DOI: https://doi.org/10.5114/ait.2019.90921

Daily sedation interruption and mechanical ventilation weaning: a literature review

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Abstract

Daily sedation interruption (DSI) is a method used since the beginning of the millennium to streamline sedation in critically ill patients under mechanical ventilation and improve clinical outcomes. The purpose was to assess whether there is a correlation between DSI and weaning from mechanical ventilation. We designed a literature review via searching PubMed, UpToDate and Google Scholar for relevant key terms from inception until March 2019. Literature retrieved included nine randomized controlled trials. When compared to usual practice, it is superior in terms of duration of mechanical ventilation, stay in the intensive care unit, hospitalization, adverse effect occurrence and total cost of therapy. Comparison with other sedation protocols produces conflicting results. DSI, and protocolized sedation in general, are safe methods to perform to facilitate earlier weaning and improved clinical outcomes. Future research should focus on minimizing bias by conducting double-blinded studies and studying different patient subgroups.

Key words: sedation, daily interruption, protocolized sedation, mechanical ventilation, weaning, intensive care unit.

Anaesthesiol Intensive Ther 2019; 51, 5: 380–389

Received: 12.11.2019, **accepted:** 22.11.2019

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Administration of sedatives is an integral part of intensive care unit (ICU) routine practice for a plethora of reasons: reduction of patient discomfort by providing anxiolysis, treating agitation but also facilitation of care, by increasing tolerance of the ventilator and preventing accidental removal of the endotracheal tube or other instrumentation (e.g. catheters, monitors and intravenous lines). Finally, sedation reduces metabolic demands during cardiovascular and respiratory instability [1]. Agents mostly in use are benzodiazepines and other nonanalgesic sedatives such as propofol. Since these have no analgesic properties, they are often combined with parallel administration of opioids. Analgesics, at high doses, may also have a sedative effect [2]. However, because of the long half-life of the most commonly used opiates and the potentially grave side effects, such as respiratory depression, hypotension, gastrointestinal complications, urine retention and histamine secretion, administration should be rather judicious. In fact, as far as benzodiazepines are concerned, the Society of Critical Care Medicine has recommended against their use in their latest clinical practice guidelines [3].

Intravenous (*i.v.*) administration of sedatives can be performed by continuous infusion or by intermittent bolus injection; between the two methods, the first provides more constant levels of sedation and higher levels of patient comfort. On first thought, that would make it an optimal method of sedation, but it has unfortunately been identified as an independent predictor of prolonged mechanical ventilation (MV) [4], an observation primarily made as soon as 1998 by Kollef *et al*. [4]. In order to prevent its associated complications, such as ventilator-associated pneumonia (VAP) [5], barotrauma, unplanned extubation and oxygen desaturation [6–9], the researchers suggested using in the future meticulous sedation protocols that might, potentially, improve clinical outcomes.

Such a sedation protocol was put to the test the following year by Brook *et al*. [10], who associated the decrease of MV duration in patients under protocol-directed sedation with the reduced duration of continuous *i.v*. sedation.

Moreover, all current sedatives are problematic in long-term sedation. Benzodiazepines and propofol accumulate unpredictably [11, 12]. High doses

of propofol may lead to occurrence of propofol infusion syndrome (PRIS), associated with a mortality rate as high as 80–85% [13]. Dexmedetomidine, according to the latest publication of SPICE III [14], when used as the sole or primary sedative in patients undergoing MV, even though it does not seem to negatively affect mortality rates, was associated with increased rates of bradycardia and hypotension and supplemental sedative requirements in order to achieve the desired level of sedation.

Other unfavorable effects of a continuous sedative infusion include hypotension, bradycardia, respiratory depression, ileus, renal failure, venous stasis and immunosuppression [15], delirium [16], presentation of delusional memories and post-traumatic stress disorder (PTSD) [17, 18], increased overall mortality [19] and impaired cognitive function [20]. Impaired cognition, however, is not exclusively a corollary of extended sedation. A change in mental status can very well be due to neurologic injury, and for the differential diagnosis physicians may be compelled to proceed with further diagnostic studies when a patient does not wake up shortly after discontinuation of sedative infusion, probably also leading to an increase of treatment costs. Finally, continuous sedative infusion has been associated with a longer ICU and hospital stay [4], both of which may further increase the cost of treatment [4, 10, 21]. On the other hand, avoiding sedatives is not always feasible, because insufficient sedation can also lead to unwanted situations, primarily hypertension, tachycardia, discomfort and dyssynchrony with the ventilator [22].

