REVIEW

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Clinical Year in Review 2014: Critical Care Medicine

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Severe sepsis is the most common cause of death among critically ill patients in non-coronary intensive care units. In 2002, the guideline titled "Surviving Sepsis Campaign" was published by American and European Critical Care Medicine to decrease the mortality of severe sepsis and septic shock patients, which has been the basis of the treatment for those patients. After the first revised guidelines were published on 2008, the most current version was published in 2013 based on the updated literature of until fall 2012. Other important revised guidelines in critical care field such as 'Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit' were revised in 2013. This article will review the revised guidelines and several additional interesting published papers of until March 2014, including the part of ventilator-induced lung injury and the preventive strategies.

Keywords: Critical Care; Review; Sepsis; Pain; Psychomotor Agitation; Delirium; Mechanical Ventilations

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012. Dellinger et al.[1] Crit Care Med 2013;41:580-637.

1. Summary and highlights

1) Diagnosis: Severe sepsis is defined as the state that reflects sepsis-induced tissue hypoperfusion or multi-organ dysfunction. Usually related with hypotension, it can be occurred in normal blood pressure state in the case of partial hypoperfusion to a specific organ or toxin-induced encephalopathy. Septic shock is defined as the persistent state that systolic blood pressure<90 mm Hg (or more decreased 40 mm Hg than initial blood pressure) and mean arterial pressure (MAP)<70 mm Hg despite of appropriate volume replacement. The appropriate volume replacement is a fluid therapy with 2 L of crystalloids in healthy patients or 10 L in severe dehydrated patients. Besides 2 pair of blood culture studies before antimicrobial therapy, 1,3-β-D-glucagon assay (2B) or mannan and antimannan antibody could be helpful to diagnose invasive candidiasis assay (2C).

2) Antimicrobial therapy: The effective intravenous antimicrobials, penetrate in adequate concentration into the tissue presume to be the source of sepsis, should be administrated within the first hour of recognition of septic shock. The antimicrobial regimen should be reassessed daily about effectiveness for consideration to change, discontinuation, and de-escalation (1B). Procalcitonin can be helpful to consider discontinuation of empirical antimicrobials, but only low risk of infection, the low procalcitonin level is associated with low risk of bacterial infection (2C).

3) Initial volume resuscitation and early goal direct therapy: Active volume resuscitation is most important role that elevates the survival rate of severe sepsis and septic shock patients as the initial management[2]. On this account, volume resuscitation must be done immediately and should be achieved the goals during the first 6 hours of resuscitation

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(1C): MAP≥65 mm Hg, central venous pressure 8–12 mm Hg (recommend 12–15 mm Hg, in the case of ventilator care or decrease ventricular compliance), hourly urine output (U/O)≥0.5 mL/kg/hr, central venous (superior vena cava) oxygen saturation ($ScvO_2$)≥70%, or mixed venous oxygen saturation (SvO_2)≥65%. Crystalloids are recommended as the initial volume resuscitation (1B). Hydroxyethy starch (hetastarch) is not recommended (1B). Although it is appropriate the volume of 30 mL/kg (1.5–3 L) crystalloids, active volume replacement is needed until last hemodynamic improvement (1C).

In spite of volume resuscitation, vasopressor therapy should be begun within initial 6 hours to maintain MAP (1C). Vasopressor should be administrated via central vein as possible, norepinephrine (NE) is recommended as the 1st choice drug (1C). Epinephrine can be replaced or added above NE (2B), vasopressin can be used to elevate MAP or to decrease use of NE by means of 0.03 units/min addition to NE. Dopamine is not recommended except low risk of tachyarrhythmia or bradycardia (2C).

Corticosteroids is suggested intravenous hydrocortisone alone at a dose of 200 mg/day if hemodynamic stability is not achievable despite of adequate fluid resuscitation and vasopressor therapy (2C).

Lactic acid level should be checked and normalized (2C) during initial resuscitation since some patients who elevated lactic acid level had been high mortality despite of normalized SvO_2[3]. Therefore, it should be considered that improve tissue perfusion by using red blood cell transfusion or dobutamin infusion when lactic acid level is over 4 mmol/L although normalized blood pressure after adequate volume resuscitation (2C).

