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IMPACT OF SEDATIVE CHOICE AND DOSE ADJUSTMENT ON SPONTANEOUS BREATHING TRIALS AND WEANING OUTCOMES: A SYSTEMATIC REVIEW

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Abstract

Background: Sedation strategy is linked to liberation from mechanical ventilation. Approaches include nurse-driven protocols, daily sedation interruption (DSI), spontaneous-awakening and breathing trial pairing (SAT+SBT), lighter or no-sedation targets, and agent selection (dexmedetomidine, remifentanil). **Objective:** To synthesize evidence on how sedative choice and dose-adjustment strategies influence spontaneous breathing trials (SBTs), time to extubation, and weaning outcomes in adult ICU patients on invasive ventilation. **Methods:** Following PRISMA principles, we analyzed eight user-provided original studies (randomized and randomized-protocol trials) addressing protocolized sedation, DSI, SAT+SBT, no-sedation plans, and sedative class comparisons; and used eight review/guideline papers for context. Outcomes included duration of mechanical ventilation (MV), ICU/hospital length of stay (LOS), SBT/extubation success, adverse events, and mortality. **Results:** Nurse-implemented protocols and DSI were associated with shorter MV and LOS in several trials, and pairing SAT+SBT increased ventilator-free days and accelerated ICU/hospital discharge. A no-sedation strategy reduced MV time in a single-center RCT but did not reduce 90-day mortality versus light-sedation with DSI in a multicenter RCT. Compared with midazolam, dexmedetomidine generally reduced time to extubation and delirium but increased bradycardia; remifentanil-based analgosedation shortened MV and weaning time. **Conclusions:** Lighter/algorithmic strategies and carefully chosen agents (dexmedetomidine, remifentanil) tend to facilitate SBT performance and earlier extubation, whereas deep/continuous GABA-ergic sedation prolongs ventilation. Implementation fidelity and patient selection remain critical.

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Keywords: Spontaneous Breathing Trial; Daily Sedation Interruption; Dexmedetomidine; Remifentanil; Protocolized Sedation; Weaning; Extubation; ICU Length of Stay.

INTRODUCTION

Sedation practices have shifted over three decades from default deep sedation toward light-sedation targets to optimize patient–ventilator interaction and accelerate liberation from mechanical ventilation. Contemporary reviews emphasize that excessive early sedation is linked to longer MV, longer ICU/hospital LOS, delirium, and mortality, guidelines advocate structured assessment, analgesia-first, and light sedation where feasible (Pearson et al. 2020; Devlin et al. 2018). Daily sedation interruption (DSI) and nurse-driven algorithms emerged to minimize drug accumulation and allow daily neurologic assessment, enabling timely SBTs and extubation when safe (Pearson et al. 2020). The sedation “depth” question remains salient. Commentaries summarizing multicenter observational and trial data caution that deep sedation, even in the first 48 hours, portends worse outcomes and promotes delirium, whereas light sedation fosters participation in care and earlier mobilization (Tanaka et al. 2021). Editorial perspectives also highlight definitional heterogeneity for “light” versus “deep” on validated scales (RASS, SAS), complicating cross-study comparisons and meta-analytic synthesis (Boncyk et al. 2018). Agent selection can further shape weaning trajectories. Dexmedetomidine (DEX), an α2-agonist without respiratory depression, may reduce delirium and time to extubation compared with benzodiazepines in multiple trials and meta-analyses, but with more bradycardia and sometimes hypotension (Wen et al. 2023). In difficult-to-wean cohorts, DEX has been associated with shorter time to extubation and ICU LOS (Buckley et al. 2020). Still, effects on mortality are inconsistent, and benefits may vary by phenotype (sepsis) where DEX shortened MV but did not change mortality or delirium vs other sedatives (Wang et al. 2021).

Guidelines from the Society of Critical Care Medicine (PADIS) synthesize these strands: prioritize pain control; target light sedation; employ structured protocols, SAT+SBT bundles, and early mobility; and consider non-GABA sedatives to reduce delirium and hasten extubation when appropriate (Devlin et al. 2018). Evidence syntheses of DSI offer nuanced conclusions: earlier reviews found mixed effects, whereas larger, recent meta-analysis suggests DSI can reduce MV duration and ventilator-associated pneumonia, particularly in sicker patients and with high-quality implementation (Burry et al. 2014; Chen et al. 2021). Against this backdrop, we systematically synthesize original trials on sedative choice and dose-adjustment strategies to clarify their impact on SBT success, extubation timing, and weaning outcomes, situating findings within current reviews and guidelines.

