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Successful resuscitation of bupivacaine systemic intoxication after intercostal block in pediatrics undergoing patent ductus arteriosus ligation (PDA) surgery

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Abstract---This article reports a 3-month-old baby girl with Patent Ductus Arteriosus (PDA) with PDA ligation surgery, performed postoperative intercostal peripheral nerve block. Cardiac toxicity occurred with features of ventricular extrasystole bigeminy and AV block with signs of cardiac depression immediately after peripheral intercostal nerve block. Administration of intravenous 20% lipid emulsion, epinephrine, and antiarrhythmics improved hemodynamic conditions after 2 hours postoperatively.

Keywords---toxicity, local anesthesia bupivacaine, pediatrics, PDA ligation, intercostal block.

Introduction

The intercostal block is a peripheral nerve block often used for postoperative analgesia in thoracotomy, upper abdominal procedures, rib fractures, and chest tube insertion. PDA surgery is performed in pediatrics who underwent thoracotomy procedure. Bupivacaine is an amide class local anesthetic that is often used in infants and pediatrics due to its long duration of action. One of the side effects of bupivacaine is cardiac toxicity when the drug enters the blood circulation directly or through absorption. The risk is more significant in pediatric population than in young adults. Previous study has reported that intralipid resuscitation is an effective therapy in patients who have received conventional resuscitation ropivacaine and bupivacaine intoxication in lumbar plexus block in pediatrics and psoas compartment block in geriatrics. (Ludot, 2008; Vadi, Patel and Stiegler, 2014)

Case

A 3-month-old baby girl weighing 5.2 kg presented with a history of term birth with a moderate large Patent Ductus Arteriosus (PDA) with Atrial Septal Defect ASD, pulmonary hypertension without cyanosis, and other congenital abnormalities. The patient was planned for PDA ligation. Initial vital signs were as follows: blood pressure 100/60 mmHg; pulse rate 120 beats/minute; respiratory rate 20 beats per minute; rectal temperature 36.8 °C. Intravenous midazolam 0.5 mg, atropine sulfate 100 mcg, and ketamine 0.5 mg were administered as premedication in the operating theatre's preparation room. After the ECG and peripheral oxygen saturation monitor was installed, the patient was pre-oxygenated with 100% oxygen for 8 minutes. Induction was performed with sevoflurane, titrated to 4 volume %. Intravenous fentanyl 10 mcg was administered as coinduction. Intravenous Atracurium 5 mg was given to facilitate intubation. Intubation was performed using endotracheal tube no. 3.5 with cuff, maintenance with 50% oxygen, 50% N₂O, and sevoflurane 1.5 volume %. During and after laryngoscopy, there was no significant hemodynamic fluctuations (systolic blood pressure 90-100 mmHg, diastolic blood pressure 55-60 mmHg, pulse 120-140 beats/minute). After intubation, the artery line was inserted in the left radial artery.

The patient was then positioned to left lateral decubitus. Intraoperative hemodynamic was stable with systolic blood pressure ranged from 108-120 mmHg, diastolic blood pressure 57-80 mmHg, pulse rate 100-110 beats/minute, and normal sinus heart rhythm. Immediately after closure of the surgical wound, an ultrasound-guided intercostal block was performed with bupivacaine 0.25% 1 ml (2.5 mg) in the 4 left anterior intercostal segments; aspiration was performed every 1 ml to ensure that the drug does not enter the blood circulation. Fifteen minutes after the intercostal injection, the patient's blood pressure dropped to 65/35 mmHg, pulse rate 110 beats/minute, and the ECG showed bigeminy Ventricular Extra Systole (VES). Oxygen fraction was increased to 100%, sevoflurane decreased to 1 volume %, N₂O was discontinued, and intravenous amiodarone 15 mcg/kg/minute was administered. After 10 minutes of observation, the blood pressure was 80/40 mmHg, pulse rate 105 beats/minute, while the ECG showed occasional VES followed by second-degree AV block.

