summary of Study Characteristics

One systematic review,[6] and five primary studies,[2,3,7-9] were included. In the literature, the terms hypoxia and hypoxemia seem to be used interchangeably. In this report the term hypoxia is used. For other outcomes (such as cardiac and respiratory outcomes), the terms as used by the authors are presented in this report. The combination of ketamine (K), propofol (P), and midazolam (M) is denoted as KPM; the combination of fentanyl (F), P, and M as FPM; combination of K and P as KP; combination of K and M as KM; and combination of M and P as MP.

The characteristics of the included publications are summarized below. Additional details are provided in Appendix 2, Table 2 (systematic review), and Table 3 (primary studies).

Study Design

The included systematic review had a broad objective to evaluate the effects of several anesthetics and opioids and included one retrospective study that was relevant for the current report. Multiple data bases were searched up to September 2014.

Of the two included RCTs,[2,7] one RCT[2] was double-blinded and another RCT[7] did not mention blinding. Of the three included non-randomized studies,[3,8,9] one was a prospective study[3] and the remaining two[8,9] were retrospective studies.

Country of Origin

The systematic review[6] was published in 2016 from the USA. One RCT[2] was published in 2017 from Israel, and another RCT[7] was published in 2014 from Turkey. Of the three non-randomized studies,[3,8,9] one study[3] was published in 2019 from India, the second study[8] was published in 2017 from the USA, and the third study[9] was published in 2015 from Turkey.

Patient Population

The included systematic review[6] included one relevant study involving 55 pediatric patients of mean age 0.5 years, undergoing flexible fiberoptic bronchoscopy; weight was not mentioned.

One RCT[2] included 80 adult patients undergoing flexible fiberoptic bronchoscopy; mean age was 57.8 years, and mean weight was 72.7 kg. The second RCT[7] included 40 pediatric patients undergoing rigid bronchoscopy; mean age was 3.6 years, and mean weight was 15.3 kg.

The three nonrandomized studies,[3,8,9] included pediatric patients undergoing flexible bronchoscopy[3,8] or adult patients undergoing endobronchial ultrasonography transbronchial needle aspiration (EBUS-TBNA), which is a type of bronchoscopy procedure;[9] the number of patients varied between 267 and 571. In one study[3] the median age was 16 months, and the median weight was 10 kg; in the second study[8] age ranged from 1.9 years to 9.8 years, and weight ranged from 11.2 kg to 33.0 kg; and in the third study[9] the mean age was 55.7 years, and the mean weight was 74.5 kg.

Interventions and Comparators

The relevant study that was included in the selected systematic review[6] assessed the use of ketamine. Ketamine in combination with other agents was used for induction, and ketamine with or without fentanyl was used for maintenance. Route of drug administration was not reported.

Of the two included RCTs,[2,7] one RCT[2] compared KPM with FPM, and another RCT[7] compared K versus P (both groups received M and remifentanil before initiating K or P). For both RCTs, the route of drug administration was intravenous.

Of the three nonrandomized studies,[3,8,9] one study[3] assessed M combined with K (i.e., all patients received M and the majority of patients received K in addition to M) majority of patients); the second study[8] compared KP versus P; and the third study[9] compared KPM

versus KP versus MP versus P. For these three studies, the route of drug administration was intravenous.

Outcomes

Outcomes reported included recovery time,[2,8,9] patient satisfaction (using the visual analog scale or a five point scoring system),[2,9] mean arterial pressure (MAP),[2,7-9] hypotension,[7,8] bradycardia,[3,9] blood pressure fluctuations,[3] hypoxia (or oxygen saturation [SpO_2]),[2,3,6,8] bronchospasm,[7] respiratory support,[2] emergence characteristics,[7] emergence agitation,[7] desaturation,[7-9] and apnea.[3,6]

Summary of Critical Appraisal

An overview of the critical appraisal of the included publications is summarized below. Additional details regarding the strengths and limitations of included publications are provided in Appendix 3, Table 4 (systematic review), and Table 5 (primary studies).

The included systematic review[6] was generally well conducted. The objective was stated, multiple databases were searched, study selection was described, a list of included studies was provided, article selection and quality assessment of the included studies were conducted independently by two reviewers, the included study characteristics were described but only briefly, and the authors mentioned that there were no conflicts of interest; publication bias does not appear to have been explored. Of note, this systematic review had a broad objective and one of the 56 studies was relevant for this current report; this study was given six stars by the authors, using the Newcastle-Ottawa Scale, but the maximum number of attainable stars was not mentioned.

In the two included RCTs,[2,7] the objective and the inclusion and exclusion criteria were stated, and patient characteristics, interventions and outcomes were described. In one RCT,[2] randomization was described and appeared to be appropriate and it was a double-blinded study. In another RCT[7] the randomization method was not described; and there appeared to be no blinding, hence there is potential for performance and detection biases. In both RCTs[2,7] sample size calculations were conducted; the appropriate number of patients was recruited in one RCT,[7] but not in the other RCT.[2] In both RCTs the authors mentioned that there were no conflicts of interest.

In the three non-randomized studies[3,8,9] the objective, and the inclusion and exclusion criteria were stated; the patient characteristics, interventions, and outcomes were described, and the study authors mentioned that there were no conflicts of interest. One study[3] was a prospective study with one treatment arm (included for safety outcomes) hence it did not present any comparative data, so safety outcomes in comparison to other agents cannot be commented on. In the other two studies[8,9] there were differences in patient characteristics (in one or more factors, such as age, weight and comorbidities) between the groups, and that could impact the findings; no adjustments appear to have been made to minimize the impact on findings. Also, as they were retrospective studies there is potential for all relevant data not being recorded. Findings from these studies need to be interpreted with caution.

Summary of Findings

The main findings are summarized below. Details of the study findings and authors' conclusions are presented in Appendix 4, Table 6 (systematic review), and Table 7 (primary studies).

