

## Optimising clinical outcomes with innovative research in the intensive care unit

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**Vijaya Patil, Muthuchellappan Radhakrishnan<sup>1</sup>, Shwethapriya Rao<sup>2</sup>, Madhuri S. Kurdi<sup>3</sup>**

Department of Anaesthesia, Critical Care and Pain, Tata Memorial Hospital, Parel, Mumbai, Maharashtra,

<sup>1</sup>Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences (NIMHANS), Hosur Road, Bengaluru, Karnataka, <sup>2</sup>Department of Critical Care, Kasturba Medical College (KMC), Manipal Academy of Higher Education, Manipal, Karnataka, <sup>3</sup>Department of Anaesthesiology, Karnataka Institute of Medical Sciences (KIMS), Hubli, Karnataka, India

**Address for correspondence:** Dr.Madhuri S. Kurdi,

Department of Anaesthesiology, Karnataka Institute of Medical Sciences (KIMS), Hubli, Karnataka, India.

E-mail: [drmadhuri\\_kurdi@yahoo.com](mailto:drmadhuri_kurdi@yahoo.com)

Patients requiring admission to intensive care units (ICUs) are generally very sick, have poor organ functional reserve, tendency for rapid clinical deterioration, often leading to multiple organ failure and many of them frequently require simultaneous multiple interventions. To improve patient survival, a thorough understanding of the disease process and treatment options is required so as to ensure that best clinical practices are followed. Nevertheless, the evidence for such practices must come from sound scientific clinical research in the ICU.

However, currently, in spite of a significant amount of research happening in critical care, the evidence identifying best practices is still scarce. Research in the critically ill is different from that in other patients and is not much touched upon especially in postgraduate dissertations in Anaesthesiology.

### THE CHALLENGES OF CONDUCTING RESEARCH IN THE ICU

A significant number of opportunities to include eligible, critically ill patients might be missed or might not be feasible in the ICU mainly because of the clinical workload, narrow time windows for inclusion, ethical considerations, difficulties in contacting families or surrogate decision-makers of the patients.<sup>[1]</sup> Considering the life-threatening scenarios, critical care physicians might often prefer to take

decisions based on their clinical experience rather than referring to complex protocols while dealing with critical patients.

The ethical principles that are followed in clinical research are in conflict when it comes to research on intensive care patients. Patients admitted to the ICU are critical and are not able to provide valid and documented informed consent because of their deranged clinical profile. There are other multiple dilemmas which hinder the consent obtaining process, including, but not limited to taking consent from relatives for certain interventions following ICU admission (e.g., treatment options in cardiac arrest, stroke thrombolysis). Similarly, studying the effect of sedatives can be challenging, because if the patient regains decision-making capacity, should the consent be obtained again retrospectively, and if the patient refuses, should these data be excluded? The debates on these issues are unending. In a recent study (NORIDES), 70% of the ICU patients were excluded from the study in spite of fulfilling the inclusion criteria.<sup>[2]</sup> Study participants in the ICU do not get direct benefit from the study as the results are useful for future generations only. However, there is a misconception that by participating in the study, patients would get the maximum benefit (therapeutic misconception). Every interventional trial has some in-built risks and limitations involved which might not be tolerated by ICU patients as their disease processes

are rapidly surfacing with multi-organ dysfunction. Sometimes it becomes difficult to ascertain the cause of deterioration (disease process or study intervention). Selecting patients for the study and control arms, though done by randomisation, is also difficult as the ICU patients are heterogeneous, and organ dysfunction is of varying degrees between patients and also within the patient over a period of time. Some trials, because of poor recruitment, run for years during which time the usual practice itself changes, thus affecting the control arm. As the institutional treatment practices differ between centres, cities and countries, it becomes even more difficult to establish standard clinical protocols in the control arm in multicentric studies.

### **CURRENT TRENDS OF RESEARCH IN THE CRITICALLY ILL**

In spite of the many challenges and obstacles, consistent improvements in critically ill patient outcomes are being observed and these are due to the increasing research centred on various aspects of the critically ill patient, including scoring systems, drugs, biomarkers and the development of new techniques and technology. Mortality and quality of life after discharge are the main outcomes in critical care research followed by ICU length of stay (LOS), hospital LOS and cost.

