Comparison between the Use of bupivacaine 0.5%alone and bupivacaine 0.5% with nefopam 20mg in sciatic n block (popliteal approach) and femoral n block in patients undergoing below knee surgery

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ABSTRACT

Objective : Sciatic nerve block (popliteal approach) and femoral N block is a new technique other than general anesthesia in below knee surgery because it provides adequate muscle relaxation, with good intraoperative and post-operative analgesia. Nefopam is non opioid, non-respiratory depressant and non-sedative was mixed with local anesthetics drug to study the effects. This study was done to compare the onset and duration of sensory and onset time and duration of action of motor block following administration of either bupivacaine alone with administration of bupivacaine and Nefopam in patients undergoing below knee lower limb surgeries under ultrasound guided regional anesthesia.

Methods: 100 patients with American society of anesthesiologists (ASA) 2 / 3/4 patients between 25 and 85 years who underwent elective and emergency lower limb surgeries randomly allocated into two group, each group has 50 patients by a sealed envelope technique to receive 20 ml of 0.5% Bupivacaine with 2 ml of normal saline in Group BS and 20 ml of 0.5% Bupivacaine with 2ml (20mg) of Nefopam in the second group (Group BN). The onset time, duration time of both sensory and motor blocking were seen and compared between the two groups.

Results : The onset time of both sensory and motor blockade was shorter in Group BN (bupivacaine with nefopam) when compared to Group BS (bupivacaine and normal saline) ($p<0.0001$). The duration of both sensory and motor blockade was longer in Group BN when compared to Group BS ($p<0.0001$). There were no significant hemodynamic changes (PR, BP,SPO2) in both groups. Also there is no any side effect or any complication.

Conclusion Nefopam when mixed with Bupivacaine in Sciatic nerve block and femoral nerve block in below knee surgeries shortens the onset time and prolongs the duration of action of both sensory and motor blockade without any systemic side effects and give excellent intra and postoperative analgesia.

Keywords: Sciatic N block, femoral N block, bupivacaine, nefopam, lower-limb surgeries

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Introduction

Elective and emergency surgeries of lower limbs were used to be done under general anesthesia and sometime under spinal anesthesia. General anesthesia usually has its own adverse side effects and its complication especially in high risk patients which include difficult intubation , aspiration ,bronchospasm, laryngospasm and sometime patient needed to be admitted to RCU for ventilator support .Spinal anesthesia also has its own morbidity and mortality especially in cardiac compromised patients like hypotension , bradycardia, postdural puncture headache……etc .So anesthesiologists in last two decades started to do these surgeries under regional anesthesia because it is safe for the patient.Befor the advent of ultrasound devices anesthesia doctors were used to do regional anesthesia using landmarks ,but nowadays after advent of ultrasound devices has revolutionized the results and efficacy of regional anesthesia .ultrasound guidance (USG) regional anesthesia has many advantage and more superior to land marks regional anesthesia because it has more successful rate ,less failure rate ,less dose of anesthetic drugs to be used and put around the nerve and hence less side effects,less chance of trauma to surrounding structures like femoral A ,femoral V,popliteal A, popliteal V ,femoral N and sciatic N so there is less chance to systemic local anesthetic drugs toxicity. In addition USG regional anesthesia has shortened the time between the start of anesthesia and the start of surgery .Bupivacaine is a long-acting local anesthetic drug, commonly used in sciatic n and femoral N blocks. Its effects last from 2 to 4 hours (1(. This will provide intra operative

anesthesia but may be insufficient to provide post- operative analgesia. Postoperative pain causes the patient to demand rescue analgesia commonly provided by opioids and no steroidal anti-inflammatory drugs. Prolonging the effect of bupivacaine can help the patients to avoid the need for this medication (opioids and NSAID) and so avoiding the side effects of the intravenous analgesic drugs. So many trials had been done throughout the world to mix bupivacaine with other agent to prolong its duration of action and potency and various drugs have been used to prolong peripheral nerves block. These include epinephrine (2(, clonidine which is alpha 2 agonist (3) and dexmedetomidine (4) midazolam(dormicum) (2) and dexamethasone (5).