Methods that may help physicians reduce the complications of under-/over-sedation include sedation protocols [10, 21], spontaneous breathing trials (SBTs) [19], early mobilization [23] or exclusive use of opioids without co-administration of sedatives [24]. Of note, regarding SBTs, newer data [25-27] support the use of decreased levels of pressure support ventilation, as inspiratory pressure augmentation of 5 to 8 cm H_2O (0.5–0.8 kPa), for instance. Use of low pressure support values also provides the advantage of overcoming the added work of breathing imposed by the resistance of the endotracheal tube.

Another method is daily interruption of sedative infusions. By awakening the patients, clinicians can keep sedation at lighter levels, without causing discomfort. This is not necessarily an exclusive choice of sedation, but is often used as a complement to other methods, as sedation-scale-based protocol-directed sedation, for example, in order to achieve the targeted light sedation levels. There have also been questions on whether daily sedation interruption (DSI) could facilitate earlier weaning and decrease the duration of MV. Several trials have been conducted to investigate a potential association and constitute the main topic of this review.

METHODS

Searching strategy and study selection

We searched the PubMed (MEDLINE), SCOPUS and ScienceDirect databases from inception to March 2019. The search was conducted by the use of the key terms "daily sedation interruption" or "daily sedative interruption" combined with the key term "mechanical ventilation" via the "AND" operator. From any primary and review articles found, we further searched for any citations for potential relevance. We excluded reviews, non-English studies, nonhuman studies, pediatric studies, protocols, guidelines, policy statements, surveys and conference abstracts. We exclusively included randomized controlled trials. To be included in our review, studies had to demonstrate utilization of DSI in their sedation protocols and measurement of MV duration as an endpoint. Screening of the articles for review eligibility based on inclusion criteria was conducted independently by two reviewers. In case of disagreement, it would be resolved by a third reviewer, which was unnecessary as group consensus was reached. We primarily aimed to elucidate whether an association between DSI and weaning of the ventilator has been established, according to the findings of the research efforts we are quoting.

Risk of bias assessment

Methodological quality assessment was conducted via the Cochrane tool of bias [28] which rates the included studies' risk of bias for the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias risk. With an overall moderate quality of evidence, the risk of bias assessment that resulted from data extraction of the included studies for the aforementioned domains is summarized in Table 1.

RESULTS

Search strategy findings

Two hundred fifty-nine articles were found through the search; 81 were excluded because they were duplicated, 49 did not meet inclusion criteria, 30 were reviews, 24 were protocols, guidelines or policy statements, 16 were written in another language, 14 were surveys and 6 analyses and 5 articles concerned the pediatric population. After primary exclusion, 34 potentially relevant articles remained which were further filtered after abstract observation, leading to exclusion of another 25 articles.

TABLE 1. Risk of bias assessment for included studies

	Selection bias: Random sequence generation	Selection bias: Allocation concealment	Performance bias: Blinding of participants and personnel	Detection bias: Blinding of outcome assessment	Attrition bias: Incomplete outcome data	Reporting bias: Selective reporting	Other bias
Kress *et al.* [21], 2000	+	+	?	?	+	+	+
Girard *et al.* [19], 2008	+	+	–	?	+	+	+
De Wit *et al.* [30], 2008	+	+	–	?	+	+	+
Anifantaki *et al.* [32], 2009	+	?	–	?	+	+	+
Yilmaz *et al.* [34], 2010	+	+	–	?	+	+	+
Strom *et al.* [24], 2010	+	+	–	?	+	+	+
Weisbrodt *et al.* [43], 2011	+	+	+	?	+	+	+
Mehta *et al.* [37], 2012	+	+	–	?	+	+	+
Nassar *et al.* [39], 2014	+	+	–	?	+	+	+
Kayir *et al.* [41], 2018	?	?	–	?	+	+	+

