WHEN LESS IS MORE IN THE INTENSIVE CARE UNIT; LESSONS LEARNED

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Abstract

In parallel to technological advances in late twentieth century, medical diagnostics and therapeutic options greatly improved. A surge of evidence-based research in intensive care medicine provided additional opportunities and the "best" medical practice has been changing rapidly. However, the primary focus of Hippocrates: "Primum non nocere" (first do no harm) is often neglected at the bedside. It became apparent that lesser intervention in the ICU may actually mean more for the patient. Multiple examples of the concept "when less is more in the ICU" are described here in an ABC format. Critical care providers have an obligation to keenly and closely follow the results of new investigative studies and to carefully incorporate those into our practice. However, they have to be sensitive to individual circumstances, patient and family preferences, and avoidance of harm.

KEY WORDS: Intensive care, evidence-based, first do no harm

Introduction

The past several decades have been marked by great technological advances, which resulted in significant improvements in the way we diagnose and treat different disease states. In the United States, we have literally become a "death-denying society", and death in the hospital and in the intensive care unit (ICU) often represented "a failure". This focus shift, from the comfort to cure, often lead us away from the primary focus of Hippocrates: "Primum non nocere" (first do no harm). Rather than a primary guiding principle of medical practice, this important concept became a historical phrase. What we mean by this is not that we, medical practitioners, actually ignore potential harms, but in our desire to achieve the cure, by all means, sometimes we neglect Hippocrates' first guiding principle. While we routinely try to weigh benefits and risks of proposed treatments, the decisions to treat despite significant (and prohibitive) risks are employed more and more commonly.

The last decade of the 20-th century was marked by a rising concept of evidence-based medicine, and what followed in the first decade of this century was unparalleled surge in good-quality research, especially in the field of intensive care medicine. The results of controlled trials provided opportunities to save more lives, by adhering our practice to the published protocols. However, the focus of research has mainly been improvement in mortality, by all means. The domino effect-protocols spread rapidly from the bench to the academia and community, sometimes, prematurely so (1) (2). Therefore, our intention with this writing is to point out most common occurrences in the intensive care medicine when less could actually mean more for the patient. The following is not all-inclusive illustration and is supposed to motivate the readers to search for moderation and individualization in their medical practice in the complex critical care environment.

When less is more...

As fellows in critical care medicine at Mayo Clinic in early 2000s, due to abundance of new data being published, we sought and found an easy way to organize our medical reasoning and application of best available data at the bed side. A concept of ABCs of evidence-based critical care medicine (3) was created, where each letter from A to G reminded a provider of the certain step in the care for critically ill patient. This tool has been taught to subsequent generations of trainees at Mayo Clinic, as it is simple to remember and use. The tool is not all-inclusive by any means but represents most commonly used interventions in the ICU. With each letter and corresponding intervention, it will be easy to appreciate how less may actually mean more for the patient.

A – Acute Respiratory Distress Syndrome (ARDS)
Mechanical ventilation saves lives and it is a therapeutic support of choice for the patients with ARDS. Traditional teaching and practice of mechanical ventilation (MV), until recently, utilized relatively large tidal volumes (TV), 10-15ml/kg of actual body weight, with the goal of normalizing partial pressure of oxygen (O_2), carbon dioxide (CO_2) and pH on the arterial blood gas analysis. However, several studies including a landmark ARDS-Net trial (4) showed that ventilation with smaller TV (6ml/kg of predicted body weight, PBW) and accepting abnormal blood gas values actually improves survival, by decreasing potential for volutrauma and ventilator induced lung injury. Patients ventilated with smaller TV had a higher CO_2 and a lower pH, which did not adversely affect the survival, hence the term "permissive hypercapnia". The small TV group was ventilated with moderately high (8-10 cm H_2O) positive end-expiratory pressure (PEEP), aiming to reduce atelectasis and "atelectrauma". Subsequent studies of MV with higher levels of PEEP failed to show further survival improvement (5-6).

