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Local-Anaesthetic-Induced Myotoxicity in Interfascial Plane Blocks: A Comparative Study between Bupivacaine and Ropivacaine

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Abstract:

Objective: Local-anaesthetic (LA)-induced myotoxicity in the use of peripheral nerve blocks has emerged as a topic of interest recently. Very few studies on human subjects have been done in this field, though the technique of nerve blocks is being widely practiced both for anaesthesia and analgesia. Studies have shown that bupivacaine induces reproducible skeletal muscle degeneration. The present study is thus aimed at comparing the myotoxicity induced by bupivacaine and ropivacaine in interfascial plane blocks.

Material and Methods: The study was a randomized comparative study done at a tertiary care hospital. The subjects were randomly assigned into 3 groups of 50 patients each:- Group B, with patients in whom bupivacaine was used; Group R, comprised of patients in which ropivacaine was used, Group N, who received no fascial plane block during their procedures. An erector spinae block (ESP block) was performed for patients undergoing unilateral lung decortication or lobectomy. Creatine phosphokinase (CPK) levels at 6 and 24 hours after completion of surgery were taken in all 3 groups and compared with baseline values using Repeated Measures Analysis of Variance.

Results: Baseline serum CPK levels were similar in all 3 study groups. Significant increases in serum CPK levels were noticed in group B compared to group R at 6 hours and 24 hours, with no increase in group N.

Conclusion: The study showed that serum CPK, a marker of skeletal muscle injury and local-anaesthetic-induced myotoxicity, significantly rose at 24 hours after an ESP block and this increase was considerably higher in group B (bupivacaine) compared to group R (ropivacaine), indicating significantly higher myotoxicity with bupivacaine.

Keywords: bupivacaine, CPK levels, erector spinae block, local-anaesthetic-induced myotoxicity, ropivacaine

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Introduction

Local-anaesthetic (LA)-induced myotoxicity in the use of peripheral nerve blocks has emerged as a topic of interest recently. Research has been done on animal models to measure the toxic changes in muscles after a LA injection, particularly in interfascial plane blocks, but to date there have been very few studies on human subjects in this field, though the technique of nerve blocks is widely practiced both for anaesthesia and analgesia. Brun[1] in the year 1959 first described LA induced myotoxicity in striated muscles. Theoretically it is believed that when LA is injected in close proximity to a muscle, it will cause inflammation and myocyte damage. However, in most of the cases it would be subclinical.

Recently a study was done by Vasundhara et al.[2] on bupivacaine-induced myotoxicity in interfascial plane blocks which concluded that there was statistically significant bupivacaine-induced myotoxicity though not severe in the majority of cases.

Bupivacaine, a long-acting LA, is being extensively used in peripheral nerve blocks. Nevertheless, the use of ropivacaine in nerve blocks has increased due to its lower cardiotoxicity compared to bupivacaine. Although studies have shown that bupivacaine induces reproducible skeletal muscle degeneration, there are very few comparative studies between bupivacaine and ropivacaine[3]. The present study thus aimed at comparing the myotoxicity induced by both the local anaesthetics. Time-tested myotoxicity markers like creatine phosphokinase (CPK), lactate dehydrogenase and aspartate amino transferase were taken into consideration for our study. Since CPK is derived mostly from the skeletal muscles and its increase is consistent with skeletal muscle injury, we decided to measure serum CPK levels to assess myotoxicity.

Material and Methods

The study was a hospital-based randomized comparative study conducted between July 2022 and January 2023 at a tertiary care referral teaching hospital. The study was approved by the Institutional Ethics Committee.

The inclusion criteria were patients of age 18-60 years of either sex categorized as American Society of Anaesthesiologists (ASA) physical status I or II admitted to the hospital for unilateral lung decortication and lobectomy. The exclusion criteria were history of bleeding disorders, allergy to LA drugs, infection at the site of needle insertion for proposed erector spinae block (ESP), pregnant or lactating females, and patients with liver, kidney or muscle diseases.