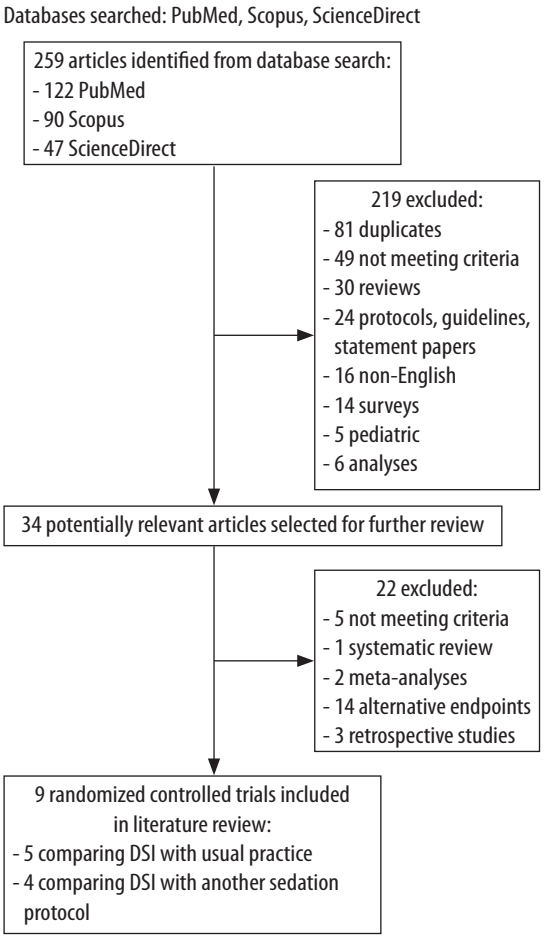

FIGURE 1. Flow chart of literature search and study selection

The remaining literature presented dates from May 2000 to January 2018 and consists of 9 RCTs conducted on adults, out of which 5 compare DSI with usual practice and 4 compare DSI with another sedation protocol. The selection process is schematized in the flow chart (Figure 1).

Description of included studies

In 2000, a landmark RCT was published by Kress *et al*. [21], implementing for the first time a DSI protocol in the 68 patients of the intervention group. To be precise, sedative infusion was ceased until patients were awake and could follow commands or became agitated/uncomfortable, at which point infusion was resumed at half the previous rate. The 60 patients of the control group had sedatives interrupted only at physician discretion. Both groups were further divided into two arms, receiving either one of two non-analgesic sedatives, propofol or midazolam, and if analgesia was necessary, morphine was used in all the 128 patients constituting the study sample.

Duration of MV was 2.4 days shorter in the intervention group ($P = 0.004$) and ICU LOS was shortened by 3.5 days ($P = 0.02$). When evaluation was conducted according to the sedative administered (propofol or midazolam), these primary end points did not differ significantly. The investigators suggested that DSI provides a simple means

to facilitate a daily neurologic examination by the clinicians, since the control group underwent 18% more frequently ($P = 0.02$) diagnostic studies, mostly fruitless, to rule out neurologic injury. Another secondary result was the smaller total doses of benzodiazepines administered to the patients of the intervention group, further cementing the prospect of this method's cost-effectiveness.

Consequently, the investigators concluded that it was safe, practical and cost-effective to treat mechanically ventilated patients with a DSI treatment. The DSI protocol, in the form devised by Kress *et al*., became the standard which almost all subsequent researchers implemented in their own trials and any adjustments they made were only minor deviations from this one. Therefore, whenever a standard DSI protocol is mentioned in the studies below, it is a reference to the present one.

In 2008, three studies were published, by Bucknall *et al*. [29], De Wit *et al*. [30] and Girard *et al*. [19], of which a DSI protocol was incorporated only in the last two, whereas in the RCT by Bucknall and colleagues, a guideline-dictated sedation protocol was compared with their ICU standard usual practice and found no significant difference in all endpoints, in contrast with other studies.

De Wit *et al*. [30] conducted a randomized study based on observations of previous investigators, i.e. that MV duration is decreased by use of DSI or other sedation algorithms, and in that context sought to compare the two methods, primarily in terms of total MV duration and survival in the 28 days following successful weaning.

The sedation algorithm was based on the one used by Brook *et al*. [10] and guidelines by the Society of Critical Care Medicine [31], aiming at minimizing continuous *i.v*. infusion and maximizing bolus injections instead and administering opioids for treatment of pain, whereas DSI was performed with the method previously used by Kress *et al*. [21].

