

Comparative Study between Using Lidocaine Alone versus Using Lidocaine Combined with Either Ketamine, Nitroglycerine or Paracetamol for Bier Block in Upper Limb Surgeries Distal to The Elbow: A Prospective Double-Blind Randomized Clinical Trial

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ABSTRACT

Background: Bier block is a good method of anaesthetizing the extremities. But it has untoward effects because anaesthesia and pain relief are satisfactory as far as the tourniquet is inflated, and once the cuff is deflated the patients experienced the loss of anaesthesia and developed severe postoperative pain (POP). So, scientists search for adjuncts to extend the duration of action and better postoperative analgesia. These adjuncts added to lidocaine like dexamethasone, ketamine, nonsteroidal anti-inflammatory drugs, narcotics, magnesium, paracetamol, nitroglycerineetc.

Objective: To assess and compare the clinical effects of Bier block, with lidocaine alone, or in a combination with ketamine, paracetamol, and nitroglycerine for anesthesia quality and better postoperative analgesia during Bier block (intravenous regional anaesthesia) for upper limb surgery distal to the elbow.

Patients and methods: One hundred patients ASA (American Society of Anesthesiologists) I and II, aged between 20 and 60 years and scheduled for any upper limb surgeries distal to the elbow were comprised in the current prospective, randomized double-blind research which was conducted at Sohag University Hospital from March to September 2023.

Results: For groups LP, LN, LK the onset of sensory and motor block were shorter while the sensory and motor block recovery times were increased in comparison with group L ($p < 0.05$). Also, there was shorter onset of the sensory and motor block in group LN than in groups LP and LK. For the sensory and motor recovery there was no significant difference between the adjuvant groups.

Conclusion: Supplementation of ketamine, nitroglycerine or paracetamol to lidocaine during Bier block reduces the onset time and improves the quality of anaesthesia, reduces tourniquet pain feeling, and also, reduces consumption of analgesics intraoperatively and postoperatively without side effects.

Keywords: Lidocaine, Lidocaine combined, Ketamine, Nitroglycerine, Paracetamol, Bier block, Upper limb surgeries, Distal to the elbow.

INTRODUCTION

Karl August Bier is the 1st one who had done regional anesthesia by intravenous injection of local anesthetic in 1908. Bier and his colleagues used procaine for iv injection and because of the usage of one tourniquet and the adverse events of procaine they faced much difficulties; so this technique gradually disappeared until Holmes in 1983 used lidocaine instead of procaine and used two tourniquet method then it started evolving. This type of regional anesthesia has the advantages of being safe, trustable, cheap method used for upper limb surgeries distal to the elbow. The anesthetic solution when injected intravenously; it spreads from large veins at site of injection to the smaller veins and venules then distributed around the large nerves and then into blood supply of the nerves, resulting in block of these nerves, after that spreads around the minor nerves, blocking them ⁽¹⁾.

Moreover, this technique quickly restored motor and sensory function, shortening patients' hospital stays ^(2,3). It gives the area of the limb just distal to the tourniquet level reliable regional anesthesia ⁽⁴⁾. Unfortunately, the tourniquet caused pain for the patients, and this approach did not sufficiently relax the muscles or reduce pain after surgery. Moreover, limb congestion was seen ⁽⁵⁾. Several studies have added medicines, such as nonsteroidal anti-inflammatory

agents like ketorolac and tenoxicam ^(6,7), paracetamol ⁽⁸⁾, opioids, dexamethasone, muscle relaxants, neostigmine, ketamine, and clonidine, as adjuvants to local anesthetics to overcome these drawbacks ⁽⁹⁾.

With these additions, a perfect prescription for Bier block should be obtained that has a quicker onset, lower total local anesthetic dose, minimizes tourniquet pain, and lasts longer after the tourniquet is deflated. Although paracetamol has a minor anti-inflammatory action, it may have a central analgesic effect. Moreover, several investigations have shown that paracetamol has peripheral anti-nociceptive characteristics that help it reduce pain. In 2002, paracetamol was administered intravenously for the first time ⁽¹⁰⁾.

Ketamine has sympathetic, sensory, and motor blocks in addition to its local anesthetic effects ⁽¹¹⁾. The noncompetitive inhibition of N-methyl-D-aspartate receptors (NMDA) seems to explain how ketamine works. These receptors have a significant impact on the pain pathway. Hence, inhibiting NMDA receptors can be used for pain relief during surgery ⁽¹²⁾.

