Original Article

Measurement of bupivacaine induced myotoxicity in interfascial plane blocks: A randomised controlled trial

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ABSTRACT

Background and Aims: Recent reports of local-anaesthetic induced myotoxicity after peripheral nerve blocks have increased interest in this less commonly known complication. Although the morphological, physiological and biochemical changes in muscle after injection of clinically used concentration of bupivacaine have been studied in animals, little research has been conducted on human subjects, especially in relation to fascial plane blocks. We conducted a study to examine the changes in circulating creatine phosphokinase (CPK) levels in patients undergoing modified radical mastectomy (MRM) or mesh hernioplasty (MH) with or without peripheral nerve blocks. The study explored local anaesthetic (bupivacaine) induced myotoxicity by measuring changes in serum CPK levels following transversus abdominis plane block (TAP) or pectoral nerve block-II (PEC- II) in patients undergoing MH or MRM, respectively. **Methods:** The study was a randomised, controlled open-label trial. Patients undergoing MH who were randomised to the intervention group received TAP block whereas those undergoing MRM received PEC-II block. Blood samples were drawn at baseline, 6 and 24 hours after surgery for serum CPK measurements. Changes in serum CPK levels between the control and intervention groups were compared using repeated-measures analysis of variance. **Results:** Baseline serum CPK levels were similar between the groups. There was a significant difference in the change in serum CPK levels between the groups. It significantly rose in the intervention group as compared to the control group ($p < 0.001$). **Conclusion:** The study shows that serum CPK levels significantly increase at 24 hours after interfascial plane block thereby indirectly indicating myotoxicity. Further research is needed to ascertain its clinical impact.

Key words: Bupivacaine, creatine kinase, local anaesthetics, myotoxicity, nerve block, neurotoxicity, peripheral nerve

INTRODUCTION

The use of peripheral nerve blockade has grown as it decreases pain and hence decreases the need for postoperative analgesia.[1] Local anaesthetics (bupivacaine) injected directly within or in close proximity to skeletal muscle cause myotoxicity, secondary to inflammation and myocyte damage; although in humans, these effects seem to be subclinical except in extremely rare cases.[2] Myotoxicity caused by local anaesthetic agents was first described by Brun in striated muscles in 1959 and has continued to gain interest as a serious complication of peripheral nerve blocks.[3] Recent reviews of local anaesthetic induced myotoxicity after peripheral nerve blocks have augmented interest in this less commonly known complication.[4] Although the morphological, physiological and biochemical changes in muscle after injection of clinically used concentration of bupivacaine have been studied in animals, little research has been conducted in humans. Animal studies have demonstrated significant local anaesthesia induced myotoxicity with biochemical

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and histological evidence whereas human studies have shown an increase in myotoxicity markers i.e., creatine phosphokinase (CPK), lactate dehydrogenase, aspartate aminotransferase.[5] Serum CPK is a marker of skeletal muscle injury as it has the highest CPK content of any tissue, more than three times as in the heart or brain, and nearly all circulating CPK activity is derived from skeletal muscle. As compared to other markers, CPK activity is more frequently abnormal in neuromuscular disease and myotoxicity.[1]

Bupivacaine is a long-acting local anaesthetic used widely in modern anaesthesia practice. Bupivacaine has specific myotoxic effects as shown in animal studies where injection of bupivacaine into muscle resulted in rapid degeneration of muscle cells without damage to the basement membrane, peripheral nerves or blood vessels and with complete regeneration reported in a small series of cases in animals.[6]

In an attempt to measure local anaesthetic-induced myotoxicity, we conducted a study wherein we measured changes in serum CPK levels after surgery in patients administered interfascial plane blocks with 0.25% bupivacaine.

METHODS

The study was a single centre, prospective, randomised, open-label, controlled trial conducted between April 2020 and March 2021. The centre is a tertiary care referral and teaching hospital. The study was approved by the Institute Ethics Committee and registered in the Clinical Trials Registry -India (CTRI/2020/03/023719).

Patients admitted to the hospital for elective mesh hernioplasty (MH) for unilateral inguinal hernia and unilateral modified radical mastectomy (MRM) were screened for inclusion in the study. Age between 18-60 years and American Society of Anesthesiologists (ASA) physical status class I or II were inclusion criteria. Exclusion criteria were history of bleeding disorder, muscle, liver, kidney, thyroid or parathyroid disease, obstructive sleep apnoea, past treatment or diagnosis of sodium or potassium disorders, allergy to local anaesthetic agents, infection at needle insertion site for proposed block in the study and lactation or pregnancy in case of females. Patients were enroled in the study after taking informed consent and were randomised by computer-generated random numbers to receive either nerve block (Group-A) or no nerve block (control Group-B) in a 1:1 ratio. Group A included patients of MRM who received general anaesthesia (GA) and pectoral nerve block (PEC-II) or patient undergoing MH who received spinal anaesthesia and transversus abdominis plane (TAP) block. Group B (Control group) included patients who underwent MRM under GA and MH under spinal anaesthesia without fascial plane block.