The results were in favor of the sedation algorithm, as patients in that group had a 7-day shorter average ICU ($P < 0.0001$) and 9-day shorter hospital LOS ($P = 0.01$) compared to patients in the DSI group. Insisting more on results regarding MV, not only was total duration shorter by 2.8 days in the sedation algorithm group ($P = 0.0003$), but so was time to successful extubation, by 4 days. Mortality was also in favor of the same group ($P = 0.04$).

The researchers were led to the conclusion that the sedation algorithm was superior to DSI and also questioned the latter's feasibility to be performed on some patient groups, such as alcohol and drug abusers, deriving from the significant occurrence of said abuse in their patient sample. That observation deserves to be pointed out, because either alcohol or drug abuse could lead to respiratory failure, making these patient groups more vulnerable and likely to require MV.

In order to assess how a DSI protocol affects time of breathing without assistance, Girard *et al*. [19] conducted a landmark multicenter RCT including a sample of 336 heterogeneous patients, in which daily SBTs were either paired with spontaneous awakening trials (intervention group, $n = 168$) or with usual sedation practice (control group, $n = 168$). Their DSI protocol was the standard one with the only exception that a 4-hour awakening trial was applied, unless the patient was in pain, agitated, uncomfortable or showed aggravating clinical signs, at which point sedatives were restarted at half the previous dose and medication was titrated to achieve patient comfort.

Patients in the intervention group were found to breathe unassisted for longer periods of time in comparison with patients of the control group. This finding was combined with a 7% reduced absolute risk of tracheostomy ($P = 0.06$), but also with a 6% higher self-extubation rate ($P = 0.03$). ICU and hospital LOS also favored the intervention group, being decreased by 3.8 ($P = 0.01$) and 4.3 ($P = 0.04$) days respectively. This group also showed a 14% lower mortality rate after one-year survival analysis ($P = 0.01$). The superiority of the intervention group's results led the researchers to conclude that a "wake up and breathe" protocol was safe and should be implemented in routine practice.

On a side note, another issue concerning ICU-hospitalized patients is the impact on long-term functional, cognitive and psychological status. Jackson *et al*. [20] compared these parameters amongst 180 patients who were assessed in a planned substudy conducted during the study mentioned above [19]. All outcomes, including cognitive impairment, composite cognitive scores, symptoms of depression/PTSD and quality of life status, were found to be similar, notwithstanding that the intervention group retained the physiological benefits of the aforementioned protocol.

In 2009, Anifantaki *et al*. [32] published an RCT in which they studied a sample of 97 mechanically ventilated, including neurosurgical, patients, over the course of almost 2 years in an ICU in Greece. The intervention group ($n = 49$) underwent DSI according to a nurse-implemented protocol mostly similar to previous ones. Contraindications excluding patients from the DSI procedure were severe haemodynamic instability, positive end expiratory pressure greater than 18 cm H_2O (2 kPa), intracranial pressure more than 18 mm Hg (2 kPa) and deteriora-

TABLE 2. The Ramsay Sedation Scale [33]

Score	Term
1	Patient anxious and agitated or restless or both
2	Patient cooperative, oriented, and tranquil
3	Patient responds to commands only
4	Patient asleep, shows brisk response to light glabellar tap or loud auditory stimulus
5	Patient asleep, shows sluggish response to light glabellar tap or loud auditory stimulus
6	Patient asleep, shows no response to light glabellar tap or loud auditory stimulus

tion of cerebral hemorrhage or edema. The control group (n = 48) received sedation per the ICU physicians' prescriptions.

Primary outcome was duration of MV, demonstrating no significant difference between the two groups. Nor did the secondary outcomes differ, ICU LOS and hospital LOS, overall mortality, total drug doses administered and Ramsay Sedation Scale [33] (RSS, described in Table 2). The researchers concluded that DSI was neither beneficial nor harmful, but was also safe and feasible for the poorly studied subgroup of neurosurgical patients.

A Turkish study [34] on a smaller scale included 50 patients who were randomly allocated to two groups of similar demographic values. One group was treated with DSI without any protocol ("Group P"); instead, instructions to cease sedation were given by physicians, after assessing the patients' hemodynamic values or blood gas analyses. The other group received sedation according to a protocol prepared by the ICU physicians ("Group N") and was administered additional sedatives at their discretion, in case of unachieved sedation levels. Sedative agents of choice were diazepam, propofol, and dexmedetomidine for both groups.

