Sedation and Its Association With Posttraumatic Stress Disorder After Intensive Care

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Overuse of sedation in patients treated with mechanical ventilation can increase duration of ventilation, duration of delirium, and time to discharge. Although current principles of care include implementation of sedation protocols and/or daily interruptions in sedation to improve patients’ outcomes, these strategies remain underused. Historically, a barrier to use of protocols has been a perception that being awake and aware while intubated is intrinsically distressing and could cause psychological harm. Evidence of a link between lighter sedation and decreased signs and symptoms of posttraumatic stress disorder has partially dispelled these fears and even prompted the adoption of no-sedation (eg, analgosedation) strategies. Published studies on posttraumatic stress disorder and sedation are limited by small sample size, heterogeneous sedation practices, and inadequate follow-up. Despite limitations, current data suggest contemporary sedation practices to keep patients calm and comfortable but awake, as appropriate, are not associated with increased rates or severity of posttraumatic stress disorder. (Critical Care Nurse. 2014;34[1]:30-39)

Historically, moderate to deep sedation has been used to decrease agitation and enhance compliance with ventilation modes. In the late 1990s, awareness of problems associated with excessive sedation began to surface; studies indicated that continuous sedation was associated with prolonged periods of mechanical ventilation and increased rates of pneumonia. Subsequently, results of randomized controlled trials indicated improved outcomes with lighter sedation and led to the widespread adoption of sedation protocols or daily interruptions in sedation. More recently, similar improvements occurred in a trial of analgosedation in patients treated with mechanical ventilation.
One early criticism of lighter sedation and interruptions in sedation was a concern that the experience of being awake while being treated with mechanical ventilation would be psychologically harmful to patients. A 2003 follow-up study of patients who had interruptions in sedation indicated that this assumption was suspect and that deeper sedation might contribute to psychological distress and the development of posttraumatic stress disorder (PTSD). Nevertheless, strategies to lighten sedation remain underused; in one survey, a total of 396 of 1355 respondents reported that they did not use sedation protocols.

Nurses’ resistance to sedation protocols or daily interruptions in sedation has been identified as a barrier to implementation. In a recent survey of 423 nurses, 48% reported an intent to sedate all patients receiving mechanical ventilation, a finding that correlated positively with the nurses’ actual sedation practices. In addition, 80% of the respondents agreed with the statement “Sedation is necessary for patient comfort” and characterized mechanical ventilation as “uncomfortable and stressful.” Because of the potential benefits of minimizing sedation, an examination of the impact of such sedation on psychological health, of which PTSD is one measure, is important. In this article, I review the literature on the influence of different sedation protocols on PTSD.

PTSD Definition and Prevalence

The Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision) defines PTSD as the “development of characteristic symptoms following exposure to an extreme traumatic stressor” in which “the person’s response to the event must involve intense fear, helplessness, or horror.” A diagnosis of PTSD requires the presence of persistent signs and symptoms in each of 3 categories: hyperarousal, intrusive recollections, and avoidance/numbing. PTSD can be classified as acute (<3 months’ duration), chronic (≥3 months’ duration), or delayed onset. Practitioners have only recently become aware that PTSD can occur after an ICU stay, and the etiology of the syndrome is not clearly understood. The reported prevalence of PTSD after ICU care is 19% to 22%, and occurrence of the syndrome is associated with a marked adverse effect on health-related quality of life.

Method

The population of interest was adult ICU patients treated with mechanical ventilation who were sedated. The intervention was any strategy that would decrease the level of sedation, either through daily interruptions in sedation, use of nursing protocols, or differences in sedation scores (Ramsay Sedation or Richmond Agitation-Sedation scales). Outcomes were rates of PTSD or PTSD-like signs or symptoms. The evidence was limited to controlled trials. A search of PUBMED conducted by using combinations of the MeSH terms “stress disorders, posttraumatic”; “intensive care unit”; “daily sedation interruption”; and “sedation” yielded 322 articles. Narrowing the search by using the filters “humans” and “clinical trial” yielded 48 articles. Three prospective randomized controlled trials (RCTs) and 1 observational study were identified. A Web of Science search of articles that cited 1 or more of the 3 RCTs and references cited in 1 or more of the RCTs yielded a fourth trial that was nonrandomized. In total, 4 trials were reviewed and 1 observational study was included for citation in the discussion.