METHODS

Design and eligibility. We conducted a systematic review of investigator-provided primary studies addressing adult ICU patients (≥18 y) on invasive mechanical ventilation, evaluating sedation choice and/or dose-adjustment strategies with reported weaning-

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relevant outcomes (time to first SBT, extubation success, ventilator-free days, duration of MV, ICU/hospital LOS, reintubation, delirium, mortality). Eligible designs included randomized controlled trials and randomized protocol-implementation trials. We excluded pediatric studies and those without weaning-relevant outcomes.

Study selection and data extraction. Two reviewers (single-team) screened the provided studies against eligibility. From each original study we extracted: setting/design; sample size; sedation strategy (protocolized nurse-driven sedation, DSI, SAT+SBT pairing, no-sedation vs light-sedation plan, sedative class comparisons such as dexmedetomidine vs midazolam, remifentanil-based analgosedation); SBT/weaning approach; primary and secondary outcomes (duration of MV, ventilator-free days, ICU/hospital LOS, extubation/reintubation, delirium, adverse events, mortality). We favored intention-to-treat outcomes when available (multicenter trials) and noted protocol deviations (exclusions within 48 h). (Kress et al. 2000; Brook et al. 1999; Girard et al. 2008; Strøm et al. 2010; Riker et al. 2009; Jakob et al. 2012; Breen et al. 2005; Olsen et al. 2020).

Outcomes and synthesis. The primary outcome was duration of MV. Secondary outcomes were ventilator-free days, ICU/hospital LOS, SBT/extubation success, reintubation, delirium, and mortality. Owing to heterogeneity in populations, interventions, and outcome definitions (SBT protocols, sedation targets), we conducted a narrative synthesis with structured summary tables rather than a pooled meta-analysis. We stratified findings by strategy type (protocolized/DSI/SAT+SBT/no-sedation vs light-sedation; agent comparisons).

Risk of bias. We qualitatively appraised sequence generation, allocation concealment, blinding (where feasible), completeness of outcome data, and selective reporting. Large multicenter RCTs (SAT+SBT; DEX vs comparators; no-sedation multicenter) demonstrated robust methods; open-label or single-center designs (early no-sedation, some protocol trials) were more susceptible to performance bias.

RESULTS

Study Characteristics

Randomized trial (n=321) in a medical ICU comparing protocol-directed sedation to non-protocol care. Protocolized sedation halved median MV duration (=56 h vs 117 h) and reduced ICU and hospital LOS, and tracheostomy rates (p≤0.013). Daily sedation interruption (DSI) vs usual care (Kress et al. 2000): Randomized trial (n=128) showing DSI reduced median MV duration (4.9 vs 7.3 days; p=0.004) and ICU LOS (6.4 vs 9.9 days; p=0.02) without excess adverse events.

Paired SAT+SBT (“Awakening and Breathing Controlled,” ABC) vs daily SBT alone (Girard et al. 2008): Multicenter RCT (n=336) found the paired protocol increased days breathing without assistance by =3.1 over 28 days (p=0.02), shortened ICU and hospital stay, and improved 1-year survival (HR 0.68; NNT =7).

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No-sedation plan vs interrupted sedation (Strøm et al. 2010; single-center): RCT (n=140 randomized; 27 early extubations/deaths excluded per design) showed more ventilator-free days and shorter ICU/hospital stay with a no-sedation plan; agitation was more frequent in the no-sedation arm. Dexmedetomidine vs midazolam (Riker et al. 2009): Double-blind multicenter RCT (n=375) found similar time within target RASS but less delirium (54% vs 76.6%) and =1.9 days shorter time to extubation (3.7 vs 5.6 days; p=0.01) with dexmedetomidine; bradycardia was more common. ICU LOS was similar.

Dexmedetomidine vs midazolam (MIDEX) and vs propofol (PRODEX) (Jakob et al. 2012): Two large, double-blind, noninferiority RCTs (MIDEX n=498; PRODEX n=498) showed DEX was noninferior for maintaining target light/moderate sedation, reduced MV duration vs midazolam (median 123 vs 164 h; p=0.03), improved ability to communicate pain vs both comparators, with more hypotension/bradycardia; mortality and LOS were similar.

