Awake Fiberoptic Intubation Protocols in the Operating Room for Anticipated Difficult Airway: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Cabrini, Luca ; Baiardo Redaelli, M ; Ball, Lorenzo ; Filippini, Martina ; Fominskiy, Evgeny ; Pintaudi, Margherita ; Putzu, Alessandro ; Votta, Carmine D ; Sorbello, Massimiliano ; Antonelli, Massimo ; Landoni, Giovanni ; Pelosi, Paolo ; Zangrillo, Alberto

Abstract: Awake fiberoptic intubation is one of the recommended strategies for surgical patients with anticipated difficult airway, especially when concurrent difficult ventilation is expected. We performed the first systematic review of randomized controlled trials assessing different protocols for awake fiberoptic intubation in anticipated difficult airway, including studies investigating elective awake fiberoptic intubation for scheduled surgery; randomized controlled trials comparing different methods for performing awake fiberoptic intubation; and adult patients with anticipated difficult airway. We excluded studies in the nonoperating theater settings, randomized controlled trials comparing awake fiberoptic intubation with other techniques, and studies based on simulation. Primary outcomes were success rate and death; secondary outcomes were major adverse events. Thirty-seven randomized controlled trials evaluating 2045 patients and 4 areas were identified: premedication, local anesthesia, sedation, and ancillary techniques to facilitate awake fiberoptic intubation. Quality of evidence was moderate-low and based on small-sampled randomized controlled trials. Overall, 12 of 2045 intubation failures (0.59%) and 7 of 2045 severe adverse events (0.34%) occurred, with no permanent consequences or death. All evaluated methods to achieve local anesthesia performed similarly well. No differences were observed in success rate with different sedatives. Dexmedetomidine resulted in fewer desaturation episodes compared to propofol and opioids with or without midazolam (relative risk, 0.51 [95% CI, 0.28-0.95]; P = .03); occurrence of desaturation was similar with remifentanil versus propofol, while incidence of apnoea was lower with sevoflurane versus propofol (relative risk, 0.43 [95% CI, 0.22-0.81]; P = .01). A high degree of efficacy and safety was observed with minimal differences among different protocols; dexmedetomidine might offer a better safety profile compared to other sedatives.

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SYSTEMATIC REVIEW ARTICLE

Awake Fiberoptic Intubation Protocols in the Operating Room for Anticipated Difficult Airway: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Luca Cabrini, MD,*† M Baiardo Redaelli, MD,* Lorenzo Ball, MD,‡ Martina Filippini, MD,* Evgeny Fominskiy, MD,* Margherita Pintaudi, MD,* Alessandro Putzu, MD,§ Carmine D. Votta, MD,* Massimiliano Sorbello, MD,‖ Massimo Antonelli, MD,¶ Giovanni Landoni, MD,*† Paolo Pelosi, MD,‡ and Alberto Zangrillo, MD*†

Awake fiberoptic intubation is one of the recommended strategies for surgical patients with anticipated difficult airway, especially when concurrent difficult ventilation is expected. We performed the first systematic review of randomized controlled trials assessing different protocols for awake fiberoptic intubation in anticipated difficult airway, including studies investigating elective awake fiberoptic intubation for scheduled surgery; randomized controlled trials comparing different methods for performing awake fiberoptic intubation; and adult patients with anticipated difficult airway. We excluded studies in the nonoperating theater settings, randomized controlled trials comparing awake fiberoptic intubation with other techniques, and studies based on simulation. Primary outcomes were success rate and death; secondary outcomes were major adverse events. Thirty-seven randomized controlled trials evaluating 2045 patients and 4 areas were identified: premedication, local anesthesia, sedation, and ancillary techniques to facilitate awake fiberoptic intubation. Quality of evidence was moderate–low and based on small-sampled randomized controlled trials. Overall, 12 of 2045 intubation failures (0.59%) and 7 of 2045 severe adverse events (0.34%) occurred, with no permanent consequences or death. All evaluated methods to achieve local anesthesia performed similarly well. No differences were observed in success rate with different sedatives. Dexmedetomidine resulted in fewer desaturation episodes compared to propofol and opioids with or without midazolam (relative risk, 0.51 [95% CI, 0.28–0.95]; $P = .03$); occurrence of desaturation was similar with remifentanil versus propofol, while incidence of apnoea was lower with sevoflurane versus propofol (relative risk, 0.43 [95% CI, 0.22–0.81]; $P = .01$). A high degree of efficacy and safety was observed with minimal differences among different protocols; dexmedetomidine might offer a better safety profile compared to other sedatives. (Anesth Analg 2019;128:971–80)

Tracheal intubation is often required for surgical interventions. A certain number of patients presents difficult airway, defined as "the clinical situation in which a conventionally trained anesthesiologist experiences difficulty with facemask ventilation of the upper airway, difficulty with tracheal intubation, or both,"[1] with an incidence ranging from 0.3% to 13%.[2] Moreover, in up to 1 of every 250 patients (0.4% of cases), difficult laryngoscopy and difficult mask ventilation might be associated, generating a risky scenario known as "cannot intubate, cannot oxygenate".[3,4] As a matter of fact, severe brain damage and death can result from inappropriate management of a difficult airway;[5,6] recently, a nationwide survey of compensation related to injuries after anesthesia and airway management in Norway revealed that more than half of the severe injuries were caused by failed intubation or a misplaced endotracheal tube.[7]

While difficult airway management can be an unexpected finding, several scores and tests with different performances have been proposed to predict the risk of its occurrence.[1,2,8] Different techniques to face anticipated difficult airway have been proposed and evaluated, and guidelines were published.[1,2,9] In such a case, the so-called awake fiberoptic intubation, performed by anesthetization of the upper airway mucosa by topical local anesthesia or regional anesthesia, and frequently facilitated by the administration of sedatives (but preserving spontaneous breathing), has a crucial role, being considered the gold standard by national societies and experts.[2,9–11] Different aspects of this technique