B - Blood transfusion
While actual blood transfusion practices varied a lot, the traditional teaching in the ICU suggested transfusing patient additional blood volume if hemoglobin (Hb) level fell below 10g/dl. This cutoff was based on early in vitro studies of blood viscosity and O_2-carrying capacity, where it was found that this relation is adversely affected if Hb level drops below 10g/dl. These preclinical studies, however did not take into consideration potential for side effects associated with blood transfusion. A Canadian Critical Care Network study showed that restrictive blood transfusion strategy with a cutoff Hb level at 7g/dl was associated with improved morbidity and trend towards improved mortality when compared with liberal transfusion practices (Hb threshold of 10 mg/dL)(7). Critically ill patients seem to benefit from restrictive transfusion strategy except perhaps in cases of active bleeding, early shock and acute coronary syndrome. Given the frequency of transfusion complications including transfusion related acute lung injury (TRALI) and transfusion associated circulatory overload (TACO) (8-9), less transfusion of blood products indeed may mean "more" for the critically ill patient.

C – Corticosteroids

A French study published in JAMA in 2002 suggested that hydrocortisone and fludrocortisone improved survival in patients with septic shock (10). Performance of an ACTH stimulation test with cosyntropin was important part of the protocol where "nonresponders" (the cortisol increased by <9 on the cosyntropin test) treated with hydrocortisone and fludrocortisone benefited the most, number needed to treat (NNT) for 1 life saved was 7. Use of steroids then became standard of care in non-selected patients with septic shock. The mortality benefit observed in the French study has not been replicated in the most recent large international multicenter double-blind placebo-controlled study of 499 patients with septic shock randomized to hydrocortisone or placebo. Moreover, cosyntropin test was not shown to be useful to determine the presence or absence of adrenal insufficiency (11). Accordingly, steroids should be reserved for treatment of the most severe cases of septic shock, not responsive to fluid resuscitation and vasopressor medications.

D – Drotrecogin alpha

Drotecogin alpha, or activated protein C (APC) marked early 2000s as the "hottest" drug in sepsis. The study by Bernard et al. showed significant reduction in mortality, a relative risk reduction (RRR) of death by 20% and an absolute risk reduction (ARR) of death by 6% if septic patients received APC 24mcg/kg/hr x 96 hours (1). However, there was higher incidence of serious bleeding in the APC group (3.5% vs. 2%). What followed was a rapid increase in use of this very expensive medication and infiltration of the industry (manufacturer of APC) in all pores of academia and community. Subsequent studies showed more risk than benefit with APC use among non-selected populations. APC did not benefit patients at low risk of death, patients with baseline bleeding risk and pediatric patients (12-15). Systematic review of Cochrane database in 2008 found no evidence suggesting that APC should be used in severe sepsis or septic shock; "APC seemed to be associated with a higher risk of bleeding and unless additional RCTs provided evidence of a treatment effect, policy-makers, clinicians and academics should not promote the use of APC".

E – EGDT, early goal directed therapy

Dr. Rivers randomized septic patients to standard or EGDT (16). Per this study protocol, patients in EGDT group were started on treatment with intravenous fluids in the emergency room. In addition, those with apparent sepsis were treated with vasopressors and or inotropes to maintain a MAP >65. The average amount of fluid given in the first 6 hours was 5 liters. This included more blood transfusions if Hb was less than 10 and more inotropes (dobutamine) then in the control group. Although the evidence that either transfusion of blood to keep Hb above 10g/dl or dobutamine, improve outcome of septic patients is lacking, these steps were part of the protocol that resulted in significantly reduced hospital mortality (46% to 30%), and the protocol was widely accepted. As mentioned earlier, restrictive blood transfusion practices appear to be safer for critically ill patients (7). Also, dobutamine has arrhythmogenic potential and may increase an already elevated heart rate in septic patients. The key component of EGDT was *early* adequate fluid resuscitation (in the emergency room); potentially this alone would have made a crucial impact and difference in outcomes (17). One should probably exercise caution before transfusing septic patients with Hb less than 10g/dl and dobutamine use should be avoided in the absence of myocardial dysfunction, particularly in the presence of tachycardia.

