Neuroanesthesia and Intensive Care

Special Article

Toronto critical care medicine symposium report

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THE Toronto Critical Care Medicine Symposium (TCCMS) is organized every October by members of the Toronto academic critical care community, with the collaboration of a group of national scientific advisors. Because of the quality of invited speakers and topics, the event is popular among Canadian and international clinicians who practice in the intensive care unit (ICU) setting (physicians, as well as nurses, and respiratory therapists). The symposium has become, over time, the premier Canadian critical care meeting. In October 2001, the conference featured several talks on cutting edge or changing issues in the area. Herein, we report selected messages of interest to critical care practitioners, and hope this summary will find favour with the Canadian Journal of Anesthesia readership. Information about the yearly symposium can be obtained on the internet at the "TCCSM" website (www.tccms.com).

The high risk pulmonary artery catheter (PAC) study

A large trial conducted in collaboration with the Canadian Critical Care (CCC) Trials Group was recently completed by Dean Sandham and colleagues. One thousand nine hundred and ninety-four ASA class III or IV patients aged 65 yr or more who underwent major noncardiac surgery were randomized to preoperative PAC and protocol-driven fluid and drug management, or a control group, managed by the ICU team, using a central venous catheter without protocolized care. Patients in the PAC group received significantly more colloids, inotropes and vasopressors. The main endpoint, hospital mortality, was the same in the two groups: 7.7% in control and 7.8% in PAC group. At one year, mortality was not significantly different. This large multicentre randomized trial suggests that peri- and postoperative management using a PAC in the ICU does not decrease mortality. The incidence of pulmonary embolism was significantly higher in the PAC group. The observed 0.8% incidence of pulmonary embolism could translate into a 12,000/yr PAC attributable incidence across North America.

Sepsis strategies/forum

Reliability/validity

Reliability and validity criteria for the terms "sepsis" and "septic shock" are not well established. A literature review of the overlap between reliability and validity criteria and diagnostic categories such as "sepsis" or even "Adult Respiratory Distress Syndrome" (ARDS) compared poorly to a number of other illnesses, including psychiatric diseases. Depression, for example, has more reliable characterizing criteria that enable correct diagnosis, thereby making the *right* diagnosis for the application of potential therapy a lot more likely across heterogeneous groups of treating physicians. The high cost of emerging therapeutic options makes the development of accurate assessment of severe sepsis more pressing.

Genomics

Some of the determinants of response to sepsis, either in terms of defense (to encapsulated organisms such as hemophilus, meningococcus or pneumococcus) or inflammation and generation of inflammatory media-

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tors, are genetically determined. TNFα (tumour necrosis factor, an inflammatory cytokine associated with severity of inflammatory response in sepsis) promoter polymorphism determines TNFα production. This in turn influences the risk of mortality among patients with similar severity of illness scores. Plasminogen-activator inhibitor 1 gene polymorphism, which influences fibrinolysis, has also been associated with increased mortality in patients with trauma or meningococcemia. These patients develop sepsis more frequently, have more multiple organ dysfunction, and have worse outcomes for comparable initial severity scores. Genetic polymorphisms and their relationship to the risk of developing sepsis, as well as the response to sepsis treatment, are currently active areas of investigation.

Treatment modalities: coagulation modulators

Inflammation and coagulation cascade abnormalities are common to sepsis and other shock states. Recognized abnormalities of coagulation and fibrinolysis have led to testing several therapeutic interventions directed at different aspects of the coagulation cascade, such as activated protein C and antithrombin. Decreased protein C levels are prevalent in patients with sepsis, and are less than 60% of normal in most patients with severe septic shock. A randomized trial of activated protein C in patients with severe sepsis demonstrated a survival benefit among patients who received the drug.[1] The number needed to treat for a 96-hr infusion is 16; that is, 16 patients with severe sepsis need to be treated with activated protein C to save one life. The drug has just undergone Federal Drug Agency (FDA) approval; in Canada (at the time of writing) it is available for compassionate use but it is not yet Health Protection Board (HPB) approved. In contrast, another agent influencing the coagulation cascade already used in clinical practice in parts of Europe showed strikingly disappointing results; antithrombin III offers no survival benefit for septic patients whether or not they receive heparin.[2]

Anti-inflammatory strategies: [bactericidal protein tissue factor pathway inhibitor (TFPI)]

Additional potentially useful therapeutic agents have also been evaluated in prospective trials. Bactericidal protein, a potent anti-endotoxin molecule, has recently been shown to be useful in meningococcal sepsis.[3] TFPI was of benefit in patients with severe septic shock and reduced mortality. Tifarcogin, the TFPI recombinant human preparation, has been tested in a large randomized trial of over 2000 patients. Preliminary results show no survival advantage.

