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Comparison of Ketamine, Clonidine, and Fentanyl as Anesthetics in the Pediatric Population: A Review of Literature

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Author's contribution

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Review Article

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ABSTRACT

This literature review examines the evidence on the safety profile and effectiveness of various adjuncts, such as clonidine, fentanyl, and ketamine, in pediatric anesthesia. Several studies were reviewed to evaluate the duration and quality of analgesia provided by these adjuncts, as well as their adverse effects. The results showed that adding clonidine to bupivacaine significantly prolonged the mean duration of analgesia compared to the fentanyl and clonidine groups. Children in the clonidine group also experienced lower pain scores and required fewer rescue medications. Furthermore, clonidine exhibited a higher safety margin with a lower incidence of adverse effects, such as urinary retention and pruritus, compared to other adjuncts. Regarding comparisons between fentanyl and clonidine, intrathecal fentanyl resulted in a better hemodynamic profile but required more propofol for sedation. On the other hand, intrathecal clonidine provided a more favorable sedation level. Adverse events like respiratory obstruction and apnea were more likely

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associated with deep sedation caused by propofol rather than the specific properties of clonidine or fentanyl.
In terms of ketamine versus clonidine, caudal blocks using ketamine were found to prolong postoperative anesthesia, particularly for lower limb and abdominal surgeries. When comparing the duration of caudal analgesia achieved by bupivacaine combined with different adjuncts, ketamine exhibited a longer duration compared to clonidine and adrenaline. However, ketamine use was found to be linked with a greater incidence of adverse effects, including urinary retention and pruritus.
In conclusion, clonidine demonstrated a relatively higher safety margin with prolonged analgesic effects in pediatric anesthesia compared to fentanyl and ketamine. Its addition to local anesthetics resulted in extended analgesia duration and reduced rescue medication requirements without significant side effects. However, careful monitoring is necessary to manage potential adverse effects.

Keywords: Ketamine; fentanyl; clonidine; anesthetics; pediatric population.

1. INTRODUCTION

The significance of proper pain relief is widely recognized in adults, but children often faced neglect and were not given the same level of importance due to their inability to express pain [1]. However, in recent times, there has been an increasing focus on managing pain in children, especially with the advancement of opioids [2].

Opioids continue to be the primary treatment for managing acute moderate to severe pain [3]. However, we can reduce their usage by incorporating additional analgesics and employing techniques that target different aspects of pain pathways [4]. This approach can provide comparable or even superior pain relief while minimizing the adverse effects associated with opioids, such as vomiting, nausea, itching, constipation, urinary retention, and respiratory depression [5]. It is important to note that the use of opioids in infants younger than 4 to 6 months can lead to apnea and hypoventilation [6]. Among the different techniques used for epidural anesthesia in children, "caudal anesthesia" is the currently most widely used method [7]. The single-dose injection in caudal anesthesia proves to be the most effective and prevalent form of regional block. This approach is straightforward, dependable, and secure, particularly for children weighing less than 10 kg [8]. The administration of a single dose of anesthetics is particularly suitable for surgical procedures below the navel [9]. When combined with general anesthesia, the caudal block is utilized for postoperative pain relief in operations below the umbilicus [10]. This technique allows for the use of lower concentrations of inhaled anesthetics and facilitates quicker recovery after the procedure [11]. Caudal block is a simple method with the lowest rate of complications [12].

Bupivacaine is commonly employed as a local anesthetic for caudal blocks in children [13]. However, its analgesic effects typically last for only 4-12 hours. As a result, additional analgesia is necessary when the block's effects diminish [14]. Various medications, including midazolam, clonidine, ketamine, fentanyl, tramadol, and morphine have been added to the caudal space to extend postoperative pain relief. These drugs have been used in different concentrations with different combinations across various studies to achieve optimal benefits [15,16].