Nefopam is derivative of benzoxazocine which is non sedative tranquilizer which discovered in 1960 and was known as fenazocine at that time .from the structural formula of nefopam, we understand that fenopam is a cyclized analogue of orphenadrine, diphenhydramine (allermine) and tofenacin(the difference between these compounds is the presence of 1 or 2 carbone atoms0 (6) (7) (.Benzoxazocine system is the structural ring system of nefopam (6). Its trade name is acupan which is available as ampules or capsules and can be given orally or intravenous or intramuscular. Till now nobody know the mechanism of action of nefopam but it acts at spinal and supraspinal center (in the brain) by three mechanisms;

1- Nefopam is triple neurotransmitter (serotonin, norepinephrine, and dopamine) reuptake inhibitors like antidepressants (8(.
2- Nefopam inhibit calcium influx by inhibition of long term excitation mediated by NMDA like anticonvulsants (8) (9)
3- Nefopam act by blocking voltage sensitive sodium channels like carbamazepine. (8((9(.

Because of the above mechanisms, nefopam has been used in the following situation:

1-It has been mainly as an analgesic drug for nociceptive pain.

2-It has been used in moderate and severe postoperative pain.

3-It has been used in neuropathic pain (9).

4-It has been used in prevention and management in intra and postoperative shivering (10) (11).

5-It has been used in treatment of hiccup (12).

6-It has been used as antihyperalgesia through modulation of glutamatergic transmission (8).

Nefopam can be given orally in dose 100-180 mg per day in 4-6 dividing dose ,intravenously as single dose 20 mg slowly over 15-20 minutes or with continuous infusion of 60-120 mg per day and can be given intramuscular. Nefopam has low tissue bioavailability(1(,it reach effective plasma concentration after .After absorption it is 70%protein bound(1(,it is metabolized in the liver by N-demethylation,part of it metabolized by other routs(1(.Its half-life is 3-6 hours, Its active metabolite(desmethylnefopam) has half-life about 0-15 hours.Nefopam usually excreted mainly by kidney and in small amount in feces (1).

Like any drug nefopam has many side effects which includedizzness,sweating,nausea,drh mouth,nervousness,headache and urinary retention.Sometime nefopam cause less common side effects like blurred vision,insomnia,convulsion,confusion,hallucination,tachycardia,exaguration of angina symptoms and rarely erythema multiformi (benign and transient pinkish discoloration of skin. But as usual these side effects are less in oral and intramuscular routs of administration.

Overdose of neopam usually cause convulsion, hallucination, hyperdynamic circulation, hypertension and tachycardia which can be treated by supportive methods,managing cardiovascular complication with B blockers and using of activated charcoal to decrease the absorption from the bowel (13) (.Sometime nefopam overdose cause death (13) (but fortunately it is less common than with opioid narcotic drugs(14(.

If we compare the potency and efficacy of nefopam to potency of morphine,20 mg of nefopam is equal to 12 mg of morphine in analgesic effects or equivalent to oxycodone, so it is less effective analgesic than morphine with fewer side effects.Nefopam does not produce respiratory depression and has less incidence of drug abuse or addiction than morphine so it is

used either as alternative choice to morphine or other narcotic drugs, or can be used as an adjunctive therapy for use with opioids to reduce the respiratory depression and abuse of opioids(15(.One study show that nefopam Is more potent as analgesic drug than aspirin (acetyl salicylic acid) [7]

Nefopam is contraindicated in convulsion, epilepsy, myocardial infarction, patients with depression who are on irreversible monoamine oxidase inhibitor (isocarboxazid,tranylcypromine and phenelzine) and in patients with depression on tricyclic antidepressant because of serotonine syndrome or hypertensive crisis.

Nefopam is also contraindicated in patients who are on anticholinergic and sympathomimetic drugs because nefopam has anticholinergic and sympathomimetic effects (13(.

Methods

This randomized controlled double blind trial was done in medical city teaching hospital and Alkindi teaching hospital Baghdad from January 2019 up to January 2020 on 100 patients scheduled for below knee elective and emergency operation like foot, ankle, leg and below knee amputation operation. All those patients underwent USG sciatic n block popliteal approach and USG femoral n block. Patients were subdivided into the following two groups:

1/first group called BS who injected with 20 ml bupivacain0.5%for sciatic n block 10 ml of bupivacaine 0.5%for femoral n block with 2ml normal saline (This is the control group).

2/second group called BN who received 20 ml bupivacain0.5%for sciatic n block 10 ml of bupivacaine 0.5%for femoral n block with 2ml nefopam 20 mg (this is the study group).

