Intensive Care Med
https://doi.org/10.1007/s00134-019-05771-2

LESS IS MORE IN INTENSIVE CARE

Less is more in critical care is supported by evidence-based medicine

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The notion that "less is (or may be) more" in intensive care medicine has been contemplated by experts for decades. However, not until Kox and Pickkers' review in 2013 had there been careful consideration of the evidence supporting this theory [1]. Their thought-provoking article focused specifically on sepsis, but the intervening years have yielded expanded evidence supporting this notion across many critical conditions. As healthcare systems seek to incentivize high-value care, transparency, and adherence to evidence-based practice guidelines, we must assess the strength of the evidence base regarding less is more. Here, we discuss recent randomized clinical trials (RCTs) that support the notion that even in intensive care units (ICUs), less intensive interventions may prove superior.

Protocolized ICU care

Perhaps the biggest giant to fall in the last six years is early-goal-directed therapy (EGDT) for sepsis care—or at least the variety of EGDT proposed by Rivers and colleagues [2]. Three separate RCTs conducted across seven countries have shown no mortality benefit to protocolized EGDT when compared to protocol-based standard therapy or usual care [3–5]. In all studies, patients in the EGDT group received increased days of vasopressor support. Mouncey et al. additionally found that EGDT was associated with increased ICU length of stay (LOS) and costs [4]. While these studies have not debunked the value of early antibiotics and resuscitation, they have been practice-changing around the more invasive components of the original EGDT protocol, specifically the routine use of central venous catheters and using central venous saturations to guide blood transfusion.

A further challenge to increasingly protocolized ICU care came from Mehta and colleagues, who found that the addition of daily sedation interruptions to protocolized sedation in mechanically ventilated patients did not reduce duration of mechanical ventilation or ICU stay [6]. While clinical outcomes were similar across groups, the addition of sedation interruption was associated with greater nursing workload.

Ventilatory support

A paradigmatic example of a less-is-more strategy is the use of low tidal volume ventilation. In the two decades following the landmark ARMA trial [7], additional evidence supports simplified versions of low tidal volume strategies for patients with ARDS over more complex and aggressive strategies. The addition of lung recruitment maneuvers and PEEP titration increased mortality when compared to low-PEEP strategy in patients with moderate to severe ARDS [8]. The aggressive ventilator strategy also decreased mean ventilator-free days (VFDs) and increased risk of pneumothorax and barotrauma.

Resuscitation fluids and transfusions

Several RCTs have also compared the administration of colloid with crystalloid solutions. In patients with severe sepsis, fluid resuscitation with hydroxyethyl starch (HES) was compared to Ringer's acetate. The trial found an increased risk of death and renal-replacement therapy (RRT) in patients randomized to the HES group [9]. In a second trial, resuscitation with HES was compared to normal saline solution in a mixed ICU population [10]. While mortality did not differ across arms, again, increased rates of RRT were noted in the HES group.

Another key example of a less-is-more approach is the guidance, since the original TRICC trial, to use a

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restrictive rather than liberal threshold for transfusing red blood cells [11]. Recent evidence solidified the less-is-more approach regarding transfusion in populations initially excluded from early trials [11, 12]. An RCT of patients with severe acute upper gastrointestinal bleeding revealed improved survival, reduced bleeding, and fewer adverse events with a restrictive transfusion approach [13]. Another RCT among patients undergoing cardiac surgery revealed the restrictive approach was generally no worse than the liberal approach despite significantly reduced transfusions, and was superior to the liberal approach among older patients [14].

Renal replacement therapy

Gaudry et al. completed a multicenter RCT of patients with severe acute kidney injury without emergent indications for dialysis to receiving renal replacement therapy (RRT) either early (immediately after randomization) or delayed (only if and when a severe complication of renal failure developed) [15]. While there was no difference in mortality between groups, the delayed strategy enabled the avoidance of RRT in 61% of survivors.

Blood pressure goals

In patients with septic shock, Asfar et al. compared a higher target of mean arterial blood pressure (80–85 mmHg) to the more traditional 65–70 mmHg [16]. The more aggressive blood pressure target had no benefit on mortality. In a sub-group of patients with baseline chronic hypertension, the higher blood pressure target was associated with decreased need for RRT without corresponding improvements in mortality. While major adverse events were similar across groups, there were higher rates of new atrial fibrillation in the high-target group. Larger, ongoing RCTs comparing various high vs low blood pressure targets in the ICU will soon shed further light on this common dilemma.