For example, research showed that the addition of morphine to caudal bupivacaine offers excellent pain relief; however, it is associated with a high incidence of side effects such as urinary retention, vomiting, nausea, and respiratory depression [17]. Other combinations, such as midazolam and clonidine improved analgesia but carry potential risks of hypotension and sedation [18]. In a similar manner, several studies have examined the effectiveness of administering clonidine and ketamine via the caudal route during the postoperative period. [19]. In this study, different doses of caudal clonidine and ketamine have been utilized, resulting in varying outcomes. The purpose of this review is to compare the effects of ketamine, clonidine, and fentanyl as an anesthetic in the pediatric population.

2. EFFICACY COMPARISON OF FENTANYL, KETAMINE AND CLONIDINE IN PEDIATRIC ANESTHESIA

The efficacy of fentanyl, ketamine, and clonidine in pediatric anesthesia has been extensively studied. These medications offer different mechanisms of action and benefits for pain management and sedation in children undergoing surgical procedures. However, their collective comparison has been only studied in two studies [1].

The research compared the effectiveness of clonidine, fentanyl, and ketamine when added to caudal bupivacaine using a single-shot technique in children, in terms of the quality and duration of analgesia they provide [20]. The group that was given bupivacaine with clonidine, experienced a noticeably longer average duration of pain relief, which was measured to be approximately 629.06 ± 286.32 minutes. This was in contrast to the other three groups that received Ketamine, Fentanyl and placebo [2]. The duration difference was determined to be statistically significant, as evidenced by a p-value of less than 0.05. Furthermore, the group receiving bupivacaine with clonidine required fewer rescue medications. According to this study, it was found that including a dose of "1 µg/kg" of clonidine alongside "0.25% bupivacaine" for "caudal analgesia" during sub-umbilical surgeries can prolong the pain-relieving effects of bupivacaine. This approach was observed to have no adverse effects, which sets it apart from the use of fentanyl or ketamine. This study concluded that administering a “0.75 ml/kg” mixture of “0.25% bupivacaine” with “1 µg/kg” of clonidine for caudal analgesia in children undergoing sub-umbilical surgery significantly increases the duration of postoperative analgesia compared to administering 0.75 ml/kg of 0.25% bupivacaine in normal saline, 0.75 ml/kg of 0.25% bupivacaine with 0.5 mg/kg of ketamine, or 0.75 ml/kg of 0.25% bupivacaine with 1 mcg/kg of fentanyl. Importantly, this extended duration of analgesia was achieved without any side effects [3].

A meta-analysis revealed that clonidine administered at a dose of 1-3 mg/kg for postoperative analgesia resulted in a longer duration of pain relief compared to other adjuncts [21]. In addition, it was observed that the group of patients who were administered clonidine with no epinephrine had a reduced number of individuals who needed extra analgesic medication [4]. The clonidine group had a higher total number of rescue analgesic administrations compared to the morphine group. Clonidine demonstrated a comparable effect to ketamine and lower requirements compared to the midazolam group. Additionally, two studies comparing clonidine with fentanyl reported motor block occurrences, with the clonidine group showing a mean difference of 0.55 hours. According to this research, it was observed that clonidine, when used alongside local anesthesia, can result in a slightly extended period of motor block in neuraxial blocks when compared to opioids [5].

3. FENTANYL VS CLONIDINE

The research evaluated and compared the effects of adding clonidine or fentanyl to intrathecal bupivacaine in pediatric patients, focusing on adverse events, hemodynamic profile, propofol consumption, and intraoperative complications [6]. The study concluded that the addition of intrathecal fentanyl resulted in a better hemodynamic profile, as it led to fewer adverse events such as diastolic hypotension, systolic hypotension, hypotension, and bradycardia. On the other hand, intrathecal clonidine resulted in a more favorable sedation level, requiring less propofol for sedation. It should be noted that complications like respiratory obstruction and apnea were more likely attributed to the deep sedation caused by a bolus of propofol rather than the specific properties of intrathecal clonidine or fentanyl as adjuvants [22].