2. Comments

The causes of sepsis were extremely wide and its mortality was still high. Therefore early recognition of progression sepsis-related syndrome is essential in the treatment of severe sepsis and septic shock. Physicians should be concerned on fungal sepsis and 1,3-β-D-glucagon assay or mannan/anti-mannan antibody would be helpful to diagnose invasive candidiasis assay depends on recent epidemiologic data[4].

Choosing the appropriate antibiotics, local anti-biogram and resistance profiles were important. And for the proper de-escalation and discontinuation of antibiotics, daily monitoring of antibiotics responsiveness and procalcitonin level can be helpful.

Active volume resuscitation is most important role that elevates the survival rate of severe sepsis and septic shock. Crystalloids are recommended as the initial volume resuscitation but hydroxyethy starch (hetastarch) is not recommended. This recommendation is based on the results of the VISEP[5], CRYSTMAS[6], 6S[7], and CHEST[8] trials. The results of the recently completed CRYSTAL trial[9] were not considered. CRYSTAL trial results were reviewed separately.

Vasopressor should be administrated via central vein as possible, NE is recommended as the 1st choice drug. Dopamine is not recommended except low risk of tachyarrhythmia or bradycardia[10].

There are debates that MAP should be maintained over at least 65 mm Hg. It is based on a study that only small number of patients (n=10) was enrolled, and there were no significant changes in hemodynamic factor, metabolite, and perfusion factor among MAP 65, 75, and 85 mm Hg groups[11]. Therefore, this guideline points out the necessity that appropriate MAP should be individualized. Namely, patients who had hypertension or artherosclerosis in the past may be needed higher MAP level.

As a marker of tissue hypoperfusion, lactic acid level should be checked and normalized during initial resuscitation. Some patients who elevated lactic acid level had been high mortality despite of normalized SvO_2[4].

Effects of Fluid Resuscitation with Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting with Hypovolemic Shock: The CRISTAL Randomized Trial. Annane et al.[9] JAMA. 2013;310:1809-17.

1. Summary and highlights

Several recent studies have shown no benefits to the use of colloids for volume resuscitations, and in aggregate suggest acute kidney injury and harmful death with starch solutions. CRISTAL investigators randomized 2,857 patients to receive colloid or crystalloid for acute hypovolemic shock blindly. Randomized colloid group had less fluid over the first 7 days (2,000 mL vs. 3,000 mL, p=0.001), lower 90 days mortality (30.7% vs. 34.2%, p=0.03), and no differences of 28-day mortality and use of renal replacement therapy. In addition, patients randomized to receive colloid had more days alive, free of mechanical ventilation, and vasopressor therapy by 7 and 28 days.

2. Comments

Administration of colloid for acute hypovolemic shock was not associated with a decrease in 28-day mortality but was associated with a decrease in 90-day mortality.

Administration of colloid was not associated with an increase in the use of renal replacement therapy. The reasons for the less renal replacement therapy compared to previous studies could be relating the total dose of starches, excluded patients with severe chronic renal failure, reduced need for vasopressor therapy, and chloride-restricted fluid relating less hyperchloremic acidosis.

However, caution should be applied to the finding that colloids were associated with decreased risk of 90 days, since this

was a secondary endpoint (primary endpoint: mortality at 28 days) and the mechanism for medium term benefit is unclear.

Effect of Heart Rate Control with Esmolol on Hemodynamic and Clinical Outcomes in Patients with Septic Shock: A Randomized Clinical Trial. Morelli et al.[12] JAMA 2013;310:1683-91.

1. Summary and highlights

Septic shock is a condition of sympathetic stress associated with high levels of plasma catecholimines. Authors tested the hypothesis that a short-acting beta-blocker could safely reduce the heart rate in patients with septic shock who required NE. Esmolol was titrated to achieve a target heart rate of 80–94 beats per minutes (BPM). Over the first 96 hours, those in esmolol group achieved a heart rate that was 28 BPM lower than baseline, compared to a 6 BPM reduction in the usual care group. Esmolol treatment group was an increase in stroke volume index and systemic vascular resistance, decrease in NE dose as well. Also, esmolol therapy was associated significant lower 28-day mortality (48.4% vs. 80.5%, p=0.001). However, there were no adverse effects on acid-base status, or kidney, liver and cardiac function.