Bupivacaine intoxication was suspected and the patient was immediately given lipid emulsion 1.5 ml/kgBW within 1 minute, followed by continuous infusion of 0.5 ml/kgBW/hour and administration of intravenous epinephrine 1 mcg/kgBW within 5 minutes after administration of lipid emulsion monitoring blood pressure 96/40 mmHg, pulse 108 beats/minute while the ECG showed second-degree AV block. Administration of lipid emulsion 3 ml/kg in 1 minute was repeated and continuous infusion of 0.5 ml/kgBW. After 15 minutes, heart rhythm and hemodynamic conditions began to improve. Postoperative treatment was carried out in the intensive room with controlled ventilation mode and continuous administration of epinephrine 0.1 mcg/kg/minute. After 2 hours of observation in the intensive care room, the heart rhythm returned to normal sinus and hemodynamic parameters were stable.

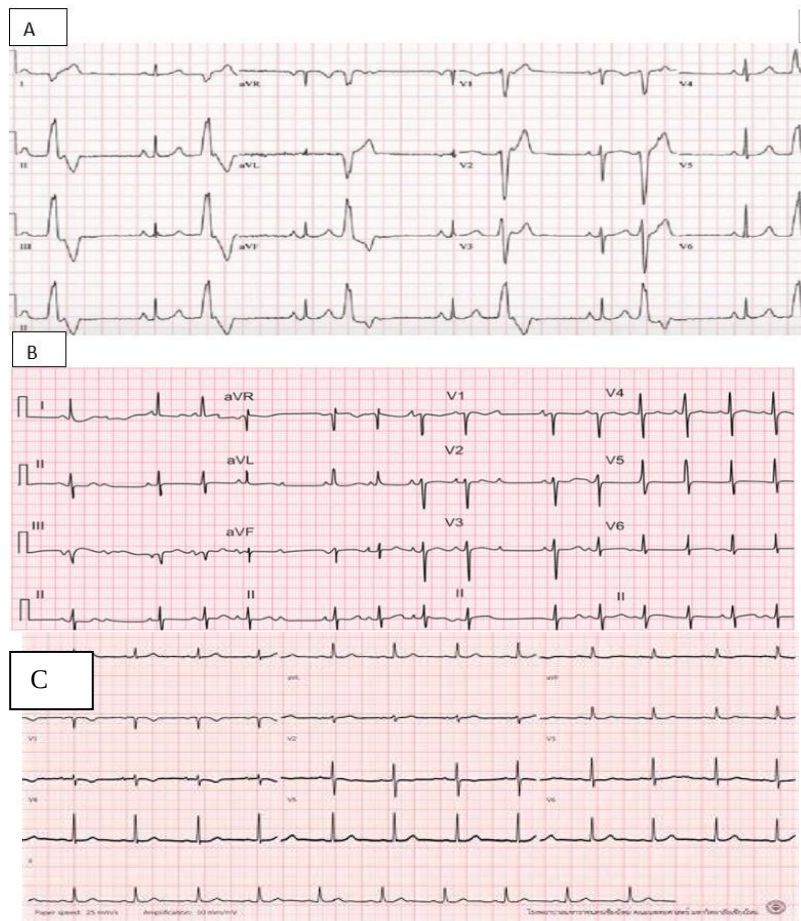


Figure 1. Electrocardiogram image after bupivacaine injection in the intercostal block. Figure 1A. shows ventricular extrasystole bigeminy that occurred 15 minutes after bupivacaine injection. Figure 1B shows an AV block electrogram after administration of the antiarrhythmic Amiodarone. Figure C. shows sinus rhythm electrogram after 2 hours of administering lipid emulsion and epinephrine

