A Fatal Case Of Bupivacaine Induced Central Nervous System Toxicity Presenting As Super Refractory Status Epilepticus : Case Report

Abstract:

Use of local anaesthetic agent for spinal anaesthesia is routinely done for various surgical procedures . While most of the cases are done without any major adverse event , Local Anaesthetic Systemic Toxicity (LAST) can occur despite giving low dose at appropriate site .We present a case report of 16 years old boy who underwent spinal anaesthesia for brodie's abscess following which he developed central nervous system toxicity manifesting as super refractory status epilepticus. His course in intensive care unit got complicated with hyperthermia , rhabdomyolysis , Acute kidney injury (AKI) and Acute Respiratory Distress Syndrome(ARDS). Despite all the efforts patient couldn't be saved and expired on day five of intensive care unit admission. Thus , one needs to be vigilant of the unpredictable and underestimated nature of bupivacaine induced central nervous system toxicity.

Keywords: Bupivacaine , LAST , super-refractory status epilepticus Introduction:

Introduction

The use of local anaesthetics(LA) is a common practice in a variety of contexts by various medical specialties. As with any other drug, their use is not without side effects or toxicity. Local anaesthetic systemic toxicity (LAST) may occur with all local anaesthetics, despite their route of administration. Although rare, it may be a life-threatening condition, and specific management and awareness are fundamental . There are only 7 case reports in the past on super refractory status epilepticus attributed to bupivacaine and out of those , six have recovered fully [1-7]. Here we present a case report of a young boy having super refractory status epilepticus with Acute respiratory distress syndrome(ARDS) and hyperthermia following spinal anaesthesia.

Case History

16 year old male was admitted as a case of Brodie's abscess on left foot and was planned for curettage of abscess at a sub district hospital in Kashmir . Patient was healthy with no co-morbidities with height 167 cm and weight 68kg (Body Mass Index =24.38 kg/m^2) . All his baseline laboratory reports were within normal limits. 12 lead electrocardiogram showed normal sinus rhythm with normal axis and chest roentogram showed normal lung parenchyma.He had no history of allergies, or previous history of seizures, or any hospital admission Therefore, his (American Society of

Anaesthesiology)ASA grade was 1. After connecting basic monitors , his baseline vitals were heart rate 78 bpm, Blood Pressure 126/72mmHg , saturation 97% on room air. 20 G intravenous cannula was secure in left dorsum of hand and an intravenous fluid (Ringer lactate 500ml) was started .After positioning patient in sitting position spinal anesthesia was given with 2.5 ml of 0.5% hyperbaric bupivacaine into L4-L5 intervertebral space. Immediately after spinal anesthesia (2-3 minutes), patient complained of peri-anal itching , and became agitated . He developed myoclonus starting from upper limbs and trunk and later involved lower limbs. Vitals recorded were heart rate 132 bpm , BP -148/98 mmHg , Saturation 98 % on room air. For abnormal body movements he was given Injection Midazolam 5mg iv initially followed by injection phenytoin 500mg. However there was no improvement seen and eventually he developed generalised tonic clonic seizures .Patient was intubated with 7.5mm cuffed endotracheal tube using thiopentone and Succinylcholine . Eventually he was referred to a tertiary care hospital for further management. As per the accompanying anesthetist , patient used to develop Generalised Tonic Clonis Seizures (GTCS) once the effect of muscle relaxant weaned off during the transportation and so was given repeated bolus doses of muscle relaxant (injection atracurium) during transportation. Patient was received in medical emergency with following status GCS E1VTM1,Pupils bilateral 3mm normally reacting to light, BP 130/80,heart rate134 bpm,saturation 98% on Artificial Manual Breathing Unit(AMBU) bag .ECG showed sinus tachycardia . Non contrast CT head was done which was normal .Patient was shifted immediately to Neuro Intensive Care Unit. On arriving to ICU ,he again developed GTCS.Injection phenytoin 1000mg (@20mg/kg)was given followed by injection levetiracetam 1.5gm . Meanwhile, the baseline investigation along with ABG was collected that showed acidosis with pH of 7.20,pco_2 49.9 mmHg, pao_2 152.7 mmHg ,Lactate*-7.4 mmol/L, Bicarbonate-18.8mmol/L, Na-141 mmol/L,K-3.53 mmol/L.Ca-1.07 mmol/L, glucose 184mg/dl . Intra-Lipid 20% infusion was given [(100 mL in three minutes and then 250 mL in 20 minutes]. Patient showed no improvement in seizure activity and was started on thiopentone infusion @ 5mg/kg/hour .Continuous EEG monitoring was done . GTCS improved after 4 hours of starting thiopentone infusion .However the electroencephalogram [EEG] showed spike waves in almost all the electrodes as shown in the below mentioned EEG [Figure 1a-Legend: EEG showing spike wave activity] and diagnosis of non convulsive status epilepticus(NCSE) was made. Injection thiamine 100mg , injection pyridoxine , injection phenobarbital, injection valproatewere added. Patient became haemodynamically unstable after starting thiopentone infusion , thus Nor-Adrenaline was started. After 20 hours of thiopentone infusion ,spike wave activity was absent and EEG waveform showed burst suppression, with improving lactates