Clinical Effectiveness and Safety of Ketamine

Adult patients

One RCT[2] and one retrospective study[9] involved adult patients.

Recovery time

One RCT[2] involving adults patients undergoing flexible fiberoptic bronchoscopy and comparing KPM to FPM found there was no statistically significant between group difference with respect to time to recovery.

One retrospective study[9] involving adult patients undergoing EBUS-TBNA compared KPM, KP, MP, and P. Recovery time was numerically shorter with KP or MP than with KPM. Recovery time was not significantly different between KP and MP (P> 0.05). Recovery time was numerically shorter with P compared with KP, MP, or KPM.

Patient satisfaction

One RCT[2] involving adults patients undergoing flexible fiberoptic bronchoscopy and comparing KPM to FPM found there was no statistically significant between group difference with respect to patient satisfaction (assessed using the visual analog scale [VAS]).

One retrospective study[9] involving adult patients undergoing EBUS-TBNA comparing KPM, KP, MP, and P found that patient satisfaction (median value) was generally high in all the groups.

Cardiac outcomes

One RCT[2] involving adults patients undergoing flexible fiberoptic bronchoscopy found that during the procedure, MAP was statistically significantly higher in the KPM group compared to the FPM group (P = 0.0001); the mean value for MAP being 101 mm Hg in the KPM group.

One retrospective study[9] involving adult patients undergoing EBUS-TBNA comparing KPM, KP, MP, and P found that during the procedure the maximum MAP (mm Hg) values among all groups were between 91 and 99, and minimum MAP (mm Hg) values were between 89 and 95. The proportions of patients experiencing high blood pressure during the procedure were numerically highest with KP followed by KPM, P, and MP respectively; the differences between MP and KP, and between MP and KPM were statistically significant (P < 0.05, P = 0.004, respectively). Bradycardia was reported in 1% of the patients in the MP and KPM groups.

Respiratory and other outcomes

One RCT[2] involving adults patients undergoing flexible fiberoptic bronchoscopy and comparing KPM to FPM found there was no statistically significant between group difference with respect to the time during which SpO_2 was less than 88% (significant hypoxia was defined as SpO_2 of 90% or less). There were no statistically significant between group differences with respect to proportions of patients requiring respiratory supports.

One retrospective study[9] involving adult patients undergoing EBUS-TBNA comparing KPM, KP, MP, and P found that the proportions of patients experiencing desaturation was

numerically highest for MP followed by KPM, and then both KP and P; however the difference between the four groups was not statistically significant (P = 0.07).

Pediatric patients

One systematic review,[6] one RCT,[7] and two non-randomized studies.[3,8] involved pediatric patients.

Recovery time

One retrospective study,[8] involving pediatric patients undergoing flexible bronchoscopy and comparing KP with P found that there was no statistically significant between group difference with respect to recovery time (P = 0.63).

Cardiac outcomes

One RCT[7] involving pediatric patients undergoing rigid bronchoscopy found that the highest MAP during bronchoscopy was 75 mm Hg or less, being numerically higher in the K group compared to the P group; and the proportion of patients experiencing hypotension was numerically lower in the K group compared to the P group (statistical significance was not reported).

One prospective observational (1-treatment arm: KM) study[3] involving pediatric patients undergoing flexible bronchoscopy found that the proportion of patients experiencing transient bradycardia, mild blood pressure fluctuations (<20% from baseline), blood pressure fluctuations (> 20% from baseline) were 1.1%, 1.1%, and 0.37% respectively.

One retrospective study,[8] involving pediatric patients undergoing flexible bronchoscopy and comparing KP with P found that at the end of the procedure, the MAP values were statistically significantly higher in the P group compared to the KP group (P = 0.04). There was no statistically significant between group difference with respect to hypotension (P = 0.4).

Respiratory and other outcomes

One relevant retrospective study (involving pediatric patients) in the included systematic review[6] reported adverse events (mild hypoxia, brief central apnea, and stridor) in 23% of the patients who were administered K in addition to M and atropine with or without fentanyl.

One RCT[7] involving pediatric patients undergoing rigid bronchoscopy found that the proportions of patients experiencing bronchospasm and emergence agitation were numerically higher in the K group compared to the P group (statistical significance was not reported; the authors reported that were no statistically significant differences in adverse events between the two groups). With respect to time to extubation, there was no statistically significant difference between the two groups. The proportion of patients needing controlled and/or assisted mask ventilation after extubation, and the duration of mask ventilation after extubation, were statistically significantly higher in the K group compared to the P group (P = 0.0095, and 0.001 respectively).

One prospective observational (1-treatment arm: KM) study[3] involving pediatric patients undergoing flexible bronchoscopy found that the proportion of patients experiencing hypoxia, apnea, and prolonged apnea were 6%, 1.8%, and 0.37% respectively.

One retrospective study,[8] involving pediatric patients undergoing flexible bronchoscopy and comparing KP with P found that there were no statistically significant between group

difference with respect to proportion of patients experiencing hypoxia (P = 0.69). The proportion of patients experiencing significant desaturation (outcome termed as "significant desaturation" by the authors) was numerically lower in the KP group compared to the P group, statistical significance was not reported.

Guidelines

No evidence-based guideline was identified; hence a summary cannot be presented.

Limitations

There was variation among the included studies with respect to population, interventions, comparators and outcomes.

Overall, the evidence base was of low quality. The majority of the studies excluded patients with severe comorbidities, hence applicability of the findings to this patient population is unclear. None of the studies were conducted in Canada, hence generalization to the Canadian context is difficult.

Findings need to be interpreted with caution considering limitations such as limited amount of evidence, and overall low quality in the body of evidence.

No evidence-based guidelines were identified.