A study was performed to assess how well Clonidine and Fentanyl work and how safe they are when added to plain bupivacaine for caudal anesthesia in children [23]. The group that only received Bupivacaine had the shortest duration of postoperative analgesia, which was 146±91.2 minutes. The BF group had a slightly longer duration of 293.5±154.5 minutes, while the BC group had the longest duration of 510±359.9 minutes. The sedation time showed a comparable pattern. The bupivacaine group had the highest mean pain scores from 2 hours to 24 hours. Following that, the BF and BC groups had slightly lower mean pain scores. In the period following the surgery, which lasted from 45 minutes to 24 hours, this study found that there were noticeable differences in sedation scores between the three groups being studied. These differences were statistically significant. Based on the findings of this study, it was recommended that the addition of clonidine at a dosage of 1µg/kg to 0.5% bupivacaine had a notable impact in extending the length of time for

postoperative pain relief following a caudal injection given as a single dose. It was found that this effect occurred without any notable side effects. The effect was noticed when it was compared to bupivacaine 0.5% by alone or when it was combined with fentanyl at a dose of 1µg/kg.

A study compared the adjuvant effects of "clonidine (2 µg/kg)" or "fentanyl (1 µg/kg)" when added to 1 ml/kg of 0.2% ropivacaine for caudal analgesia in children undergoing lower abdominal surgeries [24]. Based on the findings of this study, it was observed that the average duration of caudal analgesia was 659.5 minutes in group R, 784.5 minutes in group RF, and 960.5 minutes in group RC. These results indicate a highly significant statistical difference (P<0.01) among the three groups. The group's RF and RC had a lower total amount of rescue analgesics administered within a 24-hour period.

Additionally, the number of children in need of rescue analgesia at the 12-hour mark was significantly higher in the placebo group compared to both the fentanyl and clonidine groups (P<0.01). Group RF experienced a higher occurrence of pruritus and urinary retention, the statistical analysis did not indicate a significant difference (P=0.366). The findings of this study suggest that adding injection When Fentanyl is given at a dose of 1µg/kg or Clonidine at a dose of 2µg/kg along with Ropivacaine 0.2% at a dose of 1ml/kg, helps to make the pain relief after surgery last longer and improves its effectiveness, as compared to using only Ropivacaine. However, it has been determined that clonidine is considered to be a better addition to Ropivacaine 0.2% for single-shot caudal blocks in children who are having surgeries below the belly button. This is because clonidine has longer-lasting pain-relieving effects and causes fewer negative effects.

4. KETAMINE VS CLONIDINE

Godwin et al. conducted a study showing that combining ketamine at a dose of 0.5 mg/kg with bupivacaine resulted in prolonged postoperative anesthesia following orchidopexy compared to combining clonidine at a dose of 2µg/kg or epinephrine at a dose of 5µg/kg with bupivacaine [25]. As a result, caudal blocks utilizing basal ketamine are extensively utilized for abdominal and lower limb surgeries, particularly in uncooperative children. In a study, the effects of ketamine, clonidine, and adrenaline on the duration of caudal analgesia achieved by bupivacaine in children were compared [26]. A total of sixty boys, with ages ranging from 1 to 10 years, who were in the process of undergoing orchidopexy, were randomly divided into three groups. Each group received a different solution for caudal extradural injection. Group A received 1 ml/kg of 0.25% bupivacaine with adrenaline at a concentration of 5 µg/ml (1/200,000), group C received 1 ml/kg of 0.25% bupivacaine with clonidine at a dose of 2 µg/kg, and group K received 1 ml/kg of 0.25% bupivacaine with ketamine at a dose of 0.5 mg/kg. The researchers evaluated postoperative pain by using a modified objective pain score. If the score went above 4, they provided analgesia to manage the pain. In group K, the median duration of caudal analgesia was found to be 12.5 hours. This was compared to a duration of 5.8 hours in group C, with a statistically significant difference (P < 0.05). Additionally, the duration of caudal analgesia in group A was found to be 3.2 hours, which was significantly lower than both group K and group C (P < 0.01). The groups did not show any notable variations in urinary retention, motor block, or postoperative complications.