Thiopentone infusion was continued for 24 hours. After 24hrs ,STP was slowly tapered down, but patient again developed NCSE with worsening haemodynamics , Acute kidney injury , worsening liver enzymes , hyperthermia (Tmax- 105 °C) . Haemodynamics were supported using nor adrenaline,

infusion phenylephrine and Vasopressin . His laboratory reports showed coagulopathy and AKI with transaminitis and raised creatine kinaselevels (Creatinine* 1.37mg/dl , INR* -1.65 , ALT -600U/L , ALP- 270U/L , CK - 2543 U/L. On day two, thiopentone infusion was slowly tapered and then stopped with no features of NCSE seen on EEG. Also, lumber puncture was done and cerebrospinal fluid(CSF) analysis was sent which was normal. On day three of ICU admission patient continued to be on inotropic support to maintain haemodynamics and didn't regain his consciousness despite being off sedation for 24 hours .His EEG showed no cortical activity at that point of time [Figure 1b - EEG showing no cortical activity]. Also , he had increase requirement of FiO_2 by this time . CXR showed bilateral diffuse infiltrates suggestive of ARDS and accordingly thus, ventilatory management was set as per ARDS protocol. For worsening liver enzymes injection valproate was stopped and anti eplileptic dosages were adjusted as per creatinine clearance. Hyperthermia was treated initially with paracetamol and cold sponging and later on gold gastric lavage was done when there was no improvement seen in hyperthermia. For hyperthermia , sepsis was also considered as a differential and blood culture, CSF culture, urine culture , tracheal culture were sent which came out to be sterile after 24 hours. Despite inotropic support patient couldn't maintain his haemodynamics and had persistent hypoxemia and thus , he went into multi organ failure and expired after 5days of ICU admission.

Discussion

The overall incidence of LAST ranges from 0.87 to 1.8 per 1,000 individuals withmajor events seen in approximately 20% of the cases .[8,9] Many minor events probably go unnoticed and are unreported.Local anaesthetics prevent sodium influx into the neuronal axon thereby blocking pain conduction . The pharmacodynamic and pharmacokinetic properties change if the drug is racemic mixtures or pure enantiomer.[10] Bupivacaine, the drug used in our patient, was a racemic mixture and has a higher potential for cardiac and CNS toxicity compared with ropivacaine or levobupivacaine. [11] LAST can present as auditory change,metallic taste, circumoral numbness, , and agitation which canfurther progress to seizures or CNS depression. Cardiac toxicity usually occurs with preceding CNS toxicity, except in cases where there is inadvertent intra-vascular injection. [12] CNS toxicity leading to seizures causes cardiac excitation which presents as tachycardia, hypertension andcardiac arrhythmias. Cardiac depression is seen in cases when drug concentration is high.However, there is extreme variability in terms of onset and duration of these symptoms . Various risk factors that have been proposed for CNS toxicity are extremes of age , pregnancy , carnitine deficiency , renal insufficiency , cardiac disease , block site , drug type , dosage of drug and hepatic insufficiency. [13]

In our case, the patient developed CNS symptoms only initially. Cardiac toxicity and brainstem anaesthesiausually is apparent in the first 15 minutes after the injection. It may affect the temperature regulation and the patient can experience disorientation, aphasia, amaurosis fugax, unconsciousness, hemiplegia, convulsions, and cardio respiratory arrest.

