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Outcomes/Prediction

# Implementation of a protocol for integrated management of pain, agitation, and delirium can improve clinical outcomes in the intensive care unit: A randomized clinical trial

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ABSTRACT

*Background:* Inappropriate diagnosis and treatment of pain, agitation, and delirium (PAD) in intensive care settings results in poor patient outcomes. We designed and used a protocol for systematic assessment and management of PAD by the nurses to improve clinical intensive care unit (ICU) outcomes.
*Materials and Methods:* A total of 201 patients admitted to 2 mixed medical-surgical ICUs were randomly allocated to protocol and control groups. A multidisciplinary team approved the protocol. Pain was assessed by Numerical Rating Scale and Behavioural Pain Scale, agitation by Richmond Agitation Sedation Scale, and delirium by Confusion Assessment Method in ICU. The Persian version of the scales was prepared and tested for validity, reliability, and feasibility in a preliminary study. The patients in the protocol group were managed pharmacologically according to the protocol, whereas those in the control group were managed according to the ICU routine.
*Results:* The median (interquartile range) for the duration of mechanical ventilation in the protocol and control groups was 19 (9.3-67.8) and 40 (0-217) hours, respectively ($P = .038$). The median (interquartile range) length of ICU stay was 97 (54.5-189) hours in the protocol group vs 170 (80-408) hours in the control group ($P < .001$). The mortality rate in the protocol group was significantly reduced from 23.8% to 12.5% ($P = .046$).
*Conclusion:* The current randomized trial provided evidence for a substantial reduction in the duration of need to ventilatory support, length of ICU stay, and mortality rates in ICU-admitted patients through protocol-directed management of PAD.



## 1. Introduction

Pain is considered a dominant stressor and a main concern to critically ill patients admitted in the intensive care unit (ICU) with a quite high prevalence of 50% in medical and surgical patients [1,2], yet it is a poorly defined entity particularly because of its subjective nature, which can only be truly reported by the individual who is experiencing it. Most ICU-admitted patients are incapable of reporting their pain because of low level of consciousness, mechanical ventilation, neuromuscular blockage, or deep sedation [3]. Meanwhile, there is always concern over the development of drug dependency to pain-controlling medications, which creates great stress for the patients, their families, and health care staff [4].

Uncontrolled pain can have harmful effects on the function of different body systems, most notable of which are cardiovascular, respiratory, musculoskeletal, and, above all, mental function [5]. Several studies have demonstrated sleep deprivation, fatigue, anxiety, agitation, delirium, and increase in undesirable incidents such as self-extubation as the mental consequences of inadequate pain treatment [6,7]. The ultimate goal for pain management is producing pain-free calm patients [8] and therefore reducing pain-mediated agitation or delirious episodes. Poor pain control also results in severe agitation and further complicates the patient's condition. There are substantial consequences to inadequate control of pain and agitation such as aggressive behavior, self-removal of important tubes and catheters, and patient-ventilator asynchrony [9].

Agitation is usually treated by administration of sedatives to reduce patient's awareness to a sufficient level and induce amnesia. An inherent risk of agitation treatment is prolonged or excessive sedation, which significantly compromises caregivers' control over patient's level of consciousness and increases the duration of ICU stay [10]. Therefore, the optimal goal in agitation treatment would be

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creating manageable short episodes of tranquility, which would improve the quality of sedation and provide easier control over the patient's level of consciousness [11].

*Delirium* is defined as a syndrome characterized by acute change or fluctuation in an individual's mental status accompanied by disorganized thinking, inattention, or altered level of consciousness [12]. The prevalence of delirium has been reported from 20% to 80% in medical and surgical ICUs. However, delirious state is usually underdiagnosed [13], particularly in mechanically ventilated and deeply sedated patients because of a lack of proper patient-staff communication [14,15]. Frequent fluctuations in patient's sedation levels and changes in mental status as well as disproportionate exposure to pain medication are suggested to be linked to a rise in the incidence of delirious state [16]. Delirium is commonly accompanied by ventilation complications, nosocomial pneumonia, and self-extubation [12]. It may also prolong the duration of hospital stay and increase the need for nursing care and mortality rate [14,17,18]. Long-lasting untreated delirium could be quite dangerous by leaving long-term cognitive impairment and major psychological sequels for the patients [1].