Patients were enrolled in the study after we explained the academic purpose behind the study. They were also told that they maintained the right to withdraw from the study at any time during the process and that no physical inconvenience would cause to the patient. Patient confidentiality was maintained. Consent was obtained for being a part of the study protocol and also for the proposed procedure. Demographic data including age, sex, and past medical history were collected. The patients meeting the inclusion criteria were randomly assigned into one of 3 groups using computer generated randomized numbers: Group B, with patients in whom bupivacaine was used; Group R, comprised of patients in which ropivacaine was used, Group N, who received no fascial plane block during their procedures.Allocation concealment was done by keeping the allocated random numbers in a sealed envelope. Blood was drawn for measurement of CPK levels before surgery for all subjects randomized in these groups. In the operation theatre, two intravenous (IV) lines were secured, one on each hand. Standard patient monitoring was done using continuous electrocardiography monitoring, pulse oximetry and non-invasive blood pressure at 5-minute intervals. Resuscitation equipment was kept ready. The patient was placed in a sitting position and the site of the block cleaned and draped. Using a Fujifilm Sonosite ultrasound curvilinear probe- 3 centimetres (cm)

away from the midline in the saggital plane, the transverse process of the 5th thoracic vertebra (T5) was located and an in-plane ESP block was performed using a blunt-tip 22 gauge (G) needle in the caudal direction after injecting 2 ml of 2% lignocaine locally at the level of T4-T5. Thirty ml of the LA was injected, 0.2% bupivacaine in group B and, 0.2% ropivacaine in group R, while no ESP block was performed in group N.

After performing the block, general anaesthesia (GA) was induced with IV propofol (2 mg/kg) with premedication of 0.2 mg glycopyrrolate, 100 mcg of fentanyl and 1 mg of midazolam. The relaxant used was vecuronium 0.1 mg/kg and each patient was intubated with a double lumen tube size, with the side depending upon the patient and procedure. Anaesthesia was maintained with oxygen, nitrous oxide mixture and sevoflurane (1-2%). The neuromuscular blockade was done with vecuronium. At the time of lung isolation, 100% oxygen with an inhalational agent was used. Monitoring was done with invasive blood pressure monitoring by securing an arterial line. A central venous pressure (CVP) line was also secured for CVP monitoring, and giving drugs, and for resuscitation if needed.

After completion of the surgery, the neuromuscular blockade was reversed with IV neostigmine (50 mcg/kg) and glycopyrrolate (10 mcg/kg). The patient was monitored in the Surgical Intensive Care Unit during the post-operative period for hemodynamics, saturation and potential complications (hematoma, neurological deficit). Blood samples were drawn at 6 and 24 hours after completion of surgery for measuring CPK levels.

A sample size of 40 per group was selected based on a Cohen's effect size of 0.65 at 80.0 % power and a two-sided alpha of 0.05. A total sample size of 126 was arrived at after considering a 5.0% dropout rate.

The data were analyzed using the Statistical Package for the Social Sciences (SPSS); frequency was used to report categorical variables. Repeated measures analysis of variance was used to test the interaction of groups with respect to changes in CPK levels. The primary outcome of the study was differences in changes in serum CPK levels between the 3 groups 24 hours after surgery.

Results

One hundred seventy-five patients were screened for enrolment in the study. Twenty-three patients were excluded because either the inclusion criteria were not met or they had 1 or more exclusion criteria. Two patients declined participation. The study was commenced with 150 patients divided into three groups : group B, group R and group N with 40 members each and 10 subjects as reserve in each group in case of dropouts. The baseline demographic characteristics (age, gender, ASA physical status) were similar in all three groups. Factors that could cause increases in CPK levels (neuromuscular disorders, malignancies and metabolic disorders) were ruled out in the participants. There were significant rises in serum CPK levels in group B and group R, who had ESP blocks, compared to group N where no blocks were performed, at both 6 hours (198.2 vs 164.2 vs 138.6) and 24 hours (354.1 vs 298.7 vs 201.3). The rise of CPK levels was significantly much higher in group B compared to group RR (p-value<0.001).All study participants had uneventful intraoperative and post-operative courses. There were no significant problems with hemodynamic or monitored parameters in any of the participants. No complications or adverse events were recorded in any of the study participants.