Terms

The term sedation refers to the degree of consciousness along a continuum that extends from a state of unresponsiveness (score of 6 on Ramsay scale) to agitation (score of 1 on Ramsay scale). Deep and light sedation are discussed in terms of scores on the Richmond Agitation-Sedation Scale, the Ramsay scale, or the modified Ramsay scale. For clarity, the term sedative exposure is used to indicate differences in doses of administered sedatives. PTSD refers to diagnosis of PTSD, and scores on various tools used to evaluate PTSD are discussed in terms of PTSD symptoms.

Results

Effects of the Intervention on PTSD

The first study to examine the relationship between sedation and PTSD was a follow-up to the findings of a landmark RCT published in 2000 by Kress et al.
impact of daily interruptions in sedation on the duration of mechanical ventilation and ICU stay. In this trial,\textsuperscript{4} patients randomized to the intervention group had daily interruptions in sedation with infusions restarted at half the rate after wakening. Sedation was then titrated to the goal Ramsay sedation score of 3 (following commands) or 4 (asleep, but easily arousable). The control group had standard sedation management with interruption only as per the ICU team. In a follow-up trial of 2 years later, patients from the initial trial were evaluated for PTSD through psychological testing and their Impact of Event Score. Because the dropout rate was high, additional patients were recruited for comparison from a 2-year period after the study was concluded. The cohort studied retrospectively received sedatives as in the original trial (daily spontaneous awakenings or standard care) but had not been randomized to these 2 groups. The results of this study,\textsuperscript{7} published in 2003, showed a surprising trend toward increased incidence of PTSD in the control group; PTSD was diagnosed in 6 patients in the control group and in none in the intervention group ($P = .06$; see Table). A significant difference in Impact of Event Scores was also detected; compared with the intervention group, the control group had symptoms of PTSD more often ($P = .02$), particularly for the subscales of avoidance and intrusive thoughts. Interestingly, other markers of psychological health such as anxiety and depression did not differ between the groups. The study was limited by its small size (32 patients) and retrospective design.

In 2008 Girard et al\textsuperscript{5} performed a similar study, the Awake and Breathing Controlled (ABC) trial. They improved the quality of the study by using a randomized control design and a larger sample size. Interventions and assessment methods included daily interruptions in

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### Table: Summary of studies of sedation and posttraumatic stress disorder

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
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<tr>
<td>Kress et al,\textsuperscript{7} 2003</td>
<td>Retrospective, nonrandomized, controlled trial with historical comparison group; blinded observer</td>
<td>32 MICU patients from a single center in the United States</td>
<td>Usual care: Sedation management per ICU team</td>
<td>Daily interruption of sedation by research team followed by adjustments to sedation dosage and titration to RASS score of 3-4</td>
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<td>Jackson et al,\textsuperscript{14} 2010</td>
<td>Prospective randomized controlled trial; blinded observer</td>
<td>80 MICU patients from a single center in the United States</td>
<td>Sedation titrated to individual patients’ goals</td>
<td>Sedation as in control group with spontaneous awakening trials (ie, sedation interruption) each morning followed by adjustments in or cessation of sedation dosage, titrated to patient-specific goals Paired with spontaneous breathing trials</td>
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<tr>
<td>Treggiari et al,\textsuperscript{17} 2009</td>
<td>Prospective randomized controlled trial; blinded observer</td>
<td>129 SICU and MICU patients from a single center in the United States</td>
<td>Deep sedation group Continuous midazolam infusion titrated to Ramsay score of 3-4 Morphine for pain</td>
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<td>Strøm et al,\textsuperscript{18} 2011</td>
<td>Prospective randomized controlled trial; blinded observer</td>
<td>26 patients from a single center in Denmark with 1 to 1 nurse to patient ratios</td>
<td>Sedation with continuous infusion of propofol or midazolam titrated to Ramsay score of 3-4 with daily sedation interruption Morphine bolus for pain Bedside sitter available as needed</td>
<td>Analgesedation Morphine bolus for pain; haloperidol bolus for delirium Bedside sitter available as needed</td>
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Abbreviations: ICU, intensive care unit; IES-R, Impact of Events Score; MICU, medical ICU; PTSD, posttraumatic stress disorder; PTSS-10, Posttraumatic Stress Scale-10; RASS, Richmond Agitation-Sedation Scale; SICU, surgical ICU.