2. Comments

In an open label study of patients with septic shock, esmolol therapy was associated an improvement in 28-day mortality compared usual care without increased adverse effects of kidney, liver or myocardial injury.

Though weak strength due to open label and higher mortality in usual care group, further studies are needed to determine if these results are reproducible and what population of patients with septic shock is most likely to benefit.

Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit. Barr et al.[13] Crit Care Med 2013;41:263-306.

1. Summary and highlights

This guideline emphasizes on more patient-centered and integrated approach than that of previous guidelines concern about pain, agitation, and delirium of adult patients. The psychometric properties of pain, sedation, and delirium scales were evaluated based on item selection and content validation, reliability, validity, feasibility, and relevance or impact of implementation on patient outcomes. Especially, they mentioned about correlation between delirium occurrence and mortality and more emphasized on diagnosis and treatment.

1) Pain: A study reported that 77% of patients admitted in intensive care unit (ICU) experienced over moderate to severe pain[14]. Especially, if the pain persistent for long time, it associates with occurrence of severe degree agitation and delirium, and leads to tachyarrhythmia, hypertension, extubation failure, pneumonia, and increase mortality rate[15]. In alert patients, pain assessment is conducted by direct explanation of patients themselves[16], but Behavioral Pain Scale (BPS)[17] or Critical Care Pain Observation Tool (CPOT)[18] were used in the others.

In an observational study that daily pain assessment and management effect on mechanical ventilation period, inadequate pain management cases needed more sedative drug use and had higher mortality and prolonged in-hospital stay and ventilator period. On the other hand, adequate pain management cases were associated with a shorter duration of mechanical ventilation and a reduced duration of stay in the ICU[19]. Thus, it is necessary to assess the pain in early period and to manage pain effectively that reduce sedative drug use and minimize delirium occurrence.

This guideline recommends the use of analgesics in an interventional treatment such as chest tube removal (+1C), and prior use of analgesics in an invasive or a pain arouse procedure (+2C). Opioids are the primary medications for managing nonneurogenic pain (+1C) and analgesics such as gabapentin and carbamazenpine can be used in neurogenic pain (+1A). Non-opiate analgesics can be used if opioids dosage is reduced (+2C).

2) Agitation: It is necessary at times of sedation to maintain the proper level of sedation. If sedative level is too low, as anxiety and pain occurs, there is a possibility to remove such as a patient's own ventilator circuit or blood vessel equipment. On the other hand, in excessive sedative state, delirium, ventilator associated occurrence of pneumonia, extension of the mechanical ventilation time and ICU stay can be occurred.

In the guideline, pain control is recommended prior to sedation before. In an effort to adjust depending on the condition of the patient, high-frequency oscillation ventilation (HFOV) and the prone, deep sedation and neuromuscular blocking agents can be used, and in low tidal volume ventilation, can be avoid a relatively deep sedation, and after replacing endotracheal tube to tracheostomy, the agents such as analgesics and sedative drug can be reduced[20].

As results of the study of mechanical ventilation withdrawal, daily interruption of sedation group was shown a significant reduction in mortality and mechanical ventilation period compare to classical management group[21]. This trend was more effective to be parallel with spontaneous breathing trial (SBT)[22]. In the PAD guideline, shallow sedation level is recommended since it improves the clinical prognosis (+1B).

As an evaluation measure of sedation, the Richmond Agitation Sedation Scale (RASS)[23], Sedation Agitation Scale (SAS)[24] are recommended. Although there are methods such as, Auditory Evoked potentials (AEPS), Bispectral Index (BIS),

Narcotrend Index (NI), Patient State Index (PSI), and State Entropy (SE) as an measures of neurologic evaluation, they are not recommended as the primary evaluation method unless patients has been administered nerve root blocker with the exception of the case of coma, or if there is no paralysis. Sleep electroencephalogram can be used in patient with nonconvulsive seizure and is recommended If it means that electrosuppressive medication administration when elevate intracranial pressure. Non-benzodiazepines are preferred sedation agent of patients with mechanical ventilation because of low incidence of delirium to benzodiazepines (+2B).