Discussion

As reported in a study conducted by Hussain et al.[4] published in the British Journal of Anaesthesia, LA in therapeutic concentrations can cause myotoxicity in humans, the mechanism being disruption of calcium homeostasis.

Benoit et al.[5] did a study on the effect of LA agents on skeletal muscle and concluded that mitochondria play a crucial role in this disruption of calcium homeostasis by energy deprivation. Gomez-Arnau et al. conducted a study on anaesthesia-related diplopia after cataract surgery, and found that interventions were needed to improve post-perative muscle function which was partially lost due to LA-induced myotoxicity[6]. Three stages have been described in myotoxicity: stage I – inflammatory stage, stage II – degenerative stage, and stage III – regenerative stage, which is usually delayed.

It is worth noting that when the LA is injected outside the muscle, still there will be myotoxicity. An increased number of attempts with an increased number of injections will cause breakdown of fascial planes. A study by Nouette-Gaulain et al.[7] found that factors contributing to the severity of myotoxicity were concentration of the drug and duration of exposure to the drug. Zink et al. conducted a study on the myotoxic effects of bupivacaine and ropivacaine after continuous peripheral nerve blockade[8] and noted results similar to our study-bupivacaine resulted in increased myotoxicity compared to ropivacaine. The most probable reason to explain this fact would be the less lipophilic nature of ropivacaine compared to bupivacaine, thus the drug is less likely to penetrate large myelinated motor fibres.

Nosaka et al.[3] and Brun[1] highlighted the changes that occur in a muscle due to the myotoxicity of a LA. If an injection of LA is given intramuscularly myotoxicity starts within minutes. This is followed by an oedematous phase and then a necrotic phase within 24 hours. Diffuse inflammation will persist in the affected muscle for months.

The findings in this study were in accordance with similar studies conducted by Nosaka et al.[3] and Vasundhara et al.[2] A significant increase in plasma CPK activity was noted at various time intervals. It took more than 96 hours for CPK levels to return to baseline levels. Dorado-Velesco et at.[9] performed perineural femoral blocks for total hip replacement and reported a rise of CPK levels at 48 hours supported by magnetic resonance imaging (MRI) findings of myositis changes. In most cases myotoxicity due to LA is subclinical and many times it may go unnoticed. Holm et al.[9] reported that pain and weakness following surgery may also mask symptoms of myotoxicity. Injury to the muscle will lead to a definitive rise in CPK and glutamate levels. MRI and, electromyograms may be additional tools to establish diagnosis as per studies done by Hogan et al.[10]

Several steps have been suggested by various studies to reduce this LA myotoxicity. Neal et al.[11] concluded that by using the minimum required dose, the concentration and, the volume of the LA myotoxicity can be significantly reduced. Further, Chakraborty et al.[12] in their study pointed out that ultrasound guidance can decrease the necessity of larger volumes of LA through better localization. Adjuvants can increase the duration of LA and can further decrease the volume needed, eventually decreasing the incidence of myotoxicity. Most important is vigilant post-operative care, observing the patient closely for signs of myotoxicity and early intervention if needed.

Novette-Gaulain et al.[7] made an interesting finding concerning the use of erythropoietin 5000 U/Kg to reduce bupivacaine-induced myotoxicity. Similarly, N-acetyl cysteine may protect against reactive oxygen species production. But these findings have to be further validated.

Limitations of our study

We could not estimate serum concentrations of LA.

The sample size was 120 and a larger sample may have been helpful in giving the study a higher power.