Both the patient and the resident anesthesia doctor were blind about the technique in this prospective trial. We explained the procedure, the result and possible complication of this block to the patients and were admitted to the theater after signing the surgical consent .In the theater two venous lines were inserted and glucose saline started ,full monitoring(ECG,PR,BP,SPO2)was done .Under supine position and under aseptic technique we use ultrasound EZONA 3000 device linear probe ,and echogenic needle either 10 or 12 CM length, and we inject 20 ml bupivacaine 0.5%for sciatic n(popliteal approach) and 10 ml bupivacaine 0.5% for femoral n block with 2ml normal saline in first BS group, and we inject 20 ml bupivacaine 0.5%for sciatic n(popliteal approach) and 10 ml bupivacaine 0.5% for femoral n block with 2ml nefopam 20 mg in second BN group,

Sensory block was assessed by pinprick test using a 3-grads scale as follows:

If patient feel sharp and severe pain=0

If patient feel dull pain or dull sensation=1 this is called analgesia.

If patient feels no sensation =2 and this is called anesthesia.

Motor function was done by: hip flexion which is function of femoral nerve, flexion of knee joint which is function of sciatic nerve, foot eversion which is function of common pernoeal N. and inversion of foot which is function of tibial nerve. Motor assessment was done by using three grades scale as follow:

If patient has normal movement of all joints=0.

If patient has reduced strength of movement but he can move his toes=1.

If patient cannot move any toe =2.

Sensory and motor block was assessed every 5 min until 1hour after injection, and then every 1 hour after the surgery, until the anesthesia and motor weakness had been resolved. Onset time of sensory block was defined as the time interval between the end of local anesthetic injection to complete and full sensory block. Complete sensory block equal to score 2 on all nerve territories. Duration of sensory block was defined as the time period between the start of full sensory block and the complete resolution and disappearance of effect of anesthesia on all nerves territories. Onset of motor block (MB onset) was defined as the time interval between the end of giving all anesthetic drug to complete loss of movement (score 2). Duration of motor block (MBduration) was defined as the time period between the start of full motor block to the recovery of complete motor function of the hip and knee joints.

Heart rate (HR), systolic arterial BP, and diastolic arterial BP were recorded every 15 minutes. Adverse events such as hypotension were defined as decrease in systolic BP by 20% from baseline values.

Pain was assessed using a visual analog scale (VAS) (0–10). Nursing staff administered intramuscular diclofenac 75 mg when VAS >5. .Level of sedation was assessed by using Ramsay sedation scores as explained below:

1 anxious and agitated or restless or both
2 cooperative, oriented and quiet
3 respond to commands and orders
4 Brisk response to light forehead tap or light auditory stimulus
5 Sluggish response to light forhead tap or loud auditory stimulus
6 No response at all.

3. Sample size:

As in any statistical analysis of any research, we consider the confidence level is 95% (o.95) and we consider the confidence interval +-10% (0.1),so the width of margin of error is 20% (0.2) so E=o.1.From the table of Z scores ,we found 0.95 or o.475 are represented with 1.96 so this is the Z score.

In our trial we do not know how much percent of patients who underwent below knee surgery received bupivacaine alone or in combination with nefopam ,so we assume that 50% of total patients in Iraqi population who did below knee surgery underwent USG sciatic and femoral nerve block with bupivacaine and nefopam ,so p=50% (0,5).

The q value equal to 1-p,q=1-p,q=1-o.5=o.5 .If we multiply p with q the result will be 0.5*0.5=0.25.Now we divide Z value by E so 1.96/0.1=19.6.Now we square this value 19.6*19.6=384.16 Now we multiply this value with pq ,this mean that about 96 patient at least must be enrolled in our study. We enrolled 100 patients (50 patients per each group) because of possibility that some patient will be dropped out from the study.

. 4. Statistical analysis:

After collecting all data about onset &duration of both sensory &motor block, we use statistical package for social sciences (SPSS version 2019) to get the results. The results were presented as mean+-standard deviation. We use the unpaired t-test from compare means list to compare means of the data and variables between both groups (BS & BN).We use p value less than 0.05 as of statistical significance.