Patients with both acute and chronic pain may benefit more from the analgesic effects of various analgesic medications when prescribing nitroglycerine (NTG) with them. Also, it enhances the analgesic effects of intrathecal injections of either sufentanil or neostigmine and the analgesic quality of oral morphine

in treating persistent pain in patients with malignant tumors. Moreover, it has been documented that adding lidocaine to NTG for Bier blocks lengthens the duration of postsurgical analgesia⁽¹³⁾.

For the Bier block, we planned this study to assess the effects of adding ketamine, paracetamol, or NTG to lidocaine on pain reduction both during and after surgery, the onset of nerve block, and tourniquet pain.

PATIENTS AND METHODS

One hundred patients ASA (American Society of Anesthesiologists) I and II, aged between 20 and 60 years and scheduled for any upper limb surgeries distal to the elbow were comprised in the current prospective, randomized double-blind research which was conducted at Sohag University Hospital from March to September 2023.

Randomization was performed by utilizing a special software and cases were divided into four groups of 25 cases each. To guarantee that the allocation sequence remained secret, the randomly selected group was placed inside a sealed envelope. After transporting the patient to the operating room, the anesthesiologist who was not engaged in the study opened the sealed envelope and prepared the medication solution in accordance with randomization. This was a double blinded research in which the anesthesiologist and the nurses recording the postoperative data were blinded to patient's group.

Exclusion criteria included patient refusal, all cases with sickle cell anemia, history of allergy to drugs used in the study, Reynaud's disease, any neurological deficit in the upper limb, presence of other contraindications to Bier block as myasthenia gravis or scleroderma, crushed injuries or severe vascular injuries or compound fractures of the upper limb, inability to determine the actual location of peripheral veins, skin infections, and cellulitis.

Traditional follow up was applied, which included heart rate (HR), mean arterial pressure (MAP), oxygen saturation (SPO₂), and electrocardiogram (ECG). Then fixing two intravenous (iv) lines were done on the dorsum of hands of both limbs. Elevation of the limb of surgery was done for two minutes (min), and an elastic bandage was utilized to evacuate the venous blood in this limb as far as the patient can tolerate pain during manipulation. Then, we applied two pneumatic tourniquet in the upper arm.

The proximal one was inflated to a pressure of 100 mmHg beyond the SBP of every patient then examination of this limb for loss of radial pulse and no pulse oximetry signals of the hand of the same limb then removal of the bandage was done. In this limb, patients in Group L (lidocaine group (n=25)): we injected 2% lidocaine 2-4 mg/kg (maximal dose 4 mg/kg) for Bier block. Patients in Group LP (lidocaine and paracetamol group (n=25)): we injected 2% lidocaine 2-4 mg/kg (maximal dose 4 mg/kg) plus paracetamol 100 mg. Patients in Group LK (lidocaine and ketamine group

(n=25)): we injected 2% lidocaine 2-4 mg/kg (maximal dose 4 mg/kg) plus 40 ketamine. Patients in Group LN (lidocaine and nitroglycerine group (n=25)): we injected 2% lidocaine 2-4 mg/kg (maximal dose 4 mg/kg) plus 150 µg nitroglycerine. Normal saline was added to form an overall volume of 40 mL and the anesthesia was injected slowly over one and half minutes by an anesthesiologist blinding to the used anesthetic solution contents. The anesthetic solution was prepared by anesthesia assistant not involved in the study to prepare identical syringes containing each drug.

The distal tourniquet was inflated 10 minutes after local anesthetic injection to 100 mmHg beyond the SBP of every patient, and the proximal one was deflated and the tourniquet time and operative time were documented. The distal tourniquet was not allowed to be deflated before 20 minutes from the start of inflation and the duration of inflation was not allowed for more than 1.5 hours and at the end of surgery tourniquet deflation was conducted intermittently.

Recording of MAP, HR, and SPO₂ one minute following tourniquet inflation, and every five min after injection of drug till deflation of the tourniquet, and in the recovery room at 15, 30, 45, and 60 min. The onset of sensory block was explained as the time from administration of the anesthetic solution till sensory block in all dermatomal sensory distribution of ulnar, median and radial nerves by a pinprick test performed every 30 seconds. The motor block onset was explained as the time from administration of the anesthetic solution till reaching the total motor block. The motor block was assessed by no movement occurred on asking the patients to perform flexion and extension of the wrist and fingers every 60 seconds. The recovery period of sensory block was explained as the time from tourniquet deflation till pain sensation started.