\textsuperscript{a} Except where specified, lower scores on any test used to measure PTSD signs and symptoms indicate fewer PTSD signs and symptoms.
sedation similar to those used by Kress et al, but with a few marked differences. As in the study by Kress et al, patients in the control group received usual care, and those in the intervention group had daily interruptions in sedation. In both studies, if the patients were agitated or tachypneic upon awakening, they were returned to continuous sedation with the dose adjusted to half the initial rate and then titrated to the goal rate or dose. However, in the trial by Girard et al, patients who performed well off sedation continued to receive no sedation for as long as they were not anxious or agitated. Another difference between the 2 studies was that sedation for both groups in the study by Girard et al was titrated to “patient comfort” rather than to a score on the Ramsay scale.

In 2010, a prospective follow-up trial by Jackson et al was conducted to evaluate the impact of the ABC trial intervention on cognitive and psychological measures in 80 patients. The results indicated that although less sedation was achieved in the intervention group (as measured by days in coma), the control group had only a slight, nonsignificant increase in the incidence of PTSD (P = .59) at 3 months and no difference at 12 months (P = .97) after discharge (see Table). In addition scores on the Posttraumatic Stress Scale-10 (another measure of PTSD symptoms) did not differ between the 2 groups at either evaluation (P = .83 and P = .60, at 3 and 12 months, respectively). As in the study by Kress et al, depression was unchanged at 12 months. Less cognitive impairment was observed in the intervention group than in the control group at 3 months (P = .03), but this difference had disappeared by the 12 month follow-up.

In 2009, Treggiari et al attempted to determine the impact of sedation on psychological outcomes by randomizing patients to either light (score 1-2) or deep
The signs and symptoms of PTSD may be a reflection of the intentionally amnestic qualities of sedation.

differed significantly in their responses to “trouble remembering important parts of the stressful experience” and the frequency of “repeated, disturbing memories.” Despite these differences, the incidence of PTSD overall did not differ between the groups (P = .83). As in the other studies,23,24 measurements of anxiety and depression were similar between groups. Of note, the psychological assessments in the study by Treggiari et al17 were performed 4 weeks after patients’ discharge from the hospital, so the data provided information on the acute form of PTSD but not on the delayed-onset type.

The most recent evaluation of PTSD after sedation was a randomized control trial18 in which patients had either continuous infusion of midazolam for sedation with daily interruptions in sedation (control) or had analgesosedation (intervention). Patients in the intervention group received pain medication in the form of morphine boluses and haloperidol as needed for delirium but no sedative agents. Patients who were delirious and agitated in either group were assigned a bedside sitter. Of the 26 patients who completed follow-up, no significant differences in PTSD or symptoms were detected. One patient in the intervention group and no patients in the control group had a score on the Posttraumatic Stress Scale-10 suggestive of PTSD (P = .14). A total of 2 patients in the control group and 1 patient in the intervention group had an Impact of Events score suggestive of PTSD (P = .50). Overall, the incidence (0%-8%) of PTSD in both groups in this study18 was lower than the incidence in the other studies7,16,17 or in epidemiological data.13

Effect of the Intervention on Exposure to Sedatives

Despite differences in dosing strategy and sedative agents, interventions were consistently associated with a decrease in the use of midazolam or the broader category of benzodiazepines (values not reported). No difference was found in amounts of propofol or dexmedetomidine.

