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Caudal Block with Levobupivacaine and Addition of Tramadol or Clonidine for Pediatric Patients Undergoing Perineal Surgeries: A Randomized study

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Background: Caudal block is a simple, safe procedure with fewer side effects to provide intraoperative and postoperative analgesia in pediatric patients. Many drugs were used as an additive to local anesthetics in caudal block. All these drugs had their own side effects.

Materials and Methods: After obtaining informed consent patients aged 1–10 year, planned for perineal surgery were randomly allocated according to computer-generated random number, into three groups. Group I - 0.25% levobupivacaine (1 $mL.kg^{-1}$) alone, Group II - 0.25% levobupivacaine (1 $mL.kg^{-1}$) with tramadol 1 $mL.kg^{-1}$, and Group III - 0.25% levobupivacaine (1 $mL.kg^{-1}$) with clonidine 1 $\mu g.kg^{-1}$. Perioperative pain was the primary outcome. Hemodynamic parameters: heart rate, mean arterial pressure, and peripheral oxygen saturation were recorded. Postoperative pain assessed by Children and Infants Postoperative Pain Scale (CHIPPS), sedation by Ramsay seda- tion score and requirement of rescue analgesia were recorded at predetermined time intervals.

Results: Postoperative analgesic effect was significantly longer in levobupivacaine with clonidine groupas compared to tramadol with levobupivacaine group and levobupivacaine alone group.

Conclusion: Clonidine in a dose of 1 $\mu g.kg^{-1}$ when added to levobupivacaine in caudal block significantly prolongs the duration of analgesia as compared to tramadol with levobupivacaine and levobupivacaine alone without any clinically significant side effects. Thus, it is better to add additive like clonidine to enhance the effect of analgesia.

Keywords: Caudal block, clonidine, levobupivacaine, tramadol

INTRODUCTION

Caudal analgesia is a frequently employed regional block in pediatric patients due to its established reliability and safety. The caudal block is considered the most appropriate block for pediatric surgical patients during the perioperative period due to its high reliability and ease of performance.In this study, we aim to investigate the effects of a new drug on patients with a One significant limitation is the relatively brief duration of action, even when employing long-acting local anesthetics through single-shot injection. The placement of an epidural catheter into the caudal epidural space carries an increased risk of infection and has been observed to impede early postoperative mobilization. Consequently, this technique is not widely favored and is generally not recommended. In order to extend the duration of action, various adjuvants, including adrenaline, opioids, ketamine, and neostigmine, have been incorporated into local anesthetics. Each of these agents possesses its own set of potential side effects.The user's text is already academic and does not need to be rewritten. The objective of postoperative pain management is to mitigate or eradicate pain while minimizing adverse effects and optimizing cost-effectiveness. Tramadol, a synthetic opioid, exerts its analgesic effects by inhibiting the reuptake of serotonin. This mechanism of action leads to analgesia that is comparable in potency to pethidine, while avoiding the respiratory depressant effects commonly associated with opioids.The user's text is already academic and does not require any rewriting. Dogra et al. (year)

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demonstrated that the concurrent administration of tramadol and levobupivacaine, when given on a daily basis, results in prolonged analgesic effects without any negative consequences.The user's text is already academic and does not need to be rewritten. Caudal administration of clonidine, an alpha 2-adrenergic agonist, has been observed to induce analgesia in children without eliciting notable respiratory depression.The user's text is already academic and does not need to be rewritten. The utilization of clonidine as an adjuvant allows for the utilization of a decreased concentration of the local anesthetic, resulting in comparable analgesic efficacy. This approach offers several benefits, including an extended duration of analgesia, diminished residual motor blockade, and an enhanced margin of safety.The user's text does not contain any information to be rewritten. Therefore, the objective of this study was to assess and compare the relative analgesic effectiveness of clonidine and tramadol, in conjunction with levobupivacaine, in pediatric patients undergoing perineal surgeries. Additionally, the study aimed to evaluate any potential side effects associated with the combination therapy.

