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Contents

ABSTRACT

Background: 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.

Aim: To assess whether there is a correlation between DSI and weaning from mechanical ventilation.

Design: Systematic review.

Methods: PubMed, UpToDate and Google Scholar were searched for relevant key terms. Literature retrieved included eleven randomized controlled trials, three blinded studies and two surveys in the English language from May 2000 to January 2018.

Results: The research indicates that DSI has a reported compliance rate of up to 62% by intensive care physicians. When compared to usual practice, it is superior in terms of duration of mechanical ventilation, stay in the Intensive Care Unit, hospitalization, occurrence of adverse effects and total cost of therapy. Comparison with other sedation protocols produces conflicting results.

Conclusions: DSI, as well as protocolized sedation in general, is a safe method to perform and seems to facilitate earlier weaning process and improve clinical outcomes. Meticulous future research, however, should follow to minimize bias, to study different patient subgroups and investigate how the weaning process is affected.

Key words: Daily sedation interruption, Weaning, Mechanical ventilation, Intensive care unit

ΠΕΡΙΛΗΨΗ

Υπόβαθρο: Η ημερήσια διακοπή της καταστολής είναι μία μέθοδος που χρησιμοποιείται από την αρχή της χιλιετίας για τη βελτίωση της διαχείρισης της καταστολής των βαρέως πασχόντων ασθενών υπό μηχανικό αερισμό και τη βελτίωση της κλινικής εικόνας.

Στόχος: Ο προσδιορισμός μιας ενδεχόμενης σχέσης της ημερήσιας διακοπής της καταστολής με τον απογαλακτισμό από τον αναπνευστήρα.

Μορφή: Συστηματική ανασκόπηση.

Μέθοδοι: Αναζητήθηκε σχετική ορολογία στις βάσεις δεδομένων PubMed, UpToDate και Google Scholar. Η βιβλιογραφία που προέκυψε περιλαμβάνει έντεκα τυχαιοποιημένες ελεγχόμενες μελέτες, τρεις τυφλές μελέτες και δύο επισκοπήσεις στην Αγγλική γλώσσα από το Μάιο 2000 έως και τον Ιανουάριο 2018.

Αποτελέσματα: Η έρευνα υποδεικνύει ότι η ημερήσια διακοπή της καταστολής έχει ένα ποσοστό εφαρμογής έως και 62% από τους εντατικολόγους. Εν συγκρίσει με τη συνηθισμένη πρακτική, είναι ανώτερη όσον αφορά τη διάρκεια του μηχανικού αερισμού, της παραμονής στη ΜΕΘ και στο νοσοκομείο, τη συχνότητα των επιπλοκών και του συνολικού κόστους θεραπείας. Η σύγκριση με άλλα πρωτόκολλα καταστολής αποδίδει αβέβαια δεδομένα.

Συμπεράσματα: Η ημερήσια διακοπή της καταστολής, όπως και η καταστολή βάσει πρωτοκόλλου γενικότερα, είναι μια ασφαλής μέθοδος και φαίνεται να διευκολύνει την πρώιμη αποδέσμευση από το μηχανικό αερισμό και να βελτιώνει τα κλινικά σημεία. Ενδελεχής έρευνα, όμως, θα πρέπει να διεξαχθεί στο μέλλον για την ελαχιστοποίηση

του σφάλματος, τη μελέτη διαφορετικών υποκατηγοριών ασθενών και το πώς επηρεάζεται καθεαυτή η διαδικασία του απογαλακτισμού.

Λέξεις – Κλειδιά: Ημερήσια διακοπή καταστολής, Απογαλακτισμός, Μηχανικός αερισμός, Μονάδα εντατικής θεραπείας

INTRODUCTION

Administration of sedatives is ubiquitous and an integral part of Intensive Care Unit (ICU) routine practice for a plethora of reasons. These include 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 like propofol and 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 potential and severe side effects, such as respiratory depression, hypotension, gastrointestinal complications, urine retention and histamine secretion, administration should be rather judicious.

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),[3] increasing also the risk of ventilator-associated pneumonia (VAP).[4] This disadvantage, not being the one, is one of the most serious and it will be further analyzed below.

In fact, all current sedatives are problematic in long-term sedation. Benzodiazepines and propofol accumulate unpredictably.[5,6] High doses of propofol, furthermore, may lead to the occurrence of Propofol Infusion Syndrome, which presents with metabolic acidosis, rhabdomyolysis, lipemia (hypertriglyceridemia), arrhythmia and heart failure and is associated with a mortality rate as high as 80-85%.[7] Dexmedetomidine, with high 2-adrenoreceptor affinity and action in the locus ceruleus, was a promising alternative for sedation in ICUs, inducing a sleep state without respiratory depression; however, there were inconclusive results when its effect on duration of MV and ICU stay was studied in a meta-analysis by Tan et al.[8]

Other unfavorable effects of a continuous sedative infusion include hypotension, bradycardia, respiratory depression, ileus, renal failure, venous stasis and immunosuppression,[9] delirium,[10] presentation of delusional memories and Post Traumatic Stress Disorder (PTSD),[11,12] increased overall mortality[13] and impaired cognitive function.[14] Impaired cognition, however is not exclusively a corollary of an extended sedation. A change in mental status can very well be due to neurologic injury. Since an extended sedation can affect the clinicians' assessment of patient response to painful stimuli and the interpretation of physical examination, differentiating changes in mental status that may be due to the accumulated action of sedatives or to neurologic injury can be quite difficult. Therefore, diagnostic studies may need to be implemented

so as to rule out a new-onset neurologic injury. Frequently, physicians are compelled to proceed further with diagnostics, 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,[3] both of which may further increase cost of treatment.[3,15,16] On the other hand, avoiding sedatives is not always feasible, because insufficient sedation can also lead to unwanted situations, the primary ones being hypertension, tachycardia, discomfort and dyssynchrony with the ventilator.[17]

Obviously, the physician should take advantage of the benefits of sedation, limiting as far as possible the unwanted effects of under-/over-sedation. Methods that may help reduce these complications include sedation protocols,[15,16] spontaneous breathing trials (SBT),[13] early mobilization[18] or exclusive use of opioids without co-administration of sedatives.[19] Ideally, sedative and analgesic drug infusions begin on low doses and then titrated according to the patients' needs. Risk of overdose is minimized by streamlining medication and by evaluating consciousness states at regular intervals and at least once in every 24 hours.[20] Another method, which constitutes the main topic of this review is daily interruption of sedative infusions. By awakening the patients, clinicians are enabled to keep sedation at lighter levels, without causing discomfort. There have also been questions on whether daily sedation interruption (DSI) could decrease the duration of MV and several trials have been conducted to investigate a potential association.

Trials that have shown the efficacy of a light sedation have been conducted in developed countries, superior to developing countries in terms of nurse staffing.[21] In this

setting, adverse patient outcomes tend to be less frequent.[22] Therefore, mechanically ventilated patients who are treated in ICUs of lower nurse staffing may be more prone to care-associated risks, like unplanned extubation. This is an important issue because it questions whether lighter sedation strategies, DSI included, are applicable in these ICUs.