The recovery time of motor block was explained as the time after tourniquet deflation till the fingers start to move. Assessment of pain experienced by the patients owing to the tourniquet (tourniquet pain) was done by visual analogue scale (VAS) at 5, 10, 20, 30, 40, 50, and 60 minutes after injection of anesthesia.

Assessment of surgical pain at 1, 2, 4, 6, 12 and 24 hours postoperatively was assessed also by (VAS). Visual analogue scale assessment was done by asking the patient to put his/her finger on the faces to indicate how much pain he/she is currently feeling in which (zero) indicates 'No pain' and (ten) indicates 'Worst pain'. We used one µg/kg fentanyl injection intraoperatively to overcome tourniquet pain if VAS >3 and the fentanyl dose was documented. We used diclofenac sodium 75 mg intramuscularly for postoperative pain (POP) when VAS was >3 and total amounts of diclofenac used in the initial 24 hours was recorded.

Satisfaction of the patients about anesthetic procedure was assessed postoperatively and recorded

and graded as follows: (I) poor, (II) moderate, (III) good, (IV) excellent.

Any adverse events as GIT changes (emesis), hemodynamic changes (increase or decrease in heart rate or blood pressure), respiratory changes (respiratory depression, hypoxemia, bradypnea, and tachypnea), headache, dizziness, tinnitus, sedation, and hallucination were recorded during the operation and every hour postoperatively for 12 hours.

The primary outcome was to know the start of tourniquet pain experienced by patients. Secondary outcomes were onset of nerve block, first analgesic request intraoperatively and postoperatively, overall analgesia consumption dosage, full time of motor and sensory blockade, hemodynamic changes, and adverse effects.

Sample size:

A previous G-power analysis was performed for sample size calculation. A power of eighty percent was measured with type I error of 0.05 to obtain the analgesic differences between groups of about thirty percent to yield an overall sample size of 95 patients.

In order to get more accurate results (overcome five percent dropout) we conducted the current study on a total of 100 cases (25 patients in each group).

Ethical approval:

The Ethical Committee of Sohag University's Faculty of Medicine granted the study approval. All participants signed an informing consent following a complete explanation of the study goals. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS V 22 for Windows®. Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Quantitative data were expressed as mean ± SD (Standard deviation). Qualitative data were expressed as number (%) and were compared by chi square test. Quantitative data were presented as mean and standard deviation, if parametric, and were compared by ANOVA test with post-hoc test (LSD), or as as median and range, if nonparametric, and were compared by Kruskal–Wallis test. P value <0.05 was considered to be significant.

RESULTS

In our study, as regard to age, sex, weight, and ASA classification there were no statistically significant changes between the groups (Table 1).

Table (1): Patients age, sex, weight, and ASA class data

Items	Group L (n=25)	Group LP (n=25)	Group LK (n=25)	Group LN (n=25)	P value
Age (years)	42.3 ± 6.3	43.46 ± 5.2	40.6 ± 7.6	44.5 ± 3.8	> 0.05
Sex (M/F)	12/13	10/15	11/14	9/16	> 0.05
Weight (kg)	77.4 ± 4.2	73.2 ± 5.1	75.3 ± 9.4	76.8 ± 10.2	> 0.05
ASA class (I/II)	20/5	21/4	19/6	18/7	> 0.05

Values mentioned as mean ± SD ot ratio. M/F: male/female.

There was no statistically significant changes in between the four groups as regard to the tourniquet time and duration of surgery (Table 2).

Table (2): Data of tourniquet pain and duration of surgery

Items	Group L	Group LP	Group LK	Group LN	P value
Tourniquet time (min)	52.3 ± 12.2	50.4 ± 14.2	54.8 ± 10.8	56.1 ± 11.4	> 0.05
Duration of surgery (min)	3.5 ± 14.1	41.7 ± 11.7	45.6 ± 12.6	47.8 ± 13.7	> 0.05

Values are expressed as mean ± standard deviation.

As regard to hemodynamic changes (heart rate and MAP); there was no statistically significant difference between the four groups either preoperatively, intraoperatively, or postoperatively (Figure 1, 2). Also, the same finding was shown with oxygen saturation in all groups (Figure 3).