5. Results:

The data obtained were analyzed and the observations and results are summarized in the following tables:

The intraoperative mean pulse rate, systolic BP, and diastolic BP were comparable between the two groups at all points of observation. The difference in the two groups was found to be statistically no significant

Group Statistics

	1=BS 2=BF	N	Mean	Std. Deviation	
age	1.00	50	57.8000	20.10178	
	2.00	50	53.6400	20.47374	
1 male 2 female	1.00	50	1.4800	0.50467	
	2.00	50	1.5000	0.50508	
weight	1.00	50	71.9200	11.32244	
	2.00	50	73.6000	11.78203	
ASA	1.00	50	2.8600	0.75620	
	2.00	50	2.8800	0.79898	
SB onset	1.00	50	12.1200	1.76866	
	2.00	50	8.0800	0.69517	
SB duration	1.00	50	274.8000	20.12613	
	2.00	50	448.8000	23.61598	

MB onset	1.00	50	13.2000	1.38505	
	2.00	50	9.1200	0.71827	
MB duration	1.00	50	247.8800	18.85567	
	2.00	50	398.0000	22.94625	

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed) P value	Mean Difference	Std. Error Difference	Lower	Upper
age	Equal variances assumed	.005	.947	1.025	98	0.308	4.16000	4.05772	-3.89242	12.21242
	Equal variances not assumed			1.025	97.967	0.308	4.16000	4.05772	-3.89245	12.21245
1 male 2 female	Equal variances assumed	.079	.780	-.198	98	0.843	-.02000	.10097	-.22038	.18038
	Equal variances not assumed			-.198	98.000	0.843	-.02000	.10097	-.22038	.18038
weight	Equal variances assumed	.334	.565	-.727	98	0.469	-1.68000	2.31090	-6.26591	2.90591
	Equal variances not assumed			-.727	97.845	0.469	-1.68000	2.31090	-6.26600	2.90600
ASA	Equal variances assumed	.339	.562	-.129	98	0.898	-.02000	.15558	-.32874	.28874
	Equal variances not assumed			-.129	97.705	0.898	-.02000	.15558	-.32875	.28875
SB onset	Equal variances assumed	47.352	.000	15.032	98	0.000	4.04000	.26875	3.50667	4.57333
	Equal variances not assumed			15.032	63.787	0.000	4.04000	.26875	3.50307	4.57693
SB duration	Equal variances assumed	4.342	.040	-39.653	98	0.000	-174.00000	4.38811	-182.70806	-165.29194
	Equal variances not assumed			-39.653	95.597	0.000	-174.00000	4.38811	-182.71080	-165.28920
MB onset	Equal variances assumed	19.940	.000	18.491	98	0.000	4.08000	.22065	3.64213	4.51787
	Equal variances not assumed			18.491	73.578	0.000	4.08000	.22065	3.64031	4.51969
MB duration	Equal variances assumed	1.423	.236	-35.742	98	0.000	-150.12000	4.20016	-158.45508	-141.78492
	Equal variances not assumed			-35.742	94.451	0.000	-150.12000	4.20016	-158.45900	-141.78100

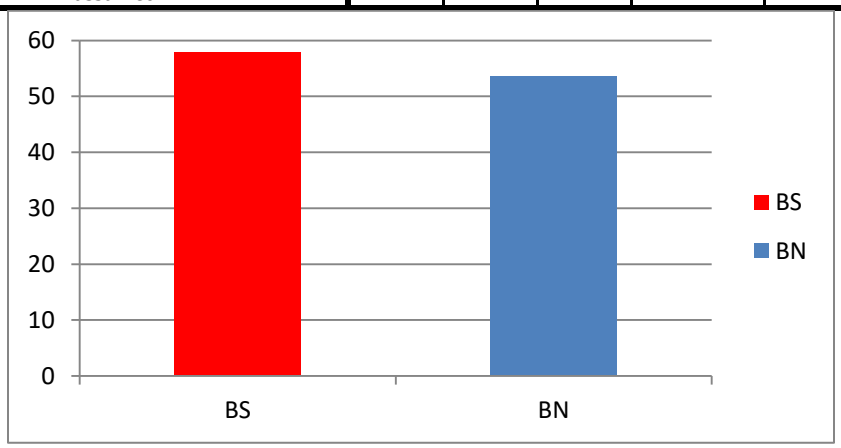


Figure (1) Bupivacaine with normal saline versus bupivacaine with nefopam in term of age in years, there is no significant statistical difference (p=0.154)

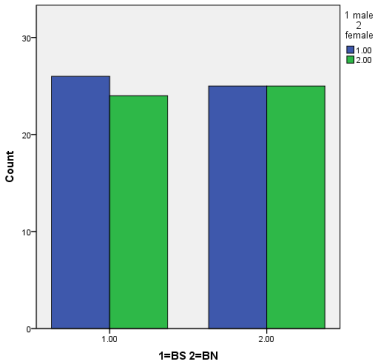


Figure (2) Bupivacaine with normal saline versus bupivacaine with nefopam in term of gender, there is no significant statistical difference (p=0.421).