Conclusions and Implications for Decision or Policy Making

Six relevant publications were identified regarding the clinical effectiveness and safety of ketamine for sedation during bronchoscopy procedures. These comprised one systematic review,[6] two RCTs,[2,7] and three non-randomized studies.[3,8,9] No evidence-based guidelines were identified.

In adult patients, the recovery time was not statistically significantly different between KPM and FPM groups,[2] or between KP and MP groups.[9] Patient satisfaction was not statistically significantly different between the KPM and FPM groups.[2] Patient satisfaction was generally high in the KPM, KP, MP, and P groups.[9] With respect to cardiovascular outcomes, MAP was statistically significantly higher in the KPM group compared to the FPM group.[2] The proportions of patients experiencing high blood pressure during the procedure were statistically significantly greater in KP compared to MP, and in KPM compared to MP.[9] There was no statistically significant difference between KPM and FPM groups with respect to hypoxia,[2] or between the KPM, KP, MP, and P groups with respect to desaturation.[9]

In pediatric patients the recovery time was not statistically significantly different between KP and P groups.[8] The proportion of patients experiencing hypotension was numerically less in the K group than in the P group[7] and not statistically significantly different between the KP and K groups;[8] and the proportion of patients experiencing bradycardia or blood pressure fluctuations were 1% or less with KM.[3] Patients treated with KM experienced complications such as hypoxia and apnea.[3,6] The proportions of patients experiencing bronchospasm and emergence agitation were numerically higher in the K group compared to the P group; and the number of patients requiring mask ventilation was statistically significantly greater in the K group.[7] The proportion of patients experiencing significant desaturation (outcome termed "significant desaturation" by authors) was numerically lower in the KP group compared to the P group.[8]

Findings need to be interpreted with caution considering there is limited number of studies for specific sedation procedures with ketamine for patients undergoing bronchoscopy. Additionally, the majority of the studies were associated with potential risk of bias. High quality studies are needed to make definitive conclusions regarding the use of ketamine for sedation during bronchoscopy.

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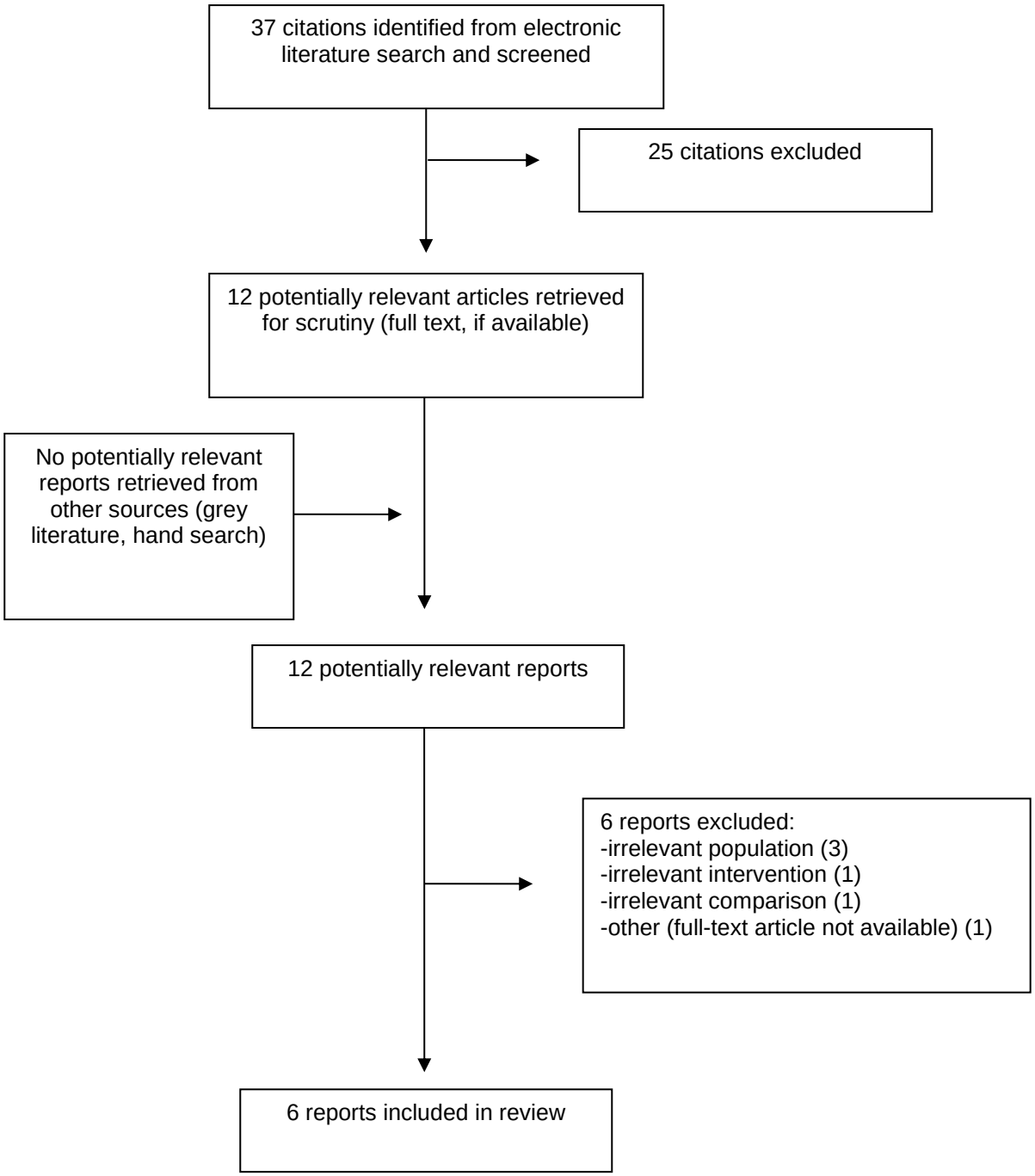
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Review