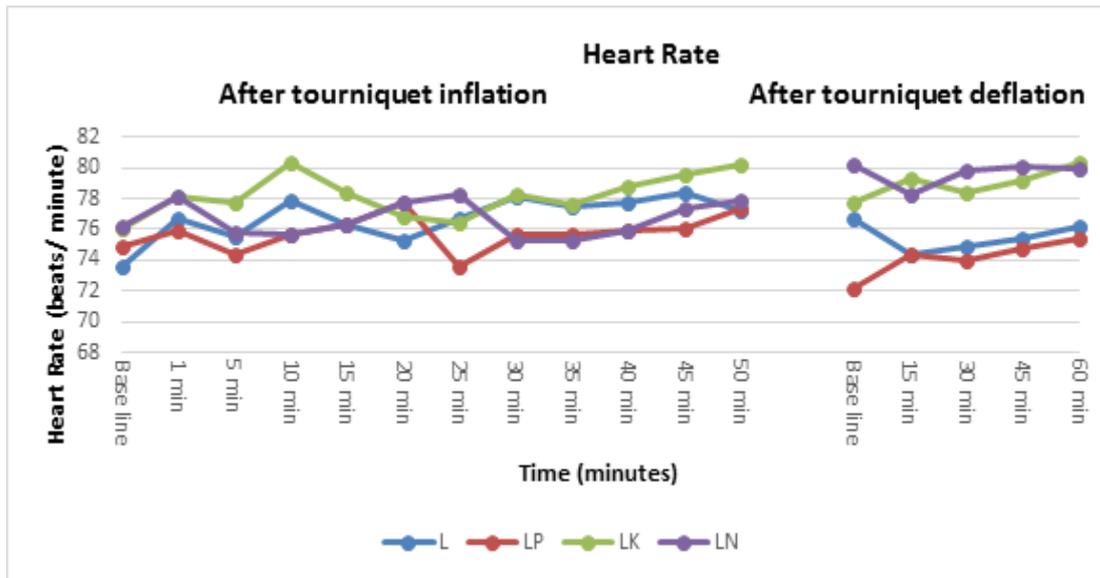


Figure (1): HR changes among the studied groups.

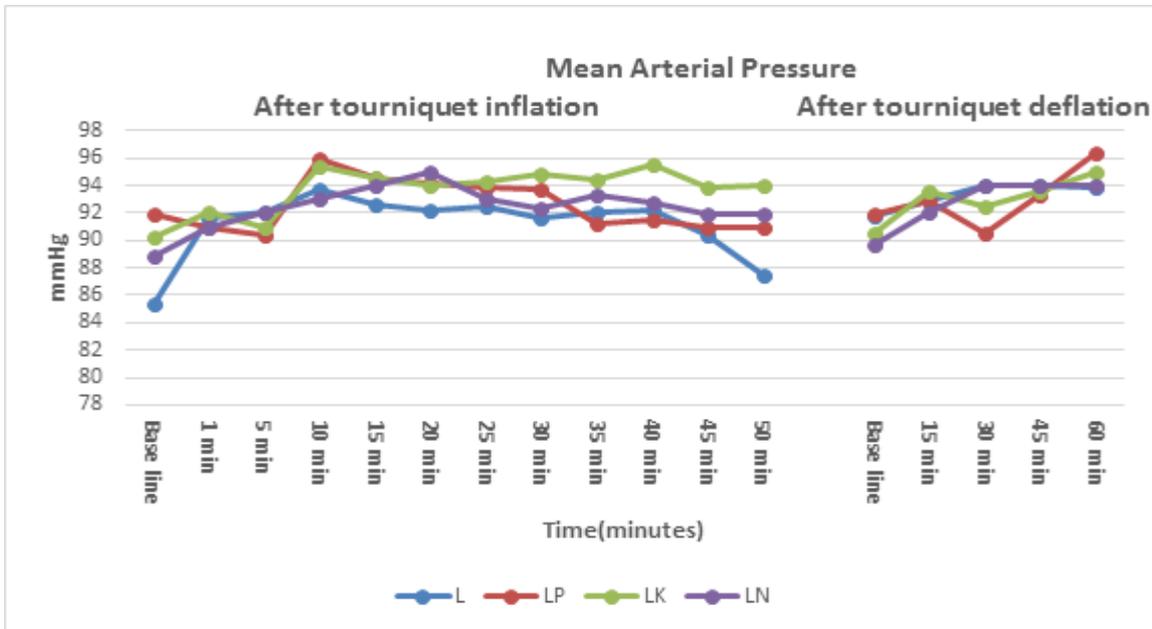


Figure (2): MAP changes in the four groups.