METHODS

In this review we have pooled the most relevant studies, to present the progress in this field, and also the most recent, providing the latest findings. PubMed, UpToDate and Google Scholar were searched for relevant key terms. Search was limited in literature regarding studies on humans and published in the English language from May 2000 to January 2018. To be included in our review, studies had to demonstrate utilization of DSI in their sedation protocols and measurement of MV as an endpoint. We have gathered material from 9 randomized controlled trials (RCT) conducted on adults, out of which 4 compare DSI with usual practice and 5 compare DSI with another sedation protocol (or no sedation at all). We also include data from 2 pediatric randomized controlled trials comparing DSI with standard care and 3 blinded studies. We also include results from 2 surveys that investigate the familiarity and compliance of ICU clinicians regarding this method of sedation. 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. Thus, primary focus will be set on duration of MV and time to start weaning, successful weaning rates or reintubation rates and respiratory complications. Simultaneously, we

also present findings that concern the total ICU length of stay (LOS), hospitalization, mortality rate, occurrence of delirium and quality of life.

RANDOMISED CONTROLLED TRIALS

The association of continuous sedation with prolonged MV had been primarily observed as soon as 1998, when Kollef and colleagues[3] were the first to suspect the negative impact of a plenteous sedative treatment on not only the duration of MV, but the patient clinical outcomes as well. In a prospective observational cohort study, 242 mechanically ventilated, adult patients were allocated in three groups: being sedated via continuous i.v. infusion (n=93), or via bolus i.v. injections (n=64) or not sedated at all (n=85).

MV was clearly shorter amongst the patients who were not receiving continuous i.v. sedation by a median difference of approximately 130 hours (185±190 hours vs 55.6±75.6 hours; $p<0.001$), with a greater divergence being recorded during the first two weeks. A statistically significant difference was also shown in ICU-LOS and hospital-LOS, with the continuously sedated group spending 8.7 days ($p<0.001$) and 8.2 days ($p<0.001$) more in the former and the latter respectively. Even though hospital mortality and tracheostomy were similar regardless of sedation technique, the continuously sedated group showed a greater incidence of other adverse effects, more specifically reintubation and organ system derangements.

This study was strictly observational and mostly included benzodiazepines and opioids as chosen sedatives, not including the use of propofol, which produces alternate

results as will be analyzed below. However, the size of the significant difference led the researchers to conclude that utilization of continuous i.v. sedation infusion may prolong MV and, in order to prevent its associated complications, such as VAP, barotrauma, unplanned extubation and oxygen desaturation,[23-26] they suggested using in the future meticulous sedation protocols that might, potentially, improve clinical outcomes.

In the following year, such a sedation protocol was put to the test by Brook et al,[15] who carried out a prospective randomized controlled trial that included 321 patients, half of which suffered from Chronic Obstructive Pulmonary Disease and about a fifth from Congestive Heart Failure. Patients were randomly assigned to receive sedation either according to the usual practice of the study ICU (control group n=159) or as determined by the study protocol (intervention group, n=162); infusion of sedatives began after assessment of the need for sedation and for analgesic treatment. The aim of the study was to test whether the sedation protocol would decrease the duration of MV.

Indeed, the median durations of MV in the two groups had an overwhelming 57-hour difference (60 hours in the intervention versus 117 in the control group). ICU and hospital LOS stay also favored the intervention group, as there was a median 1.8-day and 5.9-day reduction respectively. Finally, tracheostomy was a complication that had a smaller incidence in the protocol-sedated patients (6.2% versus 13.2% of the patients in the control group).

However, the most important observation to serve the purpose of this review is the 1.4 times greater likelihood of successful weaning in the intervention group; the investigators went on to identify the study's sedation protocol, Acute Physiology And

Chronic Health Evaluation II (APACHE II) scores, Acute Respiratory Distress Syndrome, and non-white race as independent statistical predictors of successful weaning.

Chance of bias was generated by the fact that alternative explanation of the study's results may have been ignored and by the fact that staff was not blinded to the patients' treatment groups, therefore contributing to the possibility of different practice that may favor the intervention group. However, the clinical significance of the results left little space for dismissal.

As a conclusion, the investigators associated the shorter duration of MV that was observed when protocol-directed sedation was used with the reduced duration of continuous i.v. sedation.

In 2000 followed the publication of a landmark randomized controlled trial by Kress et al,[16] implementing for the first time a DSI protocol in the 68 patients of the intervention group. To be more precise, sedative infusion was ceased until patients were awake and could follow commands or became agitated or uncomfortable, at which point infusion was resumed at half the previous rate. On the contrary, the 60 patients of the control group had their sedative treatment interrupted only at the discretion of the ICU's clinicians. Both groups were further divided into two arms, receiving either one of two non-analgesic sedatives, propofol or midazolam, and in case analgesia was necessary, morphine was utilized in all the 128 patients constituting the study sample.

The results were similar to the afore-mentioned studies. More specifically, the duration of MV was 2.4 days shorter in the intervention group (4.9 days instead of 7.3 in the control group, $p=0.004$) and ICU stay was shortened by 3.5 days ($p=0.02$). These

primary end points did not differ significantly, when evaluation was conducted according to the sedative administered (propofol or midazolam). The researchers also noticed a difference in the percentage of patients that needed to undergo diagnostic studies to assess changes in mental status and rule out any potential neurologic injury, which was 9% for the intervention and 27% for the control group (p=0.02). Most of these diagnostic tests were also fruitless, adding to the total cost of healthcare and adding to the risk associated with complications related to patient transport. The investigators suggested that DSI provides a simple means to facilitate a daily neurologic examination by the clinicians. 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.

As a consequence, the investigators concluded that it was safe, practical and cost-effective to treat mechanically ventilated patients with a DSI treatment. A limitation of this trial was the possibility of the clinical staff's awareness of the group allocation, since the intervention group's sedative infusions were openly ceased by an investigator and an evaluation of patients with interrupted sedation was performed by a research nurse, thus generating the chance of bias.

The DSI protocol, in the form devised by Kress et al became the standard which almost all future 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,[27] De Wit et al[28] and Girard et al,[13] out of which a DSI protocol was incorporated only in the last two, whereas

in the randomized controlled trial by Bucknall and colleagues, a guideline-dictated sedation protocol was compared with their ICU standard usual practice. This time the results were similar among the two groups, including durations of MV, ICU and hospital stay, occurrence of tracheostomy, unplanned extubations and mortality, providing no evidence of protocol-directed sedation superiority, as other studies did. However, practice of the ICU's highly qualified nursing staff could benefit patients of both groups. The same nursing staff took part in both protocol-directed and standard approaches and suggested therapeutic options to the clinicians; combined with the fact that neuromuscular blocking agents were more frequently used in the intervention group, thus potentially negating the positive effects of the protocol, the chance of bias may not be negligible.