Prompt recognition and early institution of treatment will ensure a more favourable outcome. Close initial observation with monitoring of vital signs will help in deciding the further course of treatment. Airway control and respiratory support with 100% oxygen supplementation and possible cardiac intervention with circulatory support in the form of fluids and vasopressors may be required.IV lipid emulsion (20%) is given as an initial bolus of 100 mL or 1.5 mL/kg over one minutes followed by an infusion @ 0.25 mL/kg/minute. The bolus can be repeated if cardiovascular stability is not achieved. The maximum total dose is 12 mL/kg. [14]

Other conditions that mimic LAST include pheochromocytoma, thyroid storm, malignant hyperthermia, anaphylaxis . Other causes of toxicity need to be excluded inorder to diagnose and treat local anesthetic toxicity . While hypotension , hypoventilation , high spinal are the common adverse consequences of spinal anesthesia ; all these were ruled out in our case scenario. His vitals were within normal range through out the procedure and even after the development of myoclonus there were no signs of hypotension or hypoventilation. Another common reason for adverse event can be drug mishap , which was ruled out by cross checking the name of drug (bupivacaine) along with its expiry date. Agitation, myoclonus of arms , trunk and legs and spike wave activity in EEG all are point towards CNS toxicity induced by intrathecal bupivacaine . Two pathways have been proposed that lead to CNS toxicity after spinal anaesthesia. One is systemic absorption of local anaesthesia which crosses blood brain barrier and happens usually at high doses of bupivacaine(>4mg/kg) . Another proposed mechanism is the cephalic diffusion to cerebral cortex which leads to neuronal excitation.[15] In this case, even if the local anaesthetic drug dose used is low , it can have adverse effect on neurons .One of the major risk factor for the CNS toxicity by local anaesthetic agent is the potency of the drug and therefore potent lipid soluble local anaesthetic agents like bupivacaine can cause CNS toxicity even at doses less than the maximum allowable limit unlike other less potent agents like levobupivacaine and ropivacaine .[16]

In a literature review by Ehelepola NDB ,et al ,[17] seven cases of super refractory status epilepticus due to bupivacaine have been described , [1-7] out of which two case reports have been from India .[5,6] In our case super refractory status epilepticus was associated with hyperthermia , rhabdomyolysis and ARDS . Rhabdomyolyisis is usually seen in status epilepticus and can cause acute kidney injury .[18] Use of antiepileptics and rhabdomyolysis further lead to hepatic dysfunction causing deranged liver enzymes . Hemodynamic instability in our case can be attributed to either use of propofol and thiopentone infusion or cardiac toxicity caused by anaesthetic agent which must have

manifested as a delayed adverse consequence. Further AKI can be attributed to rhabdomyolysis or hemodynamic instability causing acute tubular necrosis. Worsening lung mechanics can be due to neurogenic pulmonary edema or pneumonia which is usually associated with status epilepticus .[18] Absence of regain of consciousness by the patient can be attributed to nervous system injury due to super refractory status epilepticus , deranged drug metabolism owing to renal and liver dysfunction and hypoxic brain injury due to ARDS. Delay in administration of lipid emulsion due to transportation of patient from sub district hospital to tertiary care may also have lead to irreversible damage. Also, due to non availability of ECMO inour set up , we could not fully support his respiratory and circulatory system . Ours is a rare and extreme case of local anaesthetic central nervous system toxicity and very few reports have been mentioned in literature . Never the less, many cases of mild local anaesthetic toxicity have been mentioned which were self limiting.[19,20] LAST which can manifest with wide range of symptoms like feeling of impending doom which is usually ignored or slurring of speech which is usually confused with the sedation (if given any) or severe enough to cause neurological or cardiovascular instability. Also , the timing of onset can be variable - most reactions occurring within minutes or delayed upto 30-60 minutes. Despite using low drug dosage and administering drug into appropriate intrathecal space with no inadvertent intravascular administration of drug , still patient developed adverse event probably due to drug impurity itself or due to the anaesthetic agent's high potency. Prompt recognition of symptoms and timely management is pivotal inorder to prevent any severe life threatening event. Drug testing and extraction of impurity needs to be available in every state or union territory . Also ,availability of lipid emulsion as an emergency drug needs to be kept available in all hospitals so that there is no delay in its administration . Availability of ECMO is of paramount importance in a tertiary care hospitals inorder to provide high end patient care.

