Can Less be More in Intensive Care?

Seven recent randomized clinical trials (RCTs)[1-7] add momentum to a question the intensive care community is increasingly exploring; can “Less Be More” in the management of the critically ill? Practices are evolving in this direction with a preference for less invasive monitoring or intervention, less routine changing of invasive devices, and a decrease in the frequency of routine investigations. At the basic human level, it is easier to do something than to do nothing, and the pressure on clinicians to do something is much more in the context of a critically ill patient. Many clinicians have a strong intervention bias to use unproven therapies. But increasingly, clinicians are questioning if this liberal approach is effective or even harmful.[8-11]

There are nonclinical and clinical arguments to support a minimalistic approach. In the context of “less is more,” even with equivalent clinical outcomes, lesser therapies can be “more” in terms of more efficient resource utilization. This is equally relevant in the rich and poor economies, and one sees the richer countries fighting an increasingly difficult battle against runaway expenditure. Unfortunately, in the real world, there are financial incentives for clinicians, administrators, and industry to do more rather than less, regardless of the evolving scientific data. Upton Sinclair pithily observed that it is difficult to get a human to understand something, when his/her salary depends on his/her not understanding it.

The main clinical argument against doing too much is that there are adverse outcomes noted with many therapies. We have explored this[11] and cited the literature that demonstrates that less can actually be equivalent or more for multiple Intensive Care Unit (ICU) therapies including O₂ supplementation, drugs in cardiopulmonary resuscitation, and other standard ICU practices including monitoring and life support.

There is reasonable plausibility too in supporting such an approach. During the stress of an illness, many parameters may fall outside the normal range, as part of a protective response. Reversing these protective responses by targeting normal values may be detrimental. Two billion years of eukaryotic evolution and 600 millions of years of large animal evolutionary selection have resulted in complex but poorly understood physiologic adaptations that are ruthlessly efficient in ensuring healing and survival. Our add-on therapies, based on 2–3 centuries of modern medicine, are often too simplistic and superficial to impact outcomes.

Ultimately, however, the concept of “Less is More” needs to be empirically proven. Critical care trials may study surrogate end points or clinical outcomes. While numerous trials have demonstrated physiological benefit, there has been much less success when studying clinical end points. There are a large number of trials where there has been clinical harm despite success in achieving the physiological target.[11] In critical care, the main clinical outcomes are decreased mortality, decreased severity, and a faster and more complete recovery. A lesser severity can be gauged by the duration of the illness and therapy, the degree of invasive interventions needed, and the associated discomfort caused to a patient. Mortality is by far most important and we focus on this in attempting to use empiric data and prove that less is truly more in emergency and ICU patients.

If the “less is more” concept were correct, we hypothesized that, in randomized controlled trials (RCTs), the mortality in the patients in the “less” or control group (receiving placebo, restrictive, or standard therapy) would be significantly lower than in the “more” or intervention group (receiving study intervention or liberal therapy). We reviewed all RCTs related to emergency, acute, or critical care medicine with mortality as an end point published in the New England Journal of Medicine (NEJM) from 2008 onward.[12] In this list [Table 1], updated to October 2016,[1] we found 63 trials. This is not a cherry-picked list. These trials passed the NEJM review and selection process, and we included all which we felt were representative, before doing any analysis. There were a few therapies in conditions with a low (<10%) mortality, but we included them as we felt they represented intensive care practices (PRBC transfusions, thrombolysis in pulmonary embolism, and antibiotic duration).

Some studies had more than two arms, and we combined the groups together in a way that a “less” approach was compared to a “more” approach. Trials variously report ICU mortality, hospital mortality, or mortality at specified time points. We used the value reported at the longest follow-up period based on the protocol of each individual study.

