Editorial Commentary

Use of dexmedetomidine in cleft lip and palate pediatric population

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Cleft lip and palate are a congenital condition that affects approximately 8 in 10,000 births internationally (1). Cleft lip occurs when the tissues of the upper lip fail to fuse in a developing fetus during the fourth to seventh week of pregnancy, resulting in an opening in the lip either along the midline or towards either side (2). A cleft palate occurs when the roof of the mouth, also known as the palate, do not fuse during the sixth to ninth weeks of pregnancy, creating an opening between the oral and nasal cavities (2). Cleft lip and cleft palate can occur independently or concurrently, causing not only facial deformity, but also difficulties in activities such as eating and speaking. As such, children born with this condition commonly require multiple surgeries, starting from an early age and throughout their lifetimes, to improve both function and aesthetics. These surgical corrections are conducted with the patients under general anesthesia. However, the effects of anesthetic agents on emergence, respiratory depression, postoperative nausea, and other adverse events in the cleft lip and palate population are not well-studied.

Opioids along with sevoflurane anesthesia are commonly used during surgeries to repair cleft lip and palate. However, this method of anesthesia is associated with high risks of respiratory depression, postoperative emergence agitation, postoperative nausea and vomiting, prolonged hospital stay and increased hospital costs. The residual respiratory depressant and sedative effects of anesthetic agents and opioids remain a major concern in infants scheduled for cleft surgery (3). Drugs such as desflurane, which has rapid elimination from the body, and remifentanil, which has fast and predictable metabolism, may provide some advantages in minimizing post-anesthesia complications, though additional studies are needed. In addition, use of non-steroidal analgesia in the pediatric patient population is common, though further trials are needed to elucidate the most effective and safe regimens; their effect on perioperative bleeding is still disputed. In the immediate post-operative period, finding a balance between pain control and respiratory suppression is difficult. The goal is to minimize respiratory and airway compromise, which would require an awake and comfortable child. Therefore, identifying an effective a non-opioid analgesic is of particular interest in this population.

Liu *et al.* conducted a systematic review with meta-analysis to evaluate the safety and efficacy of dexmedetomidine, a potent α2-adrenergic receptor agonist, as an alternate adjuvant anesthetic agent for pediatric cleft lip and palate patients (4). Dexmedetomidine is currently approved by FDA only for sedation in adult intensive care patients. It can provide sedation and analgesia with minimal side effects and reduce additional anesthetic and opioid treatment. The use of dexmedetomidine on pediatric patients has increased due to interest in its effective analgesic and sedative properties (4). Dexmedetomidine appears to exhibit a level of efficacy similar to that seen in adults; it has also been found to be fairly well tolerated in children older than one month (5).

Emergence agitation

Liu *et al.* found that dexmedetomidine reduced the incidence of emergence agitation and the need for adjunctive pain medication, likely secondary to its sedative and analgesic effects. The sedative effect is thought to be due to presynaptic activation of α2-adrenergic receptor, which inhibits the release of norepinephrine thereby terminating the prorogation of pain signals. The mechanism of action of the analgesic effects of α2-adrenergic receptor agonists is not fully understood. One of the highest densities of α2-adrenergic receptors is in the locus coeruleus, which is known to be an important modulator of nociceptive neurotransmission. It is likely that the analgesic effect of dexmedetomidine is attributable to stimulation of α2-adrenergic receptors in this region, suppressing hyperpolarization of interneurons and reduction of the release of pronociceptive transmitters such as substance P and glutamate (5,6). One consideration in evaluating the effect of dexmedetomidine on emergence agitation in the pediatric population is distinguishing it from post-operative pain, as these two factors are difficult to separate in the pediatric population and often driven by one another.

Respiratory events

Liu *et al.* report that dexmedetomidine did not increase the incidence of breath-holding, desaturation, or airway spasm, while decreasing the incidence of cough and total respiratory adverse events. The authors suggested that these outcomes could likely be attributed to the residual sedation from the sedative effect of dexmedetomidine. They could also be due to a combination of the anesthetic-sparing, specifically opioids, and intrinsic analgesic effects of dexmedetomidine (7). These are desirable effects especially in the setting of post-operative swelling intra-orally and surrounding the nasal passageway, which may cause increased respiratory effort.

Cardiovascular adverse events

One of the main concerns regarding dexmedetomidine use is that it could cause cardiovascular depression by decreasing sympathetic outflow and augmenting vagal activity due its high selective α2-adrenergic agonist activity. Other studies have shown that it produces a typical biphasic hemodynamic response, resulting in hypotension at low plasma concentrations and hypertension at higher plasma concentrations (8). Liu *et al.* did not find a significant difference in rates of adverse cardiovascular events, specifically hypotension, bradycardia and postoperative bleeding, between the dexmedetomidine group and the placebo group. This was thought to be due to low dose, slow injection, and continuous infusion.

Postoperative nausea and vomiting

Few studies have focused on the effect of dexmedetomidine on postoperative nausea and vomiting. The authors found that dexmedetomidine did not affect the incidence of postoperative nausea and vomiting. However, this conclusion is muddled by the limited ability to assess for true incidence of nausea in children. Another potential contributing factor is the opioid-sparing effect of dexmedetomidine, which can help indirectly reducing post-operative nausea (5).

In sum, Liu *et al.* found that dexmedetomidine may be a safe and suitable perioperative agent in surgical repair for the cleft lip and palate pediatric population. The quality of evidence on the efficacy dexmedetomidine in the pediatric population leaves much to be desired. The randomized-controlled trials included in this meta-analysis had small numbers of participants and varied greatly in methodology. Current understanding of the pharmacokinetic profile of dexmedetomidine is largely limited to the adult population. As such, the indications for dexmedetomidine in the pediatric population is extrapolated from adult trials. However, children are not small adults, and many drugs exhibit very different pharmacokinetics in children compared with adults. They have immature clearance that change with age that dictate infusion rate therefore extrapolation of adult dosage may not be applicable to the pediatric population. Moving forward, this article can hopefully serve as a catalyst for further studies, particularly large-scale clinical trials, to evaluate the safety and efficacy of using dexmedetomidine in the pediatric cleft lip and palate patient population.

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