Apparently, pain, agitation, and delirium (PAD) are 3 entirely distinct but closely interrelated entities. Existence of a tight link between PAD necessitates proper management of each individual issue because underdiagnosis or mismanagement of any of them would lead to drastic complications in the other 2 and, ultimately, poor patient condition. Satisfactory outcomes can be obtained by detection, quantification, and treatment of PAD in the ICU patients with or without mechanical ventilation by using a reliable and valid policy [1,12,19]. Devising efficient and self-reliant protocols is a key to effective management strategies.

In the literature, there are a number of protocols for management of PAD, individually. The American Association of Critical Care Medicine and Society of Critical Care Medicine have recently released a multidisciplinary, evidence-based guideline for management of PAD in adult ICU patients [20]. This study started well before the publication of this document; however, the protocol used in our study is largely compatible with the provided recommendations.

Most of the studies in the field of PAD in ICU patients either focus on one of these issues or are before-after studies, comparing historical outcomes with new ones after the intervention. We aimed to design a prospective parallel-group, randomized, clinical trial after implementing a multidisciplinary generated PAD protocol in 2 mixed medical-surgical ICUs. To the best of our knowledge, this study is among the very few studies carried out in this field, thus far [21,22].

## 2. Methods

The present randomized controlled clinical trial was aimed to design and implement a collective PAD protocol and to evaluate its effects on the outcome of patients hospitalized in 2 mixed university-affiliated ICUs of Namazi Hospital, Shiraz, Iran. The study was approved by the ethics committee of the Shiraz University of Medical Sciences and registered in the Iranian Registry of Clinical Trials. All patients older than 18 years who were admitted in the 2 ICUs (central and general ICU) were screened for eligibility. Admissions were caused by trauma, surgical (postoperative), neurologic, medical, and cardiovascular problems. Written informed consents were obtained from the families (because of patients' low level of consciousness), and the patients were randomly assigned to the protocol or the control group based on a computer-generated table of random numbers. Patients were excluded if they had ICU stay less than 24 hours, were expected to die in less than 48 hours, had received muscle relaxant, received anticonvulsant drugs for convulsion, had psychological illness, or had upper extremity paralysis or immobilization in cast.

Pain was assessed by Behavioural Pain Scale (BPS) in the patients who were under the support of mechanical ventilation, BPS nonintubated in those who were noncommunicating but not under mechanical ventilation, and Numerical Rating Scale (NRS), when feasible. The level of agitation was evaluated by Richmond Agitation Sedation Scale (RASS), and the patients were assessed by Confusion Assessment Method in ICU (CAM-ICU) to determine whether delirium existed or not. Patients' Acute Physiology and Chronic Health Evaluation IV (APACHE IV) score was recorded within the first 24 hours of arrival to the ICU.

Initially, BPS, RASS, and CAM-ICU were translated to Persian by 1 of the researchers and revised by 8 experts of the field. Then, they were back translated to English by a translator familiar with medical terminology, and the draft was then compared with the original one by the first group, and the final versions were prepared. To determine the validity and reliability of the translated versions, a nurse and the researcher evaluated 30 ICU patients were evaluated using each of the scales. Each patient was simultaneously assessed by 2 investigators. Pearson correlation coefficients obtained were 0.88 and 0.92 for BPS and RASS, respectively. In addition, $\kappa$ coefficient of CAM-ICU was 0.88. All nurses working in 2 ICUs were trained to check the scores in 3 separate sections, and all questions were addressed during a 1-month period. The nurses were also encouraged to participate in the project by both financial and nonfinancial incentives.

