ORIGINAL ARTICLE

A New ICU Delirium Prevention Bundle to Reduce the Incidence of Delirium: A Randomized Parallel Group Trial

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Abstract

Introduction: Although various preventive strategies have been advocated, delirium is common in critically ill patients and is associated with increased morbidity, mortality, and long-term adverse effects. The efficacy of a novel delirium prevention bundle in mechanically ventilated critically ill patients was investigated in this study.

Methods: In this randomized controlled trial, 50 mechanically ventilated adult patients in a tertiary care medical-surgical intensive care unit (ICU) were randomized to receive either delirium prevention bundle protocol or standard of care protocol. Delirium was assessed daily using the Confusion Assessment Method for the ICU (CAM-ICU) score by an independent investigator up to 28 days or death or discharge. The primary outcome was the incidence of new-onset delirium. Secondary outcomes were duration of mechanical ventilation, ICU length of stay (ICU-LOS), hospital LOS, and other adverse events.

Results: There was a 20% reduction in the incidence of delirium in the intervention group (36 vs 56%; $p = 0.156$). The 28-day mortality (28 vs 24%; $p = 0.747$), duration of mechanical ventilation (9 vs 12 days; $p = 0.281$), ICU-LOS (11 vs 12 days; $p = 0.221$), and hospital LOS (16 vs 20 days; $p = 0.062$) were similar between the groups.

Conclusion: Implementation of delirium prevention bundle does not reduce the incidence of delirium compared to standard of care protocol in mechanically ventilated critically ill patients.

Keywords: Delirium, Intensive care unit, Mechanical ventilation.

Indian Journal of Critical Care Medicine (2021): 10.5005/jp-journals-10071-23881

Introduction

Delirium is an acute disturbance of consciousness, which is manifested by inattention, disorganization of thinking, and disturbance of perception that fluctuates over a short period of time.[1] Delirium may occur in as many as 20–50% of nonventilated and 60–80% of mechanically ventilated patients,[2-4] and it is associated with increased mortality and a multitude of adverse outcomes, including prolonged intensive care unit (ICU) and hospital stay.[5-8] Delirium may also cause functional disability, early dementia, and later cognitive disorders[9-12] and ultimately leads to increased burden of work on health-care providers and overall increased costs.[13-16] There are various risk factors that play important role in the development of delirium (Table 1),[17,18] and all these risk factors have an additive effect.

Prevention and treatment of delirium in the ICU requires the collaboration of various strategies in addition to the use of evidence-based treatment protocols. The recent pain, agitation, and delirium management guidelines have advocated for a preventive strategy, including the light level of sedation, proper analgesia, improvement in sleep quality, early physiotherapy, mobilization, etc., for decreasing the incidence and duration of delirium.[19]

Despite various proposed guidelines and recommendations, delirium continues to be common, and therefore, we believe, the institution of a bundle of care comprising of various evidence-based interventions may improve adherence to protocols and reduce the incidence of delirium. This study was designed to determine whether the new ICU delirium prevention bundle significantly reduces the incidence of delirium compared to the standard of care delirium prevention strategies in mechanically ventilated patients. Other secondary outcomes were duration of mechanical ventilation, ICU length of stay (ICU-LOS), hospital LOS, 28-day mortality ,and any adverse events.

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How to cite this article: Malik AK, Baidya DK, Anand RK, Subramaniam R. A New ICU Delirium Prevention Bundle to Reduce the Incidence of Delirium: A Randomized Parallel Group Trial. Indian J Crit Care Med 2021;25(7):754-760.

Source of support: Nil

Conflict of interest: None

Materials and Methods

Study Design

This trial was a prospective, randomized parallel-group clinical trial. Study participants were recruited after Institutional Ethics Committee clearance (Ref. No. IECPG-654/22.12.2016,RT-28/19.01.2017 dated February 1, 2017) and registration with the Clinical Trials Registry of India (www.ctri.nic.in, CTRI/2017/02/007904).

Study Setting

The trial was conducted in the combined medical and surgical ICU of the Department of Anaesthesiology, Pain Medicine and Critical Care, All India Institute of Medical Sciences, New Delhi.

