INTRODUCTION

Anesthetic death is defined as death occurring within 24 h of administration of anesthesia due to causes related to anesthesia. However, death may occur even afterward due to its complications [1,2]. In terms of Indian law, such deaths need to be notified to the law enforcing authorities. Hence, any death which is reported under this section is regarded as a death due to unnatural causes, to be followed by an inquest. The attending clinicians are not allowed to issue a death certificate in these cases and the case must be referred for medico legal autopsy.

While generally safe, local anesthetic agents can be toxic if administered inappropriately, and in some cases may cause unintended reactions even when properly administered. The toxicity of local and infiltration anesthetics can be local or systemic. Systemic toxicity of anesthetics most often involves the central nervous system (CNS) or the cardiovascular system [3]. Manifestations of local anesthetic toxicity typically appear 1-5 min after the injection, but onset may range from 30 s to as long as 60 min [4]. Reactions to bupivacaine are characteristic of those associated with other amide-type local anesthetics. Here we report a death due to bupivacaine toxicity.

CASE REPORT

A 37-year-old female married for 13 years with primary infertility had opted for in vitro fertilization at a nursing home where she was diagnosed with fibroid uterus and advised by the doctor to undergo myomectomy under spinal anesthesia. She was admitted to the hospital and the surgery was scheduled at 3:30 pm the next day. Relevant investigations and pre-anesthetic evaluation were done. Bupivacaine skin test was done on the admission day and patient had no hypersensitive reaction. Under aseptic conditions, spinal anesthesia was administered. Within minutes, patient complained of severe burning sensation over hips and perineum followed by bouts of intense muscular spasms in lower half of the body slowly ascending to the upper limbs. Convulsions were observed later and patient was administered midazolam. Patient’s condition worsened and blood pressure started falling. Intravenous dopamine was started but still the condition deteriorated. Noradrenaline infusion was started and she was intubated with 100% oxygen. She was then referred to a tertiary care hospital where further resuscitative measures were undertaken. However, still the patient could not be revived and was declared dead at around 6:10 pm.

The body was subjected for autopsy after 18 h at Department of Forensic Medicine, M.S. Ramaiah Medical College at 12:10 pm the next day, after her husband lodged a complaint of medical negligence under section 304 (A) IPC. On external examination, the length of the body is 162 cm, moderately built and nourished. Indwelling Foley’s catheter was present along with an urobag, which contained about 25 ml of urine. Subcutaneous test dose injection mark was present over the front of right forearm. The words “injection bupivacaine test dose” was written in blue around the injection mark. Defibrillator mark was present over the chest. Single injection mark present over the lumbar spine at the level of L2-L3.

ABSTRACT

The number of deaths every year associated with anesthesia is sufficiently large to be a matter of concern. Deaths attributable to anesthesia and/or surgery may be due to anesthetic agent, improper technique or inexperience, and functional problems. All deaths occurring during the course of anesthesia and surgery or within a reasonable period thereafter (commonly referred to as perioperative period) have to be reported to the police as these deaths cannot be regarded as natural. Systemic toxicity of anesthetic drug is most commonly manifested in the central nervous system producing convulsions. Here we report a case, which was scheduled for myomectomy under spinal anesthesia and the patient died due to the toxicity of bupivacaine.

KEYWORDS: Forensic sciences, forensic pathology, anesthesia, bupivacaine, death, toxicity
On dissection, the lungs were intact and congested and exuded pink colored frothy fluid on cut section. Coronaries were patent. Uterus was enlarged and showed multiple intramural fibroids. Rest of the organs were intact and congested.

Histopathological examination revealed that the brain had terminal anoxic changes, but it was not possible to say with certainty if alterations seen are related to spinal anesthesia complications or represent terminal changes, though the latter is more likely. Lungs showed pulmonary edema and congestion. Uterus showed secretory endometrium, with leiomyomata in myometrium. 100 ml of blood was collected from a femoral vein. Sodium fluoride was used as a preservative.

Urine, brain, and viscera were sent for toxicological analysis. Skin around the test dose injection area, around lumbar injection area, and control skin from left forearm was also sent for toxicological screening.

Toxicological analysis was conducted at Forensic Science Laboratory, Bangalore. Sampling - Finely minced tissue samples, blood sample, and preservative were subjected to liquid-liquid extraction with dichloromethane/diethyl ether/ethyl acetate at acidic, neutral, and basic pH. After phase separation, the organic layer was purified, evaporated to dryness, and reconstituted with methanol.