In the next step, the researchers searched the Web for protocols and guidelines for the management of PAD from 1998 up to 2010. A new protocol was designed and developed after discussions in several group meetings including 3 intensivists, a neurologist, a clinical pharmacist, a psychiatrist, and 2 ICU nurses. It is noteworthy to mention that the major part of the final protocol was extracted from ICU sedation guideline from San Diego Patient Safety Council [23]. The protocol was taught to the nurses during 3 educational sections. The knowledge and skill of the nurses on PAD scores and use of the protocol were tested twice (once during the first and another during the fourth month of the study), and appropriate feedbacks were provided.

The patients in the protocol group were evaluated by BPS/NRS and RASS every 1 hour by CAM-ICU every working shift and whenever it deemed to be needed by the nurse's discretion. Then, each patient was treated according to the approved protocol based on the scores obtained by the scales. The protocol was designed to keep BPS less than 5, NRS less than 3, and RASS score between $-1$ and $+1$ (light sedation). The protocol also followed a first-analgesia policy but did not include any daily sedation interruptions.

The nurses had the authority to adjust the analgesic and sedative drugs according to the protocol to keep the pain and agitation scores within the acceptable range. Also, if the delirium was positive, the patients were treated according to the protocol. All scores and administered medications were recorded. In the control group, pain and sedation were managed as routine according to as-needed physician orders without regular assessment for pain or sedation. No screening for delirium was done in the control group, too. All used medications in the control group were recorded in the designated forms. During the study, adherence to the protocol was monitored by 1 of the researchers and 2 assistants at all the shifts. The targeted outcomes included ICU length of stay in hours, duration of mechanical ventilation in hours, all-cause mortality rate in ICU, the number of self-extubations, the effectiveness of the protocol to control PAD, and dose of the drugs used for treating these complications.

Data were analyzed by SPSS statistical software version (SPSS, Chicago, Ill) [21] using the $\chi^2$ test, $t$ test, and the Mann-Whitney $U$ test. The differences were considered statistically significant when $P$ values were .5 or less. Data were described in mean $\pm$ SD or median and interquartile range (IQR).

## 3. Results

During the 9-month period of the study, 329 patients were admitted in these wards. One hundred seven patients did not fulfill the inclusion criteria, and 6 patients did not consent. A total of 216

**Table 1**
Comparison of the demographics and main outcomes of the study between the control and protocol groups

| | Control group (105 patients) | Protocol group (96 patients) | *P* |
|---|---|---|---|
| APACHE IV score, mean (SD) | 75 (33) | 86 (30) | .9 |
| Male (%) | 62.9 | 63.5 | .92 |
| Postoperative admission (%) | 64.7 | 77 | .064 |
| Duration of ICU stay (h), median (IQR) | 170 (80-408) | 97 (54.5-189) | <.001 |
| Duration of ventilatory support (h), median (IQR) | 40 (0-217) | 19 (9.3-67.8) | .038 |
| Mortality rate | 23.8% | 12.5% | .046 |
| Incidence of self-extubation | 2.08% | 2.98% | .684 |

patients were enrolled in the study and randomly assigned to either the control group (n = 105) or the protocol group (n = 111). Fifteen patients were excluded from the protocol group because of violation of the protocol by the nurses (13.5%). Analysis of the data was performed on 201 patients (96 in protocol group). Mean ages of the patients in the protocol and control group were 52.9 ± 20 and 52.9 ± 20.2 years, respectively ($P = .77$). The APACHE IV scores did not differ between control and protocol categories (75.5 vs 74.9, $P = .9$). In both groups, about 63% of the patients were male, and no significant difference was observed in sex distribution ($P = .92$). The admission diagnosis was surgical in 77% of the protocol group and 64.7% of the control group, respectively.

The distribution of data was not normal for ICU length of stay and duration of ventilator therapy in the 2 groups, so we used median and IQR and the Mann-Whitney test for comparison of these indices. Intensive care unit stay was longer in the control group than in the protocol group (170 [80-40.8] hours vs 97 [54.5-189] hours, respectively; $P < .001$), as was the mean ventilator time (40 [0-217] hours vs 19 [9.3-67.8] hours in the control vs protocol groups, respectively; $P = .038$). The mortality rate was higher (23.8%) in the control group than in the protocol group (12.5%; $P = .046$). There was no significant difference between the 2 study groups regarding the number of extubations (2 in control vs 4 in protocol, $P = .684$; Table 1).