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Ehsan,[6] 2016, USA. Funding: none	Systematic review. Literature search: PubMed (1950 to June 2014), CINAHL (1982 to June 2014), Evidence-Based Medicine reviews, and Scopus (1996 to June 2014) Search was updated on 24 September, 2014. Inclusion criteria: effects of anesthetic agents on the upper airway. Exclusion criteria: review articles and animal studies This systematic review had a broad aim and included 56 publications of which one publication (retrospective study) was relevant for this report and is described here. Aim: To assess the effects of anesthesia and opioids on the upper airway.	Pediatric patients undergoing flexible fiberoptic bronchoscopy N = 55 Age (years) (mean ± SD): 0.5 ± 0.2 % Female: not reported Weight: not reported	Ketamine dose (mean ± SD): 3.1 ± 1.7 mg/kg (Route of administration not reported) No comparator (Induction with ketamine and other drugs and maintenance with ketamine and with or without fentanyl. Induction: atropine 0.01 mg/kg or glycopyrrolate 0.05 to 0.01 mg/kg; midazolam 0.05 to 0.1 mg/kg; ketamine 1 mg/kg Maintenance: ketamine 0.5 to 1 mg/kg, with or without fentanyl 1mg/kg)	Adverse events (hypoxia, brief central apnea, stridor) Follow-up time: not reported

SD = standard deviation.

Table 3: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Randomized studies				
Fruchter,[2] 2017, Israel.	RCT, double blind.	Adults patients undergoing flexible	KPM versus FPM K dose	Hemodynamic and respiratory parameters

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Funding: unclear, however, it was mentioned that there were no conflicts of interest and no other disclosures	Setting: tertiary care academic medical center. Aim: To assess the efficacy and safety using K, P and M compared to F, P, and M for sedation in adult patients undergoing flexible bronchoscopy	fiberoptic bronchoscopy N = 80 (39 in KPM group and 41 in FPM group) Age (years) (mean ± SD): 55.7 ± 13.4 in KPM group, and 59.71 ± 11.5 in FPM group; P = NS. %Female: 46.1% in KPM group, and 53.7% in FPM group; P = NS Weight (kg) (mean ± SD): 76.9 ± 17.6 in KPM group and 67.8 ± 15.5 in FPM group; P = 0.0140. Exclusion criteria: Patients requiring bronchoscopy performed through an artificial airway such as endotracheal tube or tracheostomy, or allergic to the sedative drugs	(mg/kg): 0.40 ± 0.12 F (mcg/kg): 1.2 ± 0.1 P (mg/kg): 2.2 ± 1.4 in KPM group, and 2.4 ± 2.5 in FPM group. M (mg/kg): 0.04 ± 0.01 in both groups (Route of administration: intravenous) An anesthesiologist was present during the procedure (administered the sedation and monitored the patient).	(pulse, MAP, SpO_2, and $TcPO_2$). Respiratory support interventions needed (such as oxygen insufflation, and mask ventilation) Time to recovery. Patient and operator satisfaction (using VAS) Follow-up time: not reported
Bakan,[7] 2014, Turkey. Funding: not stated (It was reported that there were no conflicts of interest)	RCT Setting: not reported Aim: to assess bolus infusions of K or P as an adjuvant to remifentanil-based anesthesia for pediatric rigid bronchoscopy.	Pediatric patients undergoing rigid bronchoscopy for diagnostic (suspected foreign body aspiration, and bronchoalveolar lavage) and/or therapeutic (removal of foreign bodies and/or mucus plugs) purposes. N = 40 (20 in each group) Age (years) (mean ± SD): 3.3 ± 3 in k group, 3.9 ± 4 in P group.	K versus P. K dose (mg/kg): 2 to 3 P dose (mg/kg): 4 to 6 Both patient groups received 2 doses of M, each dose being 0.05 mg/kg. Then 1 mcg/kg per minute of R infusion was started. During the first minute of R infusion, the patients were administered either K or P.	Hemodynamic parameters (HR, SAP, MAP, and DAP). Emergence characteristics (time to extubation, assisted mask ventilation, duration of masked ventilation, time to spontaneous ventilation without assistance, and time to eye opening). Adverse events (bradycardia, hypotension, movement during

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		% Female: 35% in K group, 40% in P group. Weight (kg) (mean ± SD): 14.9 ± 6 in K group, 15.7 ± 10 in P group. Exclusion criteria: Patients with severe cardiovascular disease; cerebral, hepatic, or renal dysfuction; neuromuscular disease; predicted difficulty with laryngoscopy and intubation; SpO2 > 70%; or scheduled for additional interventions or surgery.	(Route of administration: intravenous)	bronchoscopy, and desaturation). Follow-up time: not reported
Non-randomized studies				
Bhat,[3] 2019, India. Funding: not stated (It was reported that there were no conflicts of interest)	Prospective observational study (over 3 years), 1-arm study. Setting: Department of pediatrics of a tertiary care hospital in Northern India. Aim: To assess effectiveness and safety of proceduralist give sedation in pediatric patients undergoing flexible bronchoscopy	Pediatric patients undergoing flexible bronchoscopy for diagnostic and/or therapeutic purposes. N = 267 Age (months) (median [IQR]): 16 (18). % Female: not reported. Weight (kg) (median [IQR]): 10 (7). Exclusion criteria: Pediatric patients who were on a ventilator and/or intubated were excluded	KM = M+K (of note all patients received M and majority of patients additionally received K). Patients who received K also received glycopyrrolate to decrease K-induced increased respiratory secretions. K dose (mg/kg) (median [IQR]):1.17 (0.43) M dose (mg/kg) (median [IQR]): 0.109 (0.03) Glycopyrrolate dose (mcg/kg) (median [IQR]): 5 (0.29) (Route of administration: intravenous)	Complication (hypoxia, apnea, bradycardia, and blood pressure fluctuation). Follow up time: not reported

