

# Translational research in neuroanaesthesia

Ganne S. Umamaheswara Rao

## Abstract

Translational research in anaesthesia provided great solutions to medicine, well beyond its scope, in the past. Exciting opportunities exist for neuroanaesthesiologists to conduct translational research not just in anaesthesia alone but in the wider realm of neurosciences. This research is expected to provide solutions to clinical neuroscience questions and to help understand some of the complex neurocognitive functions. Despite several technical developments, progress in translational sciences has been rather slow in the recent years. Re-orientation of the research programmes to a translational format with the involvement of all the stakeholders is likely to conserve the cost and provide rapid solutions to the healthcare.

**Key words:** Anaesthesia, neuroanaesthesia, outcome, research, translational

## INTRODUCTION

*"We must participate in interdisciplinary and translational research work. The director of the NIH has vowed that research of the future must involve research teams, and anesthesiologists must join these teams with the unique background we bring to all questions."- Reves JG in the 45<sup>th</sup> Rovenstine Lecture to the American Society of Anesthesiology in 2007.<sup>[1]</sup>*

Synchrony between basic science research and clinical research has been lacking for a long time. The result is a delay in transferring the laboratory and clinical research to the bedside. Resources have been wasted on ill-conceived clinical trials without a strong and unequivocal basic science background. Translational research aims to bridge the gap between basic and clinical research with the ultimate goal of advancing healthcare. The process of translational research encompasses several domains such as laboratory work,

clinical demands, health management policies and health economics. Successful translational research requires channelisation of all the involved research teams into a translational path.<sup>[2]</sup>

Successful translational research is a laborious process and may have to overcome scientific, financial, ethical, regulatory, legislative and practical hurdles. Among the stakeholders involved in the process, each may have a different expectation from the programme. For the academia, it is an opportunity to generate novel ideas and turn them into clinical applications. It is process of identification of novel scientific hypotheses through direct observation of humans and their diseases. For physicians, laboratory professionals and patients, it as a mechanism to close the gap between the bench and bedside and transfer of diagnostic and therapeutic advances to daily medical practice. For the industry, translational research provides the confidence to proceed with production. In simple terms, translational research increases the efficiency of determining the relevance of novel discoveries to human disease. It accelerates the rational transfer of new insights and knowledge into clinical practice for improving patient outcomes and public health.<sup>[3]</sup> Thus, translational research provides a framework through which investigators or laboratories can maximise the likelihood that their research product gets adopted into medical practice.

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Department of Neuroanaesthesia, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, Karnataka, India

### Address for correspondence:

Dr. Ganne S. Umamaheswara Rao, Department of Neuroanaesthesia, National Institute of Mental Health and Neurosciences, Bangalore - 560 029, Karnataka, India. E-mail: gsuma123@yahoo.com

The two common courses of translational research are: Investigator driven and industry enabled. Investigator-driven research has a wider scope because it does not take into account the profit margin of research, but it is a slow process. The industry-enabled model accelerates the translational research through its power for funding the process. But industry would be interested primarily in products with potential for profit.<sup>[4]</sup>

## TRANSLATIONAL SCIENCE AND ANAESTHESIA

Innovations are not new to anaesthesia. The evolution of neuroanaesthesia is a result of basic science research that could be translated into clinical practices that benefit the neurological patients in the operating rooms and intensive care units.

### Historical perspectives

Anaesthesia, by itself is a great innovation of translational nature in the history of medicine. Through translational research only, the techniques have become refined and safer over time. Anaesthetics being drugs with a potential to impact every aspect of systemic physiology, anaesthesiologists had to get involved in research that embraces several areas of medicine (physiology, pharmacology, clinical medicine and patient care delivery, etc.). Translational research by anaesthesiologists has greatly transformed patient care in several areas outside anaesthesia. The following are examples of a few major successes and failures of translational work in neuroanaesthesia in the past:

