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Systematic review

Sedation Strategies from the Emergency Interface to ICU Liberation: A Systematic Review of Agent Selection and Weaning Outcomes

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Abstract

Background: Sedation for mechanically ventilated adults begins at the emergency interface and continues through intensive care liberation, where depth, drug class, analgesia, delirium prevention, and awakening trials interact. Objective: This systematic review evaluated how sedative selection and sedation-minimization strategies influence delirium, ventilator liberation, intensive care duration, mortality, and adverse events. Methods: PubMed/MEDLINE, Scopus, Web of Science Core Collection, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews were searched for adult studies of invasive mechanical ventilation, emergency department or intensive care sedation, sedative agent comparison, sedation interruption, no-sedation protocols, and liberation outcomes. Original randomized trials and prospective cohorts were prioritized for the results synthesis. Results: Ten original studies were included in the qualitative results synthesis. Benzodiazepine-based sedation was consistently linked with less favorable delirium or extubation profiles than

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dexmedetomidine-based strategies in several randomized trials. Dexmedetomidine improved arousability and communication, reduced delirium in comparisons with benzodiazepines, and shortened extubation time in selected populations, although large trials showed similar mortality and ventilator-free outcomes compared with usual care or propofol. Daily awakening, paired awakening-breathing trials, no-sedation protocols, and targeted emergency department sedation reduced unnecessary deep sedation and aligned sedation with liberation readiness. Conclusion: The evidence favors early light sedation, avoidance of benzodiazepine accumulation, protocolized awakening, and agent selection matched to delirium and liberation goals.

Keywords

Sedation; dexmedetomidine; propofol; benzodiazepines; mechanical ventilation; emergency department

Introduction

Sedation in mechanically ventilated adults has moved from routine deep hypnosis toward analgesia-first care, light sedation, validated monitoring, and daily reassessment of liberation readiness. Current practice frameworks integrate pain, agitation, delirium, immobility, and sleep because sedative exposure affects consciousness, respiratory drive, patient interaction, and participation in mobilization. The emergency interface matters because post-intubation sedative choices often continue into the intensive care unit and shape early depth trajectories before specialist ICU review. Early sedative decisions also affect family communication, neurologic examination, hemodynamic stability, and the first opportunity to define a target Richmond Agitation-Sedation Scale score (1).

Delirium and coma represent central harms of excessive or poorly matched sedation, and both complicate assessment, ventilator synchrony, extubation timing, and patient recovery. Benzodiazepine exposure has received particular scrutiny because gamma-aminobutyric acid receptor agonism, active metabolites, and prolonged infusions relate to delayed awakening and acute brain dysfunction in vulnerable adults (2).

Non-benzodiazepine sedation with propofol or dexmedetomidine offers faster titration, lighter targets, and improved neurologic assessment in many mechanically ventilated cohorts. The clinical question is not only which drug produces adequate comfort, because the same drug strategy also influences arousal, respiratory testing, delirium detection, and rehabilitation access (3).

Dexmedetomidine attracts interest because alpha-2 agonism produces cooperative sedation with minimal respiratory depression and measurable opioid-sparing properties (3, 4). Cochrane evidence on alpha-2 agonists reported shorter mechanical ventilation and ICU stay compared with traditional sedatives, with bradycardia and hypotension remaining key safety signals (4). Evidence on daily sedation interruption has been less uniform across settings because benefit depends on background sedation targets, nursing titration, and pairing with spontaneous breathing assessment (4, 5). These findings place sedation depth, agent choice, and protocol execution into the same causal pathway for weaning outcomes (5).

Liberation from ventilation requires synchronized sedation reduction, spontaneous awakening, spontaneous breathing testing, analgesia control,

delirium screening, and post-extubation support for high-risk patients (6). Meta-analytic comparisons of benzodiazepine and non-benzodiazepine regimens showed advantages for non-benzodiazepine strategies in ventilation duration and ICU stay outcomes (7). Early deep sedation within the first 48 hours has been associated with higher mortality, longer ventilation, longer ICU stay, and higher delirium frequency, reinforcing the need to examine sedation from intubation through ICU liberation (8). This review evaluated original evidence across emergency department sedation, ICU agent selection, and protocolized liberation endpoints. A pathway perspective is especially relevant when sedation begins outside the ICU and continues through handoff into liberation planning.