Nutrition

Caloric intake seems like an area in which more should simply be more given the adverse consequences of malnutrition among the critically ill. Yet again, more aggressive strategies have not proven beneficial. Delaying initiation of parenteral nutrition to supplement caloric intake of both adult and pediatric patients not meeting their goals enterally was associated with many benefits including shorter LOS, fewer ICU infections, and decreased cost of care [17, 18]. In a trial of energy-dense vs routine enteral nutrition in mechanically ventilated patients, the more intense strategy did not show a mortality benefit, but did result in more gastrointestinal intolerance and hyperglycemia [19]. These results were similar to those seen in an earlier RCT comparing trophic enteral feeding with full dose feeding [20].

Conclusions and future directions

Together, these RCTs support the notion that less intensive management is often superior to more intensive approaches to critical care delivery. Though many of the trials were null with regard to mortality, most ICU trials lack adequate statistical power to identify plausible mortality differences [21]. Importantly, as designed, the trials above frequently demonstrate that secondary outcomes favor the less intensive approach and establish real harm associated with more intensive interventions. Statistical power is not the only limitation in many of these trials (Table 1). Development of a more personalized approach, or the design of trials with better predictive and prognostic enrichment may allow for a more nuanced understanding of when and for whom “more is more” [22, 23]. However, with currently available evidence, the uniform absence of benefits to more intensive approaches itself favors a less intensive approach—why would one use more costly strategies when less costly ones are at least as good?

Table 1 Randomized clinical trials demonstrating that "less is more"

Intervention	Effect
Protocolized ICU care	
Protocol based EGDT vs protocol-based standard therapy vs usual care [3–5]	No mortality benefit [3–5] EGDT associated with: longer ICU LOS [4] Increased days on cardiovascular support [3–5] Increased costs [4]
Protocol sedation plus daily sedation interruption vs standard protocol sedation [6]	No mortality benefit Increased nursing workload
Ventilatory support	
Lung recruitment and PEEP titration vs low PEEP [8]	Increased mortality Decreased mean ventilator-free days Increased risk of pneumothorax Increased barotrauma
Resuscitation fluids and transfusions	
Hydroxyethyl starch vs Ringers acetate [9] or normal saline [10]	Increased mortality [9] Increased need for RRT [9, 10]
Restrictive (hemoglobin of 7 g per deciliter) vs liberal (hemoglobin of 9 g per deciliter) red blood cell transfusion for acute UGIB [13]	Improved survival Decreased adverse events in restrictive strategy
Renal replacement therapy	
Early vs delayed initiation of continuous RRT in patients with AKI [15]	No benefit, avoidance of RRT 49% of patients in the delayed arm
Blood pressure goals	
MAP targets of 80–85 mmHg vs 60–70 mmHg [16]	No mortality benefit Increased new atrial fibrillation in high-target group Less RRT in sub-group of patients with chronic hypertension in the high-target group
Nutrition	
Early (within 48 h) vs late parenteral nutrition to supplement enteral nutrition [17, 18]	No mortality benefit Late initiation associated with: Shorter ICU and hospital LOS Fewer ICU infections Fewer days of RRT Decreased cost
Energy-dense vs routine enteral nutrition in mechanically ventilated patients [19]	No difference in mortality Increased upper gastrointestinal intolerance and hyperglycemia
Trophic vs full enteral feeding for the first 6 days of mechanical ventilation [20]	No difference in mortality or VFDs Increased vomiting, constipation, and need for insulin in full feeding group

AKI acute kidney injury, *EGDT* early-goal directed therapy, *LOS* length of stay, *MAP* mean arterial pressure, *PEEP* positive end-expiratory pressure, *RRT* renal replacement therapy, *TEN* total enteral nutrition, *UGIB* upper gastrointestinal bleed, *VFDs* ventilator-free-days

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Funding
Dr. Van den Berghe holds an ERC Advanced Grant (AdvG-2017-785809) from Horizon 2020 Program of the EU and receives long-term structural funding by the Methusalem Program funded by the Flemish Government (METH/14/06).

Compliance with ethical standards

Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

Publisher's Note

Received: 30 July 2019 Accepted: 29 August 2019
Published online: 18 September 2019

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