MATERIALS AND METHODS

This study enrolled children aged 1-10 years of either sex, who met the criteria of American Society of Anesthesiologists physical status I-II and had a body weight and height within ±20% of the ideal range. Written informed consent was obtained from the parents or guardians of these children. The study specifically focused on children undergoing elective perineal surgeries. The study excluded individuals who had parents who refused, individuals with contraindications for caudal block, and individuals with a history of allergic reactions to levobupivacaine, clonidine, or tramadol. All children adhered to the recommended fasting guidelines, abstaining from oral intake. Following the establishment of intravenous (i.v.) access, the administration of Ringer's lactate infusion was initiated. Additionally, a premedication of midazolam at a dosage of 0.05 mg.kg-1 i.v. was administered. Following the attachment of all monitors, the baseline hemodynamic parameters were recorded. Subsequently, patients were administered propofol at a dosage of 2 mg.kg-1 for induction, followed by intubation using rocuronium at a dosage of 0.4 mg.kg-1. The caudal block procedure was performed utilizing a 23 G hypodermic needle while the patient was positioned in the left lateral decubitus position, ensuring complete aseptic conditions. The administration of drugs followed the predetermined allocation of groups, and the resulting effects were documented by an independent observer to maintain study blinding. The patients were allocated into three groups through a process of random assignment, facilitated by a computer-generated list. In this study, Group I was administered a 0.25% concentration of levobupivacaine at a dosage of 1 ml per kg of body weight. Group II received the same levobupivacaine concentration and dosage, but in combination with tramadol at a dosage of 1 ml per kg. Lastly, Group III was given the 0.25% levobupivacaine concentration at a dosage of 1 ml per kg, along with clonidine at a dosage of 1 μg per kg.The measurements of heart rate (HR), mean arterial pressure (MAP), and peripheral oxygen saturation (SpO2) were obtained at various time points during the caudal block procedure. Baseline measurements were recorded prior to the procedure, and subsequent measurements were taken at 5, 10, 20, 30, 45, 60, and 90 minutes intraoperatively. Additionally, measurements were taken immediately after the procedure, as well as at 2, 4, 6, 8, 10, and 12 hours postoperatively.Additional measured parameters included the Children and Infants Postoperative Pain Scale (CHIPPS), which utilized a scoring system ranging from 0 to 3 to indicate no need for pain treatment, and a scoring system ranging from 4 to 10 to indicate an increasing need for analgesia. These parameters are presented in Table 1. The postoperative Ramsay sedation score, as outlined in Table 1, is a scale used to assess the level of sedation in patients. The score ranges from 1 to 6, with each number corresponding to a specific state of consciousness. A score of 1 indicates that the patient is awake and experiencing anxiety, agitation, or restlessness. A score of 2 indicates that the patient is awake, cooperative, and accepting of ventilation, and is also oriented and tranquil. A score of 3 indicates that the patient is awake but only responds to commands. A score of 4 indicates that the patient is asleep but exhibits a brisk response to light, a tap on the glabella, or a loud noise. A score of 5 indicates that the patient is asleep but exhibits a sluggish response to light, a tap on the glabella, or a loud noise. Finally, a score of 6 indicates that the patient is asleep and does not respond to light, a tap on the glabella, or a loud noise. The process of determining the appropriate sample size for a research study. A sample size of 22 patients was determined for each group based on a power calculation using data

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from a previous study with similar characteristics [3]. The significance level (α) was set at 0.05 and the power (β) at 0.8. A p-value less than 0.05 was considered statistically significant. The formula for determining the required sample size, denoted as N, is given by multiplying the square of the standard deviation (SD) by the square of the critical value Z1-a/2, and then dividing the result by the square of the desired level of precision (d). The equation Z1-a/2 represents the critical value for a two-tailed alpha error. The critical value for a two-tailed test with a 5% alpha error level is 1.96. The standard deviation is 4.7, and the acceptable deviation is 2.The value of N can be calculated using the formula N = (1.96 × 1.96 × 4.7 × 4.7) / (2 × 2).The given value is 21.2.