Table 1: Risk factors for delirium in ICU[17,18]

Modifiable risk factors	*Nonmodifiable risk factors*
Mechanical ventilation	Age
APACHE II score	Hypertension
Coma	Dementia
Polytrauma	Smoking
Acute respiratory distress	Alcohol use
Multiple organ failure	
Benzodiazepines	

Study Participants

All adult patients aged more than 18 years and requiring mechanical ventilation for more than 24 hours were included after obtaining informed written consent from the patients or their legally acceptable representatives. Exclusion criteria were: Patients with a history of prior neurological or psychiatric disorders, poor irreversible neurological status at the time of ICU admission, traumatic brain injury, and delirium at the time of ICU admission.

Grouping and Randomization

Patients were randomly allocated into two groups. Group A (intervention group) received ICU delirium prevention bundle of care protocol, and group B (control group) received the standard of care protocol. Computer-generated randomization was done by variable block method with mixed block size, and allocation concealment was done by sealed envelope method.

Blinding

An independent investigator (A.K.M), who was not part of the treating ICU team, performed daily delirium screening. He had no knowledge about the treatment group allocation of the recruited patients. To avoid further bias, he was instructed to do the delirium screening of all eligible ICU patients irrespective of their trial inclusion status. Another independent investigator (D.K.B) who was unaware of group allocation performed outcome data collection. Infusion pumps were covered by opaque papers, and modalities like earplugs and eye patches were hidden in the drawers.

Study Protocol

Details of the delirium prevention protocol followed in the intervention group and the standard of care protocol followed in the control group are provided in Table 2. Each protocol had the same seven components (sleep, analgesia and sedation, family visit, mobilization, weaning from ventilator, lines and catheters, antipsychotics, and benzodiazepines). The treating ICU physicians managed the patients with other evidence-based protocols, including fluid therapy, antibiotics, ventilator management, nutrition, insulin therapy, electrolyte replacement, and any other medical management required by the patient's condition. Staff members were instructed to continue their daily routine practices except for those mentioned in the trial design. A computerized printed leaflet with clear instructions was provided to all members of the ICU, so as to sensitize and familiarize them with the protocols in both groups. The treating physician always ensured that the respective protocols were properly implemented and followed by all the ICU caregivers.

The daily delirium screening was performed in the morning by an investigator by using the Confusion Assessment Method for the ICU (CAM-ICU) score,[20] once the patient attained a certain level of consciousness. Richmond Agitation-Sedation Scale (RASS)[21] was used for assessing the level of consciousness before proceeding with the CAM-ICU assessment. Delirium evaluation was performed only if RASS was ≥−3. In the second step of CAM-ICU assessment, pictures were used (a total of 10 pictures from the CAM-ICU training manual) to evaluate the component of inattention. Inattention was considered present if any patient committed more than two errors during this evaluation. When any patient was diagnosed with new-onset delirium, the information was conveyed to the treating ICU physician.

The treating ICU physician, according to the existing standard protocol irrespective of the study group, prescribed treatment for delirium, and it was concealed from the investigator performing delirium screening. The treatment consisted of correction of any risk factors like hypoxia, electrolyte imbalance, etc. Medical treatments included haloperidol 2.5 mg intravenous (IV) repeated over 30 minutes up to a maximum of 10 mg at 12 hours or quetiapine 50 mg per oral at 12 hourly. The treatment for delirium was continued till its resolution or according to the decision of the treating ICU physician. All the patients were evaluated daily till death or discharge or till 28 days, whichever is earlier.

Sample Size Estimation

The incidence of delirium in mechanically ventilated patients in our ICU is approximately 50%. In a previous randomized pilot study, Avendano-Cespedes[22] observed the incidence of delirium was 14.3% in the intervention group and 41.4% in the control group. To achieve a 14% incidence of delirium in our intervention group, assuming 50% incidence of delirium in the control group, with 80% power and alpha error of 0.05, the sample size was 50, with 25 patients in each group.

Statistical Analysis

All the collected data were tabulated in Microsoft Excel™ [Microsoft Corp., Redmond, Washington], and statistical analysis was performed using SPSS 20.0 software (SPSS Inc, Chicago, Illinois, USA). Continuous variables following normal distribution were analyzed by using an independent *t*-test, and their results were expressed as mean ± standard deviation. Continuous variables not following normal distribution were analyzed using the Mann-Whitney test, and data were reported as median with their minimum and maximum ranges. For the categorical variables, two groups were compared by chi-square test and Fisher's exact test, and data were presented as frequency (percentage). p-value <0.05 was considered statistically significant.