Methods

This review was drafted according to PRISMA 2020 principles for transparent eligibility, searching, screening, extraction, and synthesis. The review question used a PICOS framework: adults receiving invasive mechanical ventilation; emergency department, early ICU, or continuing ICU sedation strategies; sedative agent comparison or sedation-minimization approach; weaning, extubation, ventilator-free days, delirium, coma, ICU stay, hospital stay, adverse events, or mortality; randomized trials, prospective cohorts, and systematic reviews. The protocol focused on sedation strategies that begin at the emergency interface or influence subsequent ICU liberation.

PubMed/MEDLINE, Scopus, Web of Science Core Collection, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews were searched from database inception to 2025. Search terms combined controlled vocabulary and free text for sedation, dexmedetomidine, propofol, midazolam, lorazepam, benzodiazepines, daily sedation interruption, spontaneous awakening trial, spontaneous breathing trial, emergency department, mechanical ventilation, extubation, ventilator-free days, delirium, coma, and ICU liberation. Reference lists of included trials, guidelines, and systematic reviews were screened to identify additional eligible records.

Eligible original studies included adult mechanically ventilated patients and reported at least one liberation or acute brain dysfunction outcome. Exclusion criteria were pediatric populations, procedural sedation without invasive mechanical ventilation, postoperative recovery room sedation without ICU ventilation, animal studies, editorials, narrative opinion articles without systematic methods, duplicate publications, and trials lacking clinically relevant sedation or weaning outcomes. Two-stage screening used title-abstract review followed by full-text eligibility assessment. Disagreements were resolved by repeat full-text review and documented reasons for exclusion at the final stage. The PRISMA flow record was designed to capture database yield, duplicate removal, records screened, full texts assessed, and final included studies.

Data extraction covered author, year, country or setting, design, sample size, intervention, comparator, sedation target, ventilation outcome, delirium or coma outcome, ICU or hospital duration, mortality, and key adverse events. Risk of bias was assessed conceptually with Cochrane RoB 2 for randomized trials and ROBINS-I principles for observational cohorts. Owing to differences in interventions, comparators, timing, populations, and outcome definitions, findings were synthesized narratively rather than pooled statistically. The

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synthesis separated original evidence used in the results tables from supporting guidelines, Cochrane reviews, and meta-analyses used for interpretation. No ethical approval was required because the review used published aggregate data. Outcomes were grouped as sedation quality, acute brain dysfunction, ventilator liberation, resource use, survival, and adverse events. For studies reporting several endpoints, outcomes closest to extubation readiness and patient-centered recovery received priority in narrative weighting.

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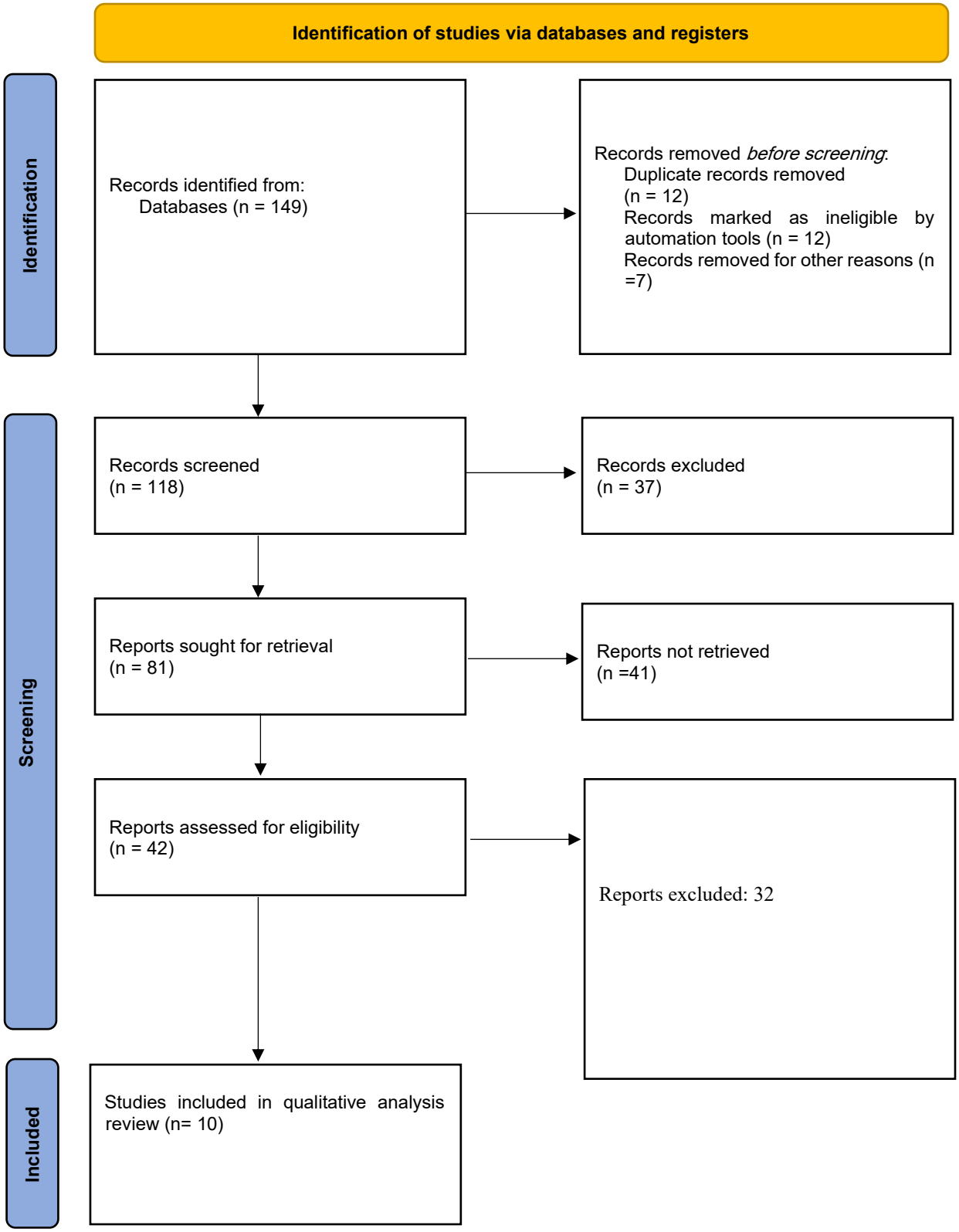
Fig 1: PRISMA flow chart