F – Fluids

While aggressive fluid resuscitation is beneficial early in the course of sepsis, especially first 6 hours and possibly first 24 hours, liberal fluid administration later in the course of critical illness may have a deleterious effect. Hemodynamic monitoring of critically ill is suboptimal, and frequently fluid challenges are used in order to determine patient's fluid responsiveness. This often results in giving more fluid than necessary with consequences ranging from hypoxemia to increased incidence of pressure ulcers. The negative impact of fluid over-administration was best demonstrated in the study that compared liberal versus conservative fluid management in ARDS (18). The group with conservative fluid administration showed trend towards lower mortality, spent less time on mechanical ventilator and in the ICU, with no adverse effects on renal function. Another important issue with fluid resuscitation is related to "the great fluid debate", i.e. crystalloids versus colloids. Crystalloids have been a mainstay of fluid therapy for decades; they are inexpensive and widely available. However as we have witnessed earlier, there has always been a push towards newer, fancier and more expensive therapeutics. Multiple studies over last several years, including systematic review of Cochrane database in 2007 and large meta-analysis have shown no overall advantages of albumin, plasma protein fraction, dextran, hydroxyethylstarch or gelatin over simple crystalloid solutions. These compounds frequently increased

complications and morbidity rates, depending on the solution used or patient population studied (19-22).

G – Glucose control

In a one of most cited medical publication of this decade, Van den Berghe et al. showed relative risk reduction in ICU mortality of 50% among postoperative, mostly cardiac surgery patients by adhering them to intensive insulin therapy (IIT) and tight glucose control between 80 and 110 mg/dl (2). There was also an overall reduction in hospital mortality by 34%, bloodstream infections by 41%, transfusions by 50% and acute renal failure by 41%. Needless to say that IIT swept the medical world and shortly became standard of care in most ICUs. Fortunately, practitioners and experts most often adopted more modest goals of glucose control (<150 mg/dL). The results of this study could not be largely replicated, and series of studies and publications including meta-analysis, showed no significant reduction in hospital mortality with IIT and an increased risk of hypoglycemia (22-27). A recently completed large international NICE SUGAR trial (28) included over 6000 patients, demonstrated an increased risk to benefit ratio of IIT (target glucose between 89-110 mg/dL) compared to more conservative approach (target glucose between 140-180 mg/dL). Early in critical illness hyperglycemia may simply be an adaptive response, providing glucose for the brain, red cells, and wound healing. Potentially more important factor than simple serum glucose concentration seems to be standard deviation of glucose measurements or glucose variation (29-30). A target glucose control should therefore be maintained between 140 and 180mg/dl for majority of patients, with avoidance of excessive glucose variability.

Discussion

Above examples are not all inclusive. Any therapeutic approach, intervention or medication has its' risks and careful consideration of risk/benefit ratio, taking into account patient preference should always be sought. Even oxygen therapy or antibiotics, which we often order without thinking twice, may exhibit adverse effects, pose toxicity to the cells or induce drug resistance. So, where do we go from here? The answer is not simple nor there a single one. As critical care providers we do have obligations to keenly and closely follow the results of new investigative studies and carefully incorporate those into our practice. However, we need to pay attention to the very details and tailor these results and their application to each and every patient individually. We have to carefully weigh the risks and harms of such treatments with their proposed benefits, and to communicate them readily to patients and their families. The ultimate goal is to improve not only "quantity" but also the quality of life, and we ought to think first not to cause more harm. Good knowledge of research results and protocols, taking into consideration individual circumstances and patient and family preferences and applied in moderation seems to be the most sensitive way for a responsible and truly evidence-based medical practice. That's when less actually may mean more for our patients.

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