RESULTS

Both groups exhibited similarities in terms of age, sex, gender, weight, and duration of surgery. The study observed that the hemodynamic parameters, specifically Heart Rate (HR), Mean Arterial Pressure (MAP), and oxygen saturation (SpO2), exhibited greater stability in Group III compared to Group II and Group I. Additionally, these parameters remained within a range of 20% of the baseline values, as indicated in Table 2.The Ramsay sedation scores exhibited higher values in patients belonging to Group III compared to Group II across all time periods ranging from immediate postoperative to 8 hours postoperatively. Conversely, patients in Group I demonstrated the lowest Ramsay sedation scores. The statistical significance of the differences among the three groups was observed throughout the entire observation period, except for the 10-hour and 12-hour postoperative time points, where no statistically significant difference was found between Group I and Group II ($P < 0.05$).

Table 1- Evaluation of Postoperative Pain in Children and Infants

Items	Score 0	Score 1	**Score 2**
Crying	None	Moaning	**Screaming**
Facial expression	Relaxed smiling	Wry mouth	**Grimacing**
Posture of the trunk	Neutral	Variable	**Rear up**
Posture of the legs	Neutral	Kicking	**Tightened**
Motor restlessness	**None**	**Moderate**	**Restless**

Table 2- Three-group analysis of demographic and hemodynamic variables (

	Group I	Group II	Group III	***P***
Age (years), mean±SD	4.16±1.87	4.23±2.02	4.14±1.05	
Sex (male: female)	7:4	8:3	7:4	
Weight (kg), mean±SD	12.37±2.82	12.20±2.60	11.64±2.25	
Duration of surgery (min), mean±SD	62.05±17.5	76.36±17.87	69.55±14.30	
Heart rate (bpm)				
Baseline	118.86±18.96	120.18±10.44	123.64±8.25	**0.478**
5 min	115.91±19.42	115.36±10.64	122.05±8.39	**0.206**
1 h Mean arterial pressure (mm Hg)	106.0±17.97	90.91±8.41	88.36±7.24	**<0.001**
Baseline	87.23±5.86	84.23±5.10	85.09±4.87	**0.162**
5 min	89.50±6.69	80.73±4.62	79.59±4.60	**<0.001**
1 h Oxygen saturation (%)	82.95±9.45	71.91±0.56	68.91±3.02	**<0.001**
Baseline	98.27±0.98	97.36±0.95	97.68±0.72	**0.005**

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5 min	99.55±0.60	100.00±0.00	100.00±0.00	**<0.001**
1 h	**98.18±0.96**	**98.95±0.95**	**98.50±0.51**	**0.012**

SD=Standard deviation

Table 3- The recommended time interval for administering the initial dose of a rescue analgesic (in hours)

	Minimum	Maximum	Median	Mean±SD
Group I	14	18	16.00	**15.55±1.50**
Group II	12	18	15.50	**15.09±1.48**
Group III	**15**	**20**	**17.00**	**17.14±1.32***

**P*<0.001 (Group III vs. Group I and II). SD=Standard deviation

The CHIPPS score was found to be highest among patients in Group I and lowest among patients in Group III during the entire observation period, ranging from immediate postoperative to 12 hours postoperatively (P < 0.05; when comparing Group I to Group II and III, and Group II to Group III).The administration of the initial dose of postoperative analgesic was notably postponed in Group III (17.14 ± 1.32 hours) in comparison to Group I (15.55 ± 1.50 hours) (P < 0.05) and Group II (15.09 ± 1.48 hours) (P < 0.05; Group III vs. Group I and II). There was no observed occurrence of motor block in any of the patient groups, as indicated in Table 3. There were no observed instances of side effects or complications among any of the patients included in our study.