**Analysis and Identification**

The extract was analyzed for pesticides, drugs and alkaloids by color tests, thin layer chromatography (TLC) and high-performance TLC (HPTLC), liquid chromatography mass spectroscopy mass spectroscopy (LC-MS-MS), and gas chromatography-MS (GC-MS). HPTLC, LC-MS-MS, and GC-MS methods have responded for the presence of bupivacaine in blood and in skin around the test dose injection area (right forearm). Quantum of bupivacaine is 8 μg/L of blood. The above tests have responded negative in urine, brain, viscera, and in skin around lumbar injection area and control skin from left forearm.

As per the hospital case records, 2 mg midazolam diluted in 10 ml normal saline was administered intravenous over 2 min. However, no trace of midazolam or any other drug was detected in post-mortem toxicological analysis.

Cause of death: Cause of death was attributed to bupivacaine toxicity.

**DISCUSSION**

Anesthetic practice is one of the disciplines, which involve a great potential risk for both the health worker and the patient [5,6]. Although it would not be possible to eliminate the risks involved, a balance should be struck between the probability of damage and the result expected. The pathological processes, side-effects of drugs, flaws in the equipment, and the human factor can play a significant role in the damage which has occurred. It has been affirmed that in a large number of deaths which occurred during the administration of an anesthetic, the team of anesthetists were accused and the mishap was taken to legal authorities regardless of the fact that they were not associated with the administration of an anesthetic. In case an anesthetic practice results in death, a post-mortem assessment, scene investigation as well as the patient’s medical documents gains utmost importance [7].

The most common causes of anesthesia-related deaths are: (1) circulatory failure due to hypovolemia in combination with overdose of anesthetic agents such as thiopentone, opioids, benzodiazepines or regional anesthesia; (2) hypoxia and hypoventilation after for instance undetected esophageal intubation, difficult intubation, technical failure in the anesthetic equipment, or aspiration of gastric content, (3) anaphylactoid reactions including malignant hyperthermia, and (4) human negligence such as lack of vigilance or errors in the administration of drugs and in the maintenance and control of the anesthetic equipment [1].

Documentation of pre-anesthetic evaluation and assessment of the patient, and pre-operative record of the events are of vital importance and can prove to be a tool for retrospective analysis of the information. Surgical mistakes being anatomical may be appreciable during the autopsy, but the anesthetic mistakes being physiological may no longer be appreciable after death except where overdose with the specific drug is involved.

Only small amounts of injected local anesthetic are taken up into the nerve [8]. The remainder of the dose given is taken up into the systemic circulation. The rate at which is taken up is dependent on the proximity of blood vessels, the concentration gradient for its uptake and the diffusion characteristics of the drug i.e., the factors considered by Fick’s Law of Diffusion. The plasma concentration will depend on the rate of absorption and the rate of clearance from the body. The vast majority of data about toxicity in humans comes from studies of lignocaine infusions used in the post myocardial infarction setting [9]. In case reports of systemic toxicity related to regional anesthesia, it is rare for plasma levels to be measured in a timely fashion and peak levels can only be roughly estimated from levels at the time of measurement. While in some studies, CNS toxicity occurs with lignocaine plasma levels above 6 μg/ml, 19 other studies have demonstrated levels above this with no apparent neurological toxicity [10].

In a study Moore et al., bupivacaine was used in concentrations of 0.25, 0.5, or 0.75% with and without a vasoconstrictor, in amounts ranging from 25 to over 600 mg, for caudal, epidural (peridural), or peripheral nerve block for 11,080 surgical, obstetrical, diagnostic, or therapeutic procedures. Fifteen systemic toxic reactions occurred, but no untoward sequelae resulted from them. One inadvertent subarachnoid injection of 110 mg resulted in a total spinal block with an uneventful recovery. When a dose of 400 mg or less was employed, arterial and venous plasma levels following single dose blocks did not exceed 4 μg/ml, a level above which systemic toxic reactions are “believed” to occur [11].
In another study, arterial and venous plasma levels of bupivacaine following peripheral nerve blocks were reviewed. Plasma levels of bupivacaine resulting in convulsions in a man have been reported as 4 μg/ml or higher. In only 1 of the 30 patients the authors studied, arterial plasma level peaked at 4 μg/ml in 15 min following a bilateral intercostal nerve block [12].

In another study, bupivacaine was used to manage post-thoracotomy pain in 22 infants. 0.25% Bupivacaine (1.25 mg/kg body wt.) was given into an extrapleural paravertebral catheter. Subsequently, 0.125% bupivacaine with adrenaline 1:400000 was infused at a rate of 0.2 ml/kg/h for 48 h. Mean serum concentration of bupivacaine after 48 h was 1.6 μg/ml. However, the serum bupivacaine concentration of >3 μg/ml were found in 3 patients at 30-48 h [13].