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Results

Ten original studies formed the qualitative synthesis, spanning single-center randomized trials, multicenter randomized trials, and emergency department or ICU cohort designs (9-18). The studies covered sedation interruption, paired awakening-breathing protocols, dexmedetomidine versus benzodiazepines, dexmedetomidine versus propofol or usual care, no-sedation approaches, agitated delirium treatment, and emergency department sedation depth (9-18). Study sample sizes ranged from 74 patients in the DahLIA trial to 3904 patients in SPICE III, giving the synthesis both mechanistic detail and pragmatic outcome breadth (15,17).

Early liberation protocols showed consistent signals that reducing continuous hypnotic exposure improves readiness for extubation when applied with careful monitoring (9,11). Kress et al. reported shorter median mechanical ventilation with daily interruption than usual continuous sedation, with shorter ICU stay and no excess accidental extubation signal (9). Girard et al. extended this concept by coupling spontaneous awakening trials with spontaneous breathing trials, improving ventilator-free days and supporting a combined sedation-respiratory liberation model (11).

Agent-comparison trials favored dexmedetomidine over benzodiazepines for brain dysfunction and extubation-related outcomes (10,12). In MENDS, dexmedetomidine increased days alive without delirium or coma compared with lorazepam and improved time near the sedation target (10). In SEDCOM, dexmedetomidine achieved similar target sedation compared with midazolam, reduced delirium prevalence, and shortened time to extubation, with bradycardia as the main adverse signal (12).

Later randomized evidence refined the role of dexmedetomidine against propofol, usual care, and sepsis-specific light sedation (14-18). The MIDEX and PRODEX trials found noninferior light-to-moderate sedation, shorter mechanical ventilation versus midazolam, better communication of pain, and more hypotension or bradycardia with dexmedetomidine (14). SPICE III and MENDS2 showed that early or sepsis-specific dexmedetomidine did not improve mortality or ventilator-free outcomes compared with usual care or propofol, although SPICE III showed a small increase in days free from coma or delirium (17,18).