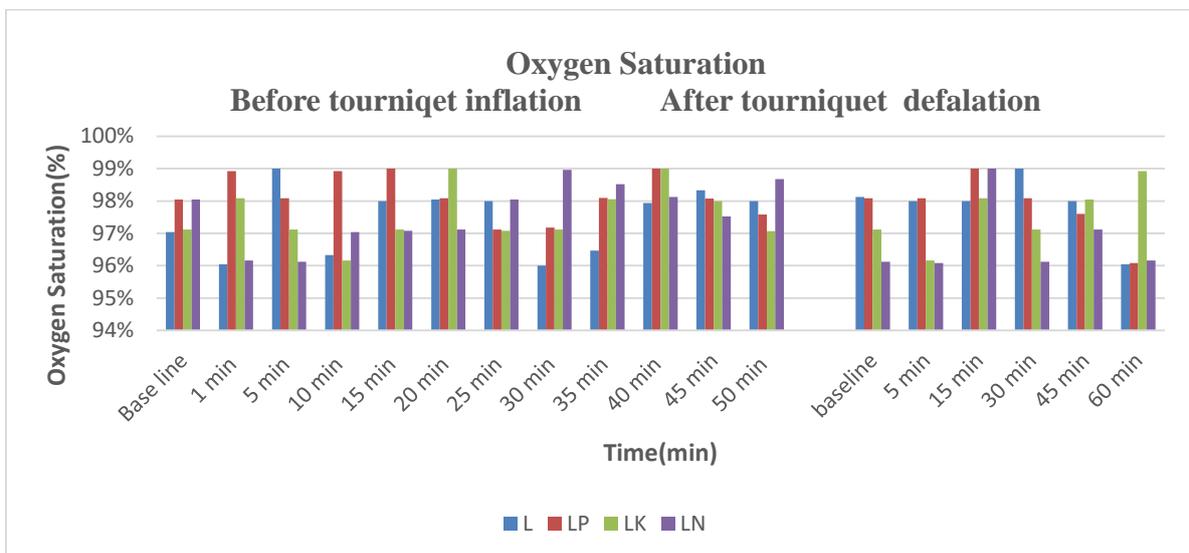


Figure (3): Changes in the oxygen saturation between the groups

As regard to the onset time for sensory block; they were statistically significantly earlier in groups LP, LK, and LN (5.1 ± 1.3 , 4.5 ± 1.1 , and 3.1 ± 1.4 min respectively) than group L (6.4 ± 1.4 min). Also the same with onset of motor block, which occurred earlier in groups LP, LK, LN (8.2 ± 3.6 , 7.4 ± 2.1 , and 3.8 ± 1.8 min respectively) than group L (9.7 ± 2.3 min). But with regard to the sensory and motor block durations they were longer in groups LP, LK, and LN groups than group L. We also found that the sensory and motor block onset times occurred earlier in group LN than in groups LK and LP. In groups LP, LK, and LP we found no statistically significant difference as regard to the durations of sensory and motor (Figure 4).