Randomisation was stratified by the type of surgery (MH or MRM). Allocation concealment was done by keeping the random allocation number enclosed in a sealed opaque envelope. The envelope was opened by an anaesthesiologist not involved in the study.

On the day of surgery, baseline samples for serum CPK were drawn before randomisation.

General anaesthesia was induced with intravenous propofol (2 mg/kg) and fentanyl (2 μg/kg). Intravenous atracurium (0.6 mg/kg) was used to facilitate intubation. Anaesthesia was maintained with isoflurane (0.6-1%) and mixture of nitrous oxide (N_2O) and oxygen (O_2) (66% and 33%, respectively). Neuromuscular block was maintained with intravenous atracurium (0.1 mg/kg).

In patients undergoing MRM who were randomised to intervention (PEC-II block), ultrasonography (USG) guided PEC-II block was performed after induction. The patient was placed in the supine position with ipsilateral upper limb (same side as planned surgery) in abducted position. Using linear USG probe (6-13 MHz, M Turbo, Fujifilm Sonosite India Pvt Ltd), axillary artery and vein were identified which was followed by the localisation of pectoralis minor and pectoralis major muscles over the first rib. Ten ml of 0.25% bupivacaine was injected under USG guidance in the fascial plane between pectoralis major and minor using 23 G short bevel needle. Thereafter, fascial plane between serratus anterior and pectoralis minor muscles (over second, third and fourth ribs towards axilla) was identified and 20 ml of 0.25% bupivacaine was injected under USG guidance.

In patients undergoing MH who were randomised to intervention (TAP block), subarachnoid block was given at L_3-L_4 interspinous space using 26 G spinal needle and 3 ml of 0.5% hyperbaric bupivacaine was injected. After confirmation of adequate level of blockade, USG guided TAP block was performed. After identifying external oblique muscle, internal oblique muscle, transversus abdominis muscle and their fascial boundaries (between twelfth rib, iliac crest and

umbilicus), a 23 G short bevel needle was advanced in the anterior axillary line in the plane between internal oblique and transversus abdominis muscle. After checking the exact location of needle tip, 1 ml of normal saline was injected to open the plane between the internal oblique and transversus abdominis muscle. This was confirmed as a hypoechoic area on USG. Thereafter, 30 ml of 0.25% bupivacaine was injected at the same site.

On completion of surgery, neuromuscular blockade was reversed with intravenous neostigmine (50 μg/kg) and glycopyrrolate (10 μg/kg).

During the surgery, non-invasive monitoring of arterial blood pressure, heart rate and oxygen saturation were done every 5 minutes. In the postoperative period, monitoring was done every 15 minutes for 1 hour. Repeat blood samples were drawn at 6 and 24 hours after surgery for serum CPK measurements.

As there was no previous data to guide sample size calculation, a sample size of 38 patients per group was calculated assuming Cohen's effect size of 0.65 at 80% power and two-sided alpha of 0.05. A total sample size of 80 (40 in each group) was arrived at after considering 5% dropout rate.

Data were analysed using Statistical Package for the Social Sciences (SPSS) software statistics, version 26 for Mac, International Business Machines Corporation (IBM), (US). Frequencies or proportions were used to report categorical variables. Continuous variables were reported as mean ± standard deviation or median with inter-quartile range. Repeated measures analysis of variance was used to test the interaction of groups with change in serum CPK levels.

The primary outcome of the study was difference in change in serum CPK levels between intervention and control groups at 24 hours after surgery.

RESULTS

Eighty-eight patients were screened for enrolment in the study. Five patients were excluded as they either did not satisfy inclusion criteria or satisfied one of the exclusion criteria, and three patients declined participation. Eighty patients were enroled in the study out of which 40 underwent MH and 40 underwent MRM. All enroled participants completed the study protocol and final outcome parameter data were available in all enroled participants [Figure 1].

