Editorial

Dexmedetomidine and Ketamine – Comrades on an eternal journey!

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Since the last few years, the desks of editors and reviewers of most anaesthesia journals have been flooded with manuscripts related to drugs like 'Dexmedetomidine', 'Clonidine', 'Ketamine', 'Gabapentin', and 'Dexamethasone'. These non-opioid drugs in anaesthesia have been a hot favourite of researchers since the past few years. Researchers have been 'courting' these drugs, especially dexmedetomidine and ketamine, which can be called as the 'all-rounders', and these courtships have culminated in many research publications with high Altmetric attention scores in journals with both low and high impact factors.

How long will these drugs be able to maintain their supremacy in research academics? Though they are a common name in anaesthesia journals, are they equally popular and effective in clinical anaesthesia practice?

There was a time when medetomidine and ketamine were both known as 'veterinary medicines'. Dexmedetomidine was approved in 1999 by the United States Food and Drug Administration (US FDA) as a short term (for <24 hours) sedative and analgesic for the intensive care unit (ICU) patients. Articles on its use in mechanically ventilated patients soon came up. In the ICU, it proved to be a novel sedative and analgesic with no respiratory depression, thus facilitating early weaning from mechanical ventilation and decreased ICU stay and decreased agitation. From the year 2000, it slowly made its way into the perioperative setting and articles contemplating its role in the perioperative setting started getting published.[1] Thus the journey of a drug which started as a short-term sedative in critical care units, soon became the favourite of researchers from the field of Anaesthesiology. Nonetheless, dexmedetomidine made its mark in perioperative management for anxiolysis, analgesia, blunting of sympathetic response to laryngoscopy and intubation, reduction in need for anaesthetic agents, cardiovascular stabilisation and decrease in post-operative shivering. Researchers proclaimed dexmedetomidine as a 'sedative -analgesic drug for the 21st century', 'a new all-in-one drug' and a 'wonder drug'.[2,3] There were widespread reports and clinical studies on its usefulness in anaesthesia and critical care and the drug steadily shaped up and made its mark as one of the most frequently used drugs in both adult and paediatric anaesthesia.[3,4]

The off-label use of dexmedetomidine as an adjuvant to local anaesthetics for regional nerve blocks, intrathecal and epidural anaesthesia, for intra-operative and post-operative analgesia, procedural sedation outside the operation room (OR) soon gained momentum. Initially, off- label IV dexmedetomidine was tried for labour analgesia and caesarean delivery in parturients who had refused neuraxial analgesia or to supplement

poorly functioning intravenous patient-controlled analgesia with fentanyl.[5,6] Efficacy and safety of dexmedetomidine in pregnancy have been highlighted by the various studies, which have been published on the use of IV dexmedetomidine before the induction of general anaesthesia (GA) to decrease the stress response to intubation in pre-eclamptics and to relieve post-operative shivering after lower segment caesarean section (LSCS).[7,8] Dexmedetomidine has been used as an intrathecal and epidural adjuvant in women undergoing caesarean section to provide good intraoperative and postoperative analgesia without any side effects/impact on APGAR scores.[9,10]

Though dexmedetomidine has been extensively studied in adults, the literary and research evidence of its safety in children is limited. It is not currently approved by the FDA for use in the paediatric population even for ICU sedation, but study findings have shown it to be effective in various clinical scenarios in children. Perioperatively, dexmedetomidine is used in children as a premedicant, as a sedative and analgesic adjunct intraoperatively for airway procedures, and to decrease emergence agitation and postoperative shivering. The peri-procedural applications of ketamine are many and include sedation during MRI procedures, lumbar puncture, central venous line placement, for extracorporeal shockwave lithotripsy, insertion of intercostal drains and procedures like frequent change of burns wound dressings.[4,11] It has been tried as an adjuvant for both peripheral and truncal blocks in children. In a study, being published in this issue of the Indian Journal of Anaesthesia (IJA), the authors used 1μg/kg dexmedetomidine as an adjunct to 0.2% ropivacaine 0.5 ml/kg in ultrasound-guided transversus abdominis plane block in children posted for laparoscopic surgeries. They found that dexmedetomidine prolonged the time to first analgesic requirement.[12]

Effectiveness of dexmedetomidine through various routes has been constantly surprising the researchers. The off-label use of dexmedetomidine in treating catheter related bladder discomfort by intra-vesical route has also been recently demonstrated.[13]

Before the advent of dexmedetomidine, ketamine was also used extensively by the researchers through whatever possible routes of administration It acquired several clinical applications through various routes including intramuscular (IM), IV, oral, nasal, intrathecal, epidural, subcutaneous, intra-osseous, rectal, gargles and nebulisation.[14] Though ketamine was widely studied and used clinically a decade back, its use in the present clinical scenario has become limited. There was a period in between, when the popularity and clinical applications of ketamine started fading because of the advent of drugs like propofol, dexmedetomidine and etomidate. It was felt that ketamine would soon be phased out. However, ketamine made its emergence in newer areas. It found applications in low doses in combination with midazolam/propofol for loco-regional procedures and sedation, paediatric premedication, as an adjunct to peripheral nerve blocks, caudal blocks, procedural sedation for adults and children, prevention of post-anaesthetic shivering, co-induction, and acute and chronic pain management.[15] Ketamine has now revolutionised research related to antidepressants and found a role in the treatment of refractory depression and post-traumatic stress disorders. Research into the network-level mechanisms of ketamine, its effect on neurobiology including modulation of the mind and neural correlates of consciousness is currently going on.[16] A new approach of ketamine conjugation to polymeric drug carriers (hydrogels, micro particles and nano particles) has been devised to develop advanced sustained release ketamine formulations in mainstream systems for use in resource constrained health care setups where injecting the drug frequently would prove to be difficult.[17]