Drugs that were used to treat PAD are shown in Table 2. According to the findings, there were no difference between the 2 groups regarding need for intravenous morphine sulfate, sufentanil, and acetaminophen for control of pain, but fentanyl was used more in the control group ($P < .001$). Also, there was no difference between the 2 groups regarding need to midazolam for control of agitation, but more propofol was used in the control group than in the protocol group ($P < .001$). The administered haloperidol for the management of delirium was not different between groups ($P < .12$; Table 1).

Overall, 84% of patients in protocol group were almost pain-free (NRS <1, BPS <4), 11% had mild pain (NRS 1-3, BPS 4-5), 3% had moderate pain (NRS 4-7, BPS 6-8), and only 2% experienced severe pain (NRS 8-10, BPS 9-12) over the total hours of the studied ICU stay. Hence, the patients in the protocol group had acceptable pain (mild or no pain) during 95% of the time of their ICU stay. Moreover, during 65% of ICU stay, the patients in the protocol group were reported to be in a calm and conscious state (RASS score 0; 65.6%) and in a desirable agitation-sedation status (RASS score −1 and +1) for their ICU stay (72% of the total hours). Delirium occurred in 8.5% of the patients in the protocol group. The frequency of PAD in the control group was not measured according to ICU routines.

## 4. Discussion

Our findings show that the design and implementation of a multidisciplinary PAD protocol in 2 mixed medical-surgical ICUs in a referral teaching hospital in a country with low allocated health care resources are both feasible and effective to improve some functional indices of the ICU. This result has a significant clinical importance because although many observational studies show that ensuring patient comfort while maintaining light levels of sedation will improve clinical outcomes [6,24-27], there are a lot of cultural, resource, and manpower differences across the world that make such quality improvement interventions difficult to implement [28-33].

To start this study, first, we needed valid and reliable bedside assessment tools to measure pain, sedation, agitation, and delirium in ICU patients. Although self-report by the patient has been considered the "gold standard" for assessment of pain, we could only use it (NRS) in just a few numbers of our patients. Although a lot of well-known scores do exist, to the best of our knowledge, there are no comparative studies regarding validity, reliability, and feasibility of different pain assessment tools in ICU.

We selected BPS because according to a recent review, it is one of the most valid and reliable tools for the evaluation of pain in ICU patients [34]. The BPS evaluates 3 behavioral domains (ie, facial expression, movements of upper limbs, and compliance with ventilator). Each domain contains 4 descriptors that are rated on a 1- to 4-point scale, and the total BPS value can range from 3 (no pain) to 12 (most pain). Because it was available in only English and French, we translated and validated it in a ministudy conducted by the researcher. We obtained assistance from 8 clinical experts and 1 linguist to translate and back-translate the BPS and found a good Spearman rank correlation coefficient of 0.88 when 2 observers assessed the patients. However, because probably this was the first time that the score was used in Persian, one should consider the need for more studies to validate this translation in our region in different settings and ICU patients.

We are not aware of the incidence of pain in the control group. We made the decision to not to evaluate pain systematically in the control group in an effort to make the least possible intervention in the comparator arm of the study. However, according to multiple previous studies, the incidence of pain in medical and surgical ICUs is more than 50% [35,36]. We noticed that the patients in the protocol group were almost pain-free in 84% of the recorded pain scores during their ICU stay. This observation, by itself, may recommend a high success rate for our pain control protocol; however, it should be interpreted with 2 limitations in mind. First, we did not evaluate the patients during the routine painful ICU procedures, and second, the pain score was just recorded in a predetermined manner—our intervals and some painful states between these intervals may have been missed.