Conclusion:

We hereby present the case of a young boy who developed CNS toxicity after spinal anesthesia presenting as super refractory status epilepticus complicated by hyperthermia, ARDS, AKI , hemodynamic instability. Intrathecal administration of a low-dose LA, especially bupivacaine, can result lethal, and unpredictable CNS toxicity and one should be vigilant about it.Apart from drug's potentiality to produce neurotoxic effects , drug impurity also needs to be considered and accordingly needs further investigation to check for its purity.

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List of Abbreviations:

Abbreviation	**Definition**
ICU	Intensive Care Unit
EEG	Electroencephalogram
ARDS	Acute respiratory distress syndrome
LAST	Local Anaesthetic Systemic toxicity
ECMO	Extracorporeal Membrane Oxygenation
CNS	Central Nervous System
CSF	Cerebro Spinal Fluid

Acknowledgements: nil

Source(s) of support: Nil

Conflicting Interest (If present, give more details):

nil

Contribution Details:

Enter the role of contributors in the first column and names of the contributors in the columns 2, 3, and so on.

Role (Concepts, Design, Definition of intellectual content, investigation, manuscript writing, etc.)	Contributor 1	Contributor 2	Contributor 3
Concepts	☑	☑	

Design	☑		☑
Definition of intellectual content	☑		☑
investigation		☑	
Manuscript writing	☑	☑	
Manuscript review	☑	☑	☑
Critical analysis	☑		

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Patient declaration of consent statement: A written consent was taking from the father of the patient inorder to publish this as a case report

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Topic	Item	Checklist item description	Yes / No
Title	**1**	The words "case report" should be in the title along with the area of focus	**Y**
Abstract	**2a**	Structured abstract with the headings: Rationale, Patient concerns, Diagnosis, Interventions, Outcomes, Lessons If unstructured abstract, all the details as per the above heading to be present	**Y**
	2b	Abstract structure outlines in the Information to Authors and contain all the information mentioned in 2a	**Y**
Introduction			
	3a	One or two paragraphs summarizing why this case is unique	**Y**
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Case report			
Patient Information	**4a**	De-identified demographic information and other patient specific information	**Y**
	4b	Main concerns and symptoms of the patient	**Y**
	4c	Medical, family, and psychosocial history including relevant genetic information (also see timeline)	**Y**
	4d	Relevant past interventions and their outcomes	**Y**
Clinical Findings	**5**	Describe the relevant physical examination (PE) and other significant clinical findings	**Y**
Diagnostic Assessment	**6a**	Diagnostic methods (such as laboratory testing, imaging, surveys)	**Y**
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	6	Prognostic characteristics (such as staging in oncology) where applicable	**Y**

	d		
Therapeutic Intervention	**7a**	Types of intervention (such as pharmacologic, surgical, preventive, self-care)	**Y**
	7 b	Administration of intervention (such as dosage, strength, duration)	**Y**
	7c	Changes in intervention (with rationale)	**Y**
Follow-up and Outcomes	**8a**	Clinician and patient-assessed outcomes (when appropriate)	**Y**
	8 b	Important follow-up diagnostic and other test results	**Y**
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	8 d	Adverse and unanticipated events	**Y**
	8e	Follow-up duration and the last known status of the patient	**Y**
Discussion	**9a**	Discussion of the strengths and limitations in your approach to this case	**Y**
	9 b	Discussion of the relevant medical literature.	**Y**
	9c	The rationale for conclusions (including assessment of possible causes)	**Y**
	9 d	The primary "take-away" lessons of this case report	**Y**
	9e	Citations adequate preferably from recent literature	**Y**
Informed Consent	**10 a**	Mention the patient (family/ legal representative) informed consent for publication of the case details. For minor (children), consent statement should mention if "parental/ legal guardian consent" was obtained.	**Y**
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Figures	**11**	Figures (full face) to be sufficiently obscured Confidential data like patient's name, date of birth, personal identification data should not be displayed in the images including the radiographs.	**Y**

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