Corticosteroids

Corticosteroids influence adrenal insufficiency common to sepsis, whether relative or absolute; act as an immune response modifier; block nitric oxide (NO) synthesis and thus improves blood pressure. Several clinical studies published recently[4–6] have suggested potential benefit to early corticosteroids, with or without mineralocorticoids, for hemodynamically unstable septic patients, with or without relative or absolute adrenal insufficiency. A French multicentre randomized trial of exogenous glucocorticoid and mineralocorticoid treatment is currently undergoing peer review; it suggests a beneficial effect on mortality with early treatment.

Sedation, analgesia, and neurocognitive issues

Sedation, delirium and sleep in the ICU are areas of emerging clinical research in critical care. The benefits of adequate analgesia and sedation must be weighed against the disadvantages of its excessive or insufficient use. Protocolized sedation and analgesia drug administration using sedation scores may render physician management more consistent, allow nurses more control in decision making in the ICU, and possibly shorten ICU stay and ventilator days. Identification of delirium is important. A newly published screening scale may be helpful.[7] Delirium risk factors differ from other populations when examined in the ICU setting. Sleep abnormalities and disruptions in the ICU are common but their attributable morbidity remains unexplored. The pharmacologic features of two new drugs, the sedative dexmedetomidine and the analgesic remifentanil, may render them useful in the ICU because of their very short half-life.

Ventilator associated pneumonia (VAP)

Observational studies have clarified risk factors for VAP. These include aspiration, older age, organ dysfunction, supine body position, enteral nutrition, increased duration of ventilation, coma, and transport out of the ICU. Noninvasive ventilation decreases the risk of nosocomial pneumonia in comparison to endotracheal intubation and conventional mechanical ventilation. However, the need for noninvasive mechanical ventilation still confers an increased risk for pneumonia compared with the ability to breathe spontaneously. The highest risk for acquiring VAP seems to occur in the first seven to ten days in the ICU. Systemic early antibiotics lower the risk for VAP. Their administration later in the ICU stay does not influence VAP, and administration late in the course of ventilation appears to be a risk factor for VAP possibly due to the emergence of superinfection and multi-resistant organisms. The CCC VAP Prevention

Guideline Group carefully and rigorously reviewed preventive measures for VAP, and their recommendations are the following:

Orotracheal intubation should be used when intubation is necessary.

Noninvasive ventilatory support should be attempted in ICUs with experienced staff, in the absence of specific contraindications.

Ventilator circuits should be changed for soiling but not routinely.

Heat and moisture exchangers are recommended rather than heated humidifiers.

Closed endotracheal suction should be used.

The 'less strong' recommendations due to insufficient evidence included consideration of the following: subglottic secretion drainage, kinetic beds, jejunal instillation of enteral nutrition, and management of patients with upper body tilted at 45 or more. Selective digestive decontamination for VAP prevention cannot be recommended (or discouraged) on the basis of currently available randomized trial literature: these trials differ with regards to populations, screening criteria, and definitions. Finally, special enteral nutrition (e.g., immune enhanced) was not recommended.

The use of bronchoscopy for the diagnosis of VAP varies widely. Randomized trials exist in support of bronchoscopy samples, and of endotracheal aspirates, for VAP diagnosis. The CCC Trials Group is currently conducting a randomized trial to test the best (invasive *vs* noninvasive) way to diagnose VAP; this study will also evaluate the outcomes of antibiotic use and costs.

Medical error

Among care givers, physicians have the highest incidence of errors. Errors are common in the critical care setting,[8] multifactorial,[9] expensive, and difficult to deal with for physicians who have committed them. Because of the benefits of computerized systems a billion dollar industry focusing on error reduction is emerging. Some systems which have the potential to reduce mistakes or oversights are already available for hand-held computer type consultation (e.g., ePocrates.com).