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Abulebda,[8] 2017, USA. Funding: not stated (It was reported that there were no conflicts of interest or financial relationship to disclose)	Retrospective study (chart review). Setting: single center, outpatient. Aim: to assess effectiveness and safety of propofol based deep procedural sedation regimens for flexible bronchoscopy in pediatric patients in an outpatient setting.	Pediatric patients N = 458 (121 with KP, and 337 with P). Age (years) (measures of central tendency and spread not reported): 3.4 (1.9 to 6.6) in KP, and 5.6 (2.8 to 9.8) in P; P value < 0.0001. % Female: 45.5% in KP, and 42.4% in P; P value = 0.57. Weight (kg) (measures of central tendency and spread were not reported): 14.7 (11.2 to 26.0) in KP, and 20.0 (14.4 to 33.0) in P; P value <0.0001. Comorbidities not significantly different between the groups (P value 0.38) Exclusion criteria: Patients who had undergone flexible bronchoscopy in the pediatric intensive care unit through tracheostomy or endotracheal tube were excluded	KP versus P. K dose: initial bolus of 0.5 mg/kg for patient weight less than 20 kg, and 0.25/kg for patient weight more than 20 kg. P dose: initial bolus of 1 to 2 mg/kg with additional boluses of 1 mg/kg as required to achieve deep sedation. (Route of administration: intravenous)	Recovery time, MAP, hypotension, hypoxia, desaturation Follow up time: not reported
Sazak,[9] 2015, Turkey. Funding: not stated (It was reported that there were no conflicts of interest)	Retrospective study. Setting: Aim: To compare data (such as clinical, hemodynamic, respiratory parameters, complications) in patients undergoing EBUS-TBNA with	Adult patients undergoing EBUS-TBNA for diagnosis and staging of lung cancer. (EBUS is a bronchoscopic method for imaging airway walls) N = 571 (103, 234, 174, and 60 in KPM,	KPM versus KP versus MP versus P. K total dose (mg) (median [range]) in the two groups: 40 (10 to 120) in KPM, and 50 (10 to 135) in KP. P total dose (mg) (median [range]) in the four groups: 50 (15 to 190) in KPM, 50 (15 to	Hemodynamic parameters (HR, MAP, and SpO_2). Patient satisfaction (using a score system: 1 to 5, higher score indicated greater satisfaction. Recovery time.

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	various types of sedation methods.	KP, MP and P groups respectively). Age (years) (mean ± SD): 55.7 ± 13.5 (54.3± 13.8, 53.9±13.9, 57.2±12.6, and 60.3±12.5 in KPM, KP, MP and P groups respectively; P = 0.002). % Female: 32% (40%, 28%, 37%, and 25% in KPM, KP, MP and P groups respectively; P = 0.048). Weight (kg) (mean ± SD): 74.5 ± 14.1 (73.7±12.7, 74.1±13.6, 75.2±14.0, and 75.4± 18.0 in KPM, KP, MP and P groups respectively; P = 0.78). Percentage of patients with comorbidities: 68%, 60%, 73%, and 82% in KPM, KP, MP and P groups respectively; P = 0.003 Exclusion criteria: not reported	220) in KP, 87.5 (20 to 400) in MP, and 100 (30 to 250) in P. M total dose (mg) (median [range]) in the two groups: 2 (1 to 5) in KPM, and 2 (1 to 10) in MP. (Route of administration: intravenous)	Complications (bleeding, pneumothorax, high BP, low BP, bradycardia), desaturation. Follow up time: not reported

BP = blood pressure; EBUS = endobronchial ultrasonography; EBUS-TBNA = EBUS transbronchial needle aspiration; DAP = diastolic arterial pressure; F = fentanyl; FPM = fentanyl+propofol+midazolam; HR = heart rate; IQR = interquartile range; K = ketamine; kg = kilogram; KM = ketamine+midazolam; KP = ketamine+propofol; KPM = ketamine+propofol+midazolam; M = midazolam; MAP = mean arterial pressure; mcg = microgram; mg = milligram; NS = not significant; P = propofol; PM = propofol+midazolam; PKM = propofol+ketamine+ midazolam; R = remifentanil; RCT = randomized controlled trial; SAP = systolic arterial pressure; SpO2 = oxygen saturation (or saturation of peripheral oxygen); TcPCO2 = transcutaneous carbon dioxide tension; VAS = visual analog scale.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Using AMSTAR 2[4]

Strengths	Limitations
Ehsan,[6] 2016, USA	
• The objective was clearly stated • Study selection was described, and a flow chart was presented • Multiple databases (PubMed, CINAHL, EBM reviews, and Scopus [all indexed years]) were searched up to September 2014. • Study selection was described, and a flow chart was presented • A list of included studies was provided • Article selection was done independently by two reviewers • Quality assessment was done independently by two reviewers using the Newcastle-Ottawa scale for non-randomized studies, and the Cochrane risk of bias tool for randomized controlled trials. The one retrospective study included for our report was given six stars (using the Newcastle-Ottawa scale) by the authors, but the maximum number of attainable stars was not mentioned. • Characteristics of the included studies were briefly described • It was mentioned that the authors had no funding, financial relationships, or conflicts of interest to disclose	• A list of excluded studies was not provided • Unclear if data extraction was done in duplicate • Publication bias does not appear to have been explored.

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2.