In this cohort from 63 RCTs, the total reported mortality in intervention group was 23,601/58,727 (40.19%), and in the...
Table 1: Randomized controlled trials published in the New England Journal of Medicine 2008-Oct 2016. \( n = 63 \)

| Category                     | \( n \) | Trial name           | Intervention and disease | Intervention mortality | Control mortality | Primary outcome | Mortality outcome | Reference                                      |
|------------------------------|--------|----------------------|--------------------------|------------------------|------------------|-----------------|------------------|-----------------------------------------------|
| Cardiovascular Shock Sepsis  | 1      | VASTT\(^a\)         | Vasopressin versus noradrenaline in septic shock | 172/392                | 188/379          | Similar         | Similar          | N Engl J Med 2008;358:877-87                  |
|                              | 2      | CORTICUS            | Steroids in septic shock | 86/251                 | 78/248           | Similar         | Similar          | N Engl J Med 2008;358:111-24                 |
|                              | 3      | SOAP II\(^a\)      | Dopamine versus noradrenaline in septic shock | 517/821                | 565/858          | Similar         | Similar          | N Engl J Med 2010;362:779-89                 |
|                              | 4      | PROWESS SHOCK       | APC in severe sepsis     | 287/842                | 269/822          | Similar         | Similar          | N Engl J Med 2012;366:2055-64                |
|                              | 5      | IABP-SHOCK-II       | IABP in cardiogenic shock | 119/300                | 123/298          | Similar         | Similar          | N Engl J Med 2012;367:1287-96                |
|                              | 6      | SEPSISPAM           | MBP target in septic shock | 142/388                | 132/388          | Similar         | Similar          | N Engl J Med 2014;370:1583-93                |
|                              | 7      | ProMISE             | EDGT                     | 184/623                | 181/620          | Similar         | Similar          | N Engl J Med 2015;372:1301-11                |
|                              | 8      | ProCESS\(^b\)      | Saline or albumin in severe pediatric sepsis | 254/2126               | 91/1044          | Adverse         | Increased        | N Engl J Med 2011;364:2483-95                |
|                              | 9      | ARISE               | Saline or albumin in severe pediatric sepsis | 129/439                | 267/902          | Similar         | Similar          | N Engl J Med 2014;370:1683-93                |
|                              | 10     | ALBIOS              | Albumin in sepsis        | 147/792                | 150/796          | Similar         | Similar          | N Engl J Med 2014;371:1496-1506              |
|                              | 11     | FEAST               | Saline or albumin in severe pediatric sepsis | 365/888                | 389/893          | Similar         | Similar          | N Engl J Med 2014;370:1412-21                |
|                              |        | FEAST Hypotensive   | Saline or albumin in severe pediatric sepsis | 9/13                  | 9/16             | Adverse         | Similar          | N Engl J Med 2016;375:1638-48                |
|                              | 12     | 6S                  | HES in shock             | 202/398                | 173/400          | Adverse         | Increased        | N Engl J Med 2012;376:124-34                |
|                              | 13     | CHEST               | Prone position in ARDS   | 597/3315               | 566/3336         | Similar         | Similar          | N Engl J Med 2012;376:1901-11                |
|                              | 14     | CARRRESS-HF         | Ultrafiltration in CCF   | 16/94                  | 13/94            | Adverse         | Similar          | N Engl J Med 2012;367:2296-304              |
| Respiratory ARDS Mechanical ventilation | 15     | LEOpards            | Levosimendan for the prevention of acute organ dysfunction in sepsis | 97/258                | 84/256           | Similar         | Similar          | N Engl J Med 2016;368:795-805               |
|                              | 16     | ACURASYS            | Neuromuscular blockers in ARDS | 56/177                 | 66/162           | Beneficial      | Decreased        | N Engl J Med 2010;363:1107-16               |
|                              | 17     | PROSEVA             | Prone position in ARDS   | 56/237                 | 94/229           | Beneficial      | Decreased        | N Engl J Med 2013;368:2159-68               |
|                              | 18     | OSCAR               | HFOV in ARDS             | 166/398                | 163/397          | Similar         | Similar          | N Engl J Med 2013;368:806-13                |
|                              | 19     | OSCILLATE           | NIV versus CPAP         | 129/275                | 96/273           | Adverse         | Increased        | N Engl J Med 2013;368:795-805               |
|                              | 20     | FLORALI\(^d\)      | NIV versus CPAP versus O\(_2\) in respiratory failure | 31/110                 | 35/200           | Beneficial (CPAP group) | Decreased (CPAP group) | N Engl J Med 2015;372:2185-96            |
|                              | 21     | HARP-2              | Simvastatin in ARDS      | 67/258                 | 90/279           | Similar         | Similar          | N Engl J Med 2014;371:1695-703              |
|                              | 22     | ROSUVASTATIN        | Rosuvastatin in ARDS     | 108/379                | 91/366           | Similar         | Similar          | N Engl J Med 2014;370:2191-200              |
| Renal                        | 23     | ATN                 | Intensity of RRT         | 302/563                | 289/561          | Similar         | Similar          | N Engl J Med 2008;359:7-20                  |
|                              | 24     | RENAL               | Intensity of RRT         | 322/721                | 352/743          | Similar         | Similar          | N Engl J Med 2009;361:1627-38               |

