UDC 617.572-089.5:615.211]-06:615.099:616-085 https://doi.org/10.26641/2307-0404.2024.4.319406

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LOCAL ANESTHETIC SYSTEMIC TOXICITY AFTER BRACHIAL PLEXUS BLOCK WITH ROPIVACAINE: A CASE REPORT

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Цитування: Медичні перспективи. 2024. Т. 29, № 4. С. 272-276
Cited: Medicni perspektivi. 2024;29(4):272-276

Keywords: *regional nerve blocks, local anesthetic systemic toxicity, ropivacaine*
Ключові слова: *регіональні блоки нервів, системна токсичність місцевого анестетика, ропівакаїн*

Abstract. Local anesthetic systemic toxicity after brachial plexus block with ropivacaine: a case report. Tutunnyk A.G., Mynka N.V., Kobelyatskyy U.U. *The aim of this article is presentation of clinical case of local anesthetic systemic toxicity (LAST). Local anesthetic systemic toxicity is a rare but life-threatening complication. Ropivacaine is widely used for the regional blocks and rarely leads to the development of LAST. LAST may develop due to intravascular injection or high dose of ropivacaine. We present the case of 48-year-old-female (ASA I, 56 kg, and 165 cm), who underwent surgery on the right shoulder under brachial plexus block. Brachial plexus nerve block was performed by interscalene access with introduction of 40 ml of 0.75% ropivacaine (300 mg). Twenty minutes after the injection, complete sensory/motor block was achieved. Twenty-five minutes after the injection, the patient complained of numbness in the tongue, tinnitus and dizziness. During this time, her blood pressure was 132/83 mmHg, heart rate 82 beats/min. oxygen saturation 97%. No changes were observed on the ECG. Suspecting ropivacaine-induced toxicity, 50 mg of thiopental sodium followed by 2 mg of midazolam were administered for seizure prophylaxis, and supplemental oxygen was given via face mask. Patient's state improved in 10 minutes. Ten minutes later 20% intralipid emulsion bolus during 2-3 min was administered followed by continuous infusion at a dose of0.25 ml/kg/min. Against clinical stablility and consciousness of the patient, decision was made to proceed with surgery, which was uneventful. Implementation of preventive measures can decrease the possibility for development of complications and emergency treatment can safe patient's health and life. Preventive measures should include implementation of ultrasound nerve location guidance, individual calculation of local anesthetic dose, taking into account sex, weight, and physical status of a patient.*

Реферат. Системна токсичність місцевого анестетика після блоку плечового сплетіння з ропівакаїном: клінічний випадок. Тютюнник А.Г., Минка Н.В., Кобеляцький Ю.Ю. *Метою цієї статті є наведення клінічного випадку виникнення системної токсичності місцевого анестетика (СТМА). Системна токсичність місцевого анестетика є рідким, але небезпечним для життя ускладненням. Ропівакаїн широко використовується для регіональних блоків та мало коли призводить до розвитку СТМА. Системна токсичність місцевого анестетика розвивається внаслідок його внутрішньосудинного введення або застосування високої дози. Ми презентуємо клінічний випадок 48-річної пацієнтки (АТА I, 56 кг, 165 см) з операцією на правому плечі під блоком плечового сплетіння. Блок плечового сплетіння був виконаний міждрабинчастим доступом з введенням 40 мл 0,75% ропівакаїну (300 мг). Через двадцять хвилин після введення був отриманий сенсорний/моторний блок. Через двадцять п'ять хвилин після введення пацієнтка поскаржилась на заніміння язика, шум у вухах та запаморочення. У цей час її артеріальний тиск був 132/83 мм рт. ст., частота серцевих скорочень 82 уд./хв., сатурація киснем 97%. На електрокардіограмі не спостерігалось змін. Запідозрено індуковану ропівакаїном токсичність, тому було введено 50 мг тіопенталу натрію та 2 мг мідазоламу з метою запобігання розвитку судом та додано кисень крізь лицьову маску. Стан пацієнтки покращився через десять хвилин. Через десять хвилин було введено болюс 20% інтраліпіду протягом 2-3 хвилин, з подальшою постійною інфузією в дозі 0,25 мл/кг/хв. На тлі клінічної стабільності та свідомості пацієнтки було ухвалено рішення щодо проведення операції, яка пройшла без ускладнень. Імплементація превентивних заходів може знизити вірогідність розвитку ускладнень, а невідкладне лікування зберегти життя та здоров'я пацієнтів. Превентивні заходи повинні включати застосування методів ультразвукової локації нервів, індивідуального розрахунку дози місцевого анестетика, враховуючи стать, вагу та фізичний статус пацієнта.*

Local anesthetic systemic toxicity (LAST) is uncommon but dangerous critical event. LAST may occur from excess local anesthetic binding of the intracellular portion of the voltage-gated sodium

(VGNa) channel. VGNa channel consists of the main alphasubunit linked to one or more beta-subunits. The alpha subunit is the functional ion channel that has binding sites for local anesthetics, and the beta subunits modulate the kinetics and voltage dependence for activation/inactivation. The binding of the local anesthetic (LA) leads to a conformational change, which inactivates the channel and creates a positive charge in the lumen of the VGNa channel, effectively blocking influx of Na [2].