#### Brain and anaesthetics

The contributions made Dr. J. D. Michenfelder and colleagues on the effects of anaesthetics on brain have profound impact on clinical practices in the neurological operating rooms and intensive care units. Extensive experimental research followed by clinical investigation provided concepts that could be incorporated into neuroanaesthetic practice. Their research provided evidence on several physiological and pharmacological aspects of anaesthetic actions. These studies provided insights into the effects of anaesthetics on cerebral blood flow, metabolism, flow-metabolism coupling, autoregulation, response to CO<sub>2</sub> changes, intracranial pressure, and brain electrical activity, the knowledge that has been extremely relevant to plan a safe anaesthetic for a patient with cerebral pathology.<sup>[5-13]</sup>

#### Cerebral ischaemia and protection

Cerebral ischaemia and cerebral protection have been two major research areas in neurosciences. Models of global and focal ischaemia<sup>[14]</sup> used in cerebral protection through anaesthetics have remained the standard models in subsequent research too. Over years, research in

neuroanaesthetic techniques for cerebral protection has involved two major streams of interventions: Anaesthetic drugs and hypothermia.

Anaesthetics: That anaesthetics cause a considerable decrease in brain metabolism provided an attractive hypothesis to use them to protect against cerebral ischaemia. A 50-60% reduction in CMRO<sub>2</sub> at a clinically-relevant anaesthetic concentration appeared to be a great solution to salvage the ischaemic neurons. Experimental studies in smaller animals and primate models of global and focal ischaemia supported the concept.<sup>[15,16]</sup> Several other potential mechanisms for protection have been unravelled in these studies. Encouraged by these results, large-scale clinical trials have been undertaken. Barbiturates have been used in clinical trials of cardiac arrest,<sup>[17]</sup> stroke,<sup>[18]</sup> traumatic brain injury<sup>[19]</sup> and cardiopulmonary bypass.<sup>[20,21]</sup> All these studies met with either disappointing results or false promises that could not be replicated. The end result was a colossal loss of time and resources and a failure of translation of laboratory studies into clinical practices. The introspection that followed offered several lessons on translational research.<sup>[22]</sup> The fundamental lesson learnt was that animal studies conducted under experimental conditions cannot be directly translated into clinical practice. Also, consistency in results of basic research should be established before undertaking large clinical trials. Clearly-defined and realistic outcome targets should be set before embarking on clinical trials to reduce the costs of translational research, avoid frustration and to hasten the translational process.

The story of mild-to-moderate hypothermia in cerebral injury is no different. Profound hypothermia has long-established beneficial effect in complex cardiac surgery. Experimental studies on mild and moderate hypothermia have documented benefit in both focal and global ischaemia. However, large-scale clinical trials have failed both in traumatic brain injury<sup>[23]</sup> and subarachnoid haemorrhage.<sup>[24]</sup> Benefit has been limited to only studies in cardiac arrest.<sup>[25,26]</sup> Hypothermia has found its place in guidelines for post-resuscitation care of survivors of paediatric cardiac arrest.<sup>[27]</sup>

Several molecules, tried for cerebral protection in various forms of brain injury, have yielded uniformly disappointing results, superoxide dismutase,<sup>[28]</sup> selfotel<sup>[29]</sup> and tirilazad,<sup>[30]</sup> just to name a few – a royal failure of translation!

#### Mechanical ventilation in neurological diseases

Work done during the European polio epidemics in the 1950s<sup>[31,32]</sup> may be considered a pioneering effort at translational science that paved the way for mechanical ventilation to save lives of patients with reversible neuromuscular diseases. Credit for successful

mechanical ventilation of patients with Guillain-Barre syndrome, myasthenia gravis, etc., in the current day neurological practice, goes to the translational work of those early years.

### **Cardiopulmonary resuscitation**

Pioneering work carried out by Peter Safar and colleagues in the 1960s transformed the chances of survival of patients of cardiac arrest.<sup>[33-37]</sup> Their innovative work improved the probability of successful restoration of circulation. Provided the ischemic-hypoxic time is short, the odds of good functional survival are very high. However, very little has been done to alleviate the cerebral outcomes of those who have sustained more severe hypoxic injury.