From the *Department of Anaesthesia and Intensive Care, Istituto di Ricovero e Cura a Carattere Scientifico San Raffaele Scientific Institute, Milan, Italy; †Università Vita-Salute San Raffaele, Milan, Italy; ‡Department of Surgical Sciences and Integrated Diagnostics, San Martino Policlinico Hospital, Istituto di Ricovero e Cura a Carattere Scientifico for Oncology, University of Genoa, Genoa, Italy; §Division of Anesthesiology, Department of Anesthesiology, Pharmacology & Intensive Care Medicine, Geneva University Hospitals, Geneva, Switzerland; ‖Anaestesia and Intensive Care, Azienda Ospedaliero-Universitaria Policlinico Vittorio Emanuele, Catania, Italy; and ¶Department of Intensive Care Medicine and Anaesthesiology, Fondazione Policlinico Universitario A. Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy.

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Address correspondence to Paolo Pelosi, MD, Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy; Policlinico San Martino Istituto di Ricovero e Cura a Carattere Scientifico per l'Oncologia, Largo Rosanna Benzi 8, 16131 Genoa, Italy. Address e-mail to ppelosi@hotmail.com.

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have been evaluated in randomized controlled trials, but no systematic review summarized their results.

We performed a systematic review of randomized controlled trials comparing different techniques and medications for awake fiberoptic intubation for anticipated difficult airway in adult surgical patients. We hypothesized that techniques and medications for awake fiberoptic intubation can impact success rate, death, and incidence of life-threatening events.

METHODS

Search Strategy

PubMed, BioMed Central, Embase, and the Cochrane Central Register of Clinical Trials were searched for pertinent studies (updated on March 21, 2018) by 5 investigators (M.B.R., M.F., M.P., A.P., C.D.V.). The detailed search strategy is reported in the Appendix A. The references of retrieved articles and pertinent reviews were checked for further studies. No language restriction was used.

Study Selection

References obtained from database and literature were first independently examined at title/abstract level by 6 investigators (L.C., M.B.R., M.F., M.P., A.P., C.D.V.), with disagreement resolved by consensus with supervision of 4 investigators (M.A., G.L., P.P., A.Z.) and, if potentially pertinent, full articles were retrieved.

The following inclusion criteria were used for potentially relevant studies: (1) elective awake fiberoptic intubation for any elective surgical procedure; (2) randomized controlled trials comparing different methods of premedication, sedation, local anesthesia, and ancillary devices or techniques for fiberoptic bronchoscopy or tracheal tube introduction; (3) involving adult patients with anticipated difficult airway management; and (4) published in peer-reviewed journals. Exclusion criteria included nonoperating theater settings, randomized controlled trials comparing awake fiberoptic intubation with other techniques, and studies based on simulation. Three investigators (L.C., L.B., G.L.) selected studies for the final analysis independently assessing compliance to selection criteria. Divergences were solved by consensus. Main outcomes were success rate, death, and potentially life-threatening adverse events.

Data Abstraction, Synthesis, and Study Characteristics

Data were independently extracted by 2 authors (M.B.R., M.F.) with disagreements resolved by discussion or involving a third reviewer when required. Two authors (L.C., L.B.) screened the trials for meaningful outcome measures that could be compared systematically. We computed the relative risks along with their 95% CIs for dichotomous outcomes. Pooled estimates were calculated with a mixed-effects model using the DerSimonian–Laird method. We analyzed several small-sampled studies with zero events reported in both arms; to include them in the mixed-effects model avoiding loss of information, we added a constant (0.5) to the event counts in these studies. Studies were stratified to reduce clinical heterogeneity. We compared subgroups with the Cochrane Q test, and residual statistical heterogeneity was assessed with the I^2 statistics and Q test. Meta-analyses were performed with R 3.2.3 and the meta-for package (The R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org).

The internal validity of each included trial was evaluated for bias according to the Cochrane Collaboration methods by 2 authors (E.F., A.P.). We assessed the risk of bias associated with the random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting, and other bias. We evaluated the potential risk of bias by applying a rating of "low," "high," or "unclear" to each study. For comparisons comprising >5 studies, we performed a formal assessment of bias using a funnel plot.

Certainty of the body of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation framework.[12] The Grading of Recommendations Assessment, Development, and Evaluation evaluation characterizes the certainty of a body of evidence on the basis of study limitations, imprecision, inconsistency, indirectness, and other considerations.[13,14]

The protocol was registered at Prospero database (CRD42018093009).

RESULTS

Database searches and references screening yielded 2150 articles. Among these, we identified and retrieved 37 randomized clinical trials for inclusion evaluating 2045 patients with anticipated difficult airway management and scheduled for elective awake fiberoptic intubation. Four different areas of investigation could be identified: premedication (1 study),[15] local anesthesia (10 studies),[16–25] sedation (23 studies),[26–48] and other ancillary devices and techniques to facilitate awake fiberoptic intubation (3 studies).[49–51] Random sequence generation was assessed as low risk of bias in 22 trials, allocation concealment in 6 trials, blinding of participants and personnel in 9 trials, blinding of outcome assessors in 12 trials, completeness of outcome data in 32 trials, selective outcome reporting in 35 trials, and other bias in 31 trials. Overall, 14 trials were judged to be at unclear risk and 23 at high risk (Supplemental Digital Content 1, Figures 1–2, http://links.lww.com/AA/C749). Overall, 12 of 2045 intubation failures (0.59%) and 7 of 2045 severe adverse events (0.34%) were reported in the randomized controlled trials, all immediately and successfully treated; no adverse events resulting in permanent damage nor death occurred.