LA can interfere with cell membrane signaling, which in turn affects multiple cellular processes of cyclic adenosine monophosphate, protein kinases**.** The LA also changes mitochondrial metabolism, adenosine triphosphate production, and ryanodine receptor. Blockade of Na channels by LA affects many sites. When Na channels are blocked, there is a decrease or cessation of conduction of action potential, which leads to vasodilation. In the heart, it leads to decreased excitability and prolonged refractory period. In central nervous system (CNS) it leads to increased excitability followed by generalized depression. The multitude of sites affected by the LA is what makes LAST have complex clinical presentation.

The cardiovascular system (CVS) and central nervous system are the most affected systems in LAST and accounted for the most of the clinical symptoms. High plasma concentration of LA in the nervous system leads to blockade of inhibitory cortical pathways by blockade of Na channels, which is presented as visual and sensory changes and eventually seizures. Increased plasma concentration affects the excitatory pathways, leading to depression of neurological activity ranging from altered level of consciousness to respiratory arrest [1, 8].

High plasma concentration of LA in the CVS leads to changes in conduction and contraction. Early tachycardia and hypertension may develop due to sympathetic activation, dysrhythmia and myocardial dysfunction. Conduction is primary affected, leading to more negative membrane potential. This leads to reentrant dysrhythmias. Bradycardia, ventricular arrhythmias, hypotension and cardiac arrest are the classic clinical features of LAST [8].

The research was conducted following the fundamental regulations stated in the "Ethical Principles for Medical Research Involving Human Subjects" as established by the Helsinki Declaration (1964-2013), ICH Good Clinical Practice (1966), Directive 609/EEC (as of 24.11.1986), and the Orders of the Ministry of Health of Ukraine No. 690 as of 23.09.2009, No. 944 as of 14.12.2009, and No. 616 as of 03.08.2012. The patient was fully informed about objectives, organization and research methods, and provided informed consent to participate in the study. All measures were taken to ensure the patient's anonymity.

The material of this study was reviewed at the meeting of the Bioethics Commission of Dnipro State Medical University and approved by the Protocol No. 13 as of 08.11.2023.

A 48-year-old-female (ASA I, 56 kg, and 165 cm) was scheduled for surgery on the right shoulder under brachial plexus block. There was no medical history of neurological or cardiovascular disease. Physical examination and electrocardiogram (ECG) were unremarkable.

The patient did not receive any sedatives before surgery. In the operating room, standard monitoring (pulse oximetry, noninvasive blood pressure cuff, and ECG) was applied. Using an insulated needle (Stimuplex A, B. Braun, Germany) and nerve stimulator (Stimuplex HNS, B. Braun, Germany) an interscalene brachial plexus nerve block was performed to provide anesthesia. Once a nerve response with a current of 0.5 mA was obtained, a total dose of 40 ml of 0.75% ropivacaine (300 mg; 5.36 mg/kg) without epinephrine was slowly injected with negative aspiration in 5 ml increments. Verbal communication was made during injection, and no early signs of systemic toxicity were noted. Ten minutes after the injection, sensory block was complete in the right shoulder. Twenty minutes after the injection, complete motor block was achieved.

Twenty-five minutes after the injection, the patient complained of numbness in the tongue, tinnitus and dizziness. During this time, her blood pressure, heart rate, and oxygen saturation was 132/84 mmHg, 80 beats/min, and 99%, respectively. No changes were observed on the ECG. Suspecting ropivacaine-induced toxicity, 50 mg of thiopental sodium followed by 2 mg of midazolam were administered for seizure prophylaxis, and supplemental oxygen was given via face mask.She recovered over 10 minutes. Patient had no recall of the preceding events, had no sequelae, and was informed. Ten minutes later 1.5 mg/kg of 20% intralipid emulsion bolus over 2 to 3 min was administered followed by continuous infusion at 0.25 ml/kg/min. As the patient remained clinically stable and her mental status had return to baseline, a decision was made to proceed with surgery, which was uneventful.