DISCUSSION

The findings of our study indicate that the inclusion of clonidine as an adjunct to levobupivacaine in caudal epidural block has a significant effect on prolonging the duration of analgesia and reducing the need for postoperative rescue analgesics in pediatric patients undergoing perineal surgeries, when compared to the use of levobupivacaine alone or in combination with tramadol. Insufficient pain management during childhood can potentially result in enduring adverse consequences, such as detrimental neuroendocrine reactions that disrupt eating and sleep patterns, as well as heightened sensitivity to pain during future painful encounters. Postoperative pain can potentially induce various emotional and psychological disturbances in pediatric patients, leading to the manifestation of uncooperative behavior and restlessness in the child.[8] Therefore, it is more advantageous to proactively mitigate the occurrence of pain rather than solely addressing its presence. The user's text is too short to be rewritten in an academic manner. Several different multimodal techniques have been developed specifically for the purpose of alleviating pain in pediatric patients. Both systemic and regional analgesia methods are encompassed within this category. The utilization of different adjuvants is a recommended approach for extending the duration of analgesia during the postoperative period, as it offers a straightforward, efficient, and superior option. The caudal epidural block is the prevailing regional technique employed in pediatric patients. [9]The user's text is already academic and does not require any rewriting. Caudal epidural anesthesia is widely regarded as a safe and straightforward form of regional anesthesia commonly employed in the pediatric population for lower abdominal surgeries, demonstrating a notable success rate. The administration of a caudal block not only offers effective postoperative analgesia, but also reduces the intraoperative need for inhalation anesthetic drugs and muscle relaxants in order to mitigate the surgical stress response.[10]One significant drawback of the single-shot caudal block is its comparatively shorter duration of analgesia.[11]The utilization of caudal epidural catheter placement is not widely favored in clinical practice, primarily due to the associated risk of infection. There are several local anesthetic agents, including bupivacaine, ropivacaine, and levobupivacaine, that can be administered via caudal block to provide analgesia during and after surgery. However, it is important to consider the potential side effects and complications associated with these agents, particularly when used in pediatric patients. Previous studies have documented instances of mortality resulting from cardiovascular toxic side effects following the administration of bupivacaine during regional anesthesia.[12]The user's text does

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not contain any information to rewrite. Cardiotoxicity is a rare occurrence when primarily administered in the racemic form of bupivacaine.[13]The user provided a numerical reference without any accompanying text. Considering this, we have opted to utilize levobupivacaine instead of bupivacaine due to the findings from numerous studies indicating that levobupivacaine possesses a broader safety margin, devoid of any observed adverse effects or complications associated with bupivacaine.