ICU LOS and mortality rates were found similar between the two groups. However, the DSI group demonstrated significantly shorter MV duration and also a 3.26-day shorter duration of sedation ($P < 0.05$). The researchers found a significant correlation between duration of sedation and duration of MV and ICU LOS. The latter two were found to be significantly correlated as well.

The effect of DSI on duration of MV was tested against no sedation at all in 2010, in a RCT by Strom *et al*. [24]. To clarify, even though no sedatives were used in the intervention group, some sedation may have been caused by the boluses of morphine that were administered to both groups of the 140-patient sample enrolled in this study. Patients in the control group underwent DSI per the usual protocol.

The primary endpoint was time of unassisted breathing, found increased by 4.2 days in the intervention group ($P = 0.0191$). Delirium was an adverse effect observed more frequently in the intervention group. As far as respiratory complications are concerned, no significant difference was found in accidental extubations or VAP between the two groups.

No sedation was mentioned to be the standard practice in the author's ICU and this study pioneered support of an even more judicious approach to sedative infusion, allowing administration only when deemed necessary. Of note, the researchers switched the sedative of choice from propofol to midazolam, which has a slower clearance rate, even more so if renal and liver failure are present [35], identifying this as a possible bias factor. Interpretation of the study's results led to the suggestion that analgesics should be considered before infusion of continuous sedation.

Beginning from the context that protocolized sedation and DSI are two methods to reduce sedation, duration of MV and ICU-LOS, Mehta *et al*. [36] combined both in a pilot trial, attempting to amplify these effects. They found that both protocolized sedation and DSI are safe and acceptable, but more importantly, their pilot trial was used to guide modifications in their protocol and served as a footing to conduct afterwards a multicenter RCT [37]. Over a 3-year period, they collected data from 430 patients hospitalized in 16 medical and surgical ICUs. Patients in the control group (n = 209) received protocolized sedation alone. The intervention group (n = 214) received sedation via the same protocol but also underwent DSI, according to the standard protocol by Kress *et al*. [21]. Levels of sedation were ideally maintained to provide a comfortable, but rousable state, or a score of -3 to 0 on the Richmond Agitation-Sedation Scale [38] (RASS, described in Table 3).

The time of successful extubation, the primary outcome, did not differ. Nor did ICU LOS, hospital LOS, unintentional endotracheal tube removal rates, delirium rates or hospital mortality rates. Instead, there was a significant increase in the total dose of drugs administered to the intervention group. The reason for this latter finding is not specified in the study; whether higher levels of sedation were used because increased doses were required or in order to resume sedation after the daily pause is not explained. Seeing that no clinical benefit was obtained to counterbalance the heavier nursing workload and the increased sedation and analgesia, the authors did not recommend implementation of DSI in patients already receiving protocolized sedation.

TABLE 3. The Richmond Agitation-Sedation Scale [38]

Score	Term	Description
+4	Combative	Overtly combative or violent and an immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent non-purposeful movement or patient ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
–1	Drowsy	Not fully alert but has sustained (> 10 seconds) awakenings, with eye contact, to voice
–2	Light sedation	Briefly (< 10 seconds) awakens with eye contact to voice
–3	Moderate sedation	Any movement (but no eye contact) to voice
–4	Deep sedation	No response to voice, but any movement to physical stimuli
–5	Unarousable	No response to voice or physical stimulation

More recently, in a Brazilian ICU with small nursing staff, Nassar *et al*. [39] conducted an RCT including comparison of DSI (per the usual protocol) to intermittent sedation in order to detect which one is superior in terms of providing more ventilator-free days. No significant difference was noted not only in the number of ventilator-free days, but also in ICU and hospital mortality, accidental extubations, delirium occurrence and psychological stress in a 6-month follow-up.

