Editorial

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Alpha 2 agonists in regional anaesthesia practice: Efficient yet safe?

Clonidine and dexmedetomidine, partial and selective alpha 2 agonists respectively are being studied and used in regional anaesthesia practice as adjuvant to local anaesthetic (LA) agents for a long period of time. Widespread presence of alpha 2 receptors in the brain, spinal lamina and peripheral nerves and their role in pain modulation explains the analgesic and LA sparing action of these agents. Despite their potential analgesic benefits it is prudent to analyse their systemic as well as neuronal safety issues in the current era of safe anaesthesia practice.

Clonidine has been used as an epidural analgesic for cancer pain relief from 1980.[1] Development of preservative free clonidine and its proven safety for neuraxial use in animal studies[2-4] have popularised its use as an adjuvant to LA agents in neuraxial[5,6] and peripheral nerve and plexus blocks.[7,8] Clonidine was used as adjuvant to LA agents via oral,[9,10] intravenous,[11] neuraxial and perineural routes to study its beneficial effect on prolonging sensory or motor block and postoperative analgesia by various regional anaesthetic techniques. Route of administration of clonidine as an adjuvant to LA agents has its own relevance in practice. Oral clonidine premedication did not prolong analgesia after hernia surgery[9] and the postoperative analgesic duration was similar to oral diazepam premedication in elderly patients undergoing ocular surgeries under peribulbar block[10] indicating minimal effect of oral clonidine in prolonging LA agents action. However, neuraxial clonidine with bupivacaine triples the duration of spinal anaesthesia (5.3 h vs. 1.8 h) in patients undergoing hip surgery and caudal clonidine prolonged the time to require first analgesic by six hours in anorectal surgery.[12] Although there was no evidence of neurotoxicity in humans, the current concern of using clonidine in regional anaesthesia is related to its haemodynamic and undesired sedative side effects. In a recent review and meta-analysis of perineural use of clonidine along with LA agents, clonidine prolonged mean duration of analgesia and motor blockade by about two hours and was associated with high incidence of hypotension (OR: 3.61; 95% CI: 1.52–8.55, number needed to harm [NNH] =11), fainting (OR: 5.07; 95% CI: 1.20–21.4, NNH = 5) with unclear dose responsiveness for beneficial or harmful effects.[13]

Dexmedetomidine, a more selective alpha 2 agonist used for many years in veterinary anaesthesia practice[14] is also studied in humans for its safety and efficacy through intravenous and combined use with LA agents as an adjunct to neuraxial and perineurally administered LA agents. A meta-analysis evaluating the effect of intravenous dexmedetomidine on spinal anaesthesia characteristics found that the duration of sensory block and motor block was prolonged by 37% and 17% respectively. The time to first analgesic request was increased by at least 53%. This was associated with 3.4-fold increase in transient bradycardia incidents without significant hypotension and sedation.[15] Another meta-analysis analysing the effects of intrathecal and intravenous dexmedetomidine in spinal anaesthesia found high incidence of bradycardia requiring atropine (OR: 7.55; 95% CI: 2.76–20.63) with significant prolongation of motor and sensory block duration.[16] Similarly a review and meta-analysis on facilitatory effect of perineurally administered dexmedetomidine along with LA agents concluded that it prolonged mean sensory block by 284 minutes with 7% incidence of reversible bradycardia.[17] In spite of unclear dose

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responsiveness for either harmful or beneficial effect, when these agents are used in the lowest effective dose, the systemic side effects seem to be minimal without affecting the benefits. Low and equipotent dose of clonidine (30 μg) and dexmedetomidine (3 μg) along with 12 mg of bupivacaine significantly improved the onset of motor blockade and prolonged the motor and sensory block regression when compared to bupivacaine alone in spinal anaesthesia without any significant hypotension.[17] The available evidences clearly show a differential block pattern while adding these agents as adjuvants to LA agents. Clonidine prolonged sensory block preferentially when compared to dexmedetomidine which prolonged both sensory and motor block duration. Prolonged motor block may delay early ambulation and discharge or may result in patient fall.[18]

United States Food and Drug Administration and Drug Controller General of India (DCGI) approved dexmedetomidine for short term sedation of mechanically ventilated patients and for ICU sedation.[19,20] Off-label clinical and investigational use of dexmedetomidine is reported in literature for perineural and neuraxial administration. If the physicians use a product for an indication other than the approved purpose they have the responsibility to be well informed about the product and its use with firm scientific rationale. It does not require the submission of an Investigational New Drug (IND) or Investigational Device Exemption (IDE) application if it is used for practice of medicine. Investigational use of approved marketed products needs submission to IND or IDE if it involves change in the route of administration or dosage level, use in subject population or other factors that significantly increases the risk.[21] The studies concerning peripheral and intrathecal usage of dexmedetomidine as an adjuvant to LA agents are mostly from middle eastern countries. A recent review on this subject questions the policies of institutional review boards and editorial boards.[17]

Neurotoxicity of perineurally administered dexmedetomidine is unclear. Demyelination of oligodentrocytes has been reported when injected epidurally.[22] However, other studies in animals demonstrated neuro protective effect of intravenous dexmedetomidine against cerebral ischemic events.[23,24] Although human studies of perineural dexmedetomidine show no evidence of neurological deficit, the safety data on the use of dexmedetomidine in perineural and neuraxial administration is limited and do not support its use in routine clinical practice.[17] Investigational use of perineural or neuraxial dexmedetomidine without approval from DCGI may place the investigator, the institute and the review board at risk of medical malpractice litigations if there are drug related adverse events. Till the safety of perineural and neuraxial dexmedetomidine is clearly proven by further approved studies it is safe to avoid its use in neuraxial and perineural routes.

To conclude, for the safe regional anaesthesia practice in patients receiving alpha 2 agonists as adjuvants to LA agents, one should monitor for bradycardia and hypotension, possible excess sedation and subsequent fall in haemoglobin saturation. Till regulatory board approved and well powered safety studies for the use of perineural dexmedetomidine are available, it is safe to restrict its use in regional anaesthesia practice as an intravenous adjuvant to LA agents for its beneficial sedative and analgesic properties without respiratory depression.

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