## **CONTEMPORARY TRANSLATIONAL RESEARCH – NEEDS, OPPORTUNITIES AND CHALLENGES**

Necessity and opportunities are driving the present day anaesthesiologists to perform research in areas, which a few decades ago would have been considered well outside the scope of the anaesthesiology. A few examples are given below:

### **Neurotoxicity of Anaesthetics**

Neurodevelopmental concerns in neonates exposed to anaesthetics have necessitated anaesthesiologists to enter the area of research on development of nervous system.<sup>[38,39]</sup> A systematic clinical review using Bayesian technique, concluded that there is a modestly elevated risk of adverse behavioural or developmental outcomes in 60,485 children who were exposed to anaesthesia/surgery during early childhood. The evidence, however, is considerably uncertain.<sup>[40]</sup> Major clinical trials are underway to explore the effect. PANDA (Pediatric Anesthesia and NeuroDevelopment Assessment) is a cohort study that will enrol 500 sibling matched pairs (1000 children) who underwent hernia surgery under general anaesthesia (ASA I-II) before 36 months of age. The children will undergo a series of neuropsychological tests between 8 and 15 years of age.<sup>[41]</sup> The results of this study could prove interesting from a clinical standpoint.

### **Neuroprotection**

Need for neuroprotection in several acute neurological situations has opened a vast scope for work into pathophysiological mechanisms and therapy of brain injury. The mechanisms, currently under investigation by several researchers in anaesthesia, include inflammation, necrosis, apoptosis and neuronal preconditioning.<sup>[42-47]</sup> This work, when translated into clinical tools, may help to protect the brain during intra-operative ischaemic events.

### **Mechanisms of Anaesthesia**

The mechanisms of anaesthetic action remain an enigma even today. It is a paradox that more than a century and a half after discovery of anaesthesia, there is no concrete understanding of its mechanism. Research, in this area implies not just exploring the mechanisms of anaesthetic action, but understanding the very basis of consciousness,<sup>[48]</sup> which neuroscientists from various disciplines have been trying to unravel. Recent approach in this area involves study of the neural net works using sophisticated gadgets like functional magnetic resonance imaging (fMRI),<sup>[49-51]</sup> positron transmission tomography.<sup>[52,53]</sup> This is also a fertile domain for collaborative research across the disciplines in neurosciences,<sup>[54,55]</sup> of which anaesthesia could play a major role.

### **Cognition and Anaesthesia**

Post-operative cognitive dysfunction remains an under-explored area. Here again, a great scope exists for research in cognitive neurosciences. This line of research may have fallouts that may answer questions in cognitive neurosciences and help understanding phenomena like ageing, dementia and Alzheimer's disease.<sup>[56,57]</sup>

### **Traumatic Brain Injury**

Hardly any definitive therapy exists for restoration of neuronal integrity after traumatic brain injury, excepting timely removal of mass lesions and prevention of secondary insults. This calls for translational research in two areas: Limiting the early secondary injury through better care-delivery processes (transportation, resuscitation) and simpler, effective and affordable systems for monitoring cerebral physiology – blood flow, oxygenation and metabolism – with the aim of limiting secondary injury.

### **Cerebral Function Monitoring**

The need to preserve the neuronal viability during surgery in the operating room and in the intensive care units demands research into innovative technologies that have better sensitivity and specificity and would preferably be non-invasive and inexpensive. Very little scope exists at this time to monitor the cerebral function and the available monitors are cumbersome, expensive and labour-intensive with limited sensitivity and specificity.

### **Monitors of the Depth of Anaesthesia**

After decades of reflection on defining the state of anaesthesia, in recent years there has been an attempt at quantification of the depth of anaesthesia, but several questions are raised about these gadgets.<sup>[58]</sup> Bringing in objectivity into prevention of intra-operative awareness requires a lot more of translational research. This research also assumes importance on the background of several

reports linking intra-operative depth of anaesthesia with adverse post-operative outcomes.<sup>[59-61]</sup>

### Sleep-Related research

Modulation of respiration during anaesthesia with its implications for peri-operative respiratory complications, is an interesting field for research.<sup>[62]</sup> Sleep apnoea and sleep-related disordered respiration have attracted anaesthesiologists for a long time. Naturally occurring NREM sleep and anaesthesia have been found to have neurophysiological similarities. EEG-based depth-of-anaesthesia monitors are being used in this area of research.<sup>[63]</sup>