Scoring systems to stratify disease severity and predict risk and indices including those developed using machine learning have now been developed for several aspects of critical care.<sup>[3-5]</sup> They take out subjectivity from patient assessment and management and help in better resource allocation and better patient management. On the diagnostic front, use of molecular biomarkers in the ICU has increased exponentially. Biomarkers such as cardiac biomarkers, autoantibodies, procalcitonin, serum cystatin C and others help in multiple ways including judging the progress of disease, response to therapy and giving warning regarding the development of organ dysfunction.<sup>[6,7]</sup>

Numerous innovations in equipment and techniques have revolutionised the critical care management. Presently, ultrasound has made a major contribution in reducing diagnostic uncertainty. In the last decade, with the availability of the bedside ultrasonography (USG) machine, the numbers of missed diagnosis and mismanagement have reduced significantly.<sup>[8]</sup> Selectively speaking, USG of the lungs

aids in the detection of pleural effusion, pneumothorax, collapse, consolidation and extra vascular lung water and also allows the optimisation of recruitment manoeuvres in mechanically ventilated patients.<sup>[9-11]</sup>

The role of USG in the ICU is ever-expanding as maximum activities in the ICU are centred around resuscitation, haemodynamic monitoring, airway management and respiratory support including mechanical ventilation and these have always attracted researchers.<sup>[12]</sup> Central line insertion has a failure rate of 22%, catheter malposition in 4% and arterial puncture in 5% cases.<sup>[13]</sup> The role of USG has gained momentum here as the in-plane approach of USG can track the actual course of the entire needle as against the out-of-plane approach where only the tip of the needle is seen. The brachiocephalic vein, being intrathoracic, was never a choice for central venous access before, but with USG it can be easily seen and cannulated under vision. In a study being published in this issue of the Indian Journal of Anaesthesia, the authors have clearly shown the superiority of brachiocephalic vein cannulation using USG.<sup>[14]</sup>

Other challenges in the ICU include weaning from mechanical ventilation, as diaphragmatic dysfunction (DD) due to disuse atrophy and microstructural changes can be a major contributor. Diagnosing DD is challenging and bilateral anterior phrenic nerve stimulation and measurement of transdiaphragmatic pressure are considered as gold standard, however these are not routinely available. USG of the diaphragm is a promising tool which helps in assessment of its excursion, and in visualisation of the diaphragmatic thickening fraction which in turn correlates with the transdiaphragmatic pressure. In another study being published in this issue, the authors have shown that bedside assessment of diaphragmatic excursion can successfully predict DD and thus help in the weaning process.<sup>[15]</sup>

### **IMPROVING THE QUALITY OF RESEARCH IN THE ICU PATIENT**

In spite of the many obstacles in implementing ethical research principles in the ICU patients, these should not deter a clinical researcher from performing good quality research. Different societies, law-makers and government establishments have come out with guidelines for researchers on how to ethically conduct research in critically ill patients, by overcoming obstacles and at the same time ensuring patient safety.<sup>[16]</sup>

Informed consent can be obtained from the patients' next of kin and later confirmed from the patients once they regain their decision-making capacity. The study population can be made homogeneous by following similar grading/severity scoring systems during patient recruitment. Safety monitoring committee and institute ethics committee play an important role in safeguarding the safety of patients. Patients and relatives in the ICU can be informed about the need for research in the ICU management as a part of routine patient counselling with emphasis on better clinical outcome.

Research in critical care is often incapacitated by the conduct of only observational studies, which have their inherent weaknesses. This has serious limitations in methodology and may generate confounding bias and unreliable findings.<sup>[17]</sup> Randomised controlled trials (RCTs) are the gold standard for effectiveness in clinical research, and are a necessity now in the field of critical care. Multicentre RCTs can be even more effective.<sup>[18]</sup> High-quality RCTs can be conducted with the help of research grants. The allocation of more resources and finances for critical care research can be a welcome move in this direction.

There are several untapped areas and much needed to be explored fields in critical care such as research in extracorporeal life support, telemedicine and artificial intelligence algorithms which involve multicentre data sharing and applicability in real time.<sup>[19]</sup> The coronavirus disease 2019 pandemic has brought in huge opportunities along with unforeseen challenges for researchers in the critical care unit as evidenced by the continuing shower of research publications.<sup>[20-25]</sup>

Nevertheless, whatever the topic and the chosen field of research, earnest, honest and high-quality innovative research in critically ill patients is now the urgent need of the hour.

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#### Conflicts of interest

There are no conflicts of interest.

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