We used RASS to assess sedation level in our patients because the validity and reliability of it have been confirmed in many studies [10,37]. It is a 10-point score from unresponsive (−5) to combative (+4). We also translated and validated the Persian version of RASS in a preliminary study in 30 adult ICU patients and found a good interrater reliability with a correlation coefficient of 0.92. Our sedation

**Table 2**
Comparison of the amounts of drugs used for controlling PAD in the control and protocol groups

| Drug used | Mean dose of drug used per each patient | | *P* |
|---|---|---|---|
| | Control group, mean (SD) | Protocol group, mean (SD) | |
| Pain | | | |
| Morphine (mg) | 24.3 (53.4) | 20.9 (11.4) | .77 |
| Fentanyl (μg) | 1002.4 (3774.4) | 63.1 (161.0) | .001 |
| Sufentanyl (μg) | 12.4 (64.2) | 28 (2) | .28 |
| Acetaminophen (mg) | 289.8 (1387.0) | 187.8 (825.7) | .65 |
| Agitation | | | |
| Midazolam (mg) | 50.4 (144.5) | 8.0 (14.2) | .061 |
| Propofol (mg) | 111.8 (487.3) | 14.4 (85) | .001 |
| Haloperidol (mg) | 3.2 (14.3) | 0.7 (3.5) | .12 |
| Delirium: haloperidol (mg) | 2.2 (20.0) | 0.1 (0.7) | .46 |

protocol included the analgesia-first policy, which means that the patients were evaluated and treated for pain as a cause of restlessness at the outset. The target of our protocol was drowsiness to restlessness (RASS −1 to +1) because many studies have shown the negative outcomes of deep and prolonged sedation and positive results of lighter sedation in adult ICU patients [38-40]. We were relatively successful to achieve this goal because in about 72% of the total observations, our patients were in the acceptable sedation range. This success may be partly explained by adequate check and control of pain and agitation of the patients by our nursing staff (every 1 hour) and a convenient PAD protocol.

Confusion Assessment Method in the ICU is among the most reliable tools for evaluating delirium in both ventilated and nonventilated adult ICU patients [41,42]. We translated and validated this test in our patients, too. This score could be used in any patient with a RASS score more than −4 (arousable) and nonverbal methods to detect major criteria of delirium (acute fluctuations of level of consciousness, inattention, and disorganized thinking) in ICU patients. Our staff checked the patients for the presence or absence of delirium according to CAM-ICU at least once in a working shift and when it deemed necessary.

We did not check the control group systematically for the detection of delirium in this study; however, the incidence of delirium, measured by CAM-ICU in a previous study in our ICU, was about 18% (unpublished data). Although 2 major risk factors for delirium—age and severity of illness on admission (APACHE score)—were similar in both groups, we cannot comment on the impact of our protocol on reducing the incidence of delirium in our patients because we are not aware of the exact incidence of this complication in the control group.

The key question of this study was if approving and implementation of a PAD protocol in our ICU is feasible and can improve major ICU outcomes. First, we detected a relatively good compliance by our ICU staff of 85% after a short course of teaching and addressing their questions. We consider this figure acceptable, a our nursing staffs were completely unfamiliar with both the scoring systems and the protocol before this study. This result was attractive because according to the previous studies, only 60% of ICUs in the United States have integrated PAD protocols, and even in those who have it, the rate of adherence to the protocol is low [43,44].

Our findings revealed that the length of ICU stay could be reduced significantly from a median of 170 hours in the control group to 97 hours in the protocol group. This means an absolute reduction in ICU length of stay by about 3 days, which is of paramount importance, especially in countries with low resources allocated to health system and low availability of ICU beds as ours. The positive influence of the implementation of PAD protocols on the ICU length of stay is well established in previous studies [19,21,38,45]. The main reason seems to be the impact of the protocol implementation on avoiding deep levels of sedation and lower incidence of delirium in patients [46].

Most previous studies have demonstrated the positive impact of ICU sedation protocols on decreasing the duration of need to mechanical ventilation [38,39]; however; we did not detect such effect in our patients. This difference could be attributed to a variety of reasons including the strong impact of other variables such as incidence of ventilator-associated pneumonia, which was not measured in this study. Moreover, we did not have an implemented ventilator weaning policy that may negatively influence the precision of our results.