Results

From February 2017 to November 2018, a total of 84 mechanically ventilated patients were screened for eligibility, 57 patients were randomized and enrolled in the study, and finally, data from 50 patients were available for analysis (Fig. 1).

The baseline characteristics like age, sex, body mass index (BMI), diagnosis, acute physiology and chronic health evaluation II (APACHE II) score, sequential organ failure assessment (SOFA) score, etc., are shown in Table 3. All the outcome data are presented in Table 4. The results show a 20% reduction in the incidence of delirium in the intervention group compared to the control group (36 vs 56%; $p = 0.156$). The 28-day mortality rate, duration of mechanical ventilation, ICU-LOS, and hospital LOS were not different between the intervention and control groups.

Table 2: Details of delirium prevention protocol in intervention group and standard of care protocol in control group

Intervention group (group A)	*Control group (group B)*
Sleep quality improvement: Ear plugs and eye patches during sleep hours. Bright lights were switched off during sleep (11 p.m.–5 a.m.). No procedures/interventions were allowed between 11 p.m. and 5 a.m. (except emergency procedures). *Analgesia and sedation:* Analgesia first sedation: Pain assessment using Critical Care Pain Observation Tool (CPOT) and treatment with intravenous fentanyl 1–2 µg/kg, if the CPOT score is ≥3. Other analgesics medications like NSAIDs and IV paracetamol were used as adjunctive. Where required local or regional blocks were also used. Sedation using IV dexmedetomidine 0.2–0.7 µg/kg/hr continuous infusion and titrated to maintain RASS of 0. Sedation interruption was given daily, at early morning (5 a.m.). Any procedure or intervention was done under adequate sedation and analgesia. *Family contacts and bonding:* Family members or relatives were allowed to meet their patients three times a day (between 5 and 6 a.m. in morning, 4 and –5 p.m. in the afternoon, and 9 and 10 p.m. in the night. Each meeting session with family members was ensured up to at least 15 minutes. They were instructed to reassure and reorient their respective patient to time, place, and persons. Patients were encouraged to wear their glasses and hearing aids, and they were allowed to watch television and read newspaper. Tender loving care by family member was allowed. They were allowed to perform small acts like holding hands, limb massaging, hair combing, feeding with spoons, etc. (under the direct supervision of ICU staff). *Early mobilization:* Patients were mobilized once they were hemodynamically stable and their requirement for respiratory support was minimal. (Not on any vasopressor drug, PEEP ≤ 5 cm H_2O, FiO_2 ≤ 40%). They were assisted to take few small steps, sit on a chair, perform limb and body movements. Patients were encouraged to perform their own limb movements during rest on a bed. A dedicated physiotherapist did daily physiotherapy, once in the morning and once in the afternoon. *Weaning from ventilator:* Daily spontaneous awakening trial (SAT) Daily spontaneous breathing trial (SBT) was given for at least 30 min. *Early removal of catheters, lines, and drains* *No prophylactic antipsychotics* *No benzodiazepine (BZD)*	*Routine sleep pattern:* No ear plugs or eye patches during sleep hours. Dim light during sleep. There was no restriction for blood sampling, ET suctioning, or any invasive procedures. *Analgesia and sedation:* For pain control, patients received either IV fentanyl or IV morphine as per the treating physician's discretion. Adjunctive analgesics were used in the form of NSAIDs or paracetamol according to the decision of the treating physician. Sedation was given with midazolam, propofol, and opioids, either alone or in combinations; according to the decision of the treating physician on duty. Sedation interruption was given according to the decision of the treating physician. The treating physician on duty decided sedation level and goal. Any procedures or intervention was done under adequate analgesia and sedation. The choice of agent was as per the treating physician. *Family visit:* Family members were allowed to visit their patients once in a day; according to the ICU family visit policy (4–5 p.m. in the afternoon). Relatives did not participate actively in providing small acts of care. Although they were allowed to provide tender loving care, it was left to their own discretion. *Mobilization:* Allowed once their trachea was extubated and they did not require any respiratory support. *Weaning from ventilator:* Patients were given SBT once they were fit for weaning, and if SBT were successful, then extubation was performed. Nasogastric tube, urinary catheter, and any drain if present were removed according to the decision of the treating ICU physician. Antipsychotic (haloperidol or quetiapine) was administered to the patients as per the discretion of the treating physician. Benzodiazepine (midazolam) infusion or bolus doses for procedural sedation were given as per the discretion of the treating physician.