Within the different areas, a high degree of heterogeneity was present in terms of protocols and reported outcomes, namely markedly different dosages, different combination of drugs and techniques, scores applied to evaluate the ease of the procedure and patient satisfaction, and safety data. Hence, formal meta-analysis was restricted to success rate, incidence of desaturation, or apnoea with different sedation regimens.

In the only randomized controlled trial focused on premedication, Yokota et al[15] compared premedication with atropine and hydroxyzine intramuscularly with oral clonidine in 30 patients: at intubation, the increase of systolic pressure and heart rate was less marked in the clonidine group.

Ten randomized controlled trials including 547 patients evaluated different techniques to perform topical anesthesia (Table). Premedication, sedatives, and collected outcomes were heterogeneous: no reliable meta-analysis could be performed. Safety and efficacy were high with all techniques: only 4 of 547 failures (0.7%) were observed, with no reported severe adverse event.

Most of the available randomized controlled trials assessed several sedation regimens in 1334 patients (Supplemental Digital Content 2, Table 1, http://links.lww.com/AA/C750). With 14 studies, dexmedetomidine was the single most evaluated drug, both as single bolus or as continuous infusion. Opioids (fentanyl, sufentanil, and remifentanil) were evaluated in 12 studies as bolus or continuous infusion (manually set or as target-controlled infusion); often, they were associated with other sedatives, usually midazolam. Propofol was evaluated in 9 studies and infused as bolus or as continuous infusion (manually regulated or as target-controlled infusion). Finally, sevoflurane was used in 2 studies, and etomidate was used in 1 study. Every randomized controlled trial reported significant differences in some clinically secondary outcome among the evaluated drugs: in particular, when not associated to benzodiazepines, opioids seemed to cause a higher incidence of recall compared to dexmedetomidine and propofol. However, all regimens showed a similarly satisfactory level of efficacy, with only 8 of 1334 (0.60%) reporting failed intubations, and high level of safety, with 7 of 1334 (0.52%) reported severe adverse events. Overall, dexmedetomidine, compared to sedation regimes based on propofol, opiates, benzodiazepines, or their combinations, resulted in fewer desaturation episodes (relative risk, 0.51; 95% CI, 0.28–0.95; $P = .03$; $I^2 = 0\%$; Grading of Recommendations Assessment, Development, and Evaluation level of evidence: low; Figure 1; funnel plot in Supplemental Digital Content 1, Figure 3, http://links.lww.com/AA/C749), but no differences were observed in the incidence of procedure failure (relative risk, 0.99; 95% CI, 0.29–3.37; $P = .98$; $I^2 = 0\%$). Remifentanil compared to propofol was associated with similar incidence of desaturation episodes (relative risk, 0.28; 95% CI, 0.04–1.92; $P = .18$; $I^2 = 0\%$; Grading of Recommendations Assessment, Development, and Evaluation level of evidence: low; Figure 2) and procedural failure (relative risk, 0.65; 95% CI, 0.11–3.96; $P = .64$; $I^2 = 0\%$; Grading of Recommendations Assessment, Development, and Evaluation level of evidence: low). Sevoflurane compared to propofol was associated with fewer episodes of apnea (relative risk, 0.43; 95% CI, 0.22–0.81; $P = .01$; $I^2 = 0\%$; Grading of Recommendations Assessment, Development, and Evaluation level of evidence: low; Figure 3) and similar procedural failure rate (relative risk, 2.90; 95% CI, 0.44–18.96; $P = .27$; $I^2 = 0\%$; Grading of Recommendations Assessment, Development, and Evaluation level of evidence: low).

Finally, 3 studies evaluated other devices and techniques to facilitate the procedure.[49–51] Bourgain et al,[49] using an endoscopy mask (VBM-Medical, Sulz am Neckar, Germany), compared the application of 10 cm H_2O of pressure support with spontaneous breathing without support in a total of 32 patients sedated with propofol; the supported group showed a significantly higher minute ventilation but longer duration of the procedure, while other parameters were similar.[49] Zou et al[50] compared a prototype mask designed for endoscopy with conventional nasal oxygen therapy in 54 patients: the mask group had a significantly better peripheral oxygen saturation and fewer episodes of desaturation <90%.[50] Mohammadzadeh et al,[51] in 48 mildly sedated patients, compared the nasal introduction of the tube only when the fiberoptic bronchoscopy reached the vocal cords with a previous introduction of the tube through a nostril for 18 cm (scope first versus tube first): the latter group required less time and fewer facilitating maneuvers.[51]

DISCUSSION

The present study is the first systematic review and meta-analyses of randomized controlled trials assessing different approaches in any phase of awake fiberoptic intubation for anticipated difficult airway in patients scheduled for elective surgery. Thirty-seven studies focusing on 4 different areas of this procedure (premedication, local anesthesia, sedation, and other ancillary devices and techniques to facilitate awake fiberoptic intubation) were included in this systematic review, while 15 were included in the meta-analyses. The present study suggests that different methods for performing awake fiberoptic intubation are similarly safe and effective: we could not identify a protocol clearly better than the others, excluding some advantage on minor outcomes for sedation protocols based on dexmedetomidine or sevoflurane. Moreover, our review observed a high level of efficacy and safety in the evaluated protocols despite the anticipated difficult airway management, with an overall success rate of 99.4%, no deaths, and an incidence of severe adverse events of 0.34% without reported permanent sequelae, confirming that awake fiberoptic intubation can be considered a reliable and well-tolerated option in this challenging condition of expected severe difficult airway management.

