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LEVOBUPIVACAINE FOR REGIONAL BLOCKADES IN ORTHOPEDICS AND TRAUMATOLOGY IN CHILDREN: RECENT EVIDENCE AND FUTURE DIRECTIONS

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Levobupivacaine is an amide anesthetic, levorotatory isomer of bupivacaine. This literature review aimed to present the possibilities of levobupivacaine in the implementation of blockades for anesthesia in traumatology and orthopedics in children. Levobupivacaine is widely used for analgesia for orthopedic interventions in adults and has become an alternative to the less safe bupivacaine. The actions of levobupivacaine, bupivacaine, and ropivacaine in the implementation of neuroaxial and peripheral blockades, and the infiltration of postoperative wounds in children were compared in the present study. Levobupivacaine has been confirmed to be safe compared with bupivacaine in pediatric patients. Studies in children of different ages comparing levobupivacaine and ropivacaine, used for anesthesia in traumatology and orthopedics, indicate the same or greater analgesic potential of levobupivacaine, with a similar level of safety. Compared with ropivacaine, levobupivacaine provides comparable pain relief at lower concentrations. The presented clinical data of levobupivacaine use in children allow the expansion of the indications for anesthesia in orthopedics and traumatology. Clinical research should be continued to compare the effectiveness of different concentrations of levobupivacaine and ropivacaine in larger groups of pediatric patients. Relevant papers were obtained by searching PubMed and Scopus databases.

Keywords: regional anesthesia in children; levobupivacaine; bupivacaine; ropivacaine, orthopedics, and traumatology.

ПЕРСПЕКТИВЫ ПРИМЕНЕНИЯ ЛЕВОБУПИВАКАИНА ДЛЯ РЕГИОНАРНЫХ БЛОКАД В ОРТОПЕДИИ И ТРАВМАТОЛОГИИ У ДЕТЕЙ

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Левобупивакаин — это амидный анестетик, левовращающий изомер бупивакаина. Целью обзора литературы является представление возможностей левобупивакаина при реализации блокад для обезболивания в травматологии и ортопедии у детей. Левобупивакаин широко применяется для обезболивания ортопедических вмешательств у взрослых и стал альтернативой менее безопасному бупивакаину. В обзоре приводится сравнение действия левобупивакаина, бупивакаина и ропивакаина при реализации нейроаксиальных и периферических блокад, инфильтрации послеоперационной раны у детей. Подтверждена бóльшая безопасность левобупивакаина по сравнению с бупивакаином у педиатрических пациентов. В исследовании у детей разного возраста, в которых сравниваются левобупивакаин и ропивакаин, применяемый для обезболивания в травматологии и ортопедии, отмечается одинаковый или больший анальгетический потенциал левобупивакаина при сходном уровне безопасности. При сравнении с ропивакаином препарат обеспечивает сопоставимое обезболивание при меньшей концентрации. Представленные данные о клинических исследованиях, связанных с применением левобупивакаина у детей, позволяют расширить показания для обезболивания в ортопедии и травматологии. Следует продолжить исследования по сравнению эффектив-

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ности разных концентраций левобупивакаина и ропивакаина на более многочисленных группах пациентов детского возраста. Релевантные статьи обзора литературы получены путем поиска в системах Pubmed и Scopus.

Ключевые слова: регионарная анестезия у детей; левобупивакаин; бупивакаин; ропивакаин; травматология и ортопедия.

Introduction

Studies aiming to improve the safety of regional anesthesia in pediatric orthopedics and traumatology enable a reduction in the number of complications associated with the toxic effects of topical anesthetics. Improving the method of performing blocks is as important as using less toxic powerful local anesthetics such as ropivacaine and levobupivacaine [1].

Levobupivacaine is an aminoamide topical anesthetic and a left-rotating enantiomer of the racemic mixture of its precursor bupivacaine [2]. Levobupivacaine was registered in the Russian Federation in June 2015 for pediatric anesthetic purposes to be used only for ilioinguinal and iliohypogastric blocks. However, it has been extensively used for other variants of regional blocks in children, including for analgesia in orthopedics and traumatology [3].

This literature review aims to present the drug capabilities in the implementation of blocks for analgesia in pediatric traumatology and orthopedics. Relevant literature review articles were obtained through searching the Pubmed and Scopus systems. The publication does not espouse the use of the drug beyond the instructions and is informative in nature, confirming the possibility of its use in traumatology and orthopedics.

Use of levobupivacaine in adults

Levobupivacaine is widely used for both neuroaxial and peripheral regional blocks in adults. The drug serves as an alternative to bupivacaine, as it is safer due to the lower risk of cardio-and neurotoxic effects with occasional intravenous administration [4–6]. Levobupivacaine 0.5% and bupivacaine 0.5% are effective and recommended for use in a 3-in-1 block [7]. Levobupivacaine provides a significantly longer duration of analgesia than ropivacaine in adults [8]. In addition, levobupivacaine allows a relatively slower restoration of the motor activity than ropivacaine after the block [9]. Prolonged sensory block combined with good analgesia and lesser toxicity make levobupivacaine the best choice for blocking the upper limbs [10]. Levobupivacaine 0.5% provides a longer duration of sensory block to the sciatic nerve using Labat approach than the same dose of ropivacaine during orthopedic interventions on the foot and lower leg [11]. Besides, a single dose of levobupivacaine 0.5% is preferred over ropivacaine 0.5% for blocking the tibial and peroneal nerves during surgery for valgus deformity of the great toe using the popliteal approach due to its good anesthesia and better control of postoperative pain [12]. Collectively, compared with ropivacaine, the potent analgesic and motor block effects as well as high safety profile of levobupivacaine favor its use in adult orthopedics and traumatology.