Results and Discussions

Systemic intoxication of local anesthetic drugs is an event associated with the increasing and growing application of regional anesthetic techniques, where the incidence reached 0.03% or 7.5 to 20 events in 10,000 peripheral nerve block procedures and about 4 events in 10,000 epidural anesthetic procedures. Systemic intoxication is caused by several factors, including the patient, type of drug, and injection site (Neal *et al.*, 2010; Birstler *et al.*, 2018; El-boghdady, Pawa and Chin, 2018). In this case report, the intoxication occurred with local anesthetic of the amide class (bupivacaine) in 10-month-old patient with PDA. Age is associated with changes in the pharmacokinetics and pharmacodynamics of local anesthetics, affecting the balance between absorption and systemic disposition of drugs. This results in pediatric patients having a higher risk of systemic intoxication than young adults. The incidence of complications associated with regional anesthesia in infants and pediatrics is relatively low, with

0.76 cases per 10,000 procedures, but remain high in peripheral nerve block procedures, with 7.5 per 10,000 procedures. Patients aged under six months have a higher risk than those aged above (Cox, 2003; Birstler *et al.*, 2018; Dontukurthy and Tobias, 2021).

The high volume of distribution in pediatrics and a faster pulse rate leads to a relatively higher cardiac output that can increase systemic drug uptake. In pediatrics, the free drug fraction was higher due to low levels of Human Serum Albumin (HSA) and 1-acid glycoprotein (AAG), which is about one-fifth of young adults. Bupivacaine is an amide local anesthetic drug that is almost 90% bound to plasma protein AAG, thus the free drug fraction will be higher until 6 to 9 months old. Systemic uptake of local anesthetics is higher while local anesthetic clearance of amide is lower. (El-boghdady, Pawa and Chin, 2018) The free or unbound fraction of local anesthetics is the active form responsible for systemic intoxication. However, some studies suggest that the total plasma drug concentration is proportional to the free drug concentration (Gantenbein *et al.*, 2000; Mather *et al.*, 2005; Christie *et al.*, 2015).

The metabolism of local anesthetics of the amide group occurs through the cytochrome P450 system located on the microsomal surface of the liver. Most of the enzyme systems involved in the metabolism of local anesthetics are the CYP3A subsystem which is then metabolized to the active metabolite 2 ',6'-pipecoloxylidide by cytochrome P450 (CYP3A4). (Gantenbein *et al.*, 2000) This enzyme system is immature before 3 weeks and is not fully effective at under one year, resulting in lower (hepatic) amide clearance in neonates and infants than in children and adults, resulting in terminal half-life of local anesthetic amides of 3-8 times longer in neonates compared to adults.

Bupivacaine is eliminated via the liver and kidneys. In the liver, elimination is rate-limited where the hepatic extraction ratio is low (20-30%) compared to young adults. The primary metabolite of bupivacaine is pipecoloxylidine (PPX); less than 3% of bupivacaine is found in the active form in the urine. The lower pH of urine in pediatrics causes alkaline local anesthetics to be more easily ionized in acidic conditions, making the drug's ionized form more challenging to pass through the tubular epithelial cells and increase the fraction of the unbound drug in the plasma. Patients with heart defects have a higher risk of systemic intoxication caused by impaired cardiac conduction and contractility. They are also at increased risk if heart valve abnormalities cause right to left shunt, acidosis, and hypoxemia. The absorption of local anesthetics from the injection site into the systemic circulation is influenced by the site of injection, the dose of the drug, the use of epinephrine, and the pharmacological characteristics of the drug.

Local anesthetic toxicity is related not only to the peak plasma concentration of the drug but also to the speed with which it reaches its peak plasma rate. The absorption rate is more consistent with causing arrhythmias than direct intravenous injection. Ventricular dysrhythmias occur minutes after injection of ropivacaine and lidocaine into the lumbar plexus with negative aspiration, indicating that the drug is not injected directly into the vasculature. (Ludot, 2008). The dose of bupivacaine used in this case was still within the pediatric therapeutic dose range of 2 mg/kg body weight. It is thought that the injection

site is in the intercostal area where the intercostal nerve runs, which is rich in vascularity (subcostal groove), causing high peak plasma drug levels and very quickly reaching peak plasma levels. The plasma toxic concentration limit for bupivacaine is 2.5 mcg/mL in pediatrics, where plasma concentrations are directly related to myocardial tissue absorption and cause cardiac toxicity. (Hori *et al.*, 2015).