Three patients developed ICU-acquired weakness (one patient in group A and two patients in group B) during the study period. Two patients in group A developed transient bradycardia and hypotension during dexmedetomidine infusion, which resolved with dose reduction. No other adverse effects were documented during the study period.

Discussion

In this randomized controlled trial, implementation of delirium prevention bundle led to an insignificant reduction in the incidence of new-onset delirium by 20%. There was a trend toward a reduction in the number of days with delirium and duration of mechanical ventilation. Other secondary outcomes like 28-day mortality and LOS in ICU and hospital were similar.

In a previous pilot study, implementation of multicomponent, nonpharmacological interventions achieved a 27.1% (14.3 vs 41.4%) reduction in the incidence of delirium.[22] However, all were noncritical hospitalized patients admitted to acute geriatric units and did not receive any mechanical ventilation. In the current study, the incidence of delirium in the control group was high (56%) and a reduction to 14% seemed too enthusiastic a target. However,

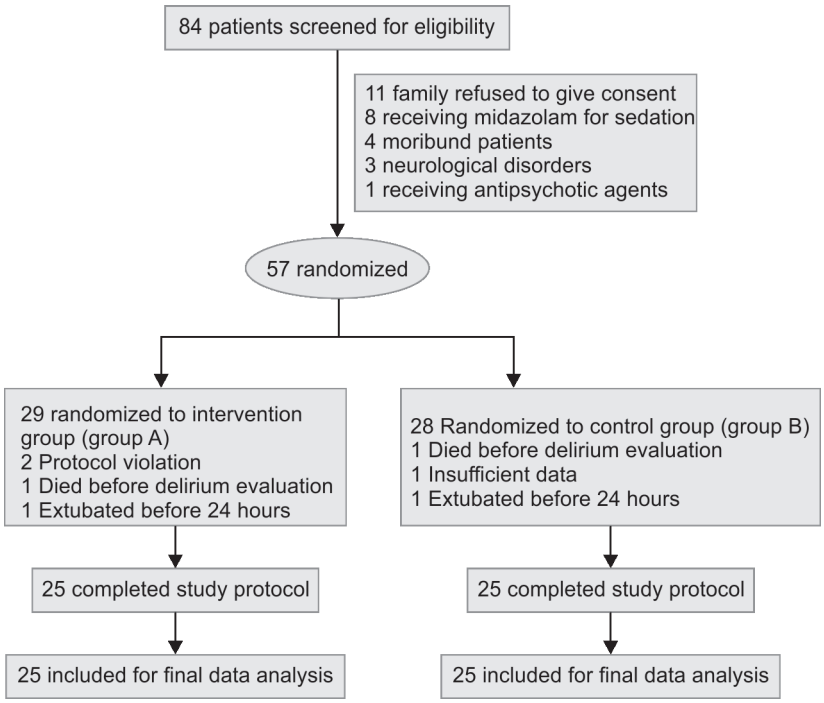

Fig. 1: CONSORT flow diagram

the goal was kept steep in the light of ample evidence available in the literature that each individual component of the bundle was associated with the reduction in the magnitude of delirium. The combination of individual components into a bundle was expected to produce a significant reduction in delirium.

In a large prospective quality improvement initiative trial involving similar multiple bundle components (ABCDEF bundle), Barnes-Daly MA showed significant improvement in survival and reduction in days with delirium and coma in ICU patients.[23] However, only 23.7% of patients received mechanical ventilation, and the duration of mechanical ventilation was short. In contrast, the current study was performed only in mechanically ventilated patients who were very sick with high SOFA and APACHE II scores at baseline. Mechanical ventilation is known to be one of the strongest risk factors of delirium,[18] and the duration of mechanical ventilation is independently associated with increased incidence of delirium.[24] In our study, the mean duration of mechanical ventilation was 12 to 14 days. However, it is interesting to note that the number of days with delirium was 2 to 4 days only, reflecting the fact that all new-onset delirium were readily treated.