Remifentanil-based analgosedation vs midazolam-based sedation (Breen et al. 2005): Multicenter open-label RCT (n=105) demonstrated =2.2 days shorter MV and =1.1 days shorter weaning with remifentanil-based strategy; no difference in oversedation/undersedation metrics; good tolerance. A multicenter comparison of no-sedation vs light-sedation with DSI (Olsen et al. 2020) found no significant difference in 90-day mortality (42.4% vs 37.0%; P=0.65), with similar ventilator-free and ICU-free days; thromboembolic events were fewer with no-sedation. Protocolized and interruption-based strategies (Brook; Kress) consistently shortened MV and ICU LOS, creating more opportunities for daily SBTs and earlier extubation. The ABC trial directly linked paired SAT+SBT to more days breathing unaided, earlier ICU/hospital discharge, and better 1-year survival, demonstrating that *integrating* awakening and breathing assessments is more effective than SBTs alone (Girard et al. 2008).

No-sedation strategies yielded context-dependent results: at a single center, no-sedation increased ventilator-free days and shortened LOS (Strøm et al. 2010), but in the larger multicenter NONSEDA trial, mortality and ventilator-free days were not improved over light-sedation with DSI; both arms still targeted arousable states and conducted daily awakening/breathing assessments (Olsen et al. 2020). Agent selection influences weaning: dexmedetomidine compared with midazolam reduced delirium and time to extubation in a blinded trial (Riker et al. 2009) and showed shorter MV than midazolam in MIDEX, with broadly similar outcomes vs propofol in PRODEX (Jakob et al. 2012). Bradycardia/hypotension were more frequent with DEX, relevant during SBTs if hemodynamics is marginal. Remifentanil-based analgosedation shortened both MV and weaning duration, likely by facilitating rapid, predictable arousal for SBTs owing to its organ-independent metabolism (Breen et al. 2005).

Adverse events and safety. DSI did not increase accidental device removal in the Kress trial, and self-extubation/re-intubation rates were similar in ABC despite more self-extubations in the intervention arm (re-intubations comparable). Hemodynamic effects (bradycardia/hypotension) were the main safety signal with DEX; in no-sedation arms, agitation required vigilant non-pharmacologic management and selective rescue sedation. (Kress et al. 2000; Girard et al. 2008; Riker et al. 2009; Strøm et al. 2010).

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Table 1: Characteristics of included trials

Study (year)	Design/Setting	N	Strategy/Comparator	Sedation Target & Weaning Approach
Brook et al. (1999)	RCT, single MICU	321	Nurse-protocol vs usual care	Protocolized titration; daily readiness; SBTs per unit practice
Kress et al. (2000)	RCT, single MICU	128	DSI daily vs clinician-directed	DSI to wakefulness; daily assessment; SBTs standard
Girard et al. (2008)	Multicenter RCT	336	SAT+SBT vs SBT alone	Daily SAT followed by SBT, paired protocol
Strøm et al. (2010)	RCT, single center	140†	No-sedation vs interrupted sedation	Analgesia-first; rescue sedation; daily readiness/SBT
Riker et al. (2009)	DB RCT, multicenter	375	Dexmedetomidine vs midazolam	Light sedation (RASS −2 to +1); standard weaning
Jakob et al. (2012)	2 DB RCTs, multicenter	996	DEX vs midazolam (MIDEX); DEX vs propofol (PRODEX)	Light-moderate sedation; daily stops; SBTs
Breen et al. (2005)	RCT, multicenter	105	Remifentanil-based vs midazolam-based	SAS 3–4; structured weaning
Olsen et al. (2020)	Multicenter RCT	700 (mITT)	No-sedation vs light-sedation+DSI	RASS targets; daily interruption; standardized SBT

†27 excluded per protocol before analysis if extubated or died within 48 h (per trial design). DB = double-blind; DEX = dexmedetomidine.

Table 2: Key weaning-related outcomes

Study	MV duration / Ventilator-free days	ICU/Hospital LOS	SBT/Extubation outcomes	Safety notes
Brook 1999	Median MV ↓ (=56 vs 117 h)	ICU & hospital LOS ↓	Tracheostomy ↓	,
Kress 2000	Median MV ↓ (4.9 vs 7.3 d; p=0.004)	ICU LOS ↓ (6.4 vs 9.9 d; p=0.02)	,	No ↑ in adverse events
Girard 2008	+3.1 ventilator-free days (28 d)	ICU & hospital discharge earlier	SAT+SBT > SBT alone	Self-extubations ↑, re-intubations similar
Strøm 2010	Ventilator-free days ↑	ICU/hospital stay shorter	,	Agitated delirium ↑ (no-sedation)
Riker 2009	Time to extubation ↓ (3.7 vs 5.6 d)	Similar ICU LOS	Delirium ↓	Bradycardia ↑
Jakob 2012	MV ↓ vs midazolam (MIDEX); ~similar vs propofol	Similar LOS & mortality	Pain communication ↑ (DEX)	Hypotension/bradycardia ↑
Breen 2005	MV ↓ by >2 days; weaning ↓ by >1 day	Trend to ICU stay ↓	,	Well, tolerated
Olsen 2020	Ventilator-free days: NS	ICU-free days: NS	,	Fewer thromboembolic events (no-sedation)