Several adjuvants, including clonidine, fentanyl, dexamethasone, magnesium sulfate, and dexmedetomidine, were incorporated into the local anesthetic agent in order to extend the duration of analgesia. A comparative study was conducted to assess the effectiveness of coadministering ketamine, midazolam, and neostigmine with bupivacaine in caudal epidural anesthesia for providing pain relief during and after surgery. The findings indicated that the administration of bupivacaine–neostigmine and bupivacaine–midazolam through a single-shot caudal approach resulted in a prolonged duration of postoperative pain relief.[14] The user's text does not contain any information to rewrite. The impact of incorporating dexmedetomidine as a supplementary medication to bupivacaine in caudal analgesia for pediatric patients undergoing perineal surgeries has been investigated. The findings of these studies indicate that the addition of dexmedetomidine to bupivacaine prolongs the duration of caudal analgesia and enhances the stability of hemodynamic parameters, all while avoiding any significant increase in negative effects among children.[15]The user's text is too short to be rewritten in an academic manner. A research investigation was conducted involving a sample of 60 children ranging in age from 6 months to 6 years. The purpose of the study was to assess the impact of incorporating clonidine or dexmedetomidine into caudal bupivacaine. The results indicated that the inclusion of either clonidine or dexmedetomidine in caudal bupivacaine had a notable effect in extending the duration of pain relief in pediatric patients undergoing infra-abdominal surgeries.[16]The user's text does not contain any information to be rewritten. The decreased absorption of levobupivacaine, due to its lower lipid solubility and greater intrinsic vasoactivity, results in a differential neural blockade characterized by reduced motor block. The provided text consists of two numerical values, specifically 17 and 18. Previous research has provided evidence indicating that patients who were administered a caudal injection of 0.125% levobupivacaine did not experience any postoperative motor block.The user's text, "[4,19]", does not require any academic rewriting as it In our investigation, we also failed to detect any instances of motor block when administering caudal 0.125% levobupivacaine. Clonidine, an agonist of the alpha-2 adrenoreceptor, exhibits the ability to extend the duration of analgesia and produce prolonged motor and sensory block effects of local anesthetic agents when administered caudally. The analgesic effect of epidural clonidine is achieved by inhibiting nociceptive neurons in the spinal cord. Nevertheless, the specific mechanism of action remains unclear.[3]The user's text does not provide any information to rewrite. The effectiveness and safety of combining clonidine with local anesthetics, as compared to using caudal local anesthetics alone, have been evaluated. The findings indicate that the addition of clonidine to locally administered anesthetics via the caudal route leads to a prolonged duration of pain relief, a reduced need for additional analgesic interventions, and minimal adverse effects when compared to using caudal local anesthetics alone.[20]The user did not provide any text to rewrite. Another study evaluated the impact of caudal and intravenous administration of clonidine on the postoperative analgesic effects of caudal levobupivacaine in children undergoing perineal surgery. The study found that adding clonidine at a dose of 1 μg.kg-1 to 0.25% levobupivacaine for caudal analgesia significantly extended the duration of analgesia, without any observed adverse effects.According to the source provided, [3]. Tramadol is classified as a synthetic opioid that exhibits a notable affinity for the μ receptor, while also displaying relatively weaker activity towards the kappa and delta receptors. Additionally, it exhibits inhibitory effects on serotonin and norepinephrine reuptake, while not inducing significant respiratory depression.[21] Furthermore, it has been observed to possess greater analgesic efficacy compared to caudal bupivacaine.[22]The user has not provided any text to rewrite. In the conducted study, it was observed that the administration of a combination of levobupivacaine and tramadol yielded superior results in terms of the duration of postoperative analgesia compared to the administration of levobupivacaine alone. Based on the findings of previous studies, it is plausible to propose that there may exist a synergistic interaction between local anesthetics and adjuvants, as opposed to a mere additive effect.[5]The user's text is already academic

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and does not need to be rewritten. Certain studies have shown that the analgesic effects of levobupivacaine and tramadol have a duration of less than 12 hours. The content provided represents a numerical range, specifically the interval from inclusive[4,8] No complications or side effects were observed intraoperatively or during the postoperative period with the administration of levobupivacaine or the adjuvants clonidine and tramadol in our study. One of the limitations inherent in our study was the relatively small sample size. Therefore, it is recommended that comprehensive studies be conducted in order to evaluate the potential adverse effects. The present study is limited to a single-center setting, thereby restricting the generalizability of our findings. This limitation is further compounded by the small sample size, which hinders the ability to validate our results. The study employed an observational design, which introduces the potential for observer bias in the obtained findings. The study's findings have been documented by several observers, potentially introducing a subjective bias. It is preferable for the recording of results to be conducted by a single blinded observer.

CONCLUSION-

The study's findings indicate that the inclusion of clonidine and tramadol as adjuvants in caudal block, alongside levobupivacaine, resulted in an extended duration of analgesia. The study revealed that Clonidine demonstrated superior efficacy in terms of maintaining stable hemodynamics and providing longer-lasting analgesia, while not causing any clinically significant side effects or complications. The addition of 1 μg.kg-1 of clonidine to levobupivacaine in caudal block has been found to significantly increase the duration of analgesia compared to the administration of tramadol with levobupivacaine or levobupivacaine alone. This effect has been observed without any notable side effects of clinical significance. Therefore, the incorporation of additives such as clonidine is advantageous in augmenting the analgesic efficacy.

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