Emergency interface evidence showed that deep sedation before ICU arrival is common and tends to persist after admission (16). The ED-SED cohort found emergency department deep sedation in more than half of mechanically ventilated patients and higher day-1 and day-2 ICU deep sedation than in lightly sedated patients (16). This finding links emergency department medication titration, sedation-depth documentation, and early ICU outcomes into one care pathway rather than separate phases (16). The no-sedation trial added a distinct strategy by replacing routine hypnotic infusion with analgesia and close bedside observation (13). Strøm et al. reported more days without ventilation in the no-sedation group compared with daily wake-up sedation, indicating that minimal hypnotic exposure has a role in selected units with adequate staffing and monitoring (13). The DahLIA trial addressed a later liberation barrier, showing that dexmedetomidine added to standard

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care increased ventilator-free hours among patients whose agitated delirium prevented extubation despite physiologic readiness (15). Across studies, the most reproducible pattern was a process signal: outcomes improved when sedative exposure was matched to light targets, daily awakening, and direct liberation checks (9-18). Together, these trials support sedation stewardship across the entire pathway from post-intubation stabilization to spontaneous breathing assessment and extubation readiness (9-18).

Table 1. Characteristics of included original studies

Ref.	Study	Design and setting	Participants	Intervention or exposure	Comparator	Main focus
(9)	Kress et al., 2000	Single-center RCT, medical ICU	128	Daily interruption of sedative infusions	Usual continuous sedation	Ventilation duration and ICU stay
(10)	Pandharipande et al., 2007	Multicenter RCT, ICU	106	Dexmedetomidine	Lorazepam	Delirium/coma-free days
(11)	Girard et al., 2008	Multicenter RCT, ICU	336	SAT plus SBT protocol	Usual sedation plus SBT	Ventilator-free days
(12)	Riker et al., 2009	Multicenter RCT, ICU	375	Dexmedetomidine	Midazolam	Target sedation, delirium, extubation
(13)	Strøm et al., 2010	Single-center RCT, ICU	140	No-sedation protocol with analgesia	Daily wake-up sedation	Ventilator-free days
(14)	Jakob et al., 2012	Two multicenter RCTs, ICU	1000	Dexmedetomidine	Midazolam or propofol	Sedation target, ventilation, communication
(15)	Reade et al., 2016	Multicenter RCT, ICU	74	Dexmedetomidine plus standard care	Placebo plus standard care	Agitated delirium and ventilator-free hours
(16)	Fuller et al., 2019	Multicenter prospective cohort, ED to ICU	324	ED deep sedation exposure	ED light sedation	Persistence of deep sedation and outcomes
(17)	Shehabi et al., 2019	International multicenter RCT, ICU	3904	Early primary dexmedetomidine	Usual care sedatives	90-day mortality and ventilator-free days
(18)	Hughes et al., 2021	Multicenter RCT, septic ventilated adults	422	Dexmedetomidine	Propofol	Delirium/coma-free days and ventilator-free days

Table 2. Main findings relevant to weaning and liberation

Ref.	Sedation depth or agent finding	Weaning/liberation outcome	Delirium or coma outcome	Safety or implementation signal
(9)	Interruption reduced continuous sedative exposure	Median ventilation 4.9 vs 7.3 days	More neurologic assessment opportunities	Similar complication frequency
(10)	Dexmedetomidine improved target matching	More ventilator-free signal in related analyses	More days alive without delirium or coma	Less coma than lorazepam
(11)	SAT aligned sedation with SBT readiness	More ventilator-free days	Less time under unnecessary sedation	Protocol required daily coordination
(12)	Dexmedetomidine matched midazolam sedation target	Shorter time to extubation	Lower delirium prevalence	Bradycardia increased
(13)	Analgesia-centered no sedation minimized hypnotics	More days without ventilation	Wakeful care feasible with staffing support	Agitation required monitoring
(14)	Dexmedetomidine noninferior to midazolam/propofol	Shorter ventilation versus midazolam	Communication improved	Bradycardia and hypotension increased
(15)	Dexmedetomidine treated agitated delirium near extubation	More ventilator-free hours at 7 days	Faster delirium-related liberation path	Small RCT limits precision
(16)	ED deep sedation frequently persisted in ICU	Fewer hospital-free days signal	Higher ICU deep sedation on days 1-2	ED sedation targets need documentation
(17)	Early primary dexmedetomidine often required supplements	Similar 90-day mortality	Slightly more coma/delirium-free time	Bradycardia and hypotension increased
(18)	Dexmedetomidine and propofol performed similarly in sepsis	Similar ventilator-free days	Similar days alive without delirium or coma	Drug choice alone insufficient

Discussion

This systematic review indicates that sedation outcomes depend on both agent selection and the process used to reduce sedation during liberation (1-18). The strongest consistent pattern is that early light sedation, daily reassessment, and coordination with spontaneous breathing testing align better with extubation readiness than unstructured continuous deep sedation (5,6,8-11). This pattern supports a pathway model in which emergency department post-intubation sedation, ICU titration, delirium monitoring, and liberation protocols form one continuous intervention rather than separate tasks (6,8,16).