Contd...
| Category | n | Trial name | Intervention and disease | Intervention mortality | Control mortality | Primary outcome | Mortality outcome | Reference |
|----------|---|------------|--------------------------|------------------------|------------------|----------------|------------------|-----------|
| Neurology CVA TBI | 25 | AKIKI | Timing of RRT | 150/311 | 153/308 | Similar | Similar | N Engl J Med 2016; 375:122-133 |
| Neurology CVA TBI | 26 | ECASS III | Thrombolysis in CVA | 32/418 | 34/403 | Beneficial | Similar | N Engl J Med 2008;359:1317-29 |
| Neurology CVA TBI | 27 | DESTINY II | Hemicranieotomy in CVA | 20/49 | 47/63 | Beneficial | Decreased | N Engl J Med 2014;370:1091-100 |
| Neurology CVA TBI | 28 | MR CLEAN | Endovascular treatment for CVA | 49/233 | 59/267 | Beneficial | Similar | N Engl J Med 2015;372:11-20 |
| Neurology CVA TBI | 29 | EXTEND IA | | 3/35 | 7/35 | Beneficial | Similar | N Engl J Med 2015;372:1009-18 |
| Neurology CVA TBI | 30 | ESCAPE | | 17/164 | 28/147 | Beneficial | Decreased | N Engl J Med 2015;372:1019-30 |
| Neurology CVA TBI | 31 | SWIFT PRIME | | 9/98 | 12/97 | Beneficial | Similar | N Engl J Med 2015;372:2285-95 |
| Neurology CVA TBI | 32 | REVASCAT | | 19/103 | 16/103 | Beneficial | Similar | N Engl J Med 2015;372:2296-306 |
| Neurology CVA TBI | 33 | MR RESCUE | | 12/64 | 13/54 | Similar | Similar | N Engl J Med 2013;368:914-23 |
| Neurology CVA TBI | 34 | SYNTHESIS | | 14/181 | 11/181 | Similar | Similar | N Engl J Med 2013;368:904-13 |
| Neurology CVA TBI | 35 | IMS III | | 83/434 | 48/222 | Similar | Similar | N Engl J Med 2013;368:893-903 |
| Neurology CVA TBI | 36 | INTERACT 2 | BP control in ICH | 166/1399 | 170/1430 | Similar | Similar | N Engl J Med 2013;368:2355-65 |
| Neurology CVA TBI | 37 | ATACH-2 | | 33/481 | 34/480 | Similar | Similar | N Engl J Med 2016; 375:1033-1043 |
| Neurology CVA TBI | 38 | TTM | Hypothermia after CPR | 235/473 | 225/466 | Similar | Similar | N Engl J Med 2013;369:2197-206 |
| Neurology CVA TBI | 39 | THAPCA | | 94/151 | 97/134 | Similar | Similar | N Engl J Med 2015;372:1898-908 |
| Neurology CVA TBI | 40 | TBI PROTECT | Progesterone in TBI | 83/442 | 69/440 | Similar | Similar | N Engl J Med 2014;371:2457-66 |
| Neurology CVA TBI | 41 | TBI SYNAPSE | | 109/591 | 95/588 | Similar | Similar | N Engl J Med 2014;371:2467-76 |
| Neurology CVA TBI | 42 | DECRA | Craniectomy in TBI | 14/73 | 15/82 | Adverse | Similar | N Engl J Med 2011;364:1493-502 |
| Neurology CVA TBI | 43 | RESCUEIcpl | | 54/201 | 92/188 | Similar | Decreased | N Engl J Med 2016;375:1119-30 |
| Neurology CVA TBI | 44 | BEST-TRIP | ICP monitoring in TBI | 56/157 | 67/167 | Similar | Similar | N Engl J Med 2012;367:2471-81 |
| Neurology CVA TBI | 45 | EUROTERM | Hypothermia in TBI | 69/194 | 51/192 | Adverse | Similar | N Engl J Med 2015;373:2403-12 |
| Neurology CVA TBI | 46 | FAST-MAG | Mg in CVA | 132/857 | 131/843 | Similar | Similar | N Engl J Med 2015;372:528-36 |
| Neurology CVA TBI | 47 | PANTER | Limited approach in pancreatitis | 7/45 | 8/43 | Beneficial | Similar | N Engl J Med 2010;362:1491-502 |
| Neurology CVA TBI | 48 | STOP-ITl | Antibiotic duration in peri-operative septic abdomen | 1249/3949 | 632/1990 | Similar (beneficial after data adjustment) | Similar | N Engl J Med 2009;360:20-31 |
| General ICU | 49 | SELECTIVE | Limited approach in pancreatitis | 1249/3949 | 632/1990 | Similar (beneficial after data adjustment) | Similar | N Engl J Med 2009;360:20-31 |
| General ICU | 50 | PROTECT | LMWH versus UFH for DVT prophylaxis | 414/1873 | 459/1873 | Similar | Similar | N Engl J Med 2011;364:1305-14 |
| General ICU | 51 | LIFENOX | LMWH in medical patients | 348/4171 | 355/4136 | Similar | Similar | N Engl J Med 2011;365:2463-72 |
In the trial (number 63) evaluating CPR, lignocaine or amiodarone was taken as the intervention and placebo as the control. In the FEAST study, in the non-hypotensive stratum, we took the placebo to be less/standard and both the saline and albumin groups to be more/intervention. In the hypotensive stratum, saline was taken as standard and albumin was taken as the intervention, dIn FLORALI, we took standard O
saline and albumin groups to be more/intervention. In the hypotensive stratum, saline was taken as standard and albumin was taken as the intervention.