When facing a predicted difficult airway management and tracheal intubation is necessary, awake fiberoptic intubation is still considered the standard approach, above all if mask ventilation is expected to be difficult.[2,53] Preserving spontaneous breathing, awake fiberoptic intubation can prevent the risk of a critical desaturation or a "cannot intubate-cannot oxygenate" scenario. In the setting of expected difficult airways, with particular reference to difficult or impossible ventilation,[5–7] awake fiberoptic intubation is highly reliable, with a low number of (mostly mild) complications[53] and a variable success rate ranging from 88% to 100%,[1] mostly related to the operator's experience

The awake fiberoptic intubation technique can be preceded by 3 subsequent steps: premedication, local anesthesia, and sedation; furthermore, the insertion of the fiberoptic bronchoscopy and the tube can be performed in different ways. A detailed description of the procedure can be found elsewhere.[53] Our aim was to identify the best approach of every step if sufficient data were available, to further improve awake fiberoptic intubation effectiveness and safety and orient future research. We found a wide heterogeneity of techniques and drugs regimens, with interpretation of their results made difficult also by the reciprocal relationships among the different steps: for example, a well-conducted

Table. Randomized Controlled Trials Comparing Different Local Anesthesia Methods for Elective Fiberoptic Tracheal Intubation in the Operating Room for Anticipated Difficult Airway

Reference	Intervention	Comparator	No. Patients Intervention	No. Patients Comparator	Premedication
Wieczorek et al[16]	Nebulized 2% lidocaine 40 mL	Nebulized 4% lidocaine 40 mL	14	13	Sodium citrate 30 mL orally, metoclopramide 10 mg, glycopyrrolate 0.3 mg, and ondansetron 4 mg IV
Woodruff et al[17]	Nebulized 1% lidocaine 40 mL	Nebulized 2% lidocaine 40 mL	11	10	Sodium citrate 30 mL orally, metoclopramide 10 mg, glycopyrrolate 0.3 mg, and ondansetron 4 mg IV
Vasu et al[18]	Nebulized 4% lidocaine 10 mL using DeVilbiss Model 163 Atomizer (DeVilbiss Health care, Somerset, PA)	Transtracheal injection 4% lidocaine 4 mL	16	17	Glycopyrrolate 0.2 mg IV; 2 sprays of 10% lidocaine into each nostril and 1 mL of 2% lidocaine jelly
Kundra et al[19]	Nebulized 4% lidocaine 4 mL	Topical anesthesia of nasal mucosa with cotton swabs soaked with 4% lidocaine + bilateral superior laryngeal nerve block (3 mL, 2%) + translaryngeal block (2 mL, 4%) with lidocaine	24	24	Diazepam (10 mg orally), morphine (0.15 mg/kg IM), glycopyrrolate (0.2 mg IM), and 2–3 drops of 0.05% xylometazoline in each nostril
Gupta et al[20]	4% lidocaine 10 mL by ultrasonic nebulizer	Blocks with 2% lidocaine of bilateral superior laryngeal nerve and transtracheal instillation of lidocaine, plus viscous xylocaine gargles twice	25	25	Oral ranitidine 150 mg, glycopyrrolate 5 μg/kg IM
Dhasmana et al[21]	2% lidocaine 10 mL by ultrasonic nebulizer	2% lidocaine 5 sprays in nasal cavity and nasopharynx, followed by 2% lidocaine with the spray-as-you-go technique (spray on the supraglottic areas, then glottic area, and finally below the cords)	30	30	IV glycopyrrolate 0.004 mg/kg and ondansetron 0.08 mg/kg. 0.1% xylometazoline 2 drops in each nostril
Xue et al[22]	2% lidocaine spray-as-you-go technique (spray on the supraglottic areas, then laryngeal area, and finally below the cords)	4% lidocaine spray-as-you-go technique (same technique)	26	26	Atropine 10 μg/kg IV + 5 intraoral sprays of 10% lidocaine
Malcharek et al[23]	Nebulization of 4% lidocaine 2 mL on the vocal cords and then by 2 mL of 4% lidocaine beneath the glottis by the fiberoptic bronchoscopy connected to the Enk Atomizer (Cook, Limerick, Ireland)	Translaryngeal injection of 4% lidocaine 4 mL	59	61	Midazolam 3.5–7 mg 1 h before surgery, orally. glycopyrrolate 0.2 mg. 5 sprays of 10% lidocaine into the oral cavity followed by nebulization of 4% lidocaine
Pirlich et al[24]	2% lidocaine by the fiberoptic bronchoscopy connected to the Enk Atomizer (Cook, Limerick, Ireland), injected along all the passages from nostril to vocal cords	2% lidocaine with the spray-as-you-go technique (spray 5 mL on the laryngeal area, and then below the cords)	48	48	Oral benzodiazepine; 2% lidocaine 1 mL plus 0.25% phenylephrine in each nostril; one 10% lidocaine spray was applied twice onto the oropharynx.
Ambi et al[25]	Ultrasound-guided block of internal branch of the superior laryngeal nerve with 2% lidocaine 1 mL	Anatomical landmark-guided block of internal branch of the superior laryngeal nerve with 2% lidocaine 1 mL	20	20	Nebulization with 3 mL of 4% lidocaine over 10 min, IV glycopyrrolate 10 μg/kg

The thick horizontal lines separate similar comparisons.
Abbreviations: BIS: bispectral index; $ETco_2$, end-tidal carbon dioxide; HR, heart rate; IM, intramuscularly; IV, intravenous; MAP, mean arterial pressure.