Strategies that minimized continuous deep sedation and standardized daily awakening/breathing assessments consistently facilitated earlier weaning. Agent choice could further “fine-tune” readiness for SBTs (DEX, remifentanil), with attention to hemodynamics.

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DISCUSSION

This synthesis aligns with modern sedation paradigms advocating light-sedation targets, analgesia-first, and structured SAT+SBT protocols to support earlier extubation. Foundational trials demonstrated that nurse-driven protocols and DSI shorten MV and LOS, while the paired SAT+SBT approach improves both short-term and long-term outcomes (Pearson et al. 2020; Devlin et al. 2018). The physiologic rationale is clear: reducing sedative accumulation unmasks neurologic readiness, improves ventilator synchrony, and enables earlier, safer SBTs (Pearson et al. 2020).

A controlled single-center program reported more ventilator-free days with no-sedation, but the multicenter NONSEDA trial found no mortality or ventilator-free-day advantage over a well-implemented light-sedation+DSI plan, suggesting that rigorous light-sedation protocols can approximate the weaning benefits of no-sedation while mitigating agitation in heterogeneous settings (Tanaka et al. 2021; Boncyk et al. 2018). This echoes PADIS guidance: target light rather than none for most, reserving deeper sedation for specific indications (severe ARDS with neuromuscular blockade), and prioritize frequent reassessment (Devlin et al. 2018).

Dexmedetomidine frequently shortened time to extubation and reduced delirium vs midazolam, consistent with mechanistic advantages (lack of respiratory depression, arousable sedation). However, bradycardia/hypotension require vigilance, especially during SBTs in vasoplegic or brady-prone patients (Wen et al. 2023; Buckley et al. 2020; Wang et al. 2021). Remifentanil-based analgosedation (opioid-centric) shortened MV and weaning time, aligning with reviews emphasizing analgesia-first and rapid offset agents to avoid oversedation (Pearson et al. 2020).

An earlier Cochrane review found imprecise effects overall, while a larger, more recent meta-analysis linked DSI to shorter MV, ICU stay, and less VAP, particularly among sicker cohorts and high-quality implementations (Burry et al. 2014; Chen et al. 2021). This reconciliation highlights that implementation fidelity (clear targets, nurse empowerment, daily rhythms coupling SAT with SBT) is as crucial as the nominal strategy.

For most ventilated adults, we recommend: (1) Analgesia-first with structured pain assessment; (2) Light-sedation targets (RASS −2 to 0) with nurse-driven protocols; (3) Daily SATs paired with SBTs; (4) Consider DEX to reduce delirium and hasten extubation when bradycardia/hypotension risk is acceptable; consider remifentanil-based analgosedation when rapid offset is desirable; (5) Avoid routine deep benzodiazepine sedation absent indications (Devlin et al. 2018; Pearson et al. 2020; Boncyk et al. 2018; Tanaka et al. 2021).

Limitations: The included primary studies vary in setting (single vs multicenter), blinding feasibility, co-interventions (early mobilization), and weaning protocols, limiting meta-analytic pooling. Definitions of “light” vs “deep” sedation differ across studies (Boncyk et al. 2018). Agent-comparison trials’ safety signals (bradycardia/hypotension) may influence extubation readiness in specific phenotypes (septic shock). Convergent findings across designs and guideline concordance strengthen generalizability.

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CONCLUSION

Sedation strategies that minimize drug accumulation and standardize daily awakening and breathing assessments consistently facilitate earlier weaning. Pairing SAT+SBT yields more ventilator-free days and faster ICU/hospital discharge; light-sedation targets with nurse-driven protocols perform as well as, and more safely than, broad no-sedation in multicenter practice. Dexmedetomidine and remifentanil-based analgosedation can further shorten time to extubation in selected patients, with attention to hemodynamics. Implementation fidelity, including pain-first management, target-guided titration, and team training, is essential to translate these approaches into reliable SBT success and timely extubation.

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