control group, it was 20,752/53,568 (38.74%). The relative risk of death in the intervention group of patients was 1.0374 (95% confidence interval: 1.0224–1.0526; *P* < 0.001). Though the absolute difference appears relatively low at 1.45%, it denotes a statistically significant higher mortality. This translates to an additional death for every 69 patients enrolled in the intervention arms of these trials. This adds empiric evidence to the concept that doing less in ICU may result in significantly lower mortality in a wide spectrum of emergency or critically ill patients.

Medicine is not a black and white field, and therapy may be beneficial even if it does not decrease mortality. For this reason, many trials report a composite end point which may or may not include mortality. To evaluate the impact of intervention on these other relevant end points, we compared the number of positive, neutral, and adverse outcomes in terms of reported primary end points. We did not include nonmortality secondary end points, *post hoc*-adjusted outcomes, or subgroup benefits in our analysis. Only eight therapies reported improved mortality or other clinically meaningful primary outcomes (continuous positive airway pressure in respiratory failure, thrombolysis in cerebrovascular accident [CVA], neuro-intervention in CVA, surgical control of intracranial pressure [ICP] in CVA, prone position ventilation in ARDS, neuro-muscular-blockers in...
acute respiratory distress syndrome [ARDS], liberal transfusion after cardiac surgery, and limited approach in pancreatitis) while seven therapies worsened outcomes (hydroxy ethyl starch solutions for fluid resuscitation, fluid bolus in pediatric nonhypotensive sepsis, high-frequency oscillatory ventilation in ARDS, glutamine supplementation, early total parenteral nutrition, surgical ICP control in traumatic brain injury, and hypothermia in traumatic brain injury). The majority had no impact on the primary outcome. This further strengthens the case for the judicious use of unproven therapies.

It is worth pointing out that “Less is More” is not a lazy approach; rather, it is a well-researched and carefully thought-out strategy aimed at getting rid of the therapies that do not improve clinical outcomes. This analysis of more than 100,000 patients from high-quality NEJM RCTs in the past decade demonstrates that the majority of studies failed to demonstrate clinical benefit. A judiciously restrictive approach, besides being resource efficient, could be associated with an overall mortality benefit. In critical care, simplicity may be the ultimate form of sophistication.

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