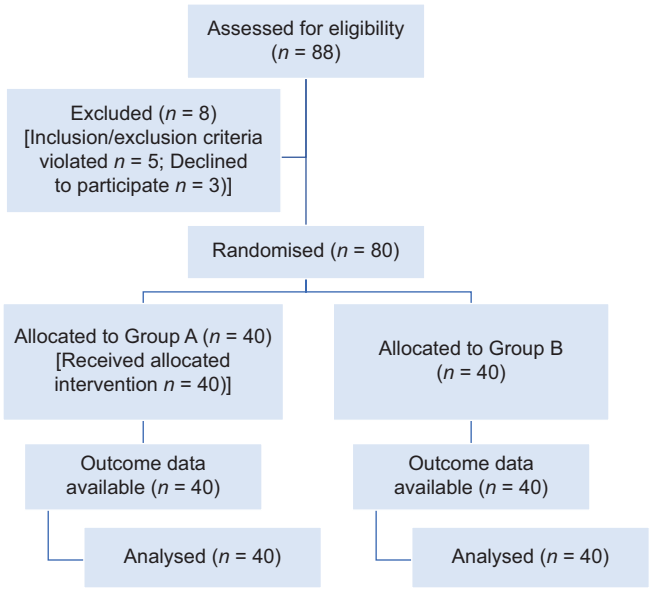

Figure 1: Patient enrolment and follow up in the study

The baseline demographic characteristics were similar in both the groups [Table 1]. There was a statistically significant difference in change in serum CPK levels between the groups [Table 2, Figure 2]. It significantly rose in the intervention group as compared to the control group [Wilk's Lambda = 0.846, F (2.638, 195.218) = 7.068 (Huynh-Feldt Correction applied), $P < 0.001$]. The results were similar in the subgroups defined by type of surgery.

All study participants had an uneventful post-operative course. The intraoperative and post-operative monitoring parameters were similar between the two groups. No major complications or adverse events were recorded in the study population.

DISCUSSION

Our study observations suggest significantly higher rise in serum CPK levels after PEC II or TAP block with 0.25% bupivacaine in patients undergoing MRM or MH, respectively. The mean serum CPK levels in the intervention group at 24 hours were almost 63% higher than that in the control group. The observations were consistent in the two subgroups (MRM and MH) classified by the type of surgery.

Local anaesthetic agents may produce myotoxicity by affecting calcium inflow and intracellular mobilisation, thereby disrupting calcium homeostasis. Mitochondria play a major role in this via energy deprivation, over-production of reactive oxygen species (ROS) and apoptosis.[7] Therapeutic concentrations of local

anaesthetics can cause myotoxic injury in human studies.[1] This myotoxicity can be classified as having three stages: an early inflammatory phase, a degenerative phase, and then a regenerative phase which can be delayed. Use of these agents in ophthalmic studies has been associated with partial or incomplete recovery after myotoxicity to the extent that intervention to improve muscle function were needed.[8] Myotoxicity can occur even when local anaesthetics are injected outside the muscle. Repeated injections may break down fascial planes, and thereby facilitate extensive spread. The severity of damage seems to be associated with the type, concentration, as well as duration of exposure to local anaesthetics.[9] Amongst local anaesthetics, bupivacaine is more strongly associated with myotoxicity as compared to lidocaine and ropivacaine.[1,10] Myotoxicity begins within minutes of intramuscular local anaesthetic injection; and myocytes become oedematous and necrotic by 24 hours. The affected muscle exhibits diffuse inflammation that may persist for months.[3]

Our observations are concordant with those reported by Nosaka K *et al.*,[5] who observed a significant increase in plasma CPK activity at 12 and 24 hours after injection ($P < 0.01$). The amount of increase in plasma CPK activity from pre injection levels varied among the subjects (274- 526 IU L^{-1}). Plasma CPK activity returned to the preinjection level by 96 hours after the injection. They also reported quadriceps weakness after continuous adductor block. Another study reported a rise in the CPK level (423 IU/L at 48 hours) following continuous adductor canal block in total knee replacement patients.[11] The authors reported extensive inflammation on magnetic resonance imaging (MRI) and the findings were compatible with myositis.

Myotoxicity due to local anaesthetics is often subclinical and confounded by concomitant clinical circumstances. Therefore, it is not surprising that the same may go unnoticed. Weakness and pain after surgery may mask symptoms of myotoxicity in many patients.[12] Muscle injury or damage leads to rise in serum CPK and glutamate levels.[13,14] Though the diagnostic utility of CPK in the present clinical context has not been validated, it is likely to be same.[15] MRI or electromyogram or biopsy can further help in establishing definitive diagnosis if required.[1,16]

Using minimum required dose, concentration and volume of local anaesthetic is desirable to prevent such subclinical or clinical complications.[4,17] Performing a nerve block under ultrasound guidance may help

Table 1: Characteristics of the study population

Parameter	Intervention group (*n*=40)	Control group (*n*=40)
Age (years)*	44.8±9.8	46.8±9.6
Gender (Male/Female)	20/20	18/22
ASA grade		
I	26	22
II	14	18
Type of surgery		
MH	20	20
MRM	20	20
Duration of surgery (minutes)*	76.45±8.54	81.1±11.67
Co-morbidities		
Diabetes mellitus	11	9
Hypertension	6	8