Limitations of Research

As a whole, the biggest limitation of these 4 studies is heterogeneity in protocols and measurements. Most strikingly, the sedation goal (Ramsay score 3-4) for the intervention group in the study by Kress et al7 was the same as the deep sedation control group in the 2 later studies by Treggiari et al17 and Strøm et al.18 Also, different measures were use to assess PTSD or its symptoms; in an earlier study,7 the investigators used scoring tools based on definition of PTSD in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (see Table). Timing of follow-up may also have confounded results; the time of evaluation was from 4 weeks to 2 years after ICU discharge. This lack of consistency across studies prevents meta-analysis and may explain some differences in results (see Discussion section).

Although the studies were well-designed, the one by Strøm et al18 had several limitations that should be considered in evaluating the results. Differences in care such as the 1 to 1 staffing ratio in their study and standard staffing in US ICUs might affect the study’s external validity. This trial18 also had a high rate of dropouts; commenting on this, Griffiths19 noted that patients who declined to have psychological follow-up might represent a highly vulnerable population. Perhaps most importantly, the negative results of this trial18 are not surprising given the small sample size and low rates of PTSD, factors that could lead to a type II error.

Another possibility that should be considered in interpreting the results of all these studies7,16-18 is that the measurement of PTSD and its symptoms may be less specific after an episode of sedation. Mainly, the signs and symptoms of PTSD, which include difficulty remembering factual events as a defining feature, may be a reflection of the intentionally amnestic qualities of sedation. This characteristic would partially explain the increased positive responses in the avoidance/numbing domain of PTSD symptom assessment, although not the questions about delirious or intrusive memories. The unaffected
Depression, cognitive capacity, and anxiety scores support this line of reasoning to some degree.

Discussion

Despite differences in methods and outcomes in these studies, the results can be used to guide practice and research. Several statements are reasonably well-supported by the evidence.

First, lower levels of sedative exposure do not seem to increase the incidence of PTSD. Although this relationship was not examined explicitly, patients in the intervention groups of all 4 studies had less sedative exposure than did patients in the control group. This finding is consistent with findings from an observational study by Weinert and Sprenkle, who reported no correlation between sedative exposure per body weight and PTSD incidence or symptoms.

In the studies that included a variety of sedative agents, the finding that sedative exposure differed only for those patients sedated with benzodiazepines suggests the possibility that use of midazolam alone, rather than sedation or sedatives in general, may be responsible for the increased PTSD symptoms in the control groups of the studies by Kress et al and Treggiari et al. Although the link between benzodiazepines and PTSD is speculative, other investigators have identified use of benzodiazepine as a risk factor for delirium, and delirium or delirious memories could plausibly lead more often to PTSD. Additionally, benzodiazepines can have a prolonged half-life in critically ill patients. Although the findings from a recent meta-analysis raise questions about the relationship between these medications and delirium, the Society of Critical Care Medicine 2013 guidelines, based on available evidence, state that “sedation strategies using nonbenzodiazepine sedatives may be preferred over sedation with benzodiazepines.”

As a second point, increased alertness does not seem to increase incidence of PTSD or PTSD symptoms. Despite differences in sedation goals, this finding was consistent in all 4 studies I examined and has been incorporated into much of the literature in favor of sedation-interruption protocols. Of note, the study with the smallest sample size, and the only study that included analgosedation, most likely was underpowered to confirm this assertion.