The ketamine-dexmedetomidine combination has attracted researchers as never before and a lot of research work on a small dose of dexmedetomidine combined with small dose ketamine to provide good analgesia and sedation with minimal side effects has got published. Most of the studies showed that dexmedetomidine prevented the rise in heart rate, blood pressure, salivation and emergence phenomena with ketamine and ketamine, in turn, prevented the bradycardia and hypotension produced with dexmedetomidine. The duo of dexmedetomidine and ketamine thus got itself established as a safe combination. Dexmedetomidine versus midazolam/propofol for sedation in ICU and intraoperatively became another hot topic of research. Researchers found themselves busy comparing dexmedetomidine through various routes and in various doses with several drugs like ketamine, dexamethasone, clonidine, midazolam-fentanyl and propofol-ketamine combination. Furthermore, the effects of both, dexmedetomidine and ketamine on postoperative sore throat have been

compared in gargles and nebulisation form.[18,19] In a study in this issue of the IJA, females undergoing minor gynaecological surgeries under propofol anaesthesia were randomised to receive IV 1 μg/kg dexmedetomidine/0.5 mg/kg ketamine/normal saline as premedication. It was found that premedication with dexmedetomidine or ketamine does not delay discharge; but stable haemodynamics and good analgesia were observed with ketamine.[20]

Gabapentin, dexamethasone and clonidine are other drugs which have been a favourite of researchers. Dexamethasone and clonidine are two drugs which have been widely used by researchers as adjuvants in peripheral nerve blocks and other miscellaneous perioperative indications. Gabapentin was approved by the FDA in 1993 for the treatment of seizures and the gabapentinoids soon found their place in perioperative management to reduce postoperative acute and chronic surgical pain, decrease perioperative opioid doses and attenuate the stress response to surgery.[21] This issue of the IJA has an article wherein the authors have compared oral gabapentin 600 mg with tramadol 100 mg and placebo given 30 min preoperatively for the prevention of post-spinal shivering in elective orthopaedic surgery patients. Both, gabapentin and tramadol were found to be equally effective for this purpose.[22]

Though the outcome of most studies was favourable for the use of these drugs in several situations, articles doubting their efficiency did come up. Few researchers have raised doubts over the use of neuraxial dexmedetomidine.[23] The FDA and Drugs Controller General of India (DGCI) still do not approve 'off-label' use of dexmedetomidine as an intrathecal/epidural drug.[23] Both gabapentin and pregabalin are not yet approved by the US FDA for the prevention and treatment of surgical pain though their use is widespread. The pain reduction and opioid-sparing effects of gabapentinoids have been now questioned. The last few years have seen the upcoming of increasing evidence on the harm and a decreasing evidence about the benefits from the perioperative use of gabapentinoids.[21] Their perioperative use is now on the decline due to the postoperative dizziness, ataxia, visual disturbances, sedation and respiratory depression produced by them.[21,24]

Though there are several systematic reviews and meta analyses on the perioperative use of dexmedetomidine and clonidine, many of the studies included have been claimed to be non-randomised, flawed and of poor quality with high heterogeneity between the studies.[25]

Authors of some systematic reviews have claimed that most of the paediatric published studies on dexmedetomidine are either observational studies with limited control groups or are small randomised controlled trials with many confounding factors and caution that adverse effects like bradycardia due to dexmedetomidine still require more detailed research, especially, with regard to different age-groups in children.[4,11]

A recent case report described hyperpyrexia following an increase in dexmedetomidine dosing to above 1.5 μg/kg/h in three patients with coronavirus disease-19 (COVID-19). Several studies have shown that hyperthermia is associated with dexmedetomidine infusion.[26] A survey of the current use of dexmedetomidine among paediatric ICU physicians revealed that 87.8% respondents had concerns over dexmedetomidine withdrawal and the primary management of this withdrawal phenomenon was with the initiation of clonidine.[27]

Ketamine is now no longer available on the counter, being a schedule III drug as per Drug Enforcement Authority. It is often used as a 'party drug/rave drug/recreational drug'. Its popularity for this purpose leaves us with doubts regarding its future availability for clinical purposes. Will its production be totally banned? It is difficult to get the answer at this stage.

All this discussion leaves us wondering – Will these 'all rounder' drugs be able to maintain their popularity in anaesthesia clinical research and practice and for how long?

Or is it time for the entry of newer drugs into the research and clinical practice arena? However, the process of drug discovery and development is long, complex and expensive and can be hampered by many efficacy and safety-related issues of clinical trials. The development of a new medicine, from biological target identification through approval for marketing takes over 12 years or longer.[28] It will not be surprising if scientific journals receive studies over the next 2-3 years comparing efficacy of anaesthetic drugs and COVID vaccination.

It is said that central nervous system drugs take a longer time to develop than other drugs and are the

most expensive to develop.[29] It is worth mentioning here that most of the anaesthesia-related drugs are related to the nervous system.

The cost of developing a new prescription drug is quite high and getting a new drug to market is costly mainly because of patenting practices and the cost in securing regulatory approval.[30]

Inspite of all this long and tedious process, newer drugs will certainly come up. As was quoted by the poet Alfred Lord Tennyson, *'The old order changeth, yielding place to new'*. So, will the all-rounders' seemingly eternal journey in anaesthesia research and clinical practice continue or soon come to an end? The answer will be obtained gradually over the next 1-2 decades. In this continual journey, efforts should be directed at the best use of the current available resources.

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