There are three forms of LAST that have been described. First is "instant" LAST from accidental intravenous injection of large volume of LA, leading to cardiovascular collapse and seizures within short time. Second scenario of "instant" LAST is accidental intra-arterial injection of LA during peripheral nerve blockade, resulting in immediate, short-lived seizures, rarely associated with cardiovascular events due

to the small volume administered. Third, "slow" LAST results from total overdosing, excessive absorption, or reduced LA metabolism and can occur up to half an hour after injection.

CNS is more susceptible to LAST than CVS. This means that the serum concentration of LA required to develop LAST symptoms is lower for the CNS then for the CVS. This is the reason that CNS toxicity is the most common and often initial symptom [9]. Different LAs have different cardiotoxicity. Lidocaine and mepivcacaine mainly represent decreased contractility, while ropivacaine and bupivacaine are negatively inotropic and highly arrhythmogenic [11]. Bupivacaine has been considered more cardiotoxic when compared with ropivacaine because smaller doses are needed to produce toxicity. It's important to take into consideration the 40 – 50% potency difference between them. Therefore, comparison has to be based on clinically equivalent doses. Basically, bupivacaine and ropivacaine are almost equal in causing CNS symptoms. It is essentially that bupivacaine occupies VGNa channel for prolonged period of time.Ropivacaine is LA with a long duration of action providing increased safety as compared to bupivacaine, because of the reduced cardiovascular and central nervous system toxicity. The lower toxicity of ropivacaine may be advantageous, enabling large doses to be used. Brachial plexus block performed by doses up to 40 ml of 0.75% ropivacaine (300 mg) provided good anesthesia without CNS and CVS toxicity.

The rate of LAST is not known, as some cases may not be reported. Nearly all available data are from case reports and retrospective analysis. Overall incidence is 0.03% or 0.27 per 1000 peripheral nerve blocks (PNB) from major retrospective studies [9].

The risk factors for LAST include age, coexisting diseases, pregnancy, agents and type of regional anesthesia technique. The pediatric and geriatric age groups are commonly recognized risk factors. Coexisting diseases such as cardiovascular, metabolic, hepatic and renal dysfunction, mitochondrial disease are reported to have a high risk of LAST. Almost all LA have been reported with LAST. The most commonly used agents, namely, bupivacaine, ropivacaine, and lidocaine, account for about 80 to 90% of all reported cases of LAST. Interscalene nerve block had the highest incidence (23%) of LAST among peripheral nerve blocks (PNBs) [9].

Strict safety measures with close monitoring and avoidance of risk factors are required to prevent or limit the severity of LAST. Restricting LA dose within the recommended dosage and customizing it to each patient depending on their clinical condition is a crucial in prevention of LAST. Incremental bolus, slow injection rate, and gentle aspiration between injections are recommended measures to avoid toxicity. Addition of epinephrine in low doses to the LA acts as a marker for intravascular injection by increasing the heart rate and systolic blood pressure. Multiple studies have shown that ultrasound guidance for PNBs reduces risk of LAST [10].

Management of LAST includes general supportive measures and specific therapeutic interventions for reducing toxicity. Management differs from other perioperative cardiac arrest scenarios. As soon as LAST is suspected, injection/infusion of LA should be stopped immediately, and more help sought to begin resuscitation measures.

Basic supportive measures to open/maintain airway, oxygenation, and ventilation are essential for survival and positive outcome. Hypoxia, hypercapnia, and acidosis have been shown to impair resuscitation and worsen the outcome [12]. Cardiac arrest or cardiovascular collapse demands immediate start of cardiopulmonary resuscitation (CPR). Effective CPR is essential to provide adequate coronary perfusion, which is the only way to decrease the local anesthetic concentration at the tissue. It has been shown that positive inotropic effects of lipid emulsion are expected only below certain levels of myocardial local anesthetic concentration. Specific therapeutic interventions differ from standart resuscitative measures. If the situation requires use of epinephrine, it is recommended in small doses, less than 1 μg/kg. Epinephrine in standard doses has been shown to impair gas exchange and cardiac function in animals with LAST. Other significant differences include avoiding vasopressin, calcium channel blockers, and beta-blockers during cardiac resuscitation in LAST. Amiodarone is the drug of choice, and lidocaine is contraindicated in these situations.

In case of seizures, airway management, mechanical ventilation, and seizures control are crucial to avoid hypoxia and acidosis. Benzodiazepines are the first choice for seizures control in these clinical cases. Propofol can control seizures but could cause further deterioration in cardiovascular stability, hence avoided. If seizures are not controlled with benzodiazepines, small doses of neuromuscular blockers can be used to prevent deterioration caused by hypoxia and acidosis [10, 11].