Table. Continued

Sedation	Success Rate Intervention	Success Rate Comparator	No. Reported Severe Adverse Events Intervention	No. Reported Severe Adverse Events Comparator	Main Findings and Statistically Significant Differences
Midazolam and fentanyl	100%	100%	0	0	No differences between groups in hemodynamics, in time to airway topicalization and in time for airway manipulation between the 2 study groups. Peak plasma lidocaine concentration was higher in the 4% group without signs of toxicity.
Midazolam 1–2 mg + fentanyl 100–150 μg	100%	100%	0	0	2% lidocaine group showed shorter time for intubation, better operator's satisfaction, and better patients' tolerance, but higher peak plasma lidocaine concentrations, without signs of toxicity. Hemodynamic response was not different.
IV fentanyl 1–2 μg/kg in incremental doses	100%	100%	0	0	Transtracheal injection resulted in lesser patient discomfort, faster intubation, and comparable hemodynamic.
Incremental doses of 2.5 mg of diazepam IV	100%	100%	0	0	No difference in intubation time or $ETco_2$ level after intubation. A higher HR and MAP increases were observed in the nebulized lidocaine group. No differences in nasal bleeding between the 2 groups.
Midazolam 20 μg/kg + fentanyl 1 μg/kg IV	100%	100%	0	0	The nebulization group showed a longer time to intubation, worse local cord opening, a higher incidence of cough and gag, a higher demand of supplemental lidocaine. No differences in hemodynamics.
Midazolam 0.05 mg/kg and fentanyl 2 μg/kg	100%	100%	0	0	No differences in hemodynamics and oxygenation. The nebulization group was more comfortable and required less lidocaine.
Fentanyl 1.5 μg/kg + midazolam	100%	100%	0	0	No difference in comfort score and coughing score, in total intubation time and hemodynamic. Higher total dosage of lidocaine was used in the 4% group.
Midazolam as clinically required	95% (3 failures)	100%	0	0	The translaryngeal technique was faster and showed less gagging and coughing, but presented more tracheal mucosal bleedings. No differences in hemodynamics, operators' satisfaction, pain, hoarseness, difficulty of swallowing, or recall
Sufentanil bolus (<60 kg: 5 μg; >60 kg: 10 μg; >100 kg: 15 μg)	98% (1 failure)	100%	0	0	Patients' comfort was better using the atomizer technique, with fewer coughs or severe coughing episodes. The atomizer technique was quicker with less lidocaine administration and a lower incidence of nasal pain 4 wk after surgery. No differences in terms gagging, grimacing or defensive movements, oxygen saturation, HR, blood pressure, depth of sedation, or BIS
Midazolam 0.03 mg/kg	100%	100%	0	0	Ultrasound-guided block showed a lower incidence of coughing and gagging, a shorter time to intubation, more stable hemodynamic and better patient's tolerance

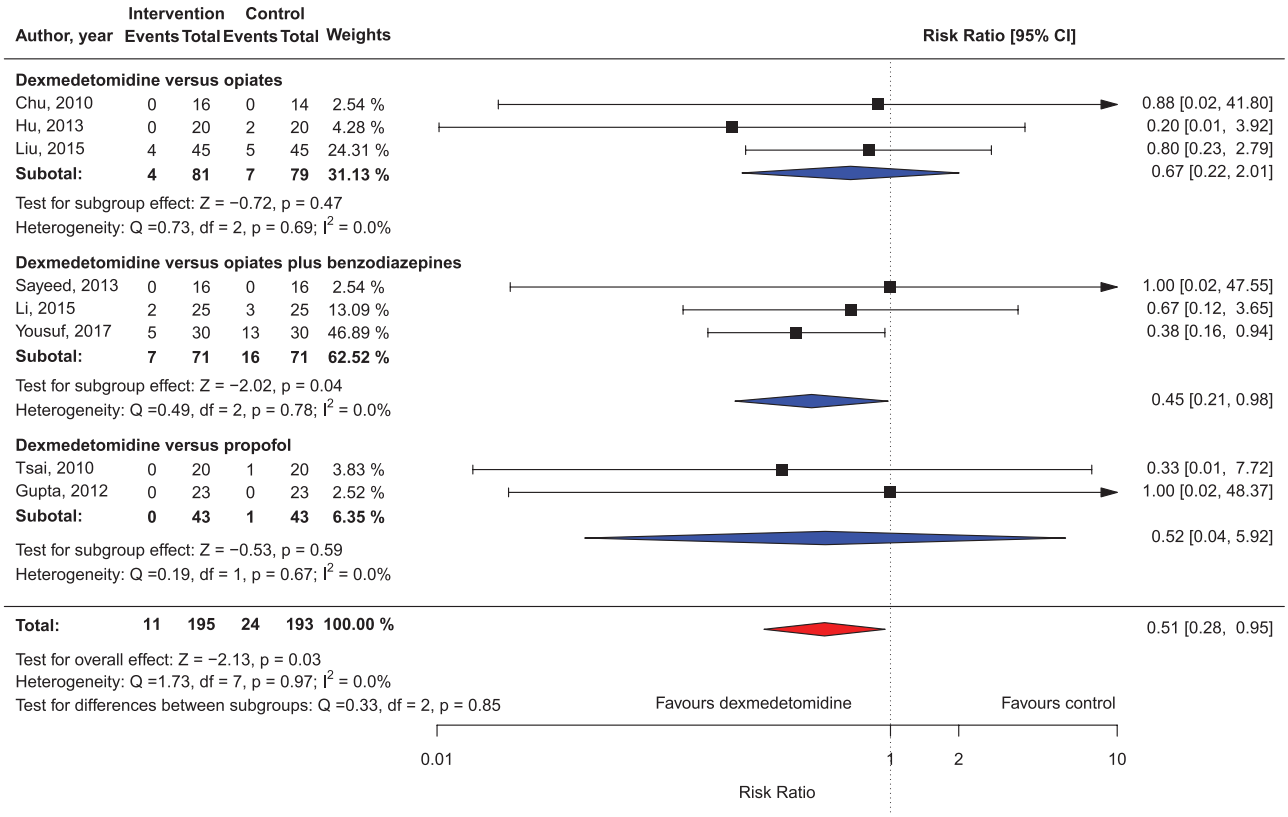

Figure 1. Forest plot for occurrence of desaturation episodes during awake fiberoptic intubation according to sedation protocol. Dexmedetomidine is compared to sedation protocols based on opiates, opiates plus benzodiazepines, or propofol. df indicates degrees of freedom.