Peripheral nerve block with levobupivacaine in children

Pioneer studies of the effectiveness of regional blocks with levobupivacaine in pediatric practice were focus on the ilioinguinal and iliohypogastric blocks for postoperative analgesia in children undergoing herniotomy (aged 6 months–12 years). A study by Gunter showed that patients in whom levobupivacaine was used exhibited lower postoperative pain and reduced dependency on analgesics [13]. In a recent study conducted in 90 children aged 1–7 years, ilioinguinal and iliohypogastric blocks using levobupivacaine were compared with transverse abdominal space and the caudal blocks, and a greater efficiency of postoperative analgesia with the latter two was shown [14].

For a safe regional anesthesia, it is important to choose a minimum effective concentration of a local anesthetic. In a study comparing three different concentrations of levobupivacaine (0.125%, 0.5%, and 0.375%) for ilioinguinal and iliohypogastric blocks in pediatric outpatient surgery (n = 73; age 1–6 years) at a dose of 0.4 mL/kg, it was evident that

the concentrations of 0.5% and 0.375% provided a significantly better quality of postoperative anesthesia [15]. Introduction of an ultrasonic navigation increases the accuracy of administration of local anesthetic and reduce its quantity when performing peripheral blocks. In 2005, Willschke et al. demonstrated that ilioinguinal or iliohypogastric block in pediatric population (age 1 month–8 years) can be achieved with a significantly smaller amount of levobupivacaine than with the traditional method of administration of a local anesthetic (0.19 mL/kg vs. 0.30 mL/kg) while maintaining a high quality of intra- and postoperative anesthesia [16].

Furthermore, a high block efficacy with levobupivacaine (0.2 mg/kg) has been demonstrated in the transverse abdominal space in 27 children aged 1–5 years who underwent surgical interventions for inguinal hernia [17]. According to Nass, bilateral intercostal block with levobupivacaine 0.25% and epinephrine (5 μg/mL) in combination with general anesthesia for minimally invasive thoracoplasty reduces the number of opioids used for analgesia in the postoperative period as well as the associated side effects [18].

Levobupivacaine along with ropivacaine in low concentrations (0.1%–0.2% solutions with an injection rate of 0.25 mg/kg/h) is recommended for prolonged blocks of peripheral nerves while continuing postoperative analgesia at home, including for the treatment of complex regional pain syndrome in children. To ensure the efficiency and safety of the regional block, it is necessary to monitor the conditions when transferring the patient home with the catheter installed; to provide training to staff, patients, and parents; and to form a special anesthesiology team [3]. Compared with ropivacaine (0.2%), levobupivacaine at a lower concentration (0.125%–0.175%) can confer comparable analgesia with a prolonged block [19].

Thus, levobupivacaine can be applied for peripheral nerves blocks both in the intra- and postoperative periods in pediatric orthopedics.

Infiltration anesthesia and infusion of levobupivacaine into postoperative wounds in children

Postoperative wound infiltration and irrigation with a topical anesthetic using a special catheter are the safest methods for regional anesthesia. The efficiency of levobupivacaine has been demonstrated in pediatric herniotomy (n = 30; age 2–12 years); infiltration of a postoperative wound, after an inguinal hernia grafting, using a 0.25% solution of levobupivacaine at a dose of 1.25 mg/kg in children weighing <16 kg and a 0.5% solution in children weighing >16 kg at a dose of 1.25 mg/kg resulted in a significantly longer and more effective postoperative analgesia compared that in children who received paracetamol 30 mg/kg via rectal route. In addition, the authors emphasized that the infiltration of the surgical wound with levobupivacaine enables a quick and reliable mobilization of the child after the surgery (within the next 2 hours) [20]. Furthermore, compared with rectal administration of paracetamol, a greater efficacy of postoperative wound infiltration with levobupivacaine for postoperative analgesia after herniotomy was demonstrated in a study on 60 children and adolescents aged 2–18 years [21]. No significant difference has been observed between the infiltration with a local anesthetic before making the incision and that at the end of the surgery [22].

This method of levobupivacaine administration may serve as an additional method of anesthesia if the peripheral nerve and neuroaxial blocks are not possible in orthopedics, or it may act as the primary type of anesthesia for low-injury intervention [23, 24].

Neuroaxial blocks with levobupivacaine in children

Over time, levobupivacaine has been more commonly used in pediatric practice for spinal anesthesia and for caudal and prolonged postoperative epidural block, including its use in orthopedic interventions [25–28].