De Wit et al[28] conducted a randomized study based on observations of previous investigators, i.e. that MV duration is decreased by utilization 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[15] and guidelines by the Society of Critical Care Medicine,[29] aiming for minimalizing 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.[16]

The results were in favor of the sedation algorithm, as the 38 patients in the sedation algorithm group had on average shorter ICU and hospital LOS compared to the 36 patients in the DSI group (8 versus 15 days, $p<0.0001$ and 12 versus 23 days,

p=0.01 correspondingly). 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 in favor of the same group, as 5 patients died in the ICU compared to the 8 patients of the DSI group (p=0.20) and 7 patients of the sedation algorithm group died in hospital versus 13 of the DSI 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 perform on some patient groups, such as alcohol and drug abusers, deriving from the fact that a significant number of their patient sample suffered from alcohol use disorders. That observation deserves to be pointed out, because either an alcohol or a 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 breathing without assistance, Girard et al[13] conducted a landmark multicenter randomized controlled study 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 of course 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, by a median difference of 3.1 days (p=0.02). This finding was combined with a 6% higher self-extubation rate (p=0.03), even though reintubation rates after self-extubation were similar between the two groups; the number of patients that required reintubation after self-extubation did not differ significantly. The absolute risk of tracheostomy was reduced by 7% in the intervention group, as occurrence of this complication was 13% versus 20% in the control group (p=0.06). ICU and hospital LOS also favored the intervention group, as they were 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).

According to the researchers, bias could be the result of the research personnel's and ICU staff's awareness of patient allocation, so they managed patients with formal protocols and used a statistical analysis plan beforehand to minimize that bias. Also, coincidentally, increased propofol dosages were administered to the intervention group before allocation, which might have a negative impact on their outcomes. However, according to the researchers, pre-enrolment propofol levels were not found to affect study outcomes (and as far as benzodiazepines are concerned, administration was similar among the two groups). 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, apart from long-term survival, another issue relating patients who have been hospitalized in ICUs is impact on long-term functional, cognitive and psychological status. Jackson and Girard et al[14] compared these parameters amongst

180 patients that were assessed in a planned sub-study conducted during the Awakening and Breathing Controlled Trial mentioned above.[13] All outcomes, including cognitive impairment, composite cognitive scores, symptoms of depression or PTSD and quality of life status were found similar, notwithstanding that the intervention group retained the physiological benefits of the aforementioned protocol.

In 2009, Anifantaki et al[30] published a randomized controlled trial, in which they studied a sample of 97 mechanically ventilated patients, including neurosurgical patients, over the course of almost 2 years in an ICU in Greece. The 49 patients of the intervention group underwent DSI according to a nurse-implemented protocol that did not differ significantly from the previous ones. There were, however, some contraindications that excluded patients from the DSI procedure: severe haemodynamic instability, Positive End Expiratory Pressure greater than 18 cm H_2O, Intracranial Pressure greater than 18 mmHg and deterioration of cerebral haemorrhage or oedema. The 48 patients of the control group received sedation per the ICU physicians' prescriptions.

Their primary outcome was duration of MV and there was no significant difference between the two groups, as the intervention group showed a median duration of 7.7 days versus the 8.7 days of the control group ($p=0.7$). Neither were the secondary outcomes any different, those of ICU-LOS and hospital-LOS, overall mortality, total drug doses administered and Ramsay Sedation Scale[31] (RSS, described in Table 1).

This study is not free of limitations either. As the staff was not blinded to the patient division, since there was a nurse present during the sedation break in the intervention group, a patient allocated in that group could possibly receive more diligent

care. Furthermore, there were patients that received only analgesia, i.e. remifentanyl was administered in order to achieve a desired RSS; that could be another source of bias. The researchers concluded at the end that DSI was neither beneficial nor harmful. They did, however, deem it safe and feasible for the subgroup of neurosurgical patients, a patient subgroup poorly studied until then.

Score	Description
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

TABLE 1. RAMSAY SEDATION SCALE[31]

A Turkish study[32] of a smaller scale included 50 patients who were randomly allocated into two groups of similar demographic values. One group was treated with DSI without any protocol (mentioned as Group P by the author) while the other group received sedation according to a protocol prepared by the ICU physicians (Group N) and was administered additional sedatives in the discretion of the physicians, in case of unachieved sedation levels. Sedative agents of choice were diazepam, propofol, and dexmedetomidine for both groups.

In this trial, DSI did not follow any protocol; instead, instructions to cease sedation were given at the physicians' discretion, after assessing the patients' haemodynamic values or blood gas analyses.

ICU-LOS and mortality rates were found similar between the two groups. However, the DSI group demonstrated significantly shorter duration of MV by a median difference of 2.86 days (6.66 versus 9.52 days in group N, $p<0.05$) and also a 3.26-day shorter duration of sedation (4.56 versus 7.82 days group N, $p<0.05$). 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.

Apart from the small sample size of the study, adding the conduction of the nursing-implementing protocol to the daily workload of the nursing staff was mentioned to be a cause of anxiety, possibly implicating the evaluation of RSS. That was the reason that, even though a nursing-implemented protocol is considered applicable, the researchers proposed it not be conducted in case of inadequate nursing staff, whereas a DSI strategy is safe and practical.

The effect of DSI on duration of MV was tested against no sedation at all in 2010, in a first of its kind randomized controlled trial by Strom et al.[19] To clarify, even though no sedatives were used in the intervention group, some sedation may have been caused by the boluses of morphine (2.5 – 5 mg) that were administered to both groups of the total 140 patients enrolled in this single-center study. The patients of the control group underwent DSI per the usual protocol.

The primary endpoint was time of unassisted breathing, which was increased in the intervention group by a median difference of 4.2 days ($p=0.0191$). Delirium was an

adverse effect observed more frequently in the intervention group but 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 to support an even more judicious approach to sedative infusion, allowing administration only when deemed necessary. Heterogeneity was a strong point of this study, which resulted from inclusion of medical and surgical patients alike. However, this might have been negated from the fact that the control group was found to suffer from slightly more severe illness, as was demonstrated after analysis of Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment (SOFA) scores. Bias might have been the result of ICU understaffing; or from switching propofol to midazolam as sedative of choice, which has a slower clearance rate, even more so if renal and liver failure are present.[33] 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 stay, Mehta et al[34] combined both these methods 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 as a guide for modifications in their protocol and was used afterwards as footing to conduct a multicenter randomized controlled trial.[35] Over a 3-year period, they collected data from 430 patients hospitalized in 16 medical and surgical ICUs. Patients were divided in the control group (n=209), receiving protocolized sedation alone and the

intervention group (n=214) which received sedation via the same protocol but also underwent DSI, according to the standard protocol by Kress et al.[16] The level of sedation was ideally maintained to provide a comfortable, but rousable state, or a score of -3 to 0 in the Richmond Agitation-Sedation Scale[36] (RASS, described in Table 2). In the intervention group, benzodiazepines and opioids were discontinued until the patient could follow certain commands and reached a RASS score of -1 to 4. Then, sedation was streamlined at the physicians' and bedside nurses' discretion; it was either stopped if patient's state allowed it, or resumed at half the previous rate if sedation was still required. In case of agitation (RASS score of 2 to 4) or clinical symptoms of discomfort, sedation was resumed at half the previous rate. The ICU team assessed daily the patients' extubation readiness and commenced weaning process at their discretion.