3) Delirium: Because the delirium in ICU is associated with increased mortality in addition to extension of admission period, and the occurrence of cognitive impairment in the future[25], it is necessary to daily assessment and management (+1B). Delirium is characterized by the acute onset of cerebral dysfunction with a change or fluctuation in baseline mental status, inattention, and either disorganized thinking or an altered level of consciousness. The major risk factors of delirium are previous history of dementia, hypertension, history of alcoholism, and a severe disease on admission[26]. Benzodiazepine-based medicine in the ICU may be increased the risk of incidence of delirium (B) and for propofol, there are still lack of results (C). When delirium occurs, it is necessary to consider minimizing the amount of analgesics or sedative agent in use and to change. In addition, as delirium is associated to pain, it has to consider together whether pain control is successful or not. The use of dexmedetomidine can reduce the risk of delirium in mechanical ventilation patient rather than the use of benzodiazepines (B).

For evaluation of delirium, Confusion Assessment Method for the ICU (CAM-ICU)[27] is mainly used. The THINK is toxic situations, hypoxemia, infection/sepsis, immobilization, nonopharmacologic interventions, and K^+/electrolyte imbalance, they are major factors associated with delirium. As the non-medical management for delirium, early mobilization is necessary in addition to assessment and management of delirium, and visual and auditory assistance with objective indicator (+1B). Meanwhile, the prevention of delirium with drugs is not recommended yet (C). Although there is no exact evidence that haloperidol can be reduce a period of delirium, atypical antipsychotics like quetiapine can be reduce the period (C). The delirium without association to withdraw alcohol or benzodiazepines can be reduced the period by dexmedetomidine rather than benzodiazepine (+2B).

2. Comments

Patients in the ICU were felt of pain over 2/3. And, it associates with occurrence of severe degree agitation and delirium, and leads to tachyarrhythmia, hypertension, extubation failure, pneumonia, and increase mortality rate. Therefore pain is routinely monitored in all adult ICU patients and pain control is recommended prior to sedation before.

Daily interruption of sedation and spontaneous awakening trial were more effective to be parallel with SBT. Therefore, shallow sedation level is recommended since it improves the clinical prognosis.

Non-benzodiazepines are preferred sedation agent of patients with mechanical ventilation because of low incidence of delirium to benzodiazepines.

The delirium in ICU is associated with increased mortality in addition to extension of admission period, and the occurrence of cognitive impairment in the future. Therefore, it is necessary to daily assessment and management of delirium.

For delirious patients, it is necessary to consider minimizing the amount of analgesics or sedative agent in use and to change. In addition, as delirium is associated to pain, it has to consider together whether pain control is successful or not.

Early mobilization of adult ICU patients whenever feasible to reduce the incidence and duration of delirium.

The use of dexmedetomidine can reduce the risk of delirium in mechanical ventilation patient rather than the use of benzodiazepines.

Ventilator-Induced Lung Injury. Slutsky and Ranieri[28] N Engl J Med 2013;369:2126-36.

1. Summary and highlights

The aim of mechanical ventilation is appropriate gas exchange and decreasing work of breathing. However, many complications occurred by mechanical ventilation itself, such as barotrauma, volutrauma, atelectotrauma, and biotrauma. Ventilator-induced lung injury (VILI) is major cause of death in the acute respiratory distress syndrome (ARDS) with multiple organ failure together[29]. Therefore, recent mechanical ventilation strategies are focused on minimizing the VILI. This article summarized clinical strategies to prevent it and mitigate its effects.

1) Low tidal volume (VT): In the study, ARDS network investigators had showed significant lower mortality rate in a group with low tidal volume (VT 6 mL/kg of predicted body weight [PBW], and plateau pressure, Ppl<30 cm H_2O) than in the other group (VT 12 mL/kg of PBW, and Ppl<50 cm H_2O)[30]. Nowadays, it became a major option in mechanical ventilation treatment to use low tidal volume for lung-protective ventilation[31].