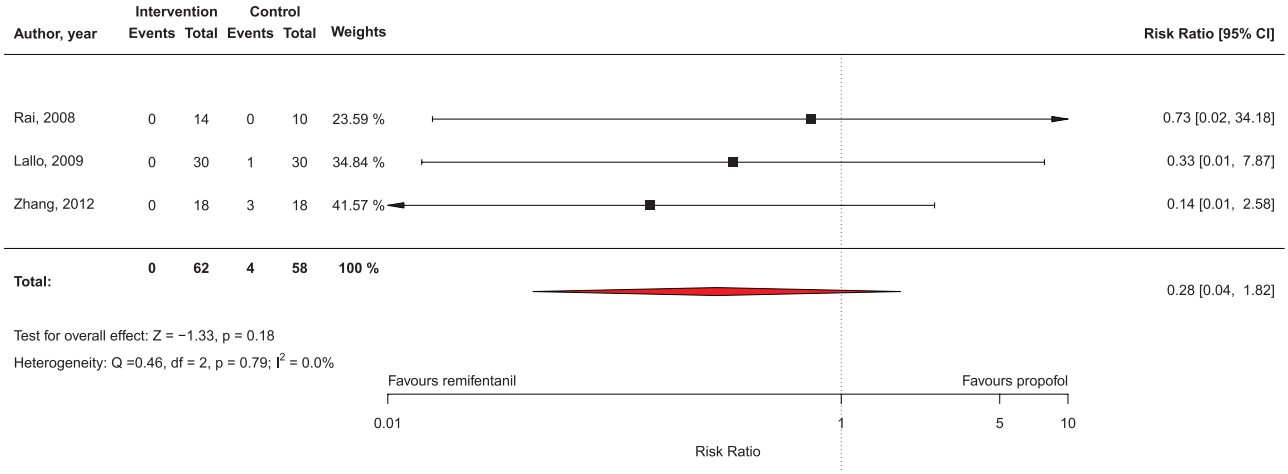

Figure 2. Forest plot for occurrence of desaturation episodes during awake fiberoptic intubation with sedation protocols based on remifentanil versus propofol. df indicates degrees of freedom.

mild sedation can limit the role of the different local anesthesia techniques under evaluation and hence can generate similar outcomes, and vice versa an optimal local anesthesia can make undetectable the potential differences of the evaluated sedatives. Nevertheless, sedation could be considered complementary to an adequate local anesthesia.

Ten studies compared different approaches to local anesthesia, including nebulization of lidocaine (with different dosages and devices), regional nerve blocks, and spray-as-you-go technique. Meta-analytic quantitative synthesis of data was hampered by the wide differences in premedication, administered sedatives, and collected outcomes. Regional blocks seem faster and slightly superior to the other approaches, but also more invasive and requiring experience; nebulization is easy and seems at least not inferior to the spray-as-you-go technique. However, no severe adverse event was reported with all the approaches, and all but 4 intubations could be completed.

Most of the available randomized controlled trials were focused on sedation. The administration of sedatives for

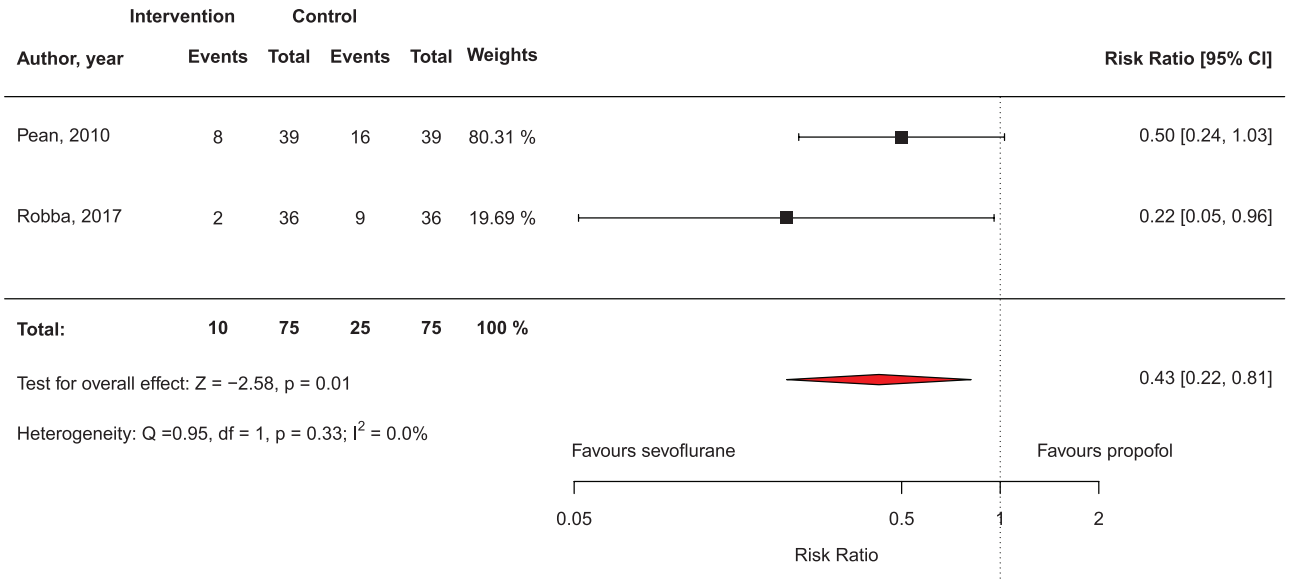

Figure 3. Forest plot for occurrence of apnea episodes during awake fiberoptic intubation with sedation protocols based on sevoflurane versus propofol. df indicates degrees of freedom.