Muscle weakness could not be objectively assessed and we depended on CPK levels which was a fairly good indicator of muscle injury and we limited our study of CPK levels to 24 hours.

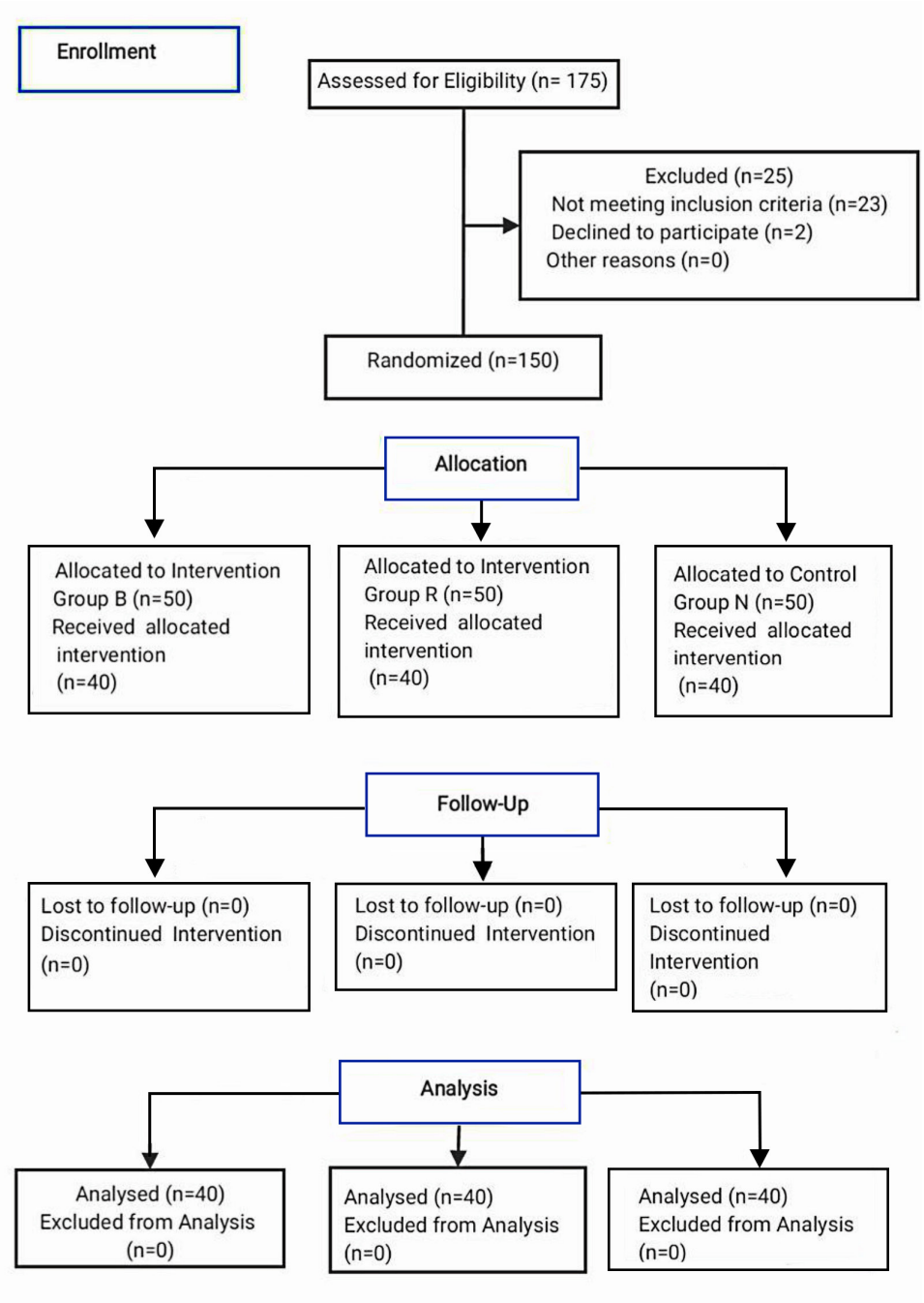


Figure 1 Consort diagram Table 1 Demographic data

Table 1 Demographic data

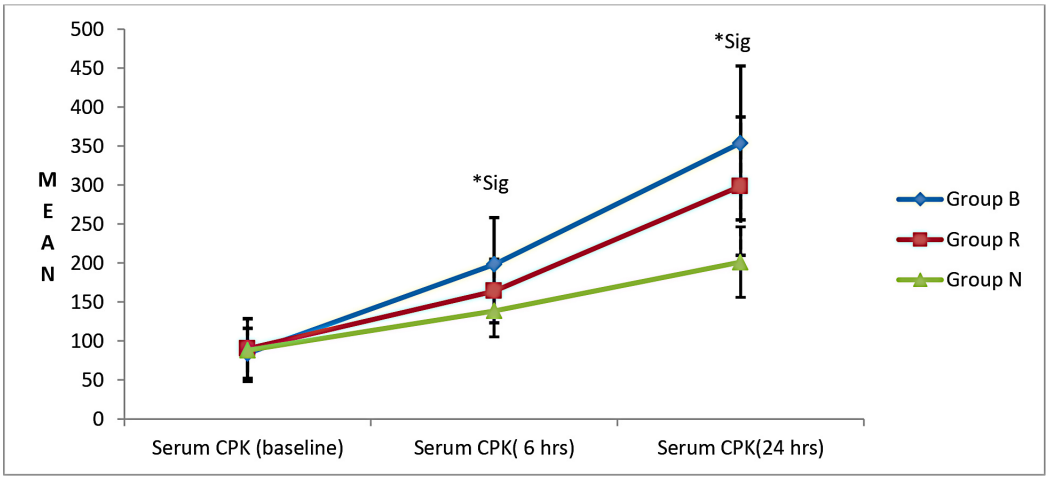
Parameter	Group B	Group R	Group N
Age in years	43.2±4.2*	44.2±3.7*	46.1±4.6*
Gender (male/female)	20/20	20/20	20/20
ASA grade I	21	22	17
ASA grade II	19	18	23

ASA=american society of anaesthesiologists physical status classification
*Expressed as mean±S.D.
Group B–ESP block done using bupivacaine 0.2% as LA
Group R–ESP block done using ropivacaine 0.2% as LA
Group N–No ESP block performed
p-value<0.001

Table 2 Primary outcome parameters in the study population

Parameter	Group B	Group R	Group N
Serum CPK (baseline)	84.2±32.1*	90.2±38.6*	88.2±40.2*
Serum CPK (6 hrs)	198.2±60.1* Serum	164.2+40.8*	138.6±33.2*
Serum CPK (24 hrs)	354.1±98.7*	298.7±88.7*	201.3+45.2*

*Expressed as mean±S.D.
S.D.=standard deviation CPK=creatine phosphokinase
Group B–ESP block done using bupivacaine 0.2% as LA
Group R–ESP block done using ropivacaine 0.2% as LA
Group N–No ESP block performed
p-value<0.001, hrs=hours



Group B–ESP block done using bupivacaine 0.2% as LA
Group R–ESP block done using Ropivacaine 0.2% as LA
Group N–No ESP block performed
hrs=hours, CPK=creatine phosphokinase–in Units/litre (U/L),*Sig=statistically significant

Figure 2 Comparison of mean CPK levels in 3 groups and Standard Deviation as Error Bars

Conclusion

This study concluded that 30 ml of 0.2% bupivacaine and 0.2% ropivacaine were notably associated with muscle injury as ascertained with elevated serum CPK levels at 24 hours after the LA injection. Bupivacaine 0.2% showed a statistically higher increase in CPK levels compared to ropivacaine 0.2%. This emphasizes the need for further studies in this field and also vigilance regarding the signs of myotoxicity.

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Conflict of interest

There are no conflicts of interest.

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