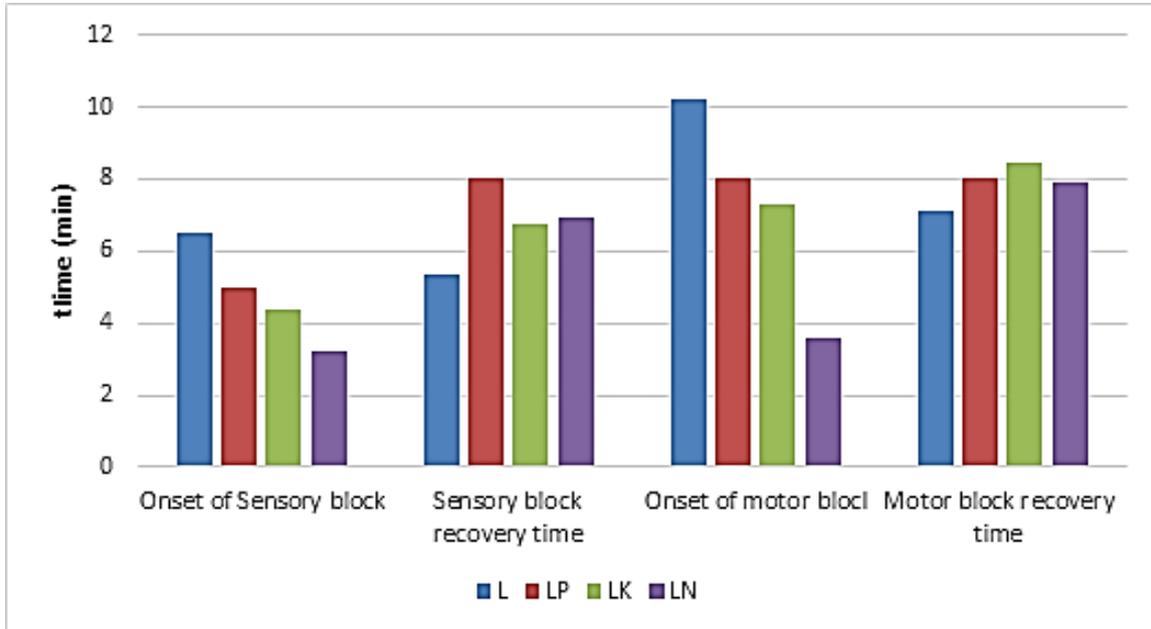


Figure (4): Data of sensory and motor changes among the studied groups

At the start of surgery no patient experienced any pain at time of incision in all the studied groups. The fentanyl amount needed to overcome tourniquet pain was less in groups LP, LK, and LN than group L. Fentanyl was needed to relief tourniquet pain in more cases in group L than in the other groups. The time for first fentanyl administration to overcome tourniquet pain was longer in the groups LP, LK, and LN than group L and also it was found to be more longer in group LK than groups LN and LP. The amount of diclofenac used for POP relief was lower in the groups LP, LK, and LN than in group L (Table 3).

Table (3): Intraoperative and postoperative analgesia

Items	Group L	Group LP	Group LK	Group LN	P value
No. of patients requiring pain relief for tourniquet pain	20/25	9/25	12/25	8/25	<0.05
Amount of intraoperative fentanyl (ug)	124.8 ± 15.1	86.3 ± 15.3	81.3 ± 13.4	90.6 ± 12.7	< 0.05
Onset of fentanyl (min)	16.1 ± 6.8	26.9 ± 5.7	40.1 ± 6.4	29.8 ± 7.2	< 0.05
Postoperative diclofenac dose (mg)	25.3 ± 53	69.5 ± 43.2	63.1 ± 38.6	60.8 ± 42.7	< 0.05

Values were shown as mean±SD or as ratios

As regard to visual analogue score (VAS) for assessment of tourniquet pain intraoperatively; we found that VAS was statistically significantly higher at all times of assessment at 10, 20, 30, 40, 50, and 60 min in group L than the other groups. Also, VAS was demonstrated to be statistically significantly higher in groups LN and LP in comparison with group LK after 30 and 40 minutes of tourniquet inflation. In the postoperative period VAS had statistically significantly higher scores for the initial 4 hours in group L in comparison with the other groups (Figure 5).