awake fiberoptic intubation aims to improve patient's comfort and cooperation, possibly making the procedure easier and safer (eg, reducing the hemodynamic response); on the other hand, spontaneous breathing must be preserved, and aspiration prevented.[2,53] Different drugs, with different dosages, administration techniques, and associations, have been evaluated in randomized controlled trials, and a clear superiority of one over the others could not be found, except for a lower incidence of episodes of desaturation or apnea using dexmedetomidine or sevoflurane; all regimens allowed a satisfactory level of efficacy and safety. Dexmedetomidine is the most studied drug in this setting; 2 recent meta-analyses[54,55] performed on 4 and 13 studies, respectively, concluded that dexmedetomidine was effective, well tolerated, and associated with better intubation conditions and reduced recall. Our systematic review of randomized controlled trials supports the safety and efficacy of dexmedetomidine and suggests some superiority when compared to propofol (in terms of ease of intubation and patient comfort) or opioids if used without benzodiazepines (in terms of postprocedure recall), even if a formal meta-analysis was not feasible for these clinically relevant outcomes; however, episodes of severe bradycardia can occur with dexmedetomidine. Opioids, administered as bolus or continuous infusion at the reported dosages, appear safe and effective with some advantage in reducing coughing and gag reflex; a high incidence of recall when they are used alone (particularly remifentanil), compared to dexmedetomidine or propofol, seems evident and has been already reported,[56] suggesting the need of a cautious association with benzodiazepines like midazolam as premedication or sedative (a frequently applied regimen in the analyzed randomized controlled trials). Moreover, the availability of antagonists of opioids and benzodiazepines can enhance their safety. Propofol and sevoflurane appeared similar when compared, but the use of sevoflurane is technically challenging and potentially associated with environmental contamination: only 1 of the 2 randomized controlled trials performed awake fiberoptic intubation through a dedicated mask.[46] Of note, no randomized controlled trial evaluated the use of benzodiazepines alone and above all the use of ketamine, whose analgesic properties could be of interest.

Among the other 4 retrieved studies, 3 reported isolated interventions without relevant results; on the contrary, the findings by Zou et al[50] on the usefulness of an intubating mask and noninvasive ventilation in improving oxygenation could be of interest in hypoxemic patients. The potential role of noninvasive ventilation during non–fiberoptic bronchoscopy-guided tracheal intubation of critically ill patients has been recently underlined,[57] but, so far, no randomized controlled trial evaluated awake fiberoptic intubation and noninvasive ventilation in hypoxemic patients with anticipated difficult airway. Interesting and promising data come from us of high-flow nasal cannula as mean of procedural oxygenation during fiberoptic intubation of difficult airway patients.[58] Based on our findings, awake fiberoptic intubation in anticipate difficult airway appears safe and effective under a wide range of protocols, with an incidence of severe adverse events or failures well below 1%. These data support the role of awake fiberoptic intubation as standard in this setting, considering the severity of the potential consequences in cannot intubate, cannot oxygenate conditions after induction of general anesthesia and suppression of spontaneous breathing.[5–7] As a consequence, training of anesthesiologist on awake fiberoptic intubation and familiarity with the local protocol should be considered a priority; unfortunately, there is evidence indicating underuse of awake fiberoptic intubation[5] and a certain reluctance by anesthetists because of unsatisfactory training and teaching.[10,52] Virtual simulators and manikins could be of help.[53]

The present review has some limitations. Its main limitation is the inability to perform a formal synthesis of most of its findings to identify the best approach for every step of awake fiberoptic intubation due to the heterogeneity of

the available studies; we performed a meta-analysis only for few, more homogeneous results, and its findings should be interpreted with caution. Moreover, given that the success rate was very high and the complications were very rare in all the randomized controlled trials, no specific strategy could be declared superior to the others and larger studies are required; furthermore, major life-threatening adverse events were collected in the different randomized controlled trials without homogeneous definitions. A second limit is the relatively low number of patients included in all randomized controlled trials. Our systematic review was focused on awake fiberoptic intubation; recently, other techniques (in particular video laryngoscopy) for awake intubations were evaluated and found to be feasible and safe.[59] Even optimal use of awake fiberoptic intubation cannot reach a success rate of 100%; alternative techniques in accordance with local and international guidelines should always be preplanned and promptly applied in case of awake fiberoptic intubation failure. On the other hand, our study has relevant strengths; it is the first systematic review on the topic, and it is based only on randomized controlled trials. To our knowledge, we describe the largest series of elective awake fiberoptic intubation, making our data original and potentially useful to guide the clinician. Moreover, even if we were unable to clearly identify a protocol superior to others, our findings suggest that a wide range of approaches can be effective and safe, and this translates in a clear message for the clinician. Finally, the present review underlines the need in this field of shared outcomes instead of unvalidated qualitative scores; furthermore, we observed that potentially useful drugs (like ketamine) or techniques (like awake fiberoptic intubation through an intubating mask in hypoxemic surgical patients) have never or poorly evaluated.