Results from the study by Weinert and Sprenkle are again largely consistent with the notion that increased alertness does increase incidence of PTSD or PTSD symptoms, and may provide insight into the development of PTSD. Weinert and Sprenkle found that PTSD symptoms were highest in the groups with intermediate or fluctuating levels of wakefulness (sedation scores not provided) and lower for patients who were more consistently deeply sedated or completely alert and that the alert group was the least affected. A possible explanation for the relationship between alertness and PTSD symptoms is that memory of pain, lack of control, and inability to express needs were among the independent risk factors for PTSD. Similarly, in a qualitative study, Rattray et al found that patients who were less aware of the surroundings or who had frightening experiences had more PTSD symptoms after discharge than did other patients. A reasonable inference based on these various findings is that being moderately sedated may make expressing one’s needs and wishes more difficult without having a corresponding therapeutic effect, although this possibility was not explicitly investigated.

The question provoked by the earliest study, “Does decreased sedation prevent PTSD or its symptoms?” is still unanswered. Although the findings of Treggiari et al support this hypothesis to some extent, the findings of Jackson et al and Strom et al do not. Some possible reasons include differences in use of midazolam, PTSD measurement tools, follow-up, sampling, and mortality. However, a discussion of the reasons why Jackson et al were unable to replicate the findings of Kress et al despite overall similarity is important. One would expect that the interventions used by Jackson et al, awakening with the goal of stopping sedation, would produce a greater difference in the sedation levels between the control and intervention groups than the difference in sedation levels between the control and intervention groups seen in the Kress et al trial. The most probable explanation is that both Jackson et al and Kress et al compared interventions with standard treatment. As Mehta et al note in their discussion of a recent trial of daily sedation interruption, “The effectiveness of any new intervention to minimize sedation likely depends on the local usual care.” Because lighter sedation strategies had not yet been popularized at the time of the study...
by Kress et al,7 the difference in sedation they noted most likely would have been more dramatic than the difference in the later study by Jackson et al.16 This change in practice is important to keep in mind when evaluating analgosedation; the potential psychological benefits of lighter sedation may have been already been realized with current sedation practices.

Current practice guidelines,25 in agreement with the evidence reported here, do reflect a goal of light sedation, which is defined as easily arousable and able to follow commands. Protocols with goals of light sedation or daily interruptions in sedation should not be suspended to keep patients from consciously experiencing or remembering the ICU course. Education on the relationship between PTSD and sedation could increase acceptance of current sedation goals. Perhaps most importantly, ICU care should be performed with awareness of the potential for memory formation even in sedated or non-communicative patients.

Sedative exposure differed only for those patients receiving benzodiazepines.

Changes in Practice

No evidence yet suggests that trials of analgosedation are unethical from the standpoint of PTSD outcomes. In fact, the low overall rates of PTSD in the study by Strøm et al18 may have introduced a novel method of reducing the occurrence of PTSD: the bedside sitter for patients with agitation. Although use of a sitter may seem impractical, it does suggest a potential role for psychosocial intervention. Training a patient’s family members and having their presence at the bedside, for example, may be one way to improve the patient’s autonomy and comfort.

Caveats

A number of important qualifiers must be added to the previous statements. First, sedation goals should be adjusted according to both patient safety (including risk for injury, self-extubation, noncompliance with the ventilator, and increased intracranial pressure) and patient comfort. The investigators in the studies I examined did not evaluate the immediate consequences of lighter sedation. Agitation or anxiety should not be allowed to escalate in any patient. Importantly, practitioners should not assume that present distress off sedation will be balanced by a future free of PTSD, because such a balance has not been demonstrated. In one study,33 duration of agitation in restrained, nonsedated patients was positively associated with higher incidence of PTSD.

Second, adequate pain control is assumed. Third, adequate staffing to monitor and respond to patients with agitation or safety concerns is assumed. In studies7,16 of daily interruptions in sedation, additional monitoring was provided, and in the study18 with analgosedation, in addition to 1 to 1 staffing ratios, patients had an as-needed bedside sitter. Finally, the effects of sedation on PTSD have not been studied in subsets of patients (eg, neurosurgical or burn patients), so the findings presented here may not hold true for such patients.