The time of successful extubation, being the primary outcome, did not differ and was 7 days on average in both groups (p=0.52). ICU-LOS, hospital-LOS, unintentional endotracheal tube removal rates, delirium rates and hospital mortality rates did not differ significantly either. Instead, there was a significant increase in the total dose of drugs administered to the intervention group (midazolam, fentanyl and daily boluses of benzodiazepines and opiates). The reason for this last 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.

Shorter acting agents such as propofol or dexmedetomidine were not tested and patients requiring deep sedation were not included in the study since the researchers targeted for lighter levels of sedation (RASS score of -3 to 0). The author also mentions not screening for drug withdrawal as another limitation of their study and considered

blinding of the caregivers not feasible. 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.

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

TABLE 2. THE RICHMOND AGITATION-SEDATION SCALE[36]

More recently, in a Brazilian ICU with low nursing staff, Nassar et al[37] conducted a randomized controlled trial comparing DSI (according to the usual protocol) to intermittent sedation in order to detect which one is superior in terms of providing more

ventilator-free days. Sixty patients underwent randomization to receive sedation with either one of the two methods mentioned above.

Not only no significant difference was noticed in the number of ventilator-free days (24 days versus 25 days for the intermittent sedation group, p=0.16), that being the primary outcome of the study, but also in ICU and hospital mortality, accidental extubations, delirium occurrence and psychological stress in a 6-month follow-up.

Apart from the small sample of the study, the authors addressed the similar levels of sedation as a potential factor for not detecting a significant difference between the two groups. Similarly to the study mentioned above,[35] increased dosages of fentanyl and midazolam were administered to the patients undergoing DSI and that observation led the authors to hypothesize that this could also increase costs, especially in the setting of developing country ICUs. There is however a finding of this study that should be emphasized and it's the fact that lighter sedation was found to be equally safe and feasible even in a lower nursing staff ICU, therefore adaptation of light sedation strategies is possible to decrease length of MV, as dictated by international guidelines.[38]

To the best of our knowledge, the most recent study on the subject was conducted by Kayir and colleagues,[39] who monitored and reviewed 100 demographically similar patients over a 5-year period. They compared DSI with continuous sedative infusion, by dividing the patients into two groups of 50 (Group D being the daily awoken patients and Group P being the patients sedated according to conventional protocol) and administering propofol, midazolam, thiopental and dexmedetomidine for sedation. In both groups, medication was adjusted according to

the patient's RSS: in case of agitation (RSS=1), i.v. boli of sedatives and opioids were administered and infusion rates were increased to achieve an RSS equal to 3.

DSI was associated with shorter MV duration, on average 4 days shorter for Group D (specifically 4.02 days was the median duration for Group D versus 8.1 days for Group P, $p<0.001$). No significant difference was noticed in successful weaning frequencies, despite a 2.92-day earlier time to start the first weaning attempt among patients in Group D ($p < 0.05$). However, rates of reintubation and VAP were both lower for the DSI group, by 18% ($p < 0.05$) and 28% ($p < 0.05$) respectively. The rest of the authors' findings concerned ICU-LOS and hospital-LOS, mortality rates, APACHE II and SOFA scores and doses of sedatives, opioids and muscle-relaxants. APACHE II, SOFA scores, ICU-LOS and fentanyl dosages differed significantly, all being lower for daily awoken patients.

The authors mentioned that in case of agitation, quick action was taken to titrate sedation levels and that may be a reason why accidental extubation and subsequent reintubation cases were fewer among the patients undergoing DSI. However, we believe that this raises the question whether the DSI group was managed with more diligent care, something that could explain the different results regarding these adverse effects, generating possibility of bias. As a conclusion the authors considered DSI to be a superior method to utilize for patients under MV and suggested it be the sedation technique chosen.

The methods compared and significant findings of all the randomized controlled trials implementing DSI protocols are summarized in Table 3 and in Table 4 we present all their results regarding the duration of MV.

Study	Sample Description	Compared Strategies	Significant Findings
Kress et al,[16] 2000	128 medical patients on MV	DSI vs. usual care	DSI led to: Fewer days on MV Fewer days in ICU
Girard et al,[13] 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,[28] 2008	74 medical patients on MV	DSI vs. Protocol based on RSS (applied by Brook et al[15])	Protocol led to: Fewer days on MV Fewer days in ICU Fewer days in hospital
Anifantaki et al,[30] 2009	97 medical & surgical patients on MV	DSI vs. usual practice	None
Yilmaz et al,[32] 2010	50 patients on MV	DSI vs. Protocol based on RSS	DSI led to: Fewer days on MV Faster wake-up
Strom et al,[19] 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
Mehta et al,[35] 2012	430 medical & surgical patients on MV	DSI + protocol vs. protocol	Protocol led to: Decreased medication
Nassar et al,[37] 2014	60 medical & surgical patients on MV	DSI + intermittent vs. Intermittent	Intermittent led to: Decreased medication
Kayir et al,[39] 2018	100 patients on MV	DSI vs. continuous	DSI led to: Fewer days on MV, in ICU & hospital Faster first weaning attempt Lower VAP, reintubation & mortality rates

TABLE 3. SUMMARY OF FINDINGS BY RANDOMIZED CONTROLLED TRIALS.

Abbreviations: DSI = Daily Sedation Interruption; MV = Mechanical Ventilation, ICU = Intensive Care Unit; RSS = Ramsay Sedation Scale; VAP = Ventilator Associated Pneumonia; SBT = Spontaneous Breathing Trial

Study	Compared Strategies	Median Duration of MV (in days) in DSI group	Median Duration of MV (in days) in control group	P value
Nassar et al[37]	DSI + intermittent vs. Intermittent	3	4	=0.16
Kayir et al[39]	DSI vs. continuous	4.02	8.1	<0.001
Kress et al[16]	DSI vs. usual care	4.9	7.3	=0.004
De Wit et al[28]	DSI vs. Protocol based on RSS (applied by Brook et al[15]	6.7	3.9	=0.0003
Yilmaz et al[32]	DSI vs. Protocol based on RSS	6.7	9.5	<0.05
Mehta et al[35]	DSI + protocol vs. protocol	7	7	=0.52
Anifantaki et al[30]	DSI vs. usual practice	7.7	8.7	=0.7
Girard et al[13]	DSI + daily SBT vs. usual practice + daily SBT	13.3	16.4	=0.02
Strom et al[19]	DSI vs. No sedation	18.4	14.2	=0.0191

TABLE 4. RESULTS OF RANDOMIZED CONTROLLED TRIALS ON MECHANICAL VENTILATION.

Abbreviations: DSI = Daily Sedation Interruption; MV = Mechanical Ventilation, RSS = Ramsay Sedation Scale; SBT = Spontaneous Breathing Trial

BLINDED STUDIES

Literature available concerning blinded studies is unfortunately not as rich. A probable explanation could be the difficulty in masking the agents administered to the patients and of course 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 been a concern on various occasions in the past. The first to make that observation were Brook et al[15] who mentioned that “it was obviously impossible to blind the staff to the patients’ group”. Girard et al[13] later made a similar statement that “blinding is not possible in a study of this kind”. Strom et al[19] mentioned the single-center and unblinded design of their study as a limitation that held risk of bias. Finally, Mehta et al[35] similarly stated that it was not feasible to blind the caregivers. There have been, however, some distinguished blinded studies that have been conducted in this field, in contrast with the afore-mentioned comments and for that reason, we believe their separate presentation is in order.

