Review Article

Future of Dexmedetomidine in Gastrointestinal Endoscopy

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Abstract

In the scenario of gastroendoscopic setup, sedation is meant to enhance the comfort of the patient and to allay anxiety associated with the procedure. Most of the procedures under gastroendoscopic setup are performed on daycare basis; hence, the drugs with shorter half-life and which are easily metabolized are preferred. Dexmedetomidine is an attractive alternative to sedatives when the patient needs to be spontaneously breathing and easily arousable from sedation.

Key words: Anesthesia, dexmedetomidine, endoscopy, gastroscopy, sedation

In today's fast-track world, diagnostic oesphago- gastroduodenal endoscopy is one of the most common outpatient procedures performed. Diagnostic as well as many therapeutic procedures are presently done in gastroenterology setup. A major volume of gastrointestinal procedures are performed routinely on daycare basis. In the scenario of gastro-endoscopic setup, sedation is meant to enhance the comfort level of the patients and allay their anxiety associated with the procedure. Sedation facilitates patient cooperation and comfort level during the procedure. An ideal sedative agent should act rapidly, have a predictable clinical effect, and should be easily titrable.[1] Respiratory and hemodynamic stability are two factors of paramount importance for procedural sedation. There is an assortment of anesthetic agents used to provide sedation. Propofol, opioids, and midazolam form the backbone of the various regimes employed in the endoscopic suites all over the world. The interaction of multiple agents has its own set of pitfalls that anesthesia providers try to overcome by titration based on individual response of patients and the practice of each endoscopic setup.

Dexmedetomidine is an imidazole compound and a pharmacologically active dextro-isomer of medetomidine. It is a selective α_2-adrenergic receptor agonist. It acts on the presynaptic receptor and regulates the release of norepinephrine through a negative feedback mechanism. In the year 1999, the US Food and Drug Administration approved the use of dexmedetomidine in the intensive care unit (ICU) for sedation and analgesia for the duration of less than 24 h.

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The sedative, hypnotic, and analgesic effects of dexmedetomidine have been attributed to the locus coeruleus in the central nervous system (CNS).[2] Locus coeruleus is a small nucleus located in the dorsal rostral pons. It is an important modulator of vigilance. The descending medullospinal noradrenergic pathway also originates from it. This pathway is an important modulator of nociceptive neurotransmission. The locus coeruleus has high density of α_2-adrenergic receptors. The presynaptic activation of α_2-adrenergic receptors inhibits the release of norepinephrine that prevents the transmission of pain signals and also inhibits the sympathetic activity, which further leads to the decrease in blood pressure and heart rate.

The analgesic effects are mediated by α_2 - alpha 2 adrenergic receptors present on the neurons of superficial dorsal horn in lamina II, by inhibiting the release of nociceptive transmitters, namely substance P and glutamate, and by hyperpolarization of spinal interneurons. Sympatholysis occurs due to the activation of postsynaptic α_2 adrenergic receptors that results in hypotension, and bradycardia thus helps in attenuating the stress response. Dexmedetomidine is also helpful in other aspects such as decreased salivation, decreased intraocular

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pressure, increased glomerular filtration, decreased shivering threshold, decreased bowel motility, and decreased release of insulin from pancreas.

The pharmacokinetic profile of dexmedetomidine is not altered by age. It exhibits linear pharmacokinetics in the dose range of 0.2–0.7 μg/kg/h intravenous infusion up to 24 h. It has poor bioavailability due to extensive first-pass metabolism. It is rapidly distributed over 2 hours. The context-sensitive half-life varies from 4 min for a 10 min infusion to 250 min for an 8 h infusion. It undergoes complete biotransformation by glucronidation and by cytochrome P-450 mediated aliphatic hydroxylation to inactive metabolites. The metabolites are excreted through urine and faeces.

It is not recommended for the pediatric age group. Its use in pregnancy, labour, and caesarean sections has still not been adequately studied. Since dexmedetomidine metabolites are excreted through the kidney, it needs to be used cautiously and at a lower dosage in patients with renal impairment. The clearance values have also been reported to be lower in the patients with hepatic impairment as compared to healthy subjects. Hence, the dose needs to be adjusted in the patients with hepatic and renal failures.

Dexmedetomidine is prepared in 0.9% sodium chloride solution to make a concentration of 4 μg/mL. Dexmedetomidine is administered as a loading dose followed by a continuous infusion. The loading dose is 1 μg/kg over a period of 10–20 min. This is followed by a maintenance infusion at 0.2–0.7 μg/kg/h titrated as per the level of sedation required. Clinically effective sedation has been reported to set in 10–15 min after the start of the loading dose.

Hypotension and bradycardia are the most common side effects of dexmedetomidine and the patient should be continuously monitored. Hypotension and bradycardia are managed by increasing the rate of intravenous fluid infusion, vasopressor agents and if required decreasing or stopping dexmedetomidine infusion. It should be cautiously used in patients with advanced heart block, severe ventricular dysfunction, and pronounced hypovolemia and in elderly patients.

In young healthy patients occasionally bolus administration is followed by transient hypertension and ensuing reflex bradycardia.[3] In order to prevent this, glycopyrrolate or atropine is administered intravenously to modify the vagal tone. Most frequently observed adverse effects include hypotension, bradycardia, dry mouth, and nausea. Many other side effects, such as rigors, cyanosis, fever, and muscle weakness, are also reported. It may lead to arrhythmias, atrioventricular (AV) block, cardiac arrest, T-wave inversion, tachycardia, angina pectoris, pulmonary edema, bronchospasm, respiratory depression, syncope, neuropathy, paraesthesia, and lactic acidosis.