Table 5: Strengths and Limitations of Clinical Studies Using the Downs and Black checklist[5]

Strengths	Limitations
Randomized controlled trial	
Fruchter,[2] 2017, Israel	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomized study. Randomization method appeared appropriate (assigned using Research Randomization online version software) • Double blinded (patients and operator were blinded) • Sample size calculation was conducted but the appropriate number of patients could not be recruited. • ITT analysis was undertaken • P values were reported • The authors mentioned that there no conflicts of interest	• The study was underpowered as the appropriate number of patients could not be recruited.
Bakan,[7] 2014, Turkey	
• The objective was clearly stated • The inclusion and exclusion criteria were stated	• Randomization method was not described • Blinding was not mentioned

Strengths	Limitations
• Patient characteristics, intervention and outcomes were described. • Randomized study but method of randomization not described • Sample size calculation was conducted, and the appropriate number of patients was recruited. • P values were reported, in most instances • The authors mentioned that there no conflicts of interest	• Unclear if ITT analysis was undertaken
Non-randomized study	
Bhat,3 2019, India	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Sample size calculation, P-value reporting, ITT analysis not applicable for this study • The authors mentioned that there no conflicts of interest	• The study was not a randomized controlled trial; it was a prospective observational study with one treatment arm.
Abulebda,[8] 2017, USA	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • P-values were reported sometimes • The authors mentioned that there no conflicts of interest or financial relationships to disclose.	• The study was not a randomized controlled trial; it was a retrospective study and there were statistically significant differences in patient characteristics (with respect to age and weight) between the different groups which could impact findings. • Sample size calculation does not appear to have been undertaken.
Sazak,[9] 2015, Turkey	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • P-values were reported • The authors mentioned that there no conflicts of interest	• The study was not a randomized controlled trial; it was a retrospective study and there were statistically significant differences in patient characteristics (with respect to age and comorbidities) between the different groups, which could impact findings. • Sample size calculation does not appear to have been undertaken.

ITT = intention to treat.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Review

Main study findings	Authors' conclusion
Ehsan,[6] 2016, USA	
Findings from one relevant retrospective study (involving pediatric patients) included in the systematic review (This systematic review evaluated various anesthetic agents and opioids; one included study was on ketamine in combination with other drugs) Adverse events occurred in 23% of the patients. Adverse events included mild hypoxia, brief central apnea, and stridor.	"Studies assessing the effect of anesthesia on the upper airway, with and without OSA, are limited and few compare effects between agents. [….] There is almost no literature describing the effect of combinations of anesthetic agents on the upper airway; this is important because most DISE protocols utilize a combination of agents (e.g., dexmedetomidine and ketamine). (p. 282)"[6]

DISE = drug-induced sleep bronchoscopy, OSA = obstructive sleep apnea.

Table 7: Summary of Findings of Included Primary Clinical Studies

Main study findings	Authors' conclusion
Randomized controlled trials	
Fruchter,[2] 2017, Israel	
Findings from RCT involving adult patients undergoing flexible fiberoptic bronchoscopy and comparing KPM to FPM; (39 patients in the KPM group, and 41 patients in the FPM group). *Hemodynamic and respiratory parameters (pulse, MAP, SpO_2, and TpCO2).* Pulse Baseline (mean ± SD): 82.9 ± 11.7 in KPM group, and 78.8 ±14.0 in FPM group; P = NS. During procedure (mean ±SD): 85.5 ± 11.6 in KPM group, and 79.2 ± 11.0 in FPM group; P = 0.02. MAP (mm Hg) Baseline (mean ± SD): 97.0 ± 13.0 in KPM group, and 96.9 ± 13.4 in FPM group; P = NS. During procedure (mean ±SD): 101.6 ± 14.8 in KPM group, and 88.6 ± 13.8 in FPM group; P = 0.0001. SpO2 (%) Baseline (mean ± SD): 99.2 ± 1.5 in KPM group, and 99.3 ± 1.5 in FPM group; P = NS. During procedure (mean ±SD): 97.6 ± 1.7 in KPM group, and 97.2 ± 2.5 in FPM group; P = NS. Time (minutes) during which SpO_2 was below 88%: 1.3 ± 2.4 in KPM group, and 1.1 ± 1.7 in FPM group; P = NS. (Significant hypoxemia was defined as SpO_2 of 90%) TcPCO2 (mm Hg) Baseline (mean ± SD): 37.8 ± 4.1 in KPM group, and 38.6 ± 4.2 in FPM group; P = NS. During procedure (mean ±SD): 47.0 ± 7.1 in KPM group, and 47.4 ± 5.7 in FPM group; P = NS.	"Ketamine is as safe and effective as fentanyl for adult analgesia and sedation during FFB. (p. 279)"[2]