A frequent, potentially lethal condition among critically ill, mechanically ventilated patients, is myocardial ischemia, as demonstrated in a prospective, blinded observational study in 2007 by Kress and colleagues.[40] They evaluated a total of 74 under MV, with established coronary artery disease factors. The researchers sought to compare DSI versus continuous sedative infusion and how these two methods fare against the risk of myocardial ischemia occurrence and to observe whether DSI was safe enough to perform in the afore-mentioned patients.

All their patients had at least two known risk factors and were monitored via a 3-lead Holter monitor. The sedatives used were midazolam or propofol and morphine was the analgesic of choice. The infusion of those drugs was interrupted on a daily basis, even if a patient had ischemia during sedation, until the awake patient could follow commands or his/her state demanded a resumption of the sedative and analgesic infusion. Interpretation of electrocardiographic recordings was blindly performed by a cardiologist, unaware of the patients' clinical condition. Vital signs, mental status as well as enzymic changes were assessed upon the interruption of infusion and by the end of it, all the while keeping in track of electrocardiographic changes, if any. The researchers also recorded Creatine Phosphokinase (CPK) criteria for defining acute myocardial infarction (increase in CPK, CPK myocardial band and CPK myocardial band above normal range).

The total number of ischemic patients was 18 and therapy included either treatment with aspirin, or beta-blocker and in fewer cases, infusion of iv heparin. One patient underwent cardiac catheterization and had a stent placement. Evidence of myocardial injury by CPK assay was observed in 6 patients (which was also documented by the Holter monitor in 3 of the cases) and in all 6 of the cases this elevation was observed before sedative interruption. Out of the eighteen ischemic patients, eight were ischemic during both the sedated and clinically awake state. Three patients were not ischemic before sedative interruption but after wake-up procedure. The seven rest were ischemic before interruption but not after waking up. The researchers also chose to analyze this percentage because the majority of the time is spent with patients under sedation (whereas DSI typically lasted a few hours). They

hypothesized that more time spent under sedation would be likely translated to more ischemic minutes during that time frame. The subgroup of the 18 ischemic patients demonstrated a 1.4% median percentage of minutes of ischemia with interrupted sedative infusion. That ratio was 11.4% when sedatives were constantly infused ($p=0.98$). That finding suggested that DSI was safe enough to implement in patients at high risk for coronary artery disease.

Even though sedative interruption was associated with a significant rise in respiratory rate, arterial pressure, heart rate and a dramatic rise in plasma adrenaline, noradrenaline and dopamine levels ($p<0.001$), what is impressive is that the occurrence of myocardial ischemia as well as the duration of ischemia was similar in both the sedated and awake state of patients. A total of 43.2% of the patients not receiving exogenous vasoactive drugs had catecholamine assays after awakening from sedative discontinuation. Given the association of myocardial ischemia with increases in heart rate, mean arterial pressure, rate–pressure product, and catecholamine levels in other circumstances, the fact that no increased prevalence was observed after awakening from sedation is a finding that surprised the researchers. Furthermore, no patient complained of angina during DSI. As far as MV duration is concerned, it was longer in patients with myocardial ischemia, as was ICU-LOS. Because the prevalence of myocardial ischemia is high among mechanically ventilated patients[41] and is also associated with increased likelihood of SBT failure[42] and, consequently, weaning failure,[43] we believe that this observation further stresses the need to shorten MV and optimize weaning process, which applies more to the main topic of this review, in order to avoid the associated adverse effects in these already gravely ill patients. The

limitations of this study mostly derived from the limited equipment available in monitoring myocardial ischemia and from the fact that all the patients were subject to DSI, thus raising the potential for falsely interpreting enzymic changes (since a morning CPK and troponin blood level might reflect myocardial injury from the previous day). That, however, was highly unlikely as almost all the enzymic elevations were observed before the first awakening. Unrecognizing the possible cumulative effects a DSI may have after a long time is another potential limitation of this study's crossover design (instead of group randomization). While the researchers acknowledged these limitations, the conclusion of this study, albeit small, is very important because it deems DSI a safe technique to utilize, even in these high-risk patients. Of course, in patients with unstable coronary disease, increased sympathetic activity is still undesirable and to the best of our knowledge, the optimal method of preventive therapy and MV duration shortening is still unknown.

In a study by Weisbrodt et al,[44] nonclinical nurses prepared normal saline to be administered by the bedside nurses instead of the prescribed sedative, in this case fentanyl and/or midazolam, in unawareness of the researchers and the clinical teams. The sample of 50 patients was thus randomly separated (by using a computer sequence) into two groups of equal size, the control group that received regular sedative infusion and the intervention group that was subject to a pause of the sedative drug infusion that lasted a maximum of 6 hours. Including propofol into the study protocol would complicate blinding due to the characteristic white appearance; in any other case excluding performance of a medical procedure or extreme agitation, the administration of its use was considered a breach of protocol, that being the case for

about a fifth of the total 50 patient sample (more specifically, 7 out of the 26 in the intervention group and 4 out of the 24 of the control group). After a daily assessment of the patients' RASS scores, cessation of sedative infusion was permitted in the cases where patients were eligible to begin weaning process.

No significant difference was noticed in the dosage of midazolam or fentanyl between the two groups (721.1 μg of fentanyl and 31.9 mg of midazolam in the intervention group versus 986.3 μg of fentanyl and 33,23 of midazolam in the control group, p=0.99 for the fentanyl comparison and p=0.41 for the midazolam comparison). Another similarity was noticed in the effects of sedation among the two groups. With the primary reason for stopping the infusion of the study drug and returning to the prescribed one being the completion of the 6-hour period of study drug administration, indeed only a few patients scored a higher than +2 RASS score (13.9% in the intervention and 7.4% in the control group correspondingly). This finding supports the safety of the blinding strategy, since patients' responses did not reveal in which group they were assigned. Spontaneous movement (+1 RASS score or higher) was noticed in grossly 50% of patients with an even allocation in both groups.

The study did not demonstrate a notable difference in the clinical outcomes of the two groups. All extubations occurred as planned and median duration of MV was the same in both groups (p=0.93). A slightly lower, but not significantly different, rate of tracheostomy was recorded in the intervention group (31% versus 54% in the control group, p=0.99) as well as a 3.1-days shorter ICU-LOS (8.2 days instead of 11.3 days in the control group, p=0.83) combined with a lower ICU mortality rate (19% versus 33%, p=0.3). Although these findings did not differ significantly, the authors admitted that their

study was by design inadequately powered to detect significant differences in clinical outcomes.