A research compared the effectiveness and duration of pain relief provided by ropivacaine 0.2% when it was combined with either clonidine (at a dose of 1 microg/kg) or ketamine (at a dose of 0.5 mg/kg), as compared to ropivacaine 0.2% by itself. Additionally, the research aimed to assess the postoperative cortisol, insulin, and glucose levels in children after caudal administration, both after induction and 1 hour later [27]. There were no notable variations found between the three study groups in terms of age, weight, or duration of surgery. On the other hand, when clonidine was given through the tail at a dose of 1 microgram per kilogram or ketamine was given at a dose of 0.5 milligrams per kilogram, it caused the pain relief to last much longer compared to just using ropivacaine alone. This difference was statistically significant with a p-value of less than 0.05. In all groups, it was observed that insulin levels were elevated, whereas cortisol levels were decreased.

Furthermore, glucose concentration showed a statistically significant increase in all groups (P < 0.05). The findings of this research indicate that adding ketamine and clonidine to caudally administered ropivacaine 0.2% at a dose of 0.75 ml/kg in children leads to a prolonged duration of postoperative analgesia. Additionally, the requirement for additional postoperative analgesics is reduced. Caudal analgesia has the

ability to moderate or partially modify the postoperative responses of cortisol, insulin, and blood glucose levels to surgery.

5. SAFETY COMPARISON BETWEEN FENTANYL, CLONIDINE AND KETAMINE IN PEDIATRIC ANESTHESIA

The most frequently reported adverse effect in the included studies was the prevention of Postoperative Nausea and Vomiting (PONV). The clonidine group demonstrated a lower relative risk (RR) of 0.49, representing a decreased incidence of PONV compared to other adjuncts commonly used with local anesthetics [28]. Out of the 421 patients, it was found that bradycardia occurred in seven cases. The group that took clonidine had a lower relative risk (RR) of 0.78. This matches what Ansermino et al. found, where a higher dose of clonidine (5 µg/kg) was linked to more severe sedation and side effects related to the heart and blood vessels. In the eight studies that investigated the occurrence of hypotension, it was found that the clonidine group experienced hypotension once. On the other hand, the fentanyl group had three occurrences of hypotension, and the midazolam group had one occurrence. The group that was given clonidine had a lower relative risk (RR) of 0.43 for hypotension [29]. Out of the 12 studies that were analyzed, respiratory depression was only mentioned in one study. In this particular study, it was observed that one patient from the clonidine group (1 µg/kg) and one patient from the midazolam group experienced respiratory depression. This discovery is consistent with earlier research carried out on premature babies and newborns, indicating that clonidine might raise the likelihood of respiratory depression [30].

In patients using clonidine, pruritus was observed [31]. Among the different groups studied (morphine, ketamine, dexmedetomidine, and fentanyl), eight patients in each group experienced pruritus. However, the incidence of pruritus was particularly high in the morphine group. In relation to urinary retention, a total of seven studies have documented its incidence. In the clonidine group, there were no instances of urinary retention among the patients [32-34]. However, both the ketamine and opioid groups had five patients each who experienced urinary retention.

In terms of hallucinations, only one study reported cases of hallucinations. In the study, it was observed that one child from the group that received a dose of 1 µg/kg of clonidine and two children from the group that received s-ketamine experienced some effects. Despite concerns about the neurotoxicity of ketamine, this meta-analysis found no evidence of neurological impairment across the included studies.

Clonidine demonstrated a relatively higher safety margin in terms of negative effects when compared to other adjuncts [35]. This conclusion is supported by a trial where clonidine was accidentally overdosed by a factor of 100, yet no major adverse effects were observed. The duration of postoperative pain relief when comparing clonidine to other additional medications showed a significant amount of variation, as indicated by this meta-analysis. There are multiple factors that contribute to this heterogeneity [36-38]. These factors include differences in the doses of clonidine used, the inclusion of epinephrine, variations in the pharmacology of other additional substances, and differences in the duration of local anesthetics.

6. CONCLUSION

In summary, clonidine appears to be a favorable adjunct in pediatric anesthesia due to its prolonged analgesic effects, lower pain scores, and fewer rescue medication requirements. It offers a relatively higher safety margin with a lower risk of adverse effects compared to other adjuncts. However, careful consideration should be given to individual patient factors, dosages, and specific surgical procedures when selecting the most appropriate adjunct for pediatric anesthesia. Further research is warranted to explore optimal dosages and combinations to maximize efficacy while minimizing potential risks.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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