Main study findings	Authors' conclusion
Other outcomes Time to recovery (minutes) (mean ± SD): 10.6 ± 3.6 in KPM group, and 9.5 ± 3.3 in FPM group; P = NS. Operator satisfaction (using VAS) (mean ± SD): 8.9 ± 1.4 in KPM group, and 9.2 ± 0.8 in FPM group; P = NS. Patient satisfaction (using VAS) (mean ± SD): 9.7 ± 0.9 in KPM group, and 9.9 ± 0.3 in FPM group; P = NS. Note: VAS scale from 0 to 10 with higher values indicating greater satisfaction. *Proportion of patients requiring cardiovascular or respiratory support* Jaw thrust: 17.9% in KPM, and 19.5% in FPM; P = NS. Oxygen insufflation: 15.4% in KPM, and 7.3% in FPM; P = NS. Nasopharyngeal airway: 19.9% in KPM, and 12.1% in FPM; P = NS. Ambu mask ventilation: 2.6% in KPM, and 0% in FPM; P = NS. Intravenous fluid administration: 0% in KPM, and 2.6% in FPM; P = NS. Any intervention: 23% in KPM, and 24% in FPM; P = NS.	
Bakan,[7] 2014, Turkey	
Findings from RCT involving pediatric patients undergoing rigid bronchoscopy and comparing K to P (Total of 40 patients; 20 in each group). *Hemodynamic parameters (SAP, MAP, DAP, and heart rate).* <u>SAP (mm Hg)</u> Baseline (mean ± SD): 106 ± 14 in K group, and 98 ± 15 in P group. Highest value during bronchoscopy: 101 ± 13 in K group, and 86 ± 8 in P group. Lowest value during bronchoscopy: 90 ± 14 in K group, and 75 ± 8 in P group. <u>DAP (mm Hg)</u> Baseline (mean ± SD): 66 ± 13 in K group, and 61 ± 13 in P group. Highest value during bronchoscopy (mean ± SD): 62 ± i12n K group, and 50 ± 8 in P group. Lowest value during bronchoscopy (mean ± SD): 50 ± 8 in K group, and 39 ± 6 in P group. <u>MAP (mm Hg)</u> Baseline (mean ± SD): 80 ± 13 in K group, and 77 ± 13 in P group. Highest value during bronchoscopy (mean ± SD): 75 ±12 in K group, and 64 ± 7 in P group. Lowest value during bronchoscopy (mean ± SD): 64 ± 10 in K group, and 53 ± 7 in P group. <u>Heart rate (beats/min)</u> Baseline (mean ± SD):132 ± 26 in K group, and 129 ± 26 in P group. Highest value during bronchoscopy (mean ± SD): 124 ± 18 in K group, and 119 ± 24 in P group. Lowest value during bronchoscopy (mean ± SD): 107 ± 21in K group, and 99 ± 22 in P group. *Emergence characteristics* Time to extubation (mean ± SD): 15.1 ± 6.9 in K group, and 18.7 ± 5.9 in P group; P = NS. Controlled and/or assisted mask ventilation after extubation (no of patients): 13 in K group, and 4 in P group; P = 0.0095. Duration of mask ventilation after extubation (mean ± SD): 6.65 ± 10.3 in K group, and 0.55 ± 1.3 in P group; P = 0.001.	"In conclusion, remifentanil-based TIVA with propofol or ketamine as an adjuvant drug along with controlled ventilation is a viable technique for pediatric RB. The intense stimulation associated with RB was well suppressed with a 1 mg/kg/min remifentanil infusion, which also secured hemodynamic stability. Propofol appeared to be more suitable in the recovery period of remifentanil-based anesthesia for RB of pediatric patients, while ketamine use instead of propofol did not provide a definite advantage when hemodynamic stability during RB is considered. (p. 376)"[7]

Main study findings	Authors' conclusion
Time to spontaneous ventilation without assistance (after decreasing remifentanil infusion) (minutes): 21.7 ± 11.2 in K group, and 19.2 ± 5.8 in P group; P = NS. Time to eye opening (after decreasing remifentanil infusion) (minutes): 30.2 ± 16 in K group, and 27 ± 9.1 in P group; P = NS. *Adverse events (number of events)* Midazolam-related agitation: 1 in K group, and 1 in P group. Bradycardia: 3 in K group, and 1 in P group. Hypotension: 3 in K group, and 5 in P group. Mild movement during rigid bronchoscopy: 2 in K group, and 9 in P group (moderate or severe movement was not observed in any group). Severe desaturation: 5 in K group, and 1 in P group Bronchopasm: 2 in K group, and 0 in P group Aryngospasm: 1 in K group, and 0 in P group Post-operative nausea and vomiting: 4 in K group, and 1 in P group Emergence agitation: 3 in K group, and 1 in P group The authors reported that were no statistically significant differences in adverse events between the two groups.	
Non-randomized study	
Bhat,[3] 2019, India	
Findings from a prospective observational study (1 treatment arm: K, M, and glycopyrrolate) involving pediatric patients undergoing flexible bronchoscopy. Patients were given M, and in addition most patients received K. *Minor complications* (proportion of patients) Hypoxia: 6% Transient bradycardia: 1.1% Mild BP fluctuations (<20% from baseline): 1.1% Apnea: 1.8% *Minor complications* (proportion of patients) BP fluctuations (>20% from baseline): 0.37% Prolonged apnea (needed intubation): 0.37%	"Flexible bronchoscopy in children can be safely performed by using midazolam and ketamine combination. The combination causes adequate sedation and analgesia for successful completion of the procedure. Furthermore, in resource-constrained settings, it is safe to use above regimen by proceduralists provided the team is adequately trained in resuscitation and airway management. (p. 217)"[3]
Abulebda,[8] 2017, USA	
Findings from a retrospective study (chart review) involving pediatric patients undergoing flexible bronchoscopy and comparing KP with P. *Recovery time* (minutes) (not specified if mean or median values): 25 (20 to 35) in KP group, and 25 (20 to 30) in P group; P = not significant. *MAP (mm Hg):* At start of the procedure MAP values (ranges) were 76.3 (68.0 to 88.7) in KP and 78.3 (71.3 to 86.3) in P; P = 0.58. At end of the procedure MAP values (ranges) were 68.7 (61.7 to 76.3) in KP, and 71.0 (64.0 to 79.3) in P; P = 0.04. *Adverse events* (proportion of patients) Hypoxia: 7.4% in KP, and 8.6% in P; P = 0.69. Hypotension (blood pressure drop greater than 20% from baseline): 26.4% in KP, and 22.6% in P; P = 0.4. Significant desaturation: 1.7%, and 4.2% in KP and P respectively; P value not reported.	"Children can be effectively sedated for outpatient flexible bronchoscopy with high rate of success. This procedure should be performed under vigilance of highly trained providers. (p180)"[8]