The unwillingness of otherwise eligible patients' next of kin to provide consent for the participation in the study narrowed down the sample of this study, but its conclusion was solid nonetheless: a double-blinded design on sedation interruption was safe and feasible to perform on patients receiving MV, but difficulties with patient recruitment and adherence to this protocol would make it difficult to apply on a multicenter study.

This prediction was only partially right, as the following year a study by Jakob et al[45] was published in the Journal of the American Medical Association, consisting of two multicenter, randomized, double-blind trials, which sought to compare dexmedetomidine against either propofol or midazolam in terms of maintaining sedation, reducing duration of MV and improving patient agitation status. Patient sedation levels were assessed by RASS scores. A blind method, similar to that of Weisbrodt et al,[44] was used, i.e. independent personnel administered the study drugs; however, in this study, propofol was also administered blindly, via nontransparent black syringes and infusion devices. Each of the three drugs was administered at six separate levels in order to cover the full dose range of said drug (dexmedetomidine 0.2-1.4 μg/kg per hour, propofol 0.3-4.0 mg/kg per hour and midazolam 0.03-0.2 mg/kg per hour). The full dose range of each of the three drugs was covered by administration at six separate levels and analgesia treatment was provided by bolus injections of fentanyl. Furthermore, DSI and SBTs were also performed.

The results regarding the total ICU and hospital LOS showed no significant difference and mortality rates between time of randomization and a 45-day follow-up

were also similar in both the dexmedetomidine/midazolam and the dexmedetomidine/ propofol trials. Dexmedetomidine seemed to affect negatively the patients' haemodynamics in comparison with midazolam, since 51/247 patients (20.6%) showed hypotension and 35/247 patients (14.2%) showed bradycardia versus 29/250 (11.6%, $p=0.007$) and 13/250 (5.2%, $p<0.001$) in the midazolam group correspondingly. Propofol fared similarly with dexmedetomidine as far as these adverse events are concerned. Even though time spent at target sedation levels was not significantly different among the 3 study drugs, patients treated with dexmedetomidine were more cooperative and arousal and interaction with the nursing staff was improved, since they had a better Visual Analogue Scale score ($p<0.001$). Dexmedetomidine also seemed to shorten MV duration in comparison with midazolam, as there was a median 41-hour difference ($p=0.03$). The same cannot be said in the comparison with propofol, as this difference was not significant ($p=0.24$).

This was a pioneering study, the first to compare dexmedetomidine to propofol on a large scale. Its conclusion was that the former was "not inferior" to midazolam or propofol in providing light to moderate sedation and the large sample size combined with the masking process minimize the chance of bias. The improved patient alertness state and the higher levels of cooperation with the nursing staff could allow, according to the researchers, earlier mobilization, a more appropriate use of opioid analgesics and a possibility of earlier extubation. The latter could facilitate an earlier weaning process, even though the duration of MV per se was not shorter when administering dexmedetomidine versus propofol.

DISCUSSION

After gathering all the evidence demonstrated by the studies included in our review, there seems to be a moderate heterogeneity among the findings. Smaller trials have sometimes contradicting results in comparison with larger ones. There is, though, unanimity on the safety of this method. This has been displayed even among patients at risk for coronary artery disease in a small study,[40] although sympathetic stimulation of unstable patients remained a concern. The conclusions that can be made is that not only DSI, but algorithm-directed sedation as well, 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 against 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.

This is not the first review to be conducted concerning how and if DSI is associated with reduction of MV duration and improvement of clinical outcomes. For instance, a more broad review on the previous work in the field of ICU sedation and analgesia for patients under MV was conducted by Patel and Kress in 2012.[46] In our review, we share some of the literature that they have presented, all the while adding the most recent relevant advances.

In a Cochrane review in 2014, by Burry et al,[47] 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 randomized controlled trials, they advised consideration of the results' instability.

Another review published in the same year in the New England Journal of Medicine by Reade and Finfer[48] demonstrated an inverse relationship between sedation and clinical benefit; their data were reconstructed from studies that strategized minimization or even elimination of sedatives in their protocol-directed sedation methods.[13,16,19] They consequently suggested minimization of sedation leads to improvement of clinical outcomes.

DSI has also become the subject of two meta-analyses, in 2011 by Augustes and Ho[49] and in 2015 by Minhas et al[50] for the Mayo Foundation. These studies share some similarities in their results in terms of clinical outcomes, possibly due to the overlapping randomized controlled trials included in both. In the former, no significant improvement was noticed as far as duration of MV, ICU-LOS and hospital-LOS or mortality are concerned. DSI was associated instead with a smaller risk of tracheostomy demand and no increase in the risk of accidental removal of the endotracheal tube. With their limited data, Augustes and Ho concluded that, even though safe, DSI was not yet to be recommended as routine practice.

That was not the case in the latter meta-analysis by Minhas et al[50] who, in sharp contrast, strongly recommended the utilization of protocolized sedation (either daily interrupted or according to algorithms). Their findings contradicted the afore-mentioned meta-analysis and the findings of the Cochrane review, as they found a significant improvement in terms of ICU-LOS and hospital-LOS and mortality; according to the authors, that contradiction was due to the previous researchers' inclusion of randomized

controlled trials in which the control groups did not receive sedation in the discretion of physicians, but according to protocol. Similarly to Augustes et al, they found a lower percentage of tracheostomy and no significant decrease in time spent under MV.

At this point, having presented the relevant literature published, we attempt to investigate how much DSI is integrated in routine practice, at least until recently. For that reason we cite two relevant surveys, in 2010 by O'Connor et al[51] and a survey in 2012 by Miller et al,[52] in form of participation in 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, that has a long-standing multidisciplinary cooperation history. In the first survey, O'Connor and colleagues explored the practices of management in Australian and New Zealand ICUs and mentioned a 62% compliance rate regarding the utilization of this method, characterizing it as common practice for the treatment of the mechanically ventilated patient. Interestingly, DSI was performed in more than 75% of patients by 23% of ICU members taking part in the survey. Contradictory to those statistics, in the 5 focus group survey by Miller et al, this intervention was mentioned to not 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 provided by literature until then, application remained sub-optimal, with the major reason for this being 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[38] 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 over sedation, they recommended application of DSI or light target 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 3 trials[32,39,45] that incorporated dexmedetomidine into the DSI protocol and, to the best of our knowledge, have never been reviewed in the past or were intentionally excluded because they did not fit the study's criteria for inclusion. For example, such was the case for the trials by Yilmaz et al[32] and Jakob et al[45] that were 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 that we have included a recent trial (also excluded from the Mayo meta-analysis for the same reason) by Nassar et al[37] who, in spite of the small size of their study, demonstrated the safety of application of DSI even in ICUs of low nurse staffing, a very important observation that could serve as footing for future trials in ICUs with a low nurse to patient ratio. Greek ICUs fall into that category and that unfortunate reality further cements the importance of this finding.