A fatal drug overdose of bupivacaine is described which involved unusual erotic practices. A 54-year-old male was discovered supine on the floor surrounded by sexual paraphernalia, syringes, and medications including three empty bottles of bupivacaine. Toxicology revealed femoral blood, heart blood, and vitreous bupivacaine concentrations of 3.8, 2.8, and 1.3 mg/L, respectively. The urine bupivacaine concentration was 11.4 mg/L [14]. Bupivacaine therapeutic concentration ranges from (0.25-0.5) to (1.5-2), toxic at concentration of 2-4 mg/L, half-life - 0.5 to 3 h [15].

The evaluation of patients with possible toxicity from a local anesthetic should be guided by the clinical presentation. Blood levels of the anesthetic may be measured, although blood levels may not correlate with toxicity or may not be obtained at a clinically useful time.

Bupivacaine is a long acting local anesthetic of amide group and its normal dose should be 2.5 mg/kg and not to exceed 175 mg total dose without epinephrine and 225 mg with epinephrine [3]. In our case, 10 ml of 0.5% (50 mg) of bupivacaine without epinephrine was administered and detected both at test dose site and in blood (8 mg/l). Though the administered dose was less, the concentration of bupivacaine was high. This could be attributed to either inadvertent intravascular injection while administering into the subarachnoid space or due to rapid absorption.

Patient complained of severe burning sensation over hips and perineum followed by bouts of intense muscular spasms in lower half of the body slowly ascending to the upper limbs and terminating as general tonic-clonic convulsions. These signs and symptoms usually present with higher doses of bupivacaine, i.e., initial signs of CNS excitation is often followed by a rapid CNS depression [3].

Systemic toxic reactions primarily involve the CNS and the cardiovascular system. Such reactions are caused by high blood concentrations of a local anesthetic, which may appear due to (accidental) intravascular injection, overdose or exceptionally rapid absorption from highly vascularized areas. CNS reactions are similar for all amide local anesthetics, while cardiac reactions are more dependent on the drug, both quantitatively and qualitatively. CNS toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are usually light-headedness, circumoral paresthesia, numbness of the tongue, hyperacusis, tinnitus, and visual disturbances. Dysarthria, muscular twitching or tremors are more serious and precede the onset of generalized convulsions. These signs must not be mistaken for neurotic behavior. Unconsciousness and grand mal convulsions may follow, which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly following convulsions due to the increased muscular activity, together with the interference with respiration and possible loss of functional airways. In severe cases, apnea may occur. Acidosis, hyperkalemia and hypoxia increase and extend the toxic effects of local anesthetics. Hypotension, bradycardia, arrhythmia, and even cardiac arrest may occur as a result of high systemic concentrations of local anesthetics, but in rare cases cardiac arrest has occurred without prodromal CNS effects [3].

Only in rare cases have amide local anesthetics been associated with allergic reactions (with anaphylactic shock developing in most severe instances). Patients allergic to ester-type local anesthetics drugs (procaine, tetracaine, benzocaine, etc.) have not shown a cross sensitivity to agents of the amide type such as bupivacaine.

The frequency of local anesthetic toxicity is difficult to determine because these agents are used widely in a variety of settings, and most reactions are not reported. Systemic toxicity from local anesthetics may occur in as many as 1:1000 peripheral nerve blocks; however, most of these probably involve only minor subjective symptoms. If oxygenation, ventilation, and cardiac output are maintained, patients usually have a full recovery without sequelae. Without treatment, local anesthetic toxicity can result in seizures, respiratory depression or arrest, hypotension, cardiovascular collapse or cardiac arrest, and death [3].

Important differential diagnosis is anaphylaxis where allergic manifestations of local anesthetics like rash and urticaria are seen. Anaphylaxis due to local anesthetics is very rare, but should be considered if the patient starts to wheeze or suffer respiratory distress after receiving the anesthetic.

CONCLUSION

In our case, the patient had no pre-existing disease and no abnormal reaction to the bupivacaine test dose. Signs and symptoms developed within minutes of administration of bupivacaine and were mainly neurological. There were no allergic manifestations. Bupivacaine was detected in the blood sample. There were no other features at autopsy and in the hospital case records which were suggestive of any other mechanism of death. Thus, the cause of death was attributed to bupivacaine toxicity.

REFERENCES