Use of intravenous lipids in treatment of LAST has been a major advancement and a real "game changer". Intravenous lipids are now a vital component of guidelines and checklists recommended for management of LAST [10]. Intravenous lipid is administered as an initial bolus and continued with a continuous infusion. In patients over 70 kg, recommended initial bolus is 100 ml over 2 to 3 min and infusion of 200 to 250 ml over 15 to 20 min. Recommendation for

bolus dose in patients less than 70 kg is 1.5 ml/kg over 2 to 3 min and continuous infusion at 0.25 ml/kg/min. The initial bolus can be repeated or infusion doubled if hemodynamic stability is not achieved. Lipid infusion should be continued for about 10 min after the patient hemodynamic is stabilized. Maximum recommended initial dose of lipid is 12 ml/kg.

Among risk factors for LAST interscalene block had the highest incidence (23%) of LAST [4].

Although the cardiovascular system and central nervous system are the most affected systems in local anesthetic systemic toxicity, in our case only central nervous system was affected clinically.

Multiple safety measures may be used including incremental bolus, slow injection over a period of time, and gentle aspiration between injections to avoid adverse effects [5].

In our case patient experienced 'slow' LAST results from overdosing, and excessive absorption occurred twenty two minutes after injection. In Finland and United States the maximum recommended dose of ropivacaine for brachial plexus block is 300 mg. However, standard doses cannot be used to every patient [10].

In our case 300 mg (5.36 mg/kg) of ropivacaine was used for interscalene block, and local anesthetic toxicity occurred on twenty five min. Plasma ropivacaine level was, unfortunately, not measured in the case presented here. However, the delayed onset of the symptoms and complete brachial plexus block suggest a nonintravascular injection, indicating rapid absorption of a large dose of ropivacaine. Therefore, 300 mg of ropivacaine may have been excessive in this patient. Several previous studies have reported that 300 mg of ropivacaine could produce local anesthetic toxicity limited to central nervous system.

Basic supportive measures to maintain airway, oxygenation were administered to prevent hypoxia, hypercapnia, and acidosis.

Administration of intravenous lipids early in the treatment is highly recommended. Lipids should be considered soon after airway management as timely administration can make a significant difference in outcome [6]. Several animal studies have shown that administration of intravenous lipids before epinephrine improves survival and cardiac stability. Over the last years, the role of lipids in the treatment of LAST has not only been established, but advances have been made in understanding the mechanism of intravenous lipids in treatment of LAST [7]. The current understanding is that the lipids have multiple mechanisms of action in reversal LAST. The first mechanism is the "scavenging effect" where lipids act as a shuttle. Lipid as a shuttle helps to redistribute LA from high-blood flow organs such as the heart and brain to organs of storage (muscles and adipose tissue) and detoxification (liver). The dual action of binding and redistribution explains the action as a "lipid shuttle" rather than a "lipid sink" as it was originally described. The second mechanism is the direct cardiac and vascular effects of intravenous lipids resulting in improved cardiac output and increased blood pressure. Third mechanism is cardio-protective effect by decreasing ischemic reperfusion injury and improving cardiac recovery. Lipid emulsion rarely causes adverse effects. Allergic reactions, hyperlipidemia, immunomodulation, hypercoagulability, and venous thrombosis have been reported with intravenous lipids. Adverse effects such as pancreatitis, acute respiratory distress syndrome, interference with laboratory analyses, renal replacement therapy, and extracorporeal membrane oxygenation have been reported [6]. These data are mostly from toxicology literature when lipids were used for the treatment of overdose of medications other than LAs, but awareness of these effects would help in the after care of patients. Next generation of lipid antidotes such as liposomes are in developmental and investigational stage.

Multiple studies have shown that ultrasound guidance for PNBs reduces risk of LAST [4]. Possible reasons for the superiority of ultrasound guidance include clear delineation of anatomy, avoidance of vascular structures, visualization of the needle, and watching the spread of anesthetic during injection [3, 10]. Use of ultrasound has not eliminated LAST but decreased its rate.

In our case nerve stimulator technic was used that limited our ability to decrease dose of ropivacaine.

CONCLUSION

1. Among risk factors for local anesthetic systemic toxicity interscalene block has the highest incidence of LAST.
2. It is difficult to recommend a safe maximum dose of ropivacaine, but dose calculations must be made on an individual basis, taking into account the sex, weight, and physical status of the patient.
3. The dose of local anesthetics should be block-specific, site-specific, and patient-specific.
4. Lipid emulsion (intralipid) is the first line for treatment of local anesthetic systemic toxicity.

Contributors:

Tutunnyk A.G. – formal analysis, writing – original draft, data curation;

Mynka N.V. – formal analysis, writing – original draft, visualization;

Kobelyatskyy Yu.Yu. – conceptualization, writing – review and editing, supervision.

Funding. This research received no external funding.

Conflict of interests. The authors declare no conflict of interest.

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Стаття надійшла до редакції 20.09.2024;
затверджена до публікації 11.12.2024