Drug dependency and abuse have been reported in animal studies but they have not been studied in human beings. Withdrawal syndrome with symptoms of headache, nervousness, agitation, and hypertension is seen due to raised catecholamines level. Atipamezole is the specific antagonist of dexmedetomidine that can be used to reverse the side effects.[4] All effects of dexmedetomidine can be easily antagonized by administering atipamezole that reverses sedation and sympatholysis and has a half-life of 1.5–2 h. The combination of dexmedetomidine and atipamezole can be the basis for a reversible intravenous anesthetic technique that could provide timely independent recovery from anesthesia and sedation in the future.

Various drug interactions have been reported with dexmedetomidine. Co-administration of anesthetics, sedatives, hypnotics, or opioids with dexmedetomidine is likely to lead to an enhancement of their effects; hence, the reduction in the dose of dexmedetomidine is required when other drugs are used. Dexmedetomidine is widely accepted in various subspecialties in anesthesia as in neuroanesthesia, cardiac anesthesia, awake fibreoptic intubation, intraoperative hypotension, and sedation in ICU. It is also widely accepted for postoperative pain relief and also for pain management and palliative care.

Dexmedetomidine is now evolving in its role in gastroenterology setup due to its favourable properties as required for such procedures. Various studies have tried to determine the efficacy of dexmedetomidine alone or in combination with other anesthetic agents for providing sedation for gastroscopy, colonoscopy, and endoscopic retrograde cholangiopancreatography (ERCP).

Demiraran *et al*. compared dexmedetomidine with midazolam in patients undergoing gastroscopy.[5] They concluded that it was a good alternative to midazolam. Similarly, Wu *et al*. compared dexmedetomidine with midazolam for upper endoscopy.[6] However, in addition they gave fentanyl citrate 1 μg/kg in both the groups. They reported better peripheral oxygen saturation and Ramsay sedation score with dexmedetomidine. They used the lower limit of recommended dose of dexmedetomidine, hence, could avoid respiratory and cardiovascular complications.

Jalowiecki *et al*. studied the efficacy of dexmedetomidine as sole agent for outpatient colonoscopy, supplemented with fentanyl whenever the analgesia was found to be inadequate.[7] They concluded that the dose of dexmedetomidine that provided adequate sedation also resulted in statistically significant hypotension and bradycardia. The hemodynamic instability was found to persist even after the procedure. They also noted a significant delay in discharge times. However, Dere *et al*. found better hemodynamic stability and higher Ramsay sedation scores on using dexmedetomidine during colonoscopy as compared to midazolam.[8] Ayazoglu *et al*. studied various propofol-based sedation regimens for colonoscopy, such as propofol and dexmedetomidine.[9] They assessed bispectral index and Ramsay sedation score. Propofol and dexmedetomidine combination was found to be most efficacious. None of their patients had severe bradycardia or hypotension requiring medical intervention.

Lee *et al*. studied the role of dexmedetomidine in ERCP.[10] Dexmedetomidine was given in addition to the midazolam

and meperidine combination in their study. They reported better sedation, analgesic effect, and patient satisfaction when dexmedetomidine was added. They did not give the loading dose of dexmedetomidine that explains absence of significant alteration in heart rate and blood pressure. However, they started the infusion 15 min before the scope was introduced. Recovery time was also shortened probably because of the reduced requirement of midazolam.

Muller *et al*. compared dexmedetomidine alone with propofol and fentanyl combination for ERCP.[11] They reported greater hemodynamic instability and a longer recovery time with dexmedetomidine. They concluded dexmedetomidine alone was inadequate for sedation in patients under ERCP. However, Sethi *et al*. found dexmedetomidine to be superior to midazolam for ERCP.[12] They used fentanyl in both the groups in their randomized control trial study. Propofol was used as a rescue drug. They found no difference in mean arterial pressure, respiratory rate, or SpO_2, though the dexmedetomidine group had significantly lower heart rate. On using dexmedetomidine there were fewer incidences of gagging and restlessness and the recovery was faster. Numerous other studies coming up at regular intervals have reported the efficacy of dexmedetomidine to be similar to the efficacy of those cited above.

Dexmedetomidine is definitely an asset in the armamentarium of an anesthesia provider. What is required is a structured regimen about its combination with other anesthetic agents that can be adopted by sedation suites all over the world. Continuous monitoring of electrocardiogram, noninvasive blood pressure, and oxygen saturation are mandatory while using dexmedetomidine. Fluid infusion is required especially in hypovolemic patients as they are more prone to hypotension. Diabetics and patients with cardiac issues need more vigilant monitoring and alteration in the infusion dose.

The role of dexmedetomidine in anesthesia is expanding day by day with more studies being published about its beneficial effects. Studies indicate that it reduces incidence of nausea, vomiting, agitation, and shivering in the postoperative period.[13-15] Dexmedetomidine is an effective sedative and analgesic agent. It has a relatively shorter duration of action and the patient can be easily aroused. All these factors make dexmedetomidine an attractive alternative to sedatives when the patient needs to be spontaneously breathing and easily arousable from sedation.

Conscious sedation is the most widely used method for the procedures performed in a gastroenterology setup, which makes the patient as well as the doctor comfortable for the procedure. Dexmedetomidine is a new drug that has been used in sedo-analgesia for short procedures, and its use has been steadily increasing worldwide. Compared to other drugs, it provides similar effects with respect to patient satisfaction, anxiety score, and recovery time but it has an added benefit with respect to endoscopist satisfaction and less number of postoperative side effects. Thus, dexmedetomidine is proved to be a promising drug for the procedures performed under gastroenterology setup in today's fast-track world.

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Conflicts of interest

There are no conflicts of interest.

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