The present review also has some limitations. As far as the primary endpoint of this review is concerned, which is how weaning is facilitated by the use of DSI, data on the method's effect on SBTs, times of first weaning attempts and weaning success rates is sadly limited and there is no concrete consensus on the reduction of MV duration. However, for the latter statement we need to take into account the fact that bias cannot

be safely excluded. First of all, the patient sample size is still inadequate; all the gathered trials are relatively small, therefore the findings may be susceptible to publication bias. Secondly, not all the studies conducted a daily screening test to ensure patients' eligibility to undergo interrupted sedation. In case of oxygenation derangement or haemodynamic instability, this method's risk of failure is increased, thus making initiation of DSI inappropriate. Thirdly, as hypothesised by de Wit et al,[28] 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.[28] Finally, in the Mayo meta-analysis,[50] a heterogeneous summary estimate was found in the findings regarding MV duration; by excluding the trial by Bucknall et al[27] from their sensitivity analysis, the heterogeneity of the results was resolved and then MV duration was found to be significantly reduced.

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 the findings of adult studies is inappropriate because of the different physiologic parameters (such as renal and hepatic clearance) and also because children are more difficult to restrain and nurse. To the best of our knowledge, only two randomized controlled trials have been published concerning DSI applied in mechanically ventilated children, in 2012 by Gupta et al[53] and by Verlaat et al,[54] in 2013. In the first, a total of 102 homogenous in terms of demographics and clinical characteristics mechanically ventilated children were

allocated in two groups, receiving either continuous infusion of sedatives or interrupted on a daily basis until awake or agitated/uncomfortable. The results favored the intervention group because length of MV (p=0.021), the length of Pediactric ICU (PICU) stay (p=0.048) and total dose of midazolam administered (p=0.002) were all significantly lower, hence the lower calculated cost of therapy (p=0.02). Occurrence of adverse effects (most commonly development of pneumothorax, in 10.9% of the DSI group and 12.5% of the continuously sedated group, p=0.79) did not differ significantly but the primary endpoint of this review, being the effect on weaning from MV, was shown to be favored by a DSI practice, since length of stay under ventilator was shorter by a median 3.3 days (7 days versus 10.3 days of the control group, p=0.021). These findings were reproduced the following year in the randomized controlled trial by Verlaat et al,[54] who used the same methods on a sample of 30 critically ill, mechanically ventilated children. Again, they observed a significant reduction in the duration of MV, by a median difference of 5 days (median duration was 4 days for the intervention and 9 for the control group, p=0.03). PICU-LOS also appeared to be significantly lower (p=0.01) and use of sedatives showed a significant decrease after 3-day course (midazolam P = 0.007 and morphine, P = 0.002). The conclusion of this study, albeit small, was similar to the study by Gupta and colleagues, that DSI is feasible and apparently safe enough to strategize in treating mechanically ventilated children, leading to earlier extubation, improved cognitive state and an earlier release from the PICU. This is something that 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 case of long-term

administration.[55] Other subgroups of patients prone to respiratory depression that DSI has been poorly studied are neurosurgical and substance-dependent patients.

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 is increased 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[44] and Jakob et al[45] presented the applicability of a blinding method in their studies, proving wrong previous claims made that conducting double-blinded trials is impossible. These studies could serve as groundwork for more future studies to optimize the quality of evidence.

CONCLUSION

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 utilize 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 as well as 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.

ABBREVIATIONS

APACHE – Acute Physiology And Chronic Health Evaluation
CPK – Creatine Phosphokinase
DSI – Daily Sedation Interruption
ICU – Intensive Care Unit
i.v. – Intravenous
LOS – Length of stay
MV – Mechanical ventilation
PICU – Pediatric Intensive Care Unit
PTSD – Post Traumatic Stress Disorder
RASS – Richmond Agitation-Sedation Scale
RCT – Randomized controlled trial
RSS – Ramsay Sedation Scale
SAPS – Simplified Acute Physiology Score
SBT – Spontaneous Breathing Trial
SOFA – Sequential Organ Failure Assessment
VAP – Ventilator associated pneumonia

REFERENCES

1. Sydow M, Neumann P. Sedation for the critically ill. Intensive Care Med. 1999;25(6):634-636.
2. Soliman HM, Melot C, Vincent JL. Sedative and analgesic practice in the intensive care unit: the results of a European survey. Br J Anaesth. 2001;87:186-192.
3. Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous i.v. sedation is associated with prolongation of Mechanical Ventilation. Chest 1998;114:541-548.
4. Cook DJ, Walter SD, Cook RJ, et al. Incidence of and risk factor for ventilator associated pneumonia in critically ill patients. Ann Intern Med. 1998;129:433-440.
5. Swart EL, Zuideveld KP, de Jongh J, Danhof M, Thijs LG, Strack van Schijndel RM. Population pharmacodynamics modelling of lorazepam- and midazolam-

induced sedation upon long-term continuous infusion in critically ill patients. Eur J Clin Pharmacol. 2006;62(3):185-194.

6. Barr J, Egan TD, Sandoval NF, et al. Propofol dosing regimens for ICU sedation based upon an integrated pharmacokinetic-pharmacodynamic model. Anesthesiology. 2001;95(2):324-333.
7. Iyer VN, Hoel R, Rabinstein AA. Propofol infusion syndrome in patients with refractory status epilepticus: an 11-year clinical experience. Crit Care Med. 2009;37: 3024-3030.
8. Tan JA, Ho KM. Use of dexmedetomidine as a sedative and analgesic agent in critically ill adult patients: a meta-analysis. Intensive Care Med. 2010;36(6):926-939.
9. Schelling G, Richter M, Roozendaal B, et al. Exposure to high stress in the intensive care unit may have negative effects on health-related quality-of-life outcomes after cardiac surgery. Crit Care Med. 2003;31:1971-1980.
10. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology. 2006;104(1):21-26.
11. Jones C, Backman C, Capuzzo M, Flaatten H, Rylander C, Griffiths RD. Precipitants of posttraumatic stress disorder following intensive care: a hypothesis generating study of diversity in care. Intensive Care Med. 2007;33(6):978-985.

12. Kress JP, Gehlbach B, Lacy M, Pliskin N, Pohlman AS, Hall JB. The long-term psychological effects of daily sedative interruption on critically ill patients. Am J Respir Crit Care Med. 2003;168(12):1457-1461.
13. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomized controlled trial. Lancet. 2008;371(9607):126-134.
14. Jackson JC, Girard TD, Gordon SM, Thompson JL, Shintani AK, Thomason JW et al. Long-term cognitive and psychological outcomes in the Awakening and Breathing Controlled trial. Am J Respir Crit Care Med. 2010;182:183-191.
15. Brook AD, Ahrens TS, Schaiff R, et al. Effect of a nursing-implemented sedation protocol on the duration of Mechanical Ventilation. Crit Care Med. 1999;27(12):2609-2615.
16. Kress JP, Pohlman AS, O'Connor MF, Hall J. Daily Interruption of Sedative Infusions in Critically Ill Patients Undergoing Mechanical Ventilation. N. Engl. J. Med. 2000;42:1471-1477.
17. Devlin JW, Fraser GL, Kanji S, et al. Sedation assessment in critically ill adults. Ann Pharmacother. 2001;35:1624-1632.
18. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009;373(9678):1874-1882.
19. Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving Mechanical Ventilation: a randomized trial. Lancet. 2010;375:475-480.