Epinephrine is used as an adjuvant to slow down drug absorption, thereby reducing peak plasma concentrations, so it is recommended to give Intercostal Block anaesthesia in areas of high vascularity. Considering that epinephrine is rate dependent which will increase the uptake of the drug in the blood and together with bupivacaine and volatile anesthetics it has the potential to cause arrhythmias, in this case no epinephrine was given during intercostal injection. Neurotoxic events cannot be evaluated in this case because the patient is under general anesthesia. Bupivacaine is more cardiotoxic, occurring almost simultaneously or earlier with neurotoxic symptoms. Cardiac toxicity is associated with peak plasma levels of 0.5-5 mcg/l on intravascular injection (Cox, 2003). Bupivacaine is abundant and rapidly binds but very slowly releases the sodium pump of the cardiac conduction system (fast-in, slow-out) as well as frequency-dependent block compared to lidocaine, resulting in blockade of conduction of the sodium, potassium, and calcium pumps, causing, ventricular dysrhythmias with a blockade. The high degree of conduction, ventricular tachycardia, decreased cardiac contractility, and peripheral vasodilation. It further impairs intracellular signals that organize metabotropic receptors and suppresses cyclic adenosine monophosphate, thereby reducing cardiac contractility (Oda, 2019).

Lipid emulsion provider in systemic events of local anesthetic intoxication is a guideline that has been established for the management of local anesthetic intoxication since 2007 in the UK and 2010 by the American Society of Regional Anesthesia and Pain Medicine (ASRA), without neglecting the importance of airway management and cardiopulmonary resuscitation. The mechanism of action of lipid emulsions is by lipid sinks, lipid shuttle, inhibiting the opening of the mitochondrial permeability membrane pore transition, activating the myocardial calcium pump, activating the PI3K/Akt/GSK-3 β pathway, inhibiting the release of Nitric Oxide, rebalancing the excitation and inhibition systems. Administration of high doses of epinephrine (>10 mcg/kg) and vasopressin can cause hyperlactate acidemia and severe acidosis, inhibiting lipid resuscitation. Hemodynamic and metabolic outcome indices during lipid resuscitation were better than adrenaline and vasopressin. In contrast, the combination of lipid and epinephrine could restore cardiac function better than lipid emulsion or epinephrine alone (Di Gregorio *et al.*, 2009).

Conclusion

In cases of systemic bupivacaine intoxication after intercostal block in pediatrics undergoing patent ductus arteriosus (PDA) ligation surgery with epinephrine immediately after lipid resuscitation and administration of amiodarone, within 15 minutes the heart rhythm began to improve and returned to normal after 2 hours.