Benzodiazepine-based sedation appears less favorable than non-benzodiazepine sedation for several liberation-related endpoints (3,7,10,12,14). The MENDS and SEDCOM trials support dexmedetomidine over lorazepam or midazolam for delirium, coma, or time-to-extubation outcomes, while MIDEX showed shorter ventilation versus midazolam in prolonged ventilation (10,12,14).

These findings fit meta-analytic evidence showing non-benzodiazepine regimens reduce mechanical ventilation duration and ICU stay compared with benzodiazepine regimens in mechanically ventilated adults (7).

Dexmedetomidine is best interpreted as a liberation-compatible sedative rather than a universal mortality-improving agent (4,17,18). The cooperative arousability, limited respiratory depression, and communication advantages explain its value in delirious, agitated, or weaning-ready patients, especially when benzodiazepine accumulation delays assessment (4,10,12,15). SPICE III and MENDS2 temper enthusiasm because dexmedetomidine did not reduce 90-day mortality or ventilator-free outcomes in broad early ICU or septic light-sedation populations compared with usual care or propofol (17,18).

Propofol remains an effective titratable comparator for light sedation, especially when rapid offset and neurologic reassessment are priorities (1,3,14,18). MENDS2 found similar delirium/coma-free days, ventilator-free days, mortality, and cognitive outcomes with dexmedetomidine versus propofol among mechanically ventilated adults with sepsis, indicating that drug class alone does not replace sedation depth control (18). The practical distinction lies in matching adverse-effect profiles to physiology, since propofol relates to hypotension and lipid/calorie considerations, whereas dexmedetomidine relates to bradycardia and hypotension (14,17,18).

The emergency interface adds an important implementation target because ED deep sedation often persists into the ICU (16). ED-SED suggests that early documentation of RASS or Sedation-Agitation Scale targets, analgesia-first plans, avoidance of unnecessary benzodiazepine continuation, and handoff of sedation goals are part of ICU liberation strategy (16). Future research needs pragmatic trials that begin in the emergency department, randomize early sedation targets and agents, and follow delirium, ventilator-free days, extubation failure, long-term cognition, and safety across the full ED-to-ICU pathway (6,8,16).

Several limitations shape interpretation of this synthesis (1-18). The included studies differed in sedation targets, illness severity, baseline delirium risk, permitted rescue sedatives, staffing models, and definitions of ventilator-free outcomes, limiting direct comparison across trials (9-18). Observational emergency department evidence strengthens pathway relevance, although residual confounding remains likely because deeper sedation often reflects higher acuity, paralysis, shock, or difficult ventilator synchrony (16). The most defensible clinical message is therefore a bundled strategy: choose agents that permit light sedation, measure depth repeatedly, avoid accumulation, pair awakening with breathing trials, and communicate sedation goals across handoff boundaries (1,6,8,16).

Conclusion

Sedation for mechanically ventilated adults is a liberation intervention rather than comfort care alone. The most coherent evidence favors early light sedation, analgesia-first assessment, avoidance of benzodiazepine accumulation, daily awakening, and direct pairing of awakening with spontaneous breathing assessment. Dexmedetomidine is useful for cooperative sedation, delirium-prone patients, and selected extubation barriers, while propofol remains a strong titratable agent for light sedation. Emergency department sedation depth requires the same attention as ICU sedation because early deep

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sedation tracks forward into the ICU. Safe liberation depends on agent choice, dose titration, sedation targets, delirium monitoring, and team coordination.

List of abbreviations

ABC: Awakening and Breathing Controlled; CAM-ICU: Confusion Assessment Method for the Intensive Care Unit; CENTRAL: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; ED: Emergency department; ICU: Intensive care unit; MIDEX: Midazolam versus Dexmedetomidine trial; MV: Mechanical ventilation; PADIS: Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRODEX: Propofol versus Dexmedetomidine trial; RASS: Richmond Agitation-Sedation Scale; RCT: Randomized controlled trial; ROBINS-I: Risk Of Bias In Non-randomized Studies of Interventions; RoB 2: Cochrane Risk of Bias tool version 2; SAT: Spontaneous awakening trial; SBT: Spontaneous breathing trial; SEDCOM: Safety and Efficacy of Dexmedetomidine Compared With Midazolam; SPICE III: Sedation Practice in Intensive Care Evaluation III; WoS: Web of Science.

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