There is a finding of this study that should be emphasized: the fact that lighter sedation was found

TABLE 4. Summary of findings from included studies

Study	Sample description	Compared strategies	Significant findings
Kress *et al.* [21], 2000	128 medical patients on MV	DSI vs. usual care	DSI led to: – fewer days on MV – fewer days in ICU
Girard *et al.* [19], 2008	336 patients on MV	DSI + daily SBT vs. usual practice + daily SBT	DSI + SBT led to: – fewer days on MV – fewer days in ICU – fewer days in hospital – lower mortality
De Wit *et al.* [30], 2008	74 medical patients on MV	DSI vs. protocol based on RSS (applied by Brook *et al.* [10])	Protocol led to: – fewer days on MV – fewer days in ICU – fewer days in hospital
Anifantaki *et al.* [32], 2009	97 medical and surgical patients on MV	DSI vs. usual practice	None
Yilmaz *et al.* [34], 2010	50 patients on MV	DSI vs. protocol based on RSS	DSI led to: – fewer days on MV – faster wake-up
Strom *et al.* [24], 2010	140 patients on MV	DSI vs. no sedation	No sedation led to: – fewer days on MV – fewer days in ICU – fewer days in hospital – more frequent delirium
Weisbrodt *et al.* [43], 2011	50 medical, surgical and trauma patients on MV	DSI vs. usual practice	None
Mehta *et al.* [37], 2012	430 medical and surgical patients on MV	DSI + protocol vs. protocol	Protocol led to: – decreased medication
Nassar *et al.* [39], 2014	60 medical and surgical patients on MV	DSI + intermittent vs. intermittent	Intermittent led to: – Decreased medication
Kayir *et al.* [41], 2018	100 patients on MV	DSI vs. continuous	DSI led to: – fewer days on MV, in ICU and hospital – faster first weaning attempt – lower VAP, reintubation and mortality rates

DSI – daily sedation interruption, MV – mechanical ventilation, ICU – intensive care unit, RSS – Ramsay Sedation Scale, VAP – ventilator associated pneumonia, SBT – spontaneous breathing trial

TABLE 5. Results of included studies regarding mechanical ventilation

Study	Compared strategies	Mean duration of MV (in days)		*P* value
		DSI group	Compared group	
Kayir *et al.* [41]	DSI vs. continuous	4.02	8.1	< 0.001
Kress *et al.* [21]	DSI vs. usual care	4.9	7.3	0.004
De Wit *et al.* [30]	DSI vs. protocol based on RSS (applied by Brook *et al.* [10])	6.7	3.9	0.0003
Yilmaz *et al.* [34]	DSI vs. protocol based on RSS	6.66	9.52	< 0.05
Mehta *et al.* [37]	DSI + protocol vs. protocol	7	7	0.52
Anifantaki *et al.* [32]	DSI vs. usual practice	7.7	8.7	0.7
Weisbrodt *et al.* [43]	DSI vs. usual practice	8	8.4	0.93
		Ventilator-free days in 28 days (mean duration)		
Nassar *et al.* [39]	DSI + intermittent vs. intermittent	24	25	0.16
Girard *et al.* [19]	DSI + daily SBT vs. usual practice + daily SBT	14.7	11.6	0.02
Strom *et al.* [24]	DSI vs. no sedation	13.8	9.6	0.0191

DSI – daily sedation interruption, MV – mechanical ventilation, RSS – Ramsay Sedation Scale, SBT – Spontaneous Breathing Trial

to be equally safe and feasible even in a smaller nursing staff ICU. Therefore adaptation of light sedation strategies is possible to decrease length of MV, as dictated by international guidelines [40].

The methods compared and significant findings of all the RCTs implementing DSI protocols are summarized in Table 4, and in Table 5 we present all their results regarding the duration of MV.

DISCUSSION

Literature concerning blinded studies is unfortunately unavailable. A probable explanation could be the difficulty in masking the agents administered to the patients and the meticulous organization and large staff required in order to blind the research staff to the methods applied in the patients enrolled in each study. The difficulty of implementing a blinding method has formerly been a concern on various occasions. The first to make that observation were Brook *et al*. [10], who mentioned that "it was obviously impossible to blind the staff to the patients' group". Girard *et al*. [19] later similarly stated that "blinding is not possible in a study of this kind". Strom *et al*. [24] accounted the single-center and unblinded design of their study as a limitation that held risk of bias. Finally, Mehta *et al*. [37] mentioned that it was not feasible to blind the caregivers. There have been, however, some distinguished studies that have been conducted in this field that applied some sort of blinding process, and for that reason, we believe their separate presentation is in order. Therefore, in our supplementary material we describe four studies [41–44] that, albeit noteworthy, did not meet the criteria for inclusion in our review.