In conclusion, in the first systematic review of randomized controlled trials focused on awake fiberoptic intubation in elective surgical patients with anticipated difficult airway, we found 37 randomized controlled trials including 2045 patients. Most studies compared different techniques of providing local anesthesia or sedation. All the approaches resulted highly safe and effective, confirming the relevance and reliability of awake fiberoptic intubation, although periprocedural protocols were highly heterogeneous. All described methods to achieve local anesthesia performed similarly well. Dexmedetomidine for sedation might be slightly safer to propofol and opioids with or without midazolam. Further, larger studies are required to identify the impact of procedural protocols on major clinical outcomes.

APPENDIX A: SEARCH STRATEGY

(bronchoscop*[tiab] OR "fiber optic"[tiab] OR fiberoptic[tiab] OR "fibre optic"[tiab] OR fibreoptic[tiab]) AND (intubat*[tiab] OR airtraq[tiab] OR airway[tiab] OR device[tiab] OR ambu[tiab] OR pressure[tiab] OR bonfils[tiab] OR bullard[tiab] OR manoeuvre[tiab] OR maneuver[tiab] OR "c-mac"[tiab] OR combitube[tiab] OR cricothyroidotomy[tiab] OR cricothyrotomy[tiab] OR "c trach"[tiab] OR mask[tiab] OR ventilation[tiab] OR catheter[tiab] OR glidescope[tiab] OR bougie[tiab] OR "i-gel"[tiab] OR laryngeal[tiab] OR oesophageal[tiab] OR esophageal[tiab] OR tracheal[tiab] OR "LMA supreme"[tiab] OR manujet[tiab] OR McCoy[tiab] OR McGrath[tiab] OR obesity[tiab] OR fastrach[tiab] OR "pentax AWS"[tiab] OR "ProSeal LMA"[tiab] OR quicktrach[tiab] OR ramping[tiab] OR cannula[tiab] OR injector[tiab] OR introducer[tiab] OR trachview[tiab] OR laryngoscop*[tiab] OR "supraglottic airway device"[tiab] OR macintosh[tiab] OR "tracheal tube"[tiab] OR "endotracheal tube"[tiab] OR "positive-pressure respiration"[tiab] OR "continuous positive airway pressure"[tiab] OR "neuromuscular blocking agents"[tiab] OR "neuromuscular blockade"[tiab] OR sedat*[tiab] OR "oxygen inhalation therapy"[tiab] OR insufflation[tiab] OR "high flow nasal cannula"[tiab] OR preoxygenation[tiab] OR "noninvasive ventilation"[tiab] OR stylet[tiab]) AND (anesthesia[tiab] OR anaesthesia[tiab] OR theatre[tiab] OR theater[tiab] OR room[tiab] OR intra operat*[tiab] OR intraoperat*[tiab] OR surg*[tiab] OR acute [tiab] OR emergen*[tiab] OR "lung injury"[tiab] OR "respiratory insufficiency"[tiab] OR "respiratory failure"[tiab] OR "airway obstruction"[tiab] OR asphyxia[tiab] OR "difficult airway"[tiab] OR hypoxia[tiab] OR hypoxemia[tiab] OR hypercapnia[tiab] OR "cardiac arrest"[tiab] OR asystole[tiab] OR anaphylaxis[tiab]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR "double-blind" [tiab] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (clinical trial[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind[tw])) OR (latin square[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[tw] OR follow-up studies[mh] OR prospective studies[mh] OR crossover studies[mh] OR control[tw] OR controls[tw] OR controlled[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]) NOT (comment[pt] OR editorial[pt] OR meta-analysis[pt] OR meta-analysis[tiab] OR practice-guideline[pt] OR review[pt] OR pediatrics[mh] OR pediatric[tiab] OR infants[tiab] OR children[tiab])).

DISCLOSURES

Name: Luca Cabrini, MD.
Contribution: This author helped design this systematic review, perform the literature search and qualitative assessment of articles, extract quantitative data, draft the manuscript, and revise and approve the final version of the manuscript.
Name: Martina Baiardo Redaelli, MD.
Contribution: This author helped perform the literature search and qualitative assessment of articles, extract quantitative data, draft the manuscript, and revise and approve the final version of the manuscript.
Name: Lorenzo Ball, MD.
Contribution: This author helped extract quantitative data, synthesize data, and revise and approve the final version of the manuscript.
Name: Martina Filippini, MD.
Contribution: This author helped perform the literature search and qualitative assessment of articles, and revise and approve the final version of the manuscript.
Name: Evgeny Fominskiy, MD.
Contribution: This author helped perform the literature search and qualitative assessment of articles, synthesize data, and revise and approve the final version of the manuscript.
Name: Margherita Pintaudi, MD.
Contribution: This author helped perform the literature search and qualitative assessment of articles, and revise and approve the final version of the manuscript.
Name: Alessandro Putzu, MD.

Contribution: This author helped perform the literature search and qualitative assessment of articles, extract quantitative data, and revise and approve the final version of the manuscript.
Name: Carmine D. Votta, MD.
Contribution: This author helped perform the literature search and qualitative assessment of articles, draft the manuscript, and revise and approve the final version of the manuscript.
Name: Massimiliano Sorbello, MD.
Contribution: This author helped draft the manuscript, and revise and approve the final version of the manuscript.
Name: Massimo Antonelli, MD.
Contribution: This author helped draft the manuscript, and revise and approve the final version of the manuscript.
Name: Giovanni Landoni, MD.
Contribution: This author helped design this systematic review, and revise and approve the final version of the manuscript.
Name: Paolo Pelosi, MD.
Contribution: This author helped draft the manuscript, and revised and approve the final version of the manuscript.
Name: Alberto Zangrillo, MD.
Contribution: This author helped design this systematic review, and revise and approve the final version of the manuscript.
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