20. Walder B, Borgeat A, Suter PM, et al. Propofol and midazolam versus propofol alone for sedation following coronary artery bypass grafting: a randomized, placebo-controlled trial. Anaesth Intensive Care. 2002;30:171-178.
21. Rothen HU, Stricker K, Einfalt J, Bauer P, Metnitz PG, Moreno RP, Takala J. Variability in outcome and resource use in intensive care units. Intensive Care Med. 2007;33:1329-1336.
22. McGahan M, Kucharski G, Coyer F. Nurse staffing levels and the incidence of mortality and morbidity in the adult intensive care unit: a literature review. Aust Crit Care. 2012;25:64-77.
23. Craven DE, Steger KA. Epidemiology of nosocomial pneumonia: new perspectives on an old disease. Chest. 1995;108:1S-16S.
24. Schnapp LM, Chin DP, Szaflarski N, et al. Frequency and importance of barotrauma in 100 patients with acute lung injury. Crit Care Med. 1995;23:272-78.
25. Colice GL, Stukel TA, Dain B. Laryngeal complications of prolonged intubation. Chest 1989;96:877-84.
26. Whelan J, Simpson SQ, Levy H. Unplanned extubation: predictors of successful termination of mechanical ventilator support. Chest. 1994;105:1 808-12.
27. Bucknall TK, Manias E, Presneill JJ. A randomized trial of protocol-directed sedation management for Mechanical Ventilation in an Australian intensive care unit. Crit Care Med. 2008;36;1444-1450.

28. De Wit M, Gennings C, Jenvey WI, and Epstein SK. Randomized trial comparing daily interruption of sedation and nursing-implemented sedation algorithm in medical intensive care unit patients. Crit Care. 2008;12(3):R70.
29. Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, Chalfin DB, Masica MF, Bjerke HS, Coplin WM, Crippen DW, Fuchs BD, Kelleher RM, Marik PE, Nasraway SA, Jr, Murray MJ, Peruzzi WT, Lumb PD. Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists (ASHP), American College of Chest Physicians Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med. 2002;30:119-141.
30. Anifantaki S, Prinianakis G, Vitsaksaki E, Katsouli V, Mari S, Symianakis A et al. Daily interruption of sedative infusions in an adult medical-surgical intensive care unit: randomized controlled trial. J Adv Nurs. 2009;65:1054-1060.
31. Ramsay MA, Savege TM, Simpson BR, et al. Controlled sedation with alphaxatonealphadolone. BMJ. 1974;2:656-659
32. Yilmaz C, Kelebek Girgin N, Özdemir N, et al. The effect of nursing-implemented sedation on the duration of Mechanical Ventilation in the ICU. Ulus Travma Acil Cerrahi Derg. 2010;16(6):521-526.
33. Clinical pharmacokinetic monitoring of midazolam in critically ill patients. Spina SP, Ensom MH. Pharmacotherapy. 2007;27:389-398.

34. Mehta S, Burry L, Martinez-Motta C, Stewart T, Hallett D, McDonald E, et al. A randomized trial of daily awakening in critically ill patients managed with a sedation protocol: A pilot trial. Crit Care Med. 2008;36:2092-9.
35. Mehta S, Burry L, Cook D, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA. 2012;308(19):1985-1992.
36. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensivecare unit patients. Am J Respir Crit Care Med. 2002;166:1338-1344.
37. Nassar Junior AP, Park M. Daily sedative interruption versus intermittent sedation in mechanically ventilated critically ill patients: a randomized trial. Ann Intensive Care. 2014;4:14.
38. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41(1):263-306.
39. Kayir S, Ulusoy H, Dogan G. The Effect of Daily Sedation-Weaning Application on Morbidity and Mortality in Intensive Care Unit Patients. Cureus. 2018;10(1):e2062.
40. Kress JP, Vinayak AG, Levitt J, Schweickert WD, Gehlbach BK, Zimmerman F, Pohlman AS, Hall JB. Daily sedative interruption in mechanically ventilated patients at risk for coronary artery disease. Crit Care Med 2007;35:365-371.

41. Landesberg G, Vesselov Y, Einav S, et al. Myocardial ischemia, cardiac troponin, and long-term survival of high-cardiac risk critically ill intensive care unit patients. Crit Care Med. 2005;33:1281-1287.
42. Srivastava S, Chatila W, Amoateng-Adjepong Y, et al. Myocardial ischemia and weaning failure in patients with coronary artery disease: An update. Crit Care Med. 1999;27:2109–2112.
43. Hurford WE, Favorito F. Association of myocardial ischemia with failure to wean from Mechanical Ventilation. Crit Care Med. 1995;23:1475-1480.
44. Weisbrodt L, McKinley S, Marshall AP, Cole L, Seppelt IM, Delaney A. Daily Interruption of Sedation in Patients Receiving Mechanical Ventilation. Am J Crit Care. 2011;20:e90-e98.21.
45. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, Bratty JR, Takala J. Dexmedetomidine vs midazolam or propofol for sedation during prolonged Mechanical Ventilation: two randomized controlled trials. JAMA. 2012;307:1151-1160.
46. Patel SB, Kress JP. Sedation and analgesia in the mechanically ventilated patient. Am J Respir Crit Care Med. 2012;185(5):486-97.
47. Burry L, Rose L, McCullagh IJ, et al. Daily sedation interruption versus no daily sedation interruption for critically ill adult patients requiring invasive Mechanical Ventilation. Cochrane Database Syst Rev. 2014;7:CD009176.
48. Reade MC, Finfer S. Sedation and delirium in the intensive care unit. N Engl J Med. 2014;370(5):444-454.

49. Augustes R, Ho KM. Meta-analysis of randomised controlled trials on daily sedation interruption for critically ill adult patients. Anaesth Intensive Care. 2011;39(3):401-409.
50. Minhas MA, Velasquez AG, Kaul A, Salinas PD, Celi LA. Effect of Protocolized Sedation on Clinical Outcomes in Mechanically Ventilated Intensive Care Unit Patients: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Mayo Clin Proc. 2015;90(5):613-23.
51. O'Connor MF, Bucknall TK, Manias E. Sedation Management in Australian and New Zealand Intensive Care Units: Doctors' and Nurses' Practices and Opinions. Am J Crit Care. 2010;19:285-295.
52. Miller MA, Bosk EA, Iwashyna TJ, Krein SL. Implementation challenges in the intensive care unit: the why, who, and how of daily interruption of sedation. J Crit Care. 2012;27(2):218.e211-218.e217.
53. Gupta K, Gupta VK, Jayashree M, Singhi S. Randomized controlled trial of interrupted versus continuous sedative infusions in ventilated children. Pediatr Crit Care Med. 2012;13(2):131-135.
54. Verlaat CW, Heesen GP, Vet NJ, et al. Randomized controlled trial of daily interruption of sedatives in critically ill children. Paediatr Anaesth. 2014;24(2):151-156.
55. de Wildt SN, de Hoog M, Vinks AA et al. Population pharmacokinetics and metabolism of midazolam in pediatric intensive care patients. Crit Care Med. 2003;31:1952-1958.