In comparison with the control group, the mortality rate was significantly lower in the protocol group in the current study. The lower mortality rate in the PAD group could be justified by a lower length of ICU stay in this group. On the other hand, according to previous studies [47-49], both the decreased length of stay and lower mortality in the protocol group could be partly explained by the possibility of a lower incidence of delirium in this group.

Our PAD protocol recommended opioids as first-line pain treatment and intravenous acetaminophen as adjuvant to opioids. According to the protocol, fentanyl or sufentanil was administered, instead of morphine, to the patients who were expected to have a short ICU stay (<48 hours), were experiencing neurologic problems and kidney failure, and were hemodynamically unstable. The average dosage of morphine, sufentanil, and acetaminophen used for control of pain in both groups was not different statistically, but less fentanyl was used in the protocol group. A significant reduction in analgesic consumption as the result of PAD protocol implementation has been reported in other studies [19,21]. This observation may warn us about inappropriate use of analgesics to control non–pain-induced agitations in the control group. To prove this theory, more confirmatory studies are needed.

Based on the designed protocol, midazolam, propofol, or haloperidol was given to the patients for control of agitation. Propofol was used in patients with neurologic problems who needed frequent evaluation of the level of consciousness, renal insufficiency, and predicted length of stay of less than 48 hours. Halopridol was preserved for sedation of patients if they had more than 3 risk factors for the development of delirium. Although midazolam and haloperidol consumption did not differ between the 2 groups, propofol consumption was significantly reduced in the protocol group. Similarly, Robinson et al [19] and Skrobik et al [21] reported considerable reductions in administered lorazepam doses in their intervention patients, too. This result is not difficult to interpret because many studies have shown that most ICUs apply an unwritten protocol of deep sedation of patients for “humanistic” reasons [20]. Hence, it is not a surprise if a PAD protocol that targeted to maintain light levels of sedation would result in less consumption of sedatives. This effect is reasonably more profound when short-acting drugs such as propofol, which are easier to titrate, are used.

We could not detect any significant difference between the 2 groups regarding the drugs used for control of delirium. This finding is not unpredictable owing to low incidence (8.5%) of delirium in the PAD group. Most probably, a larger sample size is needed to detect a significant difference, when relatively rare incidents are studied.

In addition to previously mentioned restrictions, some other limitations of our study merits to be mentioned. As a randomized clinical trial, the most undesirable problem was that both patients and health care providers were not blinded to the group assignment, so the results may be biased. The Persian version of the tools to measure PAD, BPS, RASS, and CAM-ICU was not validated robustly in separate psychometric studies. This limitation, although would require separate clinical investigations, is less likely to affect our results because the positive effect of our PAD protocol on some ICU outcomes is unarguable. We also did not monitor the patients for some short-term outcomes of the PAD protocol such as hemodynamic variability and sleep quality as well as long-term outcomes such as hospital length of stay and hospital mortality. We did not also analyze the impact of our protocol implementation on health care costs.

Overall, the findings of the present study showed that implementing a well-designed protocol that involves regular and precise monitoring of PAD, along with appropriate and timely medical therapy, can be of great help in improving the medical care provided by the ICU team. Obviously, our nursing staff had a central role in the implementation of the PAD protocol. More studies on the effect of such protocols on long-term ICU outcomes are noteworthy.