### Pain Management

Preclinical and clinical research has led to significant progress in clinical pain management. Translational pain research is a definite need as many important questions do not have definitive answers. The gap between pain research and clinical pain management is wide. Objective pain-assessment tools are far too few. The relevance of the current theories of pain mechanisms to clinical pain is not well-understood. Reliable tools for both pre-clinical and clinical pain research should be developed. Co-ordinated research is required among basic scientists, clinical investigators and pain-medicine practitioners.<sup>[64]</sup>

### Anaesthetics and Tumour-cell Invasion/Proliferation

Recent studies have shown that anaesthetics have an influence on the migration and invasion of cancer cells in the lung and colonic carcinomas.<sup>[65,66]</sup> The exact clinical relevance of these findings is not clear at this time. But when understood, this information may have a bearing on the choice of anaesthetic during surgery for cancer. The mechanisms involved may pave the way for a new line of research into anti-malignant therapy.

### Complementary Systems of Medicine

Some alternative systems of medicine have claimed ability to decrease the peri-operative pain/need for pain medications. Acupuncture and acupressure deserve systematic studies for their efficacy in providing analgesia and postoperative antiemetic effect.<sup>[67-69]</sup>

### Pharmacogenetics

There is growing evidence, in the recent years, that the susceptibility of an individual to anaesthetic actions and their side effects is dependent on the genetic polymorphism. Genetic factors seem to contribute to a majority of the severe adverse drug reactions.<sup>[70]</sup> A day may come in future when anaesthetic management is likely to be assisted by genetic factors with a view to reduce the risk of side effects and undesirable actions.<sup>[71]</sup> A similar strategy is likely in the management of acute pain relief over a shorter period of time, and prevention of acute pain becoming chronic.<sup>[72]</sup>

## HOW TO MAKE TRANSLATIONAL RESEARCH MORE EFFECTIVE?

Failure to translate potential basic sciences research into clinical practices is very conspicuous in recent years. Considering the heavy resource implications of medical research, a systematic approach is required to translational research.

When potential clinical applications of basic research findings are identified, they should be first tested in a collaborative multicenter basic research project, rather than jumping into a multicenter clinical trial. Using different animal models would be preferable. The research groups are required to disclose all their data. A collective analysis of the results is to be done to decide whether a collaborative multicenter clinical trial is justified.<sup>[73]</sup>

Journals often tend to accept studies with positive data more than those with negative data, and this trend has to change where the negative results have as much clinical relevance as the positive data.

Recently, based on the recommendation of the Royal College of Anaesthetists' Academic Strategy Report, Research Council of the National Institute of Academic Anaesthesia (NIAA) in the UK conducted a survey to identify priority areas for future research.<sup>[74]</sup> In the final analysis, the areas that emerged are as follows: (a) What interventions prevent the development of chronic pain after surgery? (b) Does epidural anaesthesia improve long-term outcomes after major elective surgery? (c) Does regional anaesthesia improve long-term outcomes after surgery? (d) What is the best management strategy for fractured neck of femur? (e) Can peri-operative interventions prevent postoperative cognitive impairment? (f) What preoperative tests can be used to modify patient care and improve outcome? (g) What interventions can prevent peri-operative cardiac complications? (h) Does tight glycaemic control improve peri-operative outcome? (i) What is the best arrangement for a pre-operative assessment clinic? (j) Does an enhanced peri-operative care package improve outcomes? (k) Does a brief period of preoperative exercise training improve outcomes after major surgery? (l) Does regional anaesthesia reduce the risk of cancer recurrence? (m) Does maintaining peri-operative blood pressure at pre-operative levels improve outcome in hypertensive patients? (n). Does hypotensive resuscitation improve outcome in active haemorrhage? (o) What peri-operative management strategies improve outcome in head injury, e.g., hyperoxia?

As can be seen, some of the areas identified concern neuroanaesthesia directly and the rest too are relevant to neuroanaesthesia as much as they are to other anaesthetics.

A similar exercise done by the neuroanaesthesiologists may provide precise ideas on the translational research priorities to improve the outcomes of neurological patients in the operating rooms and the intensive care units.

On the whole, translational research in anaesthesia provided great solutions to medicine well beyond its scope in the past. Despite all the technical developments, progress in translational sciences has been rather slow in the recent decades. Re-orientation of the research programmes to a translational format with the involvement of all the stakeholders is likely to conserve on the resources and provide rapid solutions to the healthcare.

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