2) High positive end-expiratory pressure and alveolar recruitment maneuver: Low positive end-expiratory pressure (PEEP) state is insufficient to keep of alveolar opening in severe respiratory distress state with pulmonary edema and end-expiratory alveolar collapse. In these situations, a low PEEP may be insufficient to stabilize alveoli and keep them open, thereby increasing the likelihood of ventilator-induced lung injury from atelectrauma. alveolar recruitment maneu-

ver (ARM) can suppress to develop VILI theoretically[32], there are debates about effect of ARM with hemodynamic unstable state, pneumothorax, and survival rate[33]. In the results of recent research, it is major factor of lung-protective ventilation protocol that uses low tidal volume with high PEEP[34]. Especially, in a study, they showed survival improvement as ARDS patients had been apply relatively higher PEEP than acute lung injury[35].

As the mechanical ventilation itself can take more serious in pulmonary damage through VILI, acute lung injury (ALI)/ARDS can be occurred by mechanical ventilation of non ALI/ARDS state patients. As shown in a study that compared two groups which TV 10 mL/kg of PBW used and TV 6 mL/kg of PBW used[36], and in another study that concerned about organ transplantation, compared two groups about lung harvest degree which 'TV 10–12 mL/kg of PBW, PEEP 3–5 cm H_2O' used and 'TV 6–8 mL/kg of PBW, PEEP 8–10 cm H_2O' used[37], the group of low tidal volume and relative higher PEEP group had low occurrence of ALI and higher organ harvest rate available. Therefore, ALI/ARDS patients should be apply higher PEEP and non ALI/ARDS patients also should be apply about 8 cm H_2O initially and adjusted PEEP according to required FiO_2 and hemodynamic status.

3) High-frequency oscillator ventilation: Theoretically, HFOV is possible to minimize VILI[38], and in a study of patients with ARDS results of the meta-analysis, it showed significant decrease in mortality. However, as the result of recent meta-analysis study, there are no significant advantages, therefore, it is not recommended as a primary treatment[39].

4) Prone position: In animal studies, prone position induces to increase homogenous ventilation and minimize VILI[40]. And prone position can result in improved oxygen saturation to 70% of ARDS patients[41]. As the result of a meta-analysis study, a prone position leads to decrease mortality rate of approximately 10% in severe ARDS (PaO_2:FiO_2 ratio<100 mm Hg) patients[42].

5) Extra-corporeal membrane oxygenation: To prevent VILI, mechanical ventilator supports can be minimized by use of extra-corporeal membrane oxygenation (ECMO) and CO_2 can be eliminated by use of extracorporeal circulation. As compared with total ECMO, partial combine mechanical ventilation with partial extracorporeal support assistance can reduce degree of lung injury because it has less complication and can make use of lower tidal volume[43].

6) Neuromuscular blocking agents: Neuromuscular blocking agents can make improvement of patient-ventilator synchrony and can be helpful management of tidal volume and airway pressure. In a study, patient with PaO_2:FiO_2 ratio<150 mm Hg who were applied neuromuscular blocking agent during 48 hours had significantly increasing survival rate in 90 days[44]. This effect had been significant in 16 days later and it could be interpreted that the group of neuromuscular blocking agent administration was showed low concentration of serum cytokines, that is the occurrence of less multi-organ failure to be associated with biological injury, biotrauma[45].

2. Comments

Low tidal volume is primary key in the management of mechanical ventilation in patients with or without ARDS.

More than 10 cm H_2O of PEEP for ARM would be helpful in severe ARDS.

HFOV is not recommended in primary treatment in patients with ARDS.

Taken together, the randomized control trial and meta-analysis provide evidence that prone position begun early after ARDS onset and delivered in higher dose (i.e., more hours per day) improves clinical outcomes in patients with severe ARDS. The benefit of prone positioning is largely restricted to patients with receiving low tidal volume ventilation.

For severe ARDS patients and who failed mechanical ventilation support status, short term neuromuscular blocker applying for improvement of patient-ventilator synchrony and management of tidal volume and airway pressure, total ECMO or partial ECMO will be considered.

Conclusion

The initial resuscitation such as early goal direct therapy is absolute management for survival of patients who admit medical ICU due to sepsis and septic shock. These include maintenance of MAP and close assessment of lactic acid level that evaluates tissue perfusion degree and manages according to alteration. And on the basis of main guidelines, proper management of pain and sedation, daily interruption of sedation, spontaneous awakening trial, and SBT can help to induce early self-respiration, mobilization, and prevent ICU delirium. Finally, the application of standardize protocol with lung-protective ventilation protocol minimize VILI incidence and improve survival.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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