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## References


[1] Sessler CN, Varney K. Patient-focused sedation and analgesia in the ICU. Chest 2008;133:552–65.
[2] Kaplow R, Hardin SR. Critical care nursing synergy for optimal outcomes. Jane and Batlett publishers; 2007.
[3] Shannon K, Bucknall T. Pain asessment in critical care: what have we learnt from research. Intensive Crit Care Nurs 2003;19:154–62.
[4] Marton PC, Fontaine DK, Gallo BM and Hudak CM. Critical care nursing a holistic approach. 8th ed. Lippincot Williams Wilkins; 2005.
[5] Astle SM. Pain management in critically ill obese patients. Crit Care Nurs Clin 2009;21:323–39.
[6] Mehta S, Burry L, Martinez-Motta JC, Stewart TE. A randomized trial of daily awakening in critically ill patients managed with a sedation protocol: a pilot trial. Crit Care Med 2008;36(7):2092–9.
[7] Urden LD, Stacy KM and Laugh ME. Critical care nursing diagnosis and management. 6th ed. St Louis: Mosby Elsevier; 2010.
[8] Hofso K, Coyer FM. Part 1.Chemical and physical restraints in the management of mechanically ventilated patients in the ICU: contributing factors. Intensive Crit Care Nurs 2007;23:249–55.
[9] Woien H, Stubhaug A, Bjork IT. Analgesia and sedation of mechanically ventilated patients—a national survey of clinical practice. Acta Anesthesiol Scand 2012;56: 23–9.
[10] Sessler CN, Gosnell MS, Grap MJ, Brophy GM, Oneil PV, Keane KA, et al. The Richmond Agitation Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;166:1338–44.
[11] Ramsay MAE, Savege TM, Simpson BRJ, Goodwin R. Controlled sedation with alphaxalone-alphadolone. BMJ 1974;2:656–9.
[12] Girard TD, Pandharipande PP, Ely EW. Delirium in the intensive care unit. Crit Care 2008;12(Suppl 3):S3.
[13] Ely EW, Inouye ShK, Bernard GR, Gordon Sh, Francis J, May L, et al. The validity and reliability of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). JAMA 2001;286(21):2703–10.
[14] Plaschke K, Haken R, Scholz M, Engelhardt R, Brobeil A, Eike Martin E, et al. Comparison of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) with the Intensive Care Delirium Screening Checklist (ICDSC) for delirium in critical care patients gives high agreement rate(s). Intensive Care Med 2008;34:431–6.
[15] Eijk MM J, Marum RJ, Klijn IA M, Wit N, Kesecioglu J, Slooter AJC. Comparison of delirium assessment tools in a mixed intensive care unit. Crit Care Med 2009; 37((6).
[16] Svenningsen H, Egerod I, Videbech P, Christensen D, Frydenberg M, Tonnesen EK. Fluctuations in sedation levels may contribute to delirium in ICU patients. Acta Anesthesiol Scand 2013;57:288–93.
[17] Wei LA, Fearing MA, Sternberg EJ, Inouye SK. The Confusion Assessment Method: a systematic review of current usage. JAGS 2008;56(5):823–30.
[18] Lin SH-M, Huang CH-D, Liu CH-Y, Lin H-CH, Chun-Hua W, Huang PY. Risk factors for the development of early-onset delirium and the subsequent clinical outcome in mechanically ventilated patients. J Crit Care 2008;23:372–9.
[19] Robinson BRH, Mueller EW, Henson K, Branson RD, Barsoum S, Betty J, et al. An analgesia-delirium-sedation protocol for critically ill trauma patients reduces ventilator days and hospital length of stay. J Trauma 2008;65:517–26.
[20] Barr J, Fraser GL, Puntillo K, Ely W, Gélinas C, Dasta JF, 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.
[21] Skrobik Y, Ahern S, Leblanc M, Marquis F, Awissi DK, and Kavanagh BP. Protocolized intensive care unit management of analgesia, sedation, and delirium improves analgesia and subsyndromal delirium rates. *Anesth Analg*, 2010. X.
[22] Bec l and Johnson Ch. Implementation of a nurse-driven sedation protocol in the ICU. *Dynamics*. 2008.
[23] ICU Sedation Guidelines of care. 2009. Available at: www.carefusion.com/center.
[24] Adam C, Rosser D, Manji M. Impact of introducing a sedation management guideline in intensive care. Anaesthesia 2006;61:260–3.
[25] 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;36:1444–50.