Main study findings	Authors' conclusion
(Significant desaturation was defined as oxygen saturation less than 90% for more than 30 seconds.)	
Sazak,[9] 2015, Turkey	
Findings from a retrospective study involving adults patients undergoing EBUS-TBNA and comparing KP versus MP versus KPM (same as PKM) versus P; (234, 174, 103, and 60 in KP, MP, PKM, and P respectively). *Hemodynamic and respiratory parameters (MAP, heart rate, and SpO_2).* MAP (mm Hg) Baseline (mean ± SD): 91.5 ± 12.0 in KP, 91.7 ± 12.7 in MP, 94.5 ± 12.0 in KPM, and 91.5 ± 12.9 in P; P = 0.19. First measurement during procedure (mean ± SD): 92.8 ± 12.6 in KP, 92.9 ± 14.2 in MP, 95.4 ± 10.8 in KPM, and 89.4 ± 13.1 in P; P = 0.07. Fifth measurement during procedure (mean ± SD): 97.1 ± 12.9 in KP, 89.5 ± 15.5 in MP, 97.8 ± 11.8 in KPM, and 90.7 ± 15.5 in P; P < 0.001. Maximum value during procedure (mean ± SD): 97.3 ± 13.5 in KP, 92.9 ± 14.2 in MP, 98.6 ± 12.5 in KPM, and 90.7 ± 15.5 in P Minimum value during procedure (mean ± SD): 92.8 ± 12.6 in KP, 89.5 ± 15.5 in MP, 95.4 ± 10.8 in KPM, and 89.4 ± 13.1 in P Heart rate (beats/minute) Baseline (mean ± SD): 83.9 ± 12.2 in KP, 82.7 ± 13.6 in MP, 86.4 ± 12.8 in KPM, and 82.0 ± 13.7 in P; P = 0.01. First measurement during procedure (mean ± SD): 86.0 ± 13.1 in KP, 84.3 ± 14.1 in MP, 88.2 ± 12.4 in KPM, and 83.5 ± 12.5 in P; P = 0.11. Fifth and last measurement during procedure (mean ± SD): 88.6 ± 13.7 in KP, 86.3 ± 13.5 in MP, 91.3 ± 13.0 in KPM, and 84.7 ± 11.5 in P; P = 0.01. SpO_2 (%) Baseline (mean ± SD): 96.5 ± 2.0 in KP, 95.7 ± 2.7 in MP, 96.7 ± 1.9 in KPM, and 96.4 ± 1.9 in P; P = 0.003 First measurement during procedure (mean ± SD): 96.5 ± 2.3 in KP, 96.2 ± 2.6 in MP, 96.0 ± 6.0 in KPM, and 95.9 ± 2.2 in P; P = 0.51 Fifth measurement during procedure (mean ± SD): 96.2 ± 3.3 in KP, 95.6 ± 3.2 in MP, 96.4 ± 2.1 in KPM, and 95.9 ± 2.8 in P; P = 0.28 *Other outcomes* Recovery time (minutes) (mean ± SD): 15.46 ± 3.52 in KP, 15.9 ± 3.81 in MP, 17.05 ± 3.96 in KPM, and 13.42 ± 2.94 in P. The authors concluded that the recovery time was significantly shorter with KP or MP than with KPM (however, P value not reported); was not significantly different between KP and MP (P> 0.05); and was significantly shorter with P compared with KP, MP, or KPM (however, P value not reported). Patient satisfaction score (median [range]): 5 (2 to 5), 5 (4 to 5), 5 (1 to 5), and 5 (4 to 5) for KP, MP, KPM, and P respectively; P = 0.03 for comparison between all four groups and applying Bonferroni correction. Patient satisfaction score (on a scale of 0 to 5, with higher values indicating greater satisfaction) *Adverse effects (% of patient experiencing adverse events)* Complications (includes bleeding, pneumothorax, high blood pressure, low blood pressure and bradycardia): 25% in KP, 15% in MP, 23% in KPM, and 15% in P, P = 0.045. Proportion of patients with complications were statistically significantly greater with PK compared with MP (P < 0.05).	"Independent from the sedative agent, deep sedation can be safe, and provide high patient satisfaction during EBUS-TBNA. The combination of ketamine with propofol or midazolam required lower doses of these anesthetics. However, the incidence of increased blood pressure was higher in groups administered ketamine. Recovery time was the shortest in group P, and the longest in group PKM. There was no relation between recovery time and total dose of anesthetics or presence of chronic disease. (p. 567)"[9]

Main study findings	Authors' conclusion
Bleeding: NA in KP, 1% in MP, NA in KPM, and NA in P; P = NA. Pneumothorax: 1% in KP, NA in MP, NA in KPM, and NA in P; P = NA. High blood pressure: 19% in KP, 6% in MP, 17% in KPM, and 10% in P, P < 0.001. Proportion of patients with increased blood pressure were statistically significantly greater with PK compared with MP (P < 0.05). Proportion of patients with increased blood pressure were statistically significantly greater with KPM compared with MP (P = 0.004). Low blood pressure: NA in KP, NA in MP, 1% in KPM, and NA in P; P = NA. Bradycardia: NA in KP, 1% in MP, 1% in KPM, and NA in P; P = NA. Allergy: 2% in KP, 1% in MP, NA in KPM, and NA in P, P = 0.12. Desaturation: 5% in KP, 12% in MP, 6% in KPM, and 5% in P, P < 0.07. *Multivariate regression analysis*. It was reported that there was no correlation between recovery time and gender, ASA classification, total anesthetic doses, and presence of comorbidities (P > 0.05).	

ASA = American Society of Anesthesiology; DAP = diastolic arterial pressure; EBUS = endobronchial ultrasonography; EBUS-TBNA = EBUS transbronchial needle aspiration; FFB = flexible fiberoptic bronchoscopy; FPM = fentanyl+propofol+midazolam; K = ketamine; KPM (or PKM) = ketamine+propofol+midazolam; M = midazolam; MAP = mean arterial pressure; NA = not applicable; NS = not significant; P = propofol; RB = rigid bronchoscopy; RCT = randomized controlled trial; SAP = systolic arterial pressure; SD = standard deviation; SpO_2 = oxygen saturation (or saturation of peripheral oxygen); TcPCO2 = transcutaneous carbon dioxide tension ; TIVA = total intravenous anesthesia; VAS = visual analog scale.