After gathering all the evidence provided by the studies included in our review, there seems to be moderate heterogeneity among the findings. Smaller trials have sometimes contradictory results, unlike larger ones. There is, however, unanimity on the safety of this method. This has been evident even among patients at risk for coronary artery disease [42], although the study is small and sympathetic stimulation of unstable patients remains a concern. The conclusion that can be made is that not only DSI, but also algorithm-directed sedation, in other words protocolized sedation in general, can lead to reduction of ICU LOS and hospital LOS and rates of tracheostomy and mortality, when compared to usual practice. To put it more simply, sedation management is more efficient and shows clinical benefits when it is dictated by protocol rather than the clinicians' discretion.

In a Cochrane review in 2014, by Burry *et al*. [45], the authors were skeptical of the effect of DSI in the course of MV, ICU LOS and hospital LOS, drug dosages, complications, quality of life and overall mortality. Commenting on the narrow margin between the confidence interval upper limit and the no-effect line they observed in the 9 included RCTs, they advised consideration of the results' instability. Another review published in the same year by Reade and Finfer [46] demonstrated an inverse relationship between sedation and clinical benefit.

DSI has also been the subject of two meta-analyses, in 2011 by Augustes and Ho [47] and in 2015 by Minhas *et al*. [48] for the Mayo Foundation. With their limited data, Augustes and Ho concluded that, even though safe, DSI was not yet to be recommended as routine practice.

In sharp contrast, Minhas *et al*. [48] strongly recommended the use of protocolized sedation (either DSI or algorithm-dictated). Their findings contradicted the aforementioned meta-analysis and the findings of the Cochrane review, as they

found a significant improvement in terms of ICU LOS, hospital LOS and mortality; according to the authors, that contradiction was due to the previous researchers' inclusion of RCTs in which the control groups did not receive sedation at the discretion of physicians, but according to the protocol. Similarly to Augustes and Ho, they found a lower percentage of tracheostomy and no significant decrease in time spent under MV. However, a heterogeneous summary estimate was found in the findings regarding MV duration; by excluding the trial by Bucknall *et al*. [29] from their sensitivity analysis, the heterogeneity of the results was resolved and then MV duration was found to be significantly reduced.

At this point, having presented the relevant literature published, we attempt to investigate how much DSI is integrated in routine practice. For that reason we cite two relevant surveys. In 2010, O'Connor *et al*. [49] explored the practices of management in Australian and New Zealand ICUs and reported a 62% compliance rate regarding the application of this method, characterizing it as common practice for the treatment of the mechanically ventilated patient. Interestingly, in some participating ICUs, DSI was performed in more than 75% of patients. In 2012 Miller *et al*. [50] conducted a survey in the form of participation in 5 focus groups; over a two-month period, they interviewed ICU physicians, pulmonary/critical care fellows, nurses and respiratory therapists in a 20-bed medical ICU in Chicago. Contradictory to O'Connor and colleagues' statistics, this intervention was mentioned not to be performed on a satisfactory scale. Five reasons stood out as to why ICU staff used this method of sedation: minimization of sedative dosages, conduct of a reliable neurological examination, commencing ventilator weaning, pain assessment and reduction of ICU stay duration. However, despite the evidence, application remained sub-optimal, mostly due to a lack of consensus as to why DSI should be performed, according to the researchers.

This question was answered in the following year, when Barr *et al*. [40] provided in 2013 international guidelines for pain, agitation, sedation and delirium management for critically ill adults. In order to improve clinical outcomes and to avoid the complications of oversedation, they recommended application of DSI or targeting lighter levels of sedation as routine practice for mechanically ventilated patients (+1B level of evidence).

Our study has a strong point that derives from the inclusion of 2 trials [34, 41] that incorporated dexmedetomidine into the DSI protocol and, to the best of our knowledge, have never been formerly reviewed or were intentionally excluded because they did not fit the study's criteria for inclusion. For example, such was the case for the trial by Yilmaz *et al*. [34] that was excluded in the meta-analysis by the Mayo Foundation because the control groups underwent protocolized sedation instead of being sedated at the physicians' discretion. Another point is inclusion of a recent trial by Nassar *et al*. [39] (similarly excluded from the Mayo meta-analysis), who demonstrated the safety of application of DSI even in ICUs of low nurse staffing. Trials that have shown the efficacy of light sedation have been conducted in developed countries, superior to developing countries in terms of nurse staffing [51]. In this setting, adverse patient outcomes tend to be less frequent [52]. Therefore, mechanically ventilated patients who are treated in ICUs of lower nurse staffing may be more prone to care-associated risks, such as unplanned extubation. This is an important issue because it questions whether lighter sedation strategies, DSI included, are applicable in these ICUs. Greek ICUs fall into that category and that unfortunate reality further cements the importance of the findings by Nassar *et al*.