Expressed as frequency except variables marked as * which have been expressed as mean +/- standard deviation. (ASA: American Society of Anesthesiologists, MH: Mesh hernioplasty, MRM: Modified radical mastectomy)

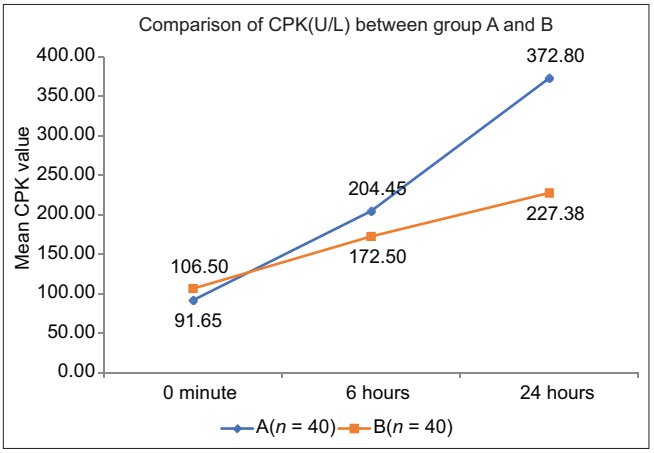

Figure 2: Change in serum creatine phosphokinase (CPK) levels (IU/L) between groups (Group A: Intervention, Group B: Control), $P < 0.001$ for comparison between groups

Table 2: Primary outcome parameter in the study population

Parameter		Baseline		6 hours after surgery		24 hours after surgery		*P*
		Group A	Group B	Group A	Group B	Group A	Group B	
SerumCPK (U/L)*	Overall study population	91.6±34.1	106.5±44.7	204.4±84.1	172.5±57.2	372.8±107.5	227.4±94.7	<0.001
	MH subgroup	100.8±37.5	115.2±51.1	201.5±82.1	183.5±56.7	386.1±127.6	232.10±83.5	<0.001
	MRM subgroup	82.5±28.3	97.7±36.5	207.4±88.1	161.4±56.9	359.5±84.2	222.6±106.7	<0.001

* Expressed as mean +/- standard deviation. (Group A: Intervention, Group B: Control. CPK: creatine phosphokinase, MH: mesh hernioplasty, MRM: modified radical mastectomy)

reduce volume used through better localisation.[18,19] The duration of continuous nerve blocks can be increased by other options (e.g., combination with other drugs etc.) and finally, vigilant postoperative follow up to look for signs of myotoxicity might also help to pick up complications early.

Recent studies suggest that drug-induced protection may also be considered to reduce bupivacaine induced myotoxicity.[20] Erythropoietin (5000 U/kg) administered with bupivacaine prevents the alterations of mitochondrial structure and bioenergetics. This effect is time-dependent, which suggests an interaction with the regulatory pathway of mitochondrial autophagy. However, the doses of erythropoietin used in these experiments were greater than those used clinically (600 U/kg) in the perioperative period for its haematopoietic effect. This intervention still requires rigorous evaluation before clinical use. Similarly, N-acetyl cysteine given with bupivacaine, protects against ROS production, but its clinical significance is yet to be ascertained.[21] The observations reported in our study need to be validated in other patient populations to ascertain their true clinical significance. This would also help us to assess whether therapeutic preventive strategies are needed or not. In current clinical practice, we use lower doses as compared to those reported in the past. Therefore, further validation and assessment are needed to preclude clinical significance and consequences of myotoxicity.

There are certain limitations of our study. Ours was a single-centre hospital-based study with a small sample size. We did not estimate the serum concentrations of bupivacaine. In our study, we used only serum CPK levels as markers of myotoxicity. We enroled patients who received nerve blocks that involved the chest wall and abdominal muscles; hence it was not possible to objectively assess muscle weakness. We did not measure serum CPK levels beyond 24 hours. Overall, these limitations still do not take us away from the strengths of our study. As per our knowledge,there are not many studies on local anaesthetic induced myotoxicity in interfascial plane blocks like PEC-II and TAP blocks. Our study enroled relatively homogenous population by restricting to two types of surgeries, had a control group without use of nerve blocks and randomised design. The consistent significant difference in CPK levels in the overall study population and across subgroups reinforce the potential for myotoxicity in peripheral blocks using bupivacaine.

CONCLUSION

Use of 0.25% bupivacaine for interfascial nerve blocks is associated with elevation in serum CPK levels. The systematic design of our study highlights the myotoxic potential of local anaesthetics agents and underlines the need for exploring this observation further to ascertain its true clinical significance. Till that time, clinicians need to be aware about this rare entity.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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