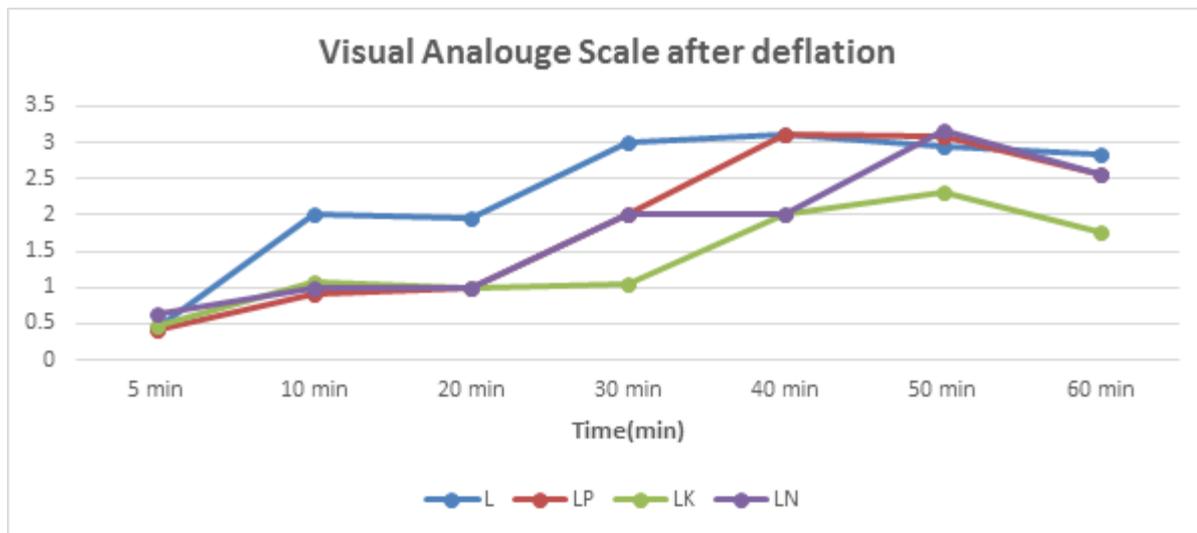


Figure (5): Visual analogue scores for all groups of the study

On assessing patient satisfaction for this type of block, this study showed statistically significant higher satisfaction in groups LP, LK, and LN when compared with Group L (Table 4).

Table (4): Patient satisfaction

Item	Group L	Group LP	Group LK	Group LN	P value
Patient satisfaction	2 (2-3)	3 (3-4)	4 (3-4)	3 (3-4)	< 0.05

Values are shown as median (range)

All patients in the four groups completed the study under Bier block without conversion to general anesthesia and no side effects were recorded.

DISCUSSION

Bier block has already lost some of its luster and brilliance as a regional anesthetic for limb surgeries due to its undesirable effects, such as delayed onset, tourniquet pain, and a swift loss of analgesia following the tourniquet deflation, but the addition of certain medications to the local anesthetic enhances the block's effectiveness and lessens these undesirable effects⁽¹⁴⁾.

During upper limb procedures distal to the elbow, our study examined the effects of adding paracetamol, ketamine, or nitroglycerine to lidocaine during the Bier block technique. Our findings demonstrated that the use of these adjuvants decreased tourniquet discomfort and postoperative analgesic use, enhanced the quality of the nerve blocks, shortened the time before the first patient requested analgesia after surgery, and had no negative side effects. However, our study also demonstrated that ketamine was more effective than NTG and paracetamol at reducing tourniquet pain, as evidenced by the longer time it took for patients to request their first analgesic to relieve tourniquet discomfort and the lower intraoperative VAS score.

However, we discovered that NTG was superior to ketamine and paracetamol in that it sped up the period before sensory and motor blocks appeared. This finding can be attributed to NTG's vasodilator effect, which enables lidocaine to reach the nerves more quickly⁽¹⁴⁾.

Regarding paracetamol, it has relatively little anti-

inflammatory impact since it is a weak inhibitor of prostaglandin formation⁽¹⁵⁾. Many research have proposed paracetamol's analgesic modes of action, which explain both its central and peripheral effects. The inhibition of nitric oxide (NO) production, as well as the inhibition of hyperalgesia brought on by either N-methyl-D-aspartate (NMDA) or substance P^(16,17), as well as the effect on cannabinoid receptors, can be used to explain these suggestions. It was shown that cannabinoid receptor (CB1) antagonists, such as CB1 and CB2 receptor antagonists, completely eliminated the analgesic action of paracetamol⁽¹⁸⁾. The results of a study carried out by **Canbay et al.**⁽¹⁹⁾, are similar to ours in that paracetamol has a peripheral analgesic effect, also showed that iv paracetamol reduced the discomfort during the injection of propofol.

Since its mode of action is a noncompetitive blocking effect of NMDA receptor, ketamine has significant roles with regard to pain management by preventing central sensitization that results from peripheral nociceptive stimulation and reducing hypersensitivity⁽²⁰⁾.

In a study carried out by **Durrani et al.**⁽²¹⁾, the researchers utilized diluted ketamine (0.6 mg/kg) as the sole anesthetic solution for Bier blocks to demonstrate its peripheral analgesic effects. They discovered that while this approach completely blocked sensory and motor functions, it also resulted in undesirable side

effects (hallucinations and disorientation) after the tourniquet was deflated.

Opoda et al. ⁽²²⁾ recorded that the addition of ketamine 50 mg to lidocaine for Bier block has shortened the onset of both sensory and motor blocks and increased their durations as well as it prolonged the time of first tourniquet pain sensation with better analgesia postoperatively. This agrees with our findings as well, even though their values are comparable to ours.