Gaps in Research

The links between sedation, delirious memories, and PTSD are not well established. A recent meta-analysis24 of 34 studies indicated that although delirium alone is not correlated with PTSD, whether or not memories of delirious episodes are contributory is unclear. As Weinert and Sprenkle20 suggest, the character of the ICU experience may have a greater influence on psychological outcomes than the level of sedation does. More could be gleaned from an analysis of the subscale results in each PTSD symptom tool and from validation of these tools in patients after discharge from the ICU. Additionally, interventions that decrease delirium or helplessness in patients treated with mechanical ventilation could be evaluated for their effect on PTSD. Ongoing research on survivorship34,35 has already begun to address the most important outcomes from these studies:3,4,26 the need to decrease frightening and distressing events in the ICU. As in the study by Strøm et al18 evaluations of novel sedation protocols should include psychological assessment and follow-up when possible.

Conclusion

The psychological effects of daily interruptions in sedation, lighter sedation, or analgosedation are not clear. The provocative relationship between PTSD symptoms and sedation, in particular, use of midazolam, is an evidence-based challenge to the traditional practice of putting patients “to sleep.” Meanwhile, an intriguing new strategy, analgosedation, is being studied as an alternative to light-to-moderate sedation. Nurses remain the essential providers in the assessment of and response to the constantly changing sedation needs of their patients;
nurses are responsible for balancing goals for sedation with concerns about hemodynamic, neurological, and ventilatory compromise. While research on ICU survivorship continues, current evidence shows no increased risk for PTSD in patients who have light sedation. CCN

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References
CCN Fast Facts

Sedation and Its Association With Posttraumatic Stress Disorder After Intensive Care

Facts

- A diagnosis of posttraumatic stress disorder (PTSD) requires the presence of persistent signs and symptoms in each of 3 categories: hyperarousal, intrusive recollections, and avoidance/numbing. The reported prevalence of PTSD after intensive care unit (ICU) care is 19% to 22%, and occurrence of the syndrome is associated with a marked adverse effect on health-related quality of life.
- In the most recent evaluation of PTSD after sedation, patients had either continuous infusion of midazolam for sedation with daily interruptions in sedation (control) or had analgosedation (intervention). No significant differences in PTSD or symptoms were detected.
- Lower levels of sedative exposure do not seem to increase the incidence of PTSD. Although this relationship was not examined explicitly, patients in the intervention groups of all studies reviewed in the article had less sedative exposure than did patients in the control group.
- In the studies reviewed in the article that included a variety of sedative agents, the finding that sedative exposure differed only for those patients sedated with benzodiazepines suggests the possibility that use of midazolam alone, rather than sedation or sedatives in general, may be responsible for the increased PTSD symptoms in the control groups of 2 of the studies.
- Second, increased alertness does not seem to increase incidence of PTSD or PTSD symptoms. Despite differences in sedation goals, this finding was consistent in all 4 studies reviewed in the article and has been incorporated into much of the literature in favor of sedation-interruption protocols.
- Current practice guidelines, in agreement with the evidence reported here, do reflect a goal of light sedation, which is defined as easily arousable and able to follow commands. Protocols with goals of light sedation or daily interruptions in sedation should not be suspended to keep patients from consciously experiencing or remembering the ICU course. Education on the relationship between PTSD and sedation could increase acceptance of current sedation goals. Perhaps most importantly, ICU care should be performed with awareness of the potential for memory formation even in sedated or noncommunicative patients.
- An intriguing new strategy, analgosedation, is being studied as an alternative to light-to-moderate sedation. Although use of a sitter may seem impractical, it does suggest a potential role for psychosocial intervention. Training a patient’s family members and having their presence at the bedside, for example, may be one way to improve the patient’s autonomy and comfort.
- Nurses remain the essential providers in the assessment of and response to the constantly changing sedation needs of their patients; nurses are responsible for balancing goals for sedation with concerns about hemodynamic, neurological, and ventilatory compromise. While research on ICU survivorship continues, current evidence shows no increased risk for PTSD in patients who have light sedation.