[26] Elliott R, McKinley S, Aitken LM, et al. The effect of an algorithm-based sedation guideline on the duration of mechanical ventilation in an Australian intensive care unit. Intensive Care Med 2006;32:1506–14.
[27] Treggiari MM, Romand JA, Yanez ND, et al. Randomized trial of light versus deep sedation on mental health after critical illness. Crit Care Med 2009;37:2527–34.
[28] Rello J, Lode H, Cornaglia G, et al. VAP Care Bundle Contributors: a European care bundle for prevention of ventilator-associated pneumonia. Intensive Care Med 2010;36:773–80.
[29] Tufano R, Piazza O, De Robertis E. Guidelines and the medical "art". Intensive Care Med 2010;36:1612–3.
[30] Bellomo R, Stow PJ, Hart GK. Why is there such a difference in outcome between Australian intensive care units and others? Curr Opin Anaesthesiol 2007;20: 100–5.
[31] Rello J, Lorente C, Bodí M, et al. Why do physicians not follow evidence-based guidelines for preventing ventilator-associated pneumonia? A survey based on the opinions of an international panel of intensivists. Chest 2002;122:656–61.
[32] Hicks P, Cooper DJ. The Australian and New Zealand Intensive Care Society (ANZICS) Board and Clinical Trials Group Executive Committee: the Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2008. Crit Care Resusc 2008;10:8.
[33] Orford NR, Faulkner C, Flintoff W, et al. Implementation and outcomes of a severe sepsis protocol in an Australian tertiary hospital. Crit Care Resusc 2008;10: 217–24.
[34] Pudas-Tähkä SM, Axelin A, Aantaa R, et al. Pain assessment tools for unconscious or sedated intensive care patients: a systematic review. J Adv Nurs 2009;65: 946–56.
[35] Chanques G, Sebbane M, Barbotte E, et al. A prospective study of pain at rest: Incidence and characteristics of an unrecognized symptom in surgical and trauma versus medical intensive care unit patients. Anesthesiology 2007;107:858–60.
[36] Payen JF, Chanques G, Mantz J, et al. Current practices in sedation and analgesia for mechanically ventilated critically ill patients: a prospective multicenter patient-based study. Anesthesiology 2007;106:687–95 quiz 891.
[37] Schulte-Tamburen AM, Scheier J, Briegel J, et al. Comparison of five sedation scoring systems by means of auditory evoked potentials. Intensive Care Med 1999; 25:377–82.
[38] 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: 2609–15.
[39] 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 randomised controlled trial. Lancet 2008;371:126–34.
[40] Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342: 1471–7.
[41] Tobar E, Romero C, Galleguillos T, et al. Confusion Assessment Method for diagnosing delirium in ICU patients: cultural adaptation and validation of the Spanish version. Med Intensiva 2010;34:4–13.
[42] Larsson C, Axell AG, Ersson A. Confusion Assessment Method for the Intensive Care Unit (CAM-ICU): translation, retranslation and validation into Swedish intensive care settings. Acta Anaesthesiol Scand 2007;51:888–92.
[43] Mehta S, McCullagh I, Burry L. Current sedation practices: lessons learned from international surveys. *Crit Care Clin* 2009; 25:471–488, vii.
[44] Tanios MA, de Wit M, Epstein SK, et al. Perceived barriers to the use of sedation protocols and daily sedation interruption: a multidisciplinary survey. J Crit Care 2009;24:66–73.
[45] Brattebø G, Hofoss D, Flaatten H, Muri AK, Gjerde S, and Plsek PE. Effect of a scoring system and protocol for sedation on duration of patients' need for ventilator support in a surgical intensive care unit. *BMJ*. 2002 8(324(7350)):1386–1389.
[46] Ouimet S, Kavanagh BP, Gottfried SB, et al. Incidence, risk factors and consequences of ICU delirium. Intensive Care Med 2007;33:66–73.
[47] Shehabi Y, Riker RR, Bokesch PM, et al. SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group: delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. Crit Care Med 2010;38:2311–8.
[48] Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291: 1753–62.
[49] Ely EW, Gautam S, Margolin R, et al. The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med 2001;27:1892–900.