The number of days with delirium in the intervention groups was half of that of the control group, although this was not statistically significant. Once the independent investigator diagnosed the delirium, it was communicated to the ICU team and the ICU physicians who treated delirium in similar fashion in both groups, mostly with the use of antipsychotics. The trend toward the reduced incidence of delirium in the intervention groups suggests that the multicomponent intervention bundle may have a role not only in prevention but also in the treatment of delirium in ICU.

Dexmedetomidine was the sedative drug of choice in the intervention bundle. Previous studies have demonstrated that the use of dexmedetomidine as a sedative resulted in reduced incidence of delirium compared to benzodiazepines,[25,26] but not when compared to propofol.[27,28] In fact, dexmedetomidine patients had a longer duration of mechanical ventilation, ICU, and hospital LOS compared to propofol.[27] In the current study, propofol was allowed as sedatives in the control group, and this could have improved the outcome in the control group and reduced the magnitude of difference in duration of mechanical ventilation and ICU or hospital stay with the intervention group.

Another important finding in our study was prolonged hospital LOS in both groups. Increased incidence of delirium is strongly associated with pronged hospitalization. In a multicenter study, Emond found that the occurrence of delirium increased hospital LOS by 4 days in emergency department patients.[29] Prolonged hospitalization had also contributed to the death of patients after ICU discharge as approximately half of the deaths in the current study occurred during hospital stay after ICU discharge.

Strengths and Limitations

The strengths of the study were proper randomization and blinding. Blinding was achieved despite the fact that patients received multiple interventions that were difficult to conceal. This study included only mechanically ventilated patients with severe illness, whereas most of the previous studies have been performed in all critically ill patients. Delirium assessment was performed by an independent physician and a standard objective assessment scale was used, which reduced the chances of bias and any interobserver variation. Moreover, there was strict adherence to study protocols in ICU and no loss of data in follow-up. Lastly, all the patients were followed up till their hospital discharge, which provided an insight into the course of illness and outcome even after their discharge from the ICU.

There are various limitations in our study. It was a single-center study. A multicenter study with a larger sample size can alter the results. Secondly, the study aimed to achieve a steep reduction in the delirium incidence, which may not be practical in mechanically ventilated patients. The patient population was very sick with high

Table 3: Baseline characteristics

Characteristics	*Group A (n = 25)*	*Group B (n = 25)*	*p-value*
Age, years (mean ± SD)	37.72 ± 15.926	46.40 ± 18.053	0.078
Gender, *n* (%)			
Male	13 (52)	10 (40)	0.395
Female	12 (48)	15 (60)	
BMI (mean ± SD)	24.53 ± 2.396	24.60 ± 2.887	0.924
APACHE II (mean ± SD)	19.40 ± 5.972	19.52 ± 5.001	0.939
SOFA (mean ± SD)	8.44 ± 3.417	7.96 ± 1.947	0.545
Admission diagnosis, *n* (%)*			
Sepsis	6 (24)	10 (40)	0.364
Shock	9 (36)	8 (32)	1.000
Pneumonia/ARDS	11 (44)	10 (40)	1.000
AECOPD	3 (12)	5 (20)	0.702
AFI	7 (28)	2 (8)	0.138
Others[a]	5 (20)	6 (24)	1.000
Associated comorbidities, *n* (%)#			
DM	4 (16)	4 (16)	1.000
HTN	4 (16)	4 (16)	1.000
Hypothyroidism	3 (12)	2 (8)	1.000
Others[b]	2 (8)	2 (8)	1.000
Number of comorbidities, *n* (%)			
0	15 (60)	10 (40)	0.153
1	6 (24)	9 (36)	
2	1 (4)	5(20)	
3	3 (12)	1 (4)	
AKI, *n* (%)	5 (20)	7 (28)	0.742
Number of organ failure, *n* (%)			
0	1 (4)	1 (4)	0.709
1	8 (32)	11 (44)	
2	12 (48)	8 (32)	
3	4 (16)	5 (20)	