The present review also has some limitations. As far as the primary endpoint of this review is concerned, there is no concrete consensus on the reduction of MV duration and data concerning the way in which weaning is facilitated by the use of DSI, the method's effect on SBTs, times of first weaning attempts and weaning success rates are sadly limited. However, for the latter statement we need to take into account the fact that bias cannot be safely excluded. First of all, patient sample size is still inadequate; all the gathered trials are relatively small, so the findings may be susceptible to publication bias. Secondly, not all studies conducted a daily screening test to ensure patients' eligibility to undergo interrupted sedation. In the case of oxygenation derangement or hemodynamic instability, this method's risk of failure is increased, thus making initiation of DSI inappropriate. Thirdly, as hypothesized by de Wit *et al*. [30], DSI may not be well tolerated by drug or alcohol addicted patients suffering from withdrawal syndrome. That raises the suspicion whether high prevalence of these disorders is responsible for outcome discrepancies in the studies included in this review and also raises the question whether this method of sedation is applicable in certain patient groups [30]. Finally, in the Mayo meta-analysis [48], exclusion of the RCT by Bucknall *et al*. [29] resulted in demonstration of significant reduction of MV duration.

Another limitation is that we cannot provide enough evidence to resolve whether these results are reproducible in children, due to the little material available in the current literature. Of course, extrapolation of adult studies' findings is inappropri-

ate because of the children's different physiologic parameters and increased difficulty to restrain and nurse. To the best of our knowledge, only two RCTs applying DSI in mechanically ventilated children have been published, in 2012 by Gupta *et al*. [53] and by Verlaat *et al*. [54], in 2013. In the first, 102 patients were allocated to two groups, receiving sedatives either continuously or daily interrupted until awake or agitated/uncomfortable. The results favored the intervention group in terms of MV, PICU LOS, total dose of midazolam administered, and hence also in terms of cost. Occurrence of adverse effects did not differ. These findings were reproduced the following year by Verlaat *et al*. [54], who compared the same methods on a sample of 30 critically ill children. Again, they observed a significant reduction in durations of MV, PICU LOS and use of sedatives. Therefore they concluded that DSI is feasible and apparently safe enough to strategize in treating mechanically ventilated children, leading to earlier extubation, improved cognitive state and earlier release from the PICU. This merits further research, even more so because of the potential benefit of interrupting sedation in children, due to lower renal and hepatic clearance rates, which makes them more susceptible to accumulation of sedatives, especially in long-term administration [55]. Other subgroups of patients, prone to respiratory depression, in which DSI has been poorly studied, are neurosurgical patients, neuromuscular disease sufferers or substance abusers.

A final limitation addresses the overall quality of evidence. There is no material presented in conferences included in our review that could provide another perspective and unblinded studies included in this review are vulnerable to performance and detection bias because there is the possibility of a patient receiving less or more thorough care. This possibility increases if the same clinicians treated patients in both groups of the study. In the future, elimination of bias should be prioritized, especially because Weisbrodt *et al*. [43] and Jakob *et al*. [44] presented the applicability of a blinding method in their studies, disproving previous claims that conducting double-blinded trials is impossible. These studies could serve as groundwork for more future studies to optimize the quality of evidence.

CONCLUSIONS

In summary, strategizing DSI in the treatment of the mechanically ventilated patient is not only safe, but also seems beneficial to the facilitation of the weaning process. Previous surveys have displayed incomplete rates of this method's inclusion in routine practice and thus we stress our recommendation to use protocolized sedation, especially since there are formal tools to direct the sedation management. More blinded trials should follow and future research should also focus on different patient subgroups and on meticulous observation of how weaning parameters (such as tidal volume, maximum inspiratory pressure, PaO_2/FiO_2, respiratory rate, vital capacity and minute ventilation) are affected by implementation of DSI protocols.

ACKNOWLEDGEMENTS

1. Financial support and sponsorship: none.
2. Conflicts of interest: none.

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