Neurological monitoring

An array of technological devices is available to aid in the monitoring of neurologic function in critical illness. The evidence supporting their usefulness is sparse. Intracranial pressure monitoring is useful in trauma patients with basal cisterns compression. Low jugular vein oxygen saturation ($SvjO_2$) is associated with poor outcome, but its predictive power has not been clearly shown. Transcranial Doppler (TCD) techniques are probably most beneficial in the assessment of cerebral perfusion pressure, and in differentiating vasospasm from hyperemia. Evoked potentials (EP) may be added to the limited examination in comatose patients. Prognostication is best served by the somatosensory EP, and age remains the most important influence on functional recovery and survival. Microdialysis catheters threaded in the subdural space allow the measurement of variables that may be more sensitive (e.g., glutamate and lactate release as well as glucose levels) than standard clinical evaluations as an index of tissue or cell suffering. Genetic prediction of adverse outcome following traumatic injury is enhanced by presence of the phi epsilon 4 gene.[10]

Comatose survivors following hypoxic-ischemic events can be assessed using a number of methods including clinical, electrophysiologic, biochemical and imaging techniques. Lack of normal brainstem findings is a poor prognostic indicator; however, myoclonus is not; and even an early Glasgow coma scale of 3 can be associated with a good outcome. Valproic acid *iv* may be useful for myoclonus without affecting level of consciousness.

Mechanical ventilation and ARDS

A recent study described 304 hypoxemic patients with criteria of acute lung injury (ALI) or ARDS on admission that were randomized to control or prone ventilation.[11] Patients were prone six hours a day. The end points were mortality, discharge from ICU and discharge from hospital. Prone positioning offered no advantage in terms of mortality in hospital or at six months. Prone patients had better oxygenation and a lower incidence of aspiration. Endotracheal tube removal (10%) was no different in the two groups. In a post-hoc subgroup analysis the most severely hypoxic patient, with high illness severity, and high tidal volumes, benefited from prone positioning. The study was underpowered, as it would have required 700 patients to demonstrate a 20% difference in effect.

A session addressing nonventilatory approaches to management of patients with ARDS focused on four areas. Mechanical ventilation affects surfactant biochemistry. Lung injury is associated with a shift in the appearance of surfactant from "beneficial" large aggregates to nonfunctional smaller aggregates. This, coupled with the inhibition of surfactant due to exuded serum proteins into the alveolar airspace, results in pulmonary surfactant that is largely ineffective. Early laboratory studies suggest hyper-osmolar solutions can exert marked protective effects against postresuscitation lung injury. These effects can be duplicated by the use of hyper-oncotic solutions; there seems to be

an immunologic basis for these protective effects. "Therapeutic hypercapnia" may be highly effective in selected experimental models. However, the model-specificity was emphasized. Given the risks and benefits of therapeutic hypercapnia in the experimental setting, clinical testing of therapeutic hypercapnia in the current level of knowledge would be premature. Liquid ventilation, despite the negative outcomes from recent ARDS studies, may have multiple other potential applications including use for application of gene therapy, and lung growth in lung hypoplasia.

Transfusion practice

Transfusion practice varies widely between different physicians and centres. The Transfusion Requirement in Critical Care Trial[12] suggested that transfusion to hemoglobin levels of 10–12 $g \cdot dL^{-1}$ is associated with increased organ dysfunction compared to lower hemoglobin (7–9 $g \cdot dL^{-1}$) in ICU patients. In patients with ischemic heart disease, a higher hemoglobin is possibly preferable, although randomized trials are needed in this population. Erythropoietin administration is also being evaluated as a potential alternative to transfusion and several randomized trials are now underway.

Blood substitutes are available in two forms: hemoglobin based oxygen carriers or perfluorocarbons. Clinical trials of blood substitutes in cardiac and non-cardiac surgery to date suggest that these products may help patients to avoid transfusion and augment O_2 delivery. One trauma trial showed a higher mortality in the blood substitute group. From a scientific perspective, the interest lies in the blood substitutes' ability to normalize microcirculatory physiology. Whether this is truly beneficial is debated, as cellular down regulation in the context of low perfusion may be protective of organ function. This active area of clinical research has many ongoing or completed phase II and III trials. There is accumulating data on the safety profile; some products may soon be available for use in North America.

Conclusion

Critical care provides constant challenges to the practitioner whose attempt to remain up to date is made more difficult by the breadth and amount of new information available. This critical care symposium aptly captured bench-to-bedside areas of interesting new basic research, reviewed clinical trials with potential practical impact on day-to-day practice, and revisited older scientific questions (such as steroids in sepsis) which are now being re-evaluated in a new light.

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