*Few patients had more than one conditions; #Few patients had more than one comorbidity; [a]Includes postsurgical patients, postrenal transplant graft failure, systemic lupus erythematosus flare, snake bite, acute gastroenteritis, diabetic ketoacidosis, poisonings; [b]Systemic lupus erythematosus, obstructive sleep apnea, multiple myeloma, dilated cardiomyopathy. *Abbreviations*: BMI, body mass index; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; AFI, acute febrile illness; DM, diabetes mellitus; HTN, hypertension; AKI, acute kidney injury

Table 4: Outcome parameters

Parameters	*Group A (n = 25)*	*Group B (n = 25)*	*p value*
Delirium incidence, *n* (%)	9 (36)	14 (56)	0.156
Days to delirium onset (mean ± SD*)	5.67 ± 2.179	5.93 ± 2.868	0.807
Number of days with delirium (mean ± SD)	1.92 ± 3.081	3.88 ± 6.346	0.219
Delirium-free days in ICU (mean ± SD)	7.84 ± 6.053	7.40 ± 4.725	0.93
28-day mortality, *n* (%)	7 (28)	6 (24)	0.747
Death after ICU discharge, *n* (%)	3 (12)	4 (16)	1.000
Duration of MV (mean ± SD) Median (min–max)	11.6 ± 10.308 9 (2–41)	14.84 ± 15.562 12 (3–73)	0.281
ICU LOS (mean ± SD) Median (min–max)	12.92 ± 9.725 11 (3–40)	15.72 ± 11.66 12 (4–58)	0.221
Hospital LOS (mean ± SD) Median (min–max)	23 ± 17.559 16 (7–66)	32 ± 30.918 20 (12–160)	0.062

*SD, standard deviation; $p < 0.05$. *Abbreviations:* MV, mechanical ventilation; LOS, length of stay

disease severity scores and multiple associated comorbidities, which might have affected the incidence of delirium.

Conclusion

To conclude, the implementation of a new ICU delirium prevention bundle does not significantly reduce the incidence of delirium compared to standard of care protocol in mechanically ventilated critically ill patients. Moreover, it does not affect 28-days mortality, duration of mechanical ventilation, ICU-LOS, and hospital LOS.

Acknowledgments

Authors would like to acknowledge the contribution of Dr. Maroof Ahmed Khan, Mr. Kulwant Singh Kapoor, and Mr. Vishwajeet Singh for performing the statistical analysis for this study.