In children, levobupivacaine has a clinical efficacy equivalent to that of racemic bupivacaine for spinal anesthesia. A study of the efficacy of levobupivacaine 0.5% (average dose is 0.3 mg/kg) for spinal anesthesia in pediatric surgeries of the lower abdominal cavity or lower limbs (n = 40; aged 1–14 years) has demonstrated a good level of anesthesia in 39 children. The average level of the sensory block was T_4, and the average time taken for the regression of the sensory block to T_{10} was 90 min. Full motor block was achieved in 36 children [29].

A study of newborns by Frawley et al. has revealed that to achieve comparable spinal block effects, a higher dose of isobaric levobupivacaine 0.5% (1.2 mg/kg) than of bupivacaine and eopivacaine (1 mg/kg) is required [30].

In a study conducted in 307 children aged 2 months–10 years, no difference was found in the potencies of bupivacaine and levobupivacaine for caudal epidural block. The recommended dose of levobupivacaine for effective caudal anesthesia is 2.5 mg/kg. Prolonged postoperative epidural block with 0.125% levobupivacaine or ropivacaine in children is accompanied by a significantly lower motor blockage than that with a similar dose of bupivacaine with equally good analgesia [31].

In a randomized, double-blind, controlled study by Ivani et al. ($n = 60$; age 1–7 years), caudal block with 1 mL/kg of levobupivacaine 0.25%, ropivacaine 0.2%, and bupivacaine 0.25%, along with inhalation anesthesia with sevoflurane, were compared. Levobupivacaine, ropivacaine, and bupivacaine demonstrated a comparable time of onset of action and duration of anesthesia after surgery. Compared with ropivacaine 0.2%, a significant difference was observed in residual motor block after the application of bupivacaine 0.25% and levobupivacaine 0.25%. No significant difference was observed between levobupivacaine 0.25% and bupivacaine 0.25% [32].

In another study, levobupivacaine 0.25% and ropivacaine 0.25% did not show any differences in the onset time, intraoperative efficacy, postoperative analgesia, and residual motor block in children (age 2–6 years) [33]. In addition, Ingelmo et al. have demonstrated that no significant differences exist in the analgesic potential of levobupivacaine and ropivacaine when performing a caudal block under inhalation anesthesia with sevoflurane [34].

In a randomized blind study by Ivani et al., three different concentrations of levobupivacaine (0.125%, 0.2%, and 0.25%) were compared in children aged 1–7. The dose–response relationship was analyzed taking into account the average duration of postoperative analgesia and the number of patients with early postoperative motor blockade. The concentration of 0.125% provided a significantly lower level of early motor block than the other two concentrations. The authors suggested that a 0.2% solution could be the best clinical option for caudal block with levobupivacaine in children [35].

The pharmacokinetics of levobupivacaine in children (aged <3 months) with caudal block have been studied by measuring its plasma concentration following a single injection of its 0.25% solution at a dose of 2 mg/kg. The median time taken to reach the peak plasma concentration was 30 min (range 5–60 min); the time taken to reach the peak was longer in children aged <3 months. The peak plasma concentration for racemic bupivacaine was within the acceptable range, 0.41–2.12 μg/mL. Moreover, the authors revealed that plasma clearance of bupivacaine is half of its value in adults (mainly due to the immaturity of the isoenzymes CYP3A4 and CYP1A2 isoforms of cytochrome P450) and T_{max} is slowed down (50 min after the injection), but to a lesser extent than that of ropivacaine (120 min in the same age group) [36].

Studies have demonstrated contradictory data on the difference between levobupivacaine and ropivacaine in neuroaxial blocks in children, in contrast to the results obtained in adults; thus, further research in more extensive groups is warranted.

Conclusion

Levobupivacaine is a safer local anesthetic than bupivacaine and is effective in regional blocks in adult and pediatric traumatology and orthopedics. Efforts to minimize the risk of complications during regional anesthesia administration in children should be focused on the measures to reduce accidental intravenous and intraosseous injections, reduce the total amount of local anesthetics used, and the use of drugs with lower toxic potential. Compared with bupivacaine, levobupivacaine can be used at higher doses and the risk of intoxication remains relatively lower. In clinical situations that require prolonged topical anesthesia for caudal block in newborns and young children, levobupivacaine is a safer alternative to bupivacaine. Most studies in children, unlike those in adults, show no significant differences in the potency and duration of motor block between levobupivacaine and ropivacaine. In studies of children of different ages, in which levobupivacaine and ropivacaine were used for anesthesia in traumatology and orthopedics, an equal or greater analgesic potential of levobupivacaine has been observed with a similar level of safety. Several authors recommend continuing the research to

compare the efficiency of different concentrations of levobupivacaine and ropivacaine in larger groups of pediatric patients [37, 38].

None of the above studies in children demonstrate a difference in the incidence of complications associated with the use of levobupivacaine and ropivacaine.

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Contribution of the authors

G.E. Ulrich created the concept and design of the study and prepared the manuscript.

D.V. Zabolotsky, Yu.S. Aleksandrovich, V.A. Koryachkin were involved in collection and processing of data.

S.N. Nezabudkin performed data analysis.

D.G. Ulrich translated the articles and designed the material.

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