Elmetwaly et al. ⁽²³⁾ findings, which match with our work, showed that adding ketamine to lidocaine during Bier block resulted in a reduction in tourniquet discomfort at a dose of 0.1 mg/kg (our study utilized a dosage of 60 mg), and they observed no neurological effects following the deflation of the tourniquet.

Nitric oxide (NO) increases cellular levels of cyclic guanosine monophosphate (cGMP) inside the cells, which in turn affects how the CNS and PNS respond to pain ^(23,24). Moreover, when given topically, NO inhibits hyperalgesia and blocks the neurogenic element of inflammatory oedema, which has anti-inflammatory and analgesic effects ⁽²⁵⁾. The metabolism of nitroglycerine (NTG) within cells results in the production of NO, and this is how it works as an analgesic.

Several researches findings about the function of NTG as an adjuvant in the Bier block agreed with our findings, however they utilized a dose of 200 ug whereas we used 150 ug to achieve the same effects. When compared to the use of lidocaine alone, they discovered that adding NTG 200 ug to the Bier block accelerated the onset of the sensory and motor blockade and occurred earlier, increased the duration of the sensory and motor block, decreased the VAS of tourniquet pain and POP, prolonged the time of first analgesic request, and also decreased the postsurgical analgesic consumption without the occurrence of any adverse events ^(8,13,23).

Ewieda et al. ⁽²⁶⁾ findings, declared that the addition of NTG to LA (lidocaine 3 mg/kg versus 1.5 mg/kg) during the Bier block resulted in a quicker start to surgery and less need for intraoperative and postoperative analgesics, are consistent with our investigation. The claimed better anesthetic outcome was unaffected by reducing the LA dose.

In agreement with our findings, multiple studies found that ketamine was superior to NTG and paracetamol in reducing tourniquet pain, which was demonstrated by the patients' requests for their first analgesics lasting longer and their lower intraoperative VAS scores ^(8,12,23,27).

In our study we found that paracetamol supplementation to lidocaine during Bier block lowered the tourniquet pain, the analgesic requirements during and after surgery, and the intraoperative VAS when compared with lidocaine alone.

In agreement with our study; **Ko et al.** ⁽²⁸⁾ compared paracetamol (300 mg) versus ketorolac (10

mg) addition to lidocaine during Bier block. They found an earlier onset of sensory block in paracetamol group than ketorolac group, reduced intraoperative analgesia need, and lowered intraoperative and postsurgical VAS than the control group. But their results reported that the onset time of 1st tourniquet pain was (34.6 ± 7.8 min), which is longer than our results (26.9 ± 5.7 min) and also the amount of fentanyl in their study was (22 ± 28.7 ug), which is less than ours (65.3 ± 15.3 ug), which can be attributed to larger dose of paracetamol (300 mg) in their study than ours (100 mg) and this also revealed that the analgesic efficacy of paracetamol is dose dependent.

Also, in agreement with our study **Abdelrady et al.** ⁽²⁹⁾ concluded that paracetamol supplementation to lidocaine in Bier block reduces tourniquet pain and lowers VAS score and the analgesic consumption throughout and after elective hand surgical approaches were decreased too.

On the opposite side our findings did not match with a study done by **Akdogan and Eroglu** ⁽³⁰⁾ who demonstrated that the supplementation of acetaminophen and dexketoprofen to the lidocaine in Bier block does not add any statistically significant difference.

A study conducted by **Abdel-Rahman et al.** ⁽³¹⁾ compared various dosages of paracetamol (100, 200, and 300 mg) during Bier block and they concluded that doses of 200 and 300 mg when added to lidocaine during Bier block provided statistically significant shorter onset of sensory and motor blocks, longer duration of their recoveries, longer duration of analgesic request, and lower amount of analgesic consumption when compared with dose of 100 mg. they recommended that actaminophen 200 mg could be utilized appropriately as an adjuvant to lidocaine during Bier block and no need for the increased dose to 300 mg. On the other hand, in our study we used a concentration of 100 mg.

CONCLUSION

We came to the conclusion that adding either paracetamol, ketamine, or nitroglycerine to lidocaine during a Bier block shortens the time it takes for anesthesia to start and improves its quality, lessens tourniquet pain, and reduces the need for intraoperative and postoperative analgesics without having any noticeable side effects.

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