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References

- Birstler, J., Wolf, C., Bosenberg, A.T., Ch, B., Suresh, S., Taenzer, A.H. and Polaner, D.M. (2018) 'Complications in Pediatric Regional Anesthesia', (4), pp. 721–732.
- Christie, L.E., Hons, M., Mrcp, H., Picard, J., Ma, B.A., Bm, D.E.A., Frca, B. and Weinberg, G.L. (2015) 'Local anaesthetic systemic toxicity', 15(July 2014), pp. 136–142. Available at: <https://doi.org/10.1093/bjaceaccp/mku027>.
- Cox, B. (2003) 'Toxicity of local anaesthetics', 17(1), pp. 111–136. Available at: <https://doi.org/10.1053/bean.2003.0275>.
- Di Gregorio, G., Schwartz, D., Ripper, R., Kelly, K., Feinstein, D.L., Minshall, R.D., Massad, M., Ori, C. and Weinberg, G.L. (2009) 'Lipid emulsion is superior to vasopressin in a rodent model of resuscitation from toxin-induced cardiac arrest', *Critical Care Medicine*, 37(3), pp. 993–999. Available at: <https://doi.org/10.1097/CCM.0b013e3181961a12>.
- Dontukurthy, S. and Tobias, J.D. (2021) 'Update on local anesthetic toxicity, prevention and treatment during regional anesthesia in infants and children', *Journal of Pediatric Pharmacology and Therapeutics*, 26(5), pp. 445–454. Available at: <https://doi.org/10.5863/1551-6776-26.5.445>.
- El-boghdadly, K., Pawa, A. and Chin, K.J. (2018) 'Local anesthetic systemic toxicity: current perspectives', pp. 35–44.
- Gantenbein, M., Attolini, L., Bruguerolle, B., Villard, P.H., Puyooou, F., Durand, A., Lacarelle, B., Hardwigsen, J. and Le-Treut, Y.P. (2000) 'Oxidative metabolism of bupivacaine into pipecolylxylidine in humans is mainly catalyzed by CYP3A', *Drug Metabolism and Disposition*, 28(4), pp. 383–385.
- Hori, K., Matsuura, T., Tsujikawa, S., Mori, T., Kuno, M. and Nishikawa, K. (2015) 'The significant contribution of the partitioning effect in lipid resuscitation for bupivacaine-induced cardiotoxicity: Evaluation using centrifuged solution in vivo and in isolated hearts', *British Journal of Anaesthesia*, 115(6), pp. 935–937. Available at: <https://doi.org/10.1093/bja/aev386>.
- Ludot, H. (2008) 'Successful Resuscitation After Ropivacaine and Lidocaine-Induced Ventricular Arrhythmia Following Posterior Lumbar Plexus Block in a Child CASE REPORT', 106(5), pp. 1572–1574. Available at: <https://doi.org/10.1213/01.ane.0000286176.55971.f0>.
- Mather, L.E., Ph, D., Copeland, S.E., Ladd, L.A., Vsc, B. and Editorial, S. (2005) 'Acute Toxicity of Local Anesthetics: Underlying Pharmacokinetic and Pharmacodynamic Concepts', 30(6), pp. 553–566. Available at: <https://doi.org/10.1016/j.rapm.2005.07.186>.
- Neal, J.M., Bernards, C.M., John, F., Gregorio, G. Di, Drasner, K., Hejtmanek, M.R., Michael, F., Rosenquist, R.W. and Weinberg, G.L. (2010) 'SPECIAL ARTICLE ASRA Practice Advisory on Local Anesthetic Systemic Toxicity', 35(2), pp. 152–161. Available at: <https://doi.org/10.1097/AAP.0b013e3181d22fcd>.
- Oda, Y. (2019) 'Local anesthetic systemic toxicity: proposed mechanisms for lipid resuscitation and methods of prevention', *Journal of Anesthesia*, 33(5), pp. 569–571. Available at: <https://doi.org/10.1007/s00540-019-02648-y>.

- Shamma, R. A., Hosni, Y. A., Hassan, M. M., Hassan, N. A., & Khedr, D. (2022). Role of optical coherence tomography angiography in early detection of retinal microvascular changes in adolescents with type 1 diabetes. *International Journal of Health Sciences*, 6(S4), 1337–1353. <https://doi.org/10.53730/ijhs.v6nS4.6049>
- Sofyan, M., Cakra, I. G. L. O., & Putra, I. G. A. A. (2020). Consumption, nutrient digestibility and nitrogen retention in pe goats received ransum with various levels of gamal (gliricidiasepium) balance versus concentrate. *International Journal of Life Sciences*, 4(1), 50–57. <https://doi.org/10.29332/ijls.v4n1.380>
- Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2021). Get vaccinated when it is your turn and follow the local guidelines. *International Journal of Health Sciences*, 5(3), x-xv. <https://doi.org/10.53730/ijhs.v5n3.2938>
- Vadi, M.G., Patel, N. and Stiegler, M.P. (2014) 'Case scenario: Local anesthetic systemic toxicity after combined psoas compartment-sciatic nerve block: Analysis of decision factors and diagnostic delay', *Anesthesiology*, 120(4), pp. 987–996. Available at: <https://doi.org/10.1097/ALN.0000000000000154>.