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References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV. 4th ed. Washington (DC): American Psychiatric Association; 1994. 866 p. Available from: http://www.psychiatryonline.com/DSMPDF/dsm-iv.pdf.
2. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 2001;286(21):2703–2710. DOI: 10.1001/jama.286.21.2703.
3. Pandharipande P, Cotton BA, Shintani A, Thompson J, Pun BT, Morris JA Jr, et al. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. J Trauma 2008;65(1):34–41. DOI: 10.1097/TA.0b013e31814b2c4d.
4. Page VJ, Navarange S, Gama S, McAuley DF. Routine delirium monitoring in a UK intensive care unit. Crit Care 2009;13(1):R16. DOI: 10.1186/cc7714.
5. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291(14):1753–1762. DOI: 10.1001/jama.291.14.1753.
6. Salluh JI, Wang H, Schneider EB, Nagaraja N, Yenokyan G, Damluji A, et al. Outcome of delirium in critically ill patients: systemic review and meta-analysis. BMJ 2015;350:h2538. DOI: 10.1136/bmj.h2538.
7. Lin SM, Liu CY, Wang CH, Lin HC, Huang CD, Huang PY, et al. The impact of delirium on the survival of mechanically ventilated patients. Crit Care Med 2004;32(11):2254–2259. DOI: 10.1097/01.ccm.0000145587.16421.bb.
8. Pompei P, Foreman M, Rudberg MA, Inouye SK, Braund V, Cassel CK. Delirium in hospitalized older persons: outcomes and predictors. J Am Geriatr Soc 1994;42(8):809–815. DOI: 10.1111/j.1532-5415.1994.tb06551.x.
9. O'Keeffe S, Lavan J. The prognostic significance of delirium in older hospital patients. J Am Geriatr Soc 1997;45(2):174–178. DOI: 10.1111/j.1532-5415.1997.tb04503.x.
10. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. N Engl J Med 2013;369:1306–1316. DOI: 10.1056/NEJMoa1301372.
11. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of post discharge mortality, institutionalization, and dementia: a meta-analysis. JAMA 2010;304(4):443–451. DOI: 10.1001/jama.2010.1013.
12. McCusker J, Cole MG, Voyer P, Monette J, Champoux N, Ciampi A, et al. Prevalence and incidence of delirium in long-term care. Int J Geriatr Psychiatry 2011;26(11):1152–1161. DOI: 10.1002/gps.2654.
13. Buss MK, Vanderwerker LC, Inouye SK, Zhang B, Block SD, Prigerson HG. Associations between caregiver-perceived delirium in patients with cancer and generalized anxiety in their caregivers. J Palliat Med 2007;10(5):1083–1092. DOI: 10.1089/jpm.2006.0253.
14. Shankar KN, Hirschman KB, Hanlon AL, Naylor MD. Burden in caregivers of cognitively impaired elderly adults at time of hospitalization: a cross-sectional analysis. J Am Geriatr Soc 2014;62(2):276–284. DOI: 10.1111/jgs.12657.
15. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. Arch Intern Med 2008;168(1):27–32. DOI: 10.1001/archinternmed.2007.4.
16. Milbrandt EB, Deppen S, Harrison PL, Shintani AK, Speroff T, Stiles RA, et al. Costs associated with delirium in mechanically ventilated patients. Crit Care Med 2004;32(4):955–962. DOI: 10.1097/01.ccm.0000119429.16055.92.
17. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. JAMA 1996;275(11):852–857. PMID: 8596223.
18. Zaal IJ, Devlin JW, Peelen LM, Slooter AJ. A systematic review of risk factors for delirium in the ICU. Crit Care Med 2015;43(1):40–47. DOI: 10.1097/CCM.0000000000000625.
19. Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas 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. DOI: 10.1097/CCM.0b013e3182783b72.
20. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2001;29(7):1370–1379. DOI: 10.1097/00003246-200107000-00012.
21. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care patients. Am J Respir Care Med 2002;166(10):1338–1344. DOI: 10.1164/rccm.2107138.
22. Avendano-Cespedes A, Garcia-Cantos N, Gonzalez-Teruel Mdel M, Martinez-Garcia M, Villarreal-Bocanegra E. Pilot study of a preventive multicomponent nurse intervention to reduce the incidence and severity of delirium in hospitalized older adults. Maturitas 2016;86:86–94. DOI: 10.1016/j.maturitas.2016.02.002.
23. Barnes-Daly MA, Phillips D, Ely EW. Improving hospital survival and reducing brain dysfunction at seven California community hospital: Implementing PAD guidelines via the ABCDEF bundle in 6,064 patients. Crit Care Med 2017;45(2):171–178. DOI: 10.1097/CCM.0000000000002149.
24. Sanchez-Hurtado LA, Hernandez-Sanchez N, Moral-Armengol MD, Guevara-Garcia H, Garcia-Guillen FJ, Herrera-Gomez A, et al. Incidence of delirium in critically ill cancer patients. Pain Res Manag 2018;Article ID 4193275. DOI: 10.1155/2018/4193275.
25. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298(22):2644–2653. DOI: 10.1001/jama.298.22.2644.
26. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009;301(5):489–499. DOI: 10.1001/jama.2009.56.
27. Jiang YK, Wang S, Lam TS, Hanna A, DeMuro JP, Calixte R, et al. Prevalence of delirium and coma in mechanically ventilated patients sedated with dexmedetomidine or propofol. Pharm Therapeut 2016;41(7):442–445. PMID: 27408521, PMCID: PMC4927019.

28. Louie JM, Lonardo NW, Mone MC, Stevens VW, Deka R, Shipley W, et al. Outcomes when using adjunct dexmedetomidine with propofol sedation in mechanically ventilated surgical intensive care patients. Pharmacy 2018;6(3):93. DOI: 10.3390/pharmacy6030093.

29. Emond M, Boucher V, Carmichael PH, Voyer P, Pelletier M, Gouin E, et al. Incidence of delirium in the Canadian emergency department and its consequences on hospital length of stay: a prospective observational multicenter cohort study. BMJ Open 2018;8(3):e018190. DOI: 10.1136/bmjopen-2017-018190.