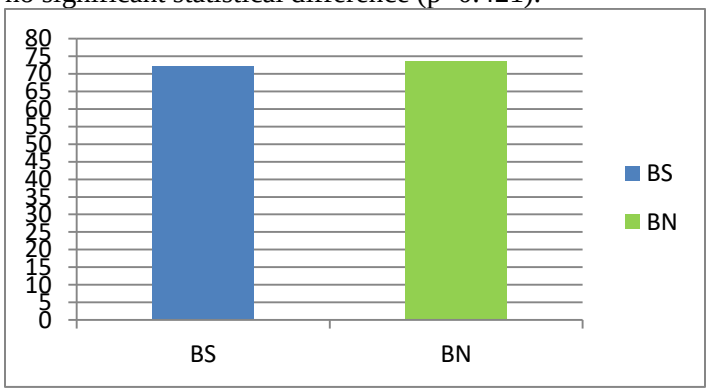


Figure (3) Bupivacaine with normal saline versus bupivacaine with nefopam in term of weight in kilogram, there is no significant statistical difference (p=0.234).

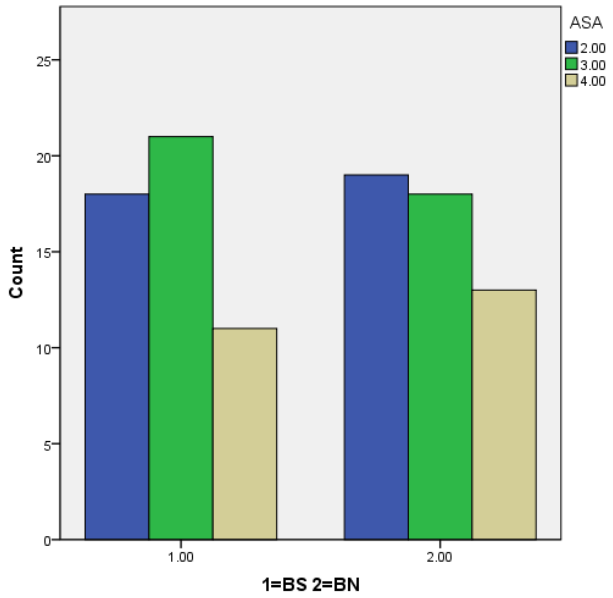


Figure (4) Bupivacaine with normal saline versus bupivacaine with nefopam in term of American society of anesthesiologists (ASA), there is no significant statistical difference (p=0.449).

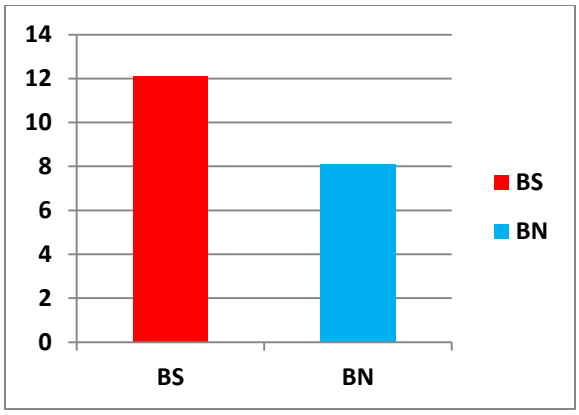


Figure (5) Bupivacaine with normal saline versus bupivacaine with nefopam in term of sensory block onset in minutes, bupivacaine with nefopam show significant statistical difference ($p<0.001$).

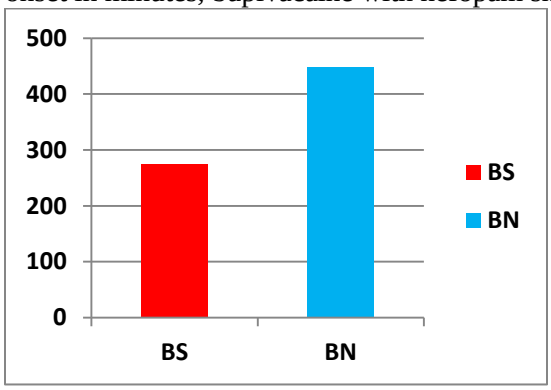


Figure (6) Bupivacaine with normal saline versus bupivacaine with nefopam in term of sensory block duration in minutes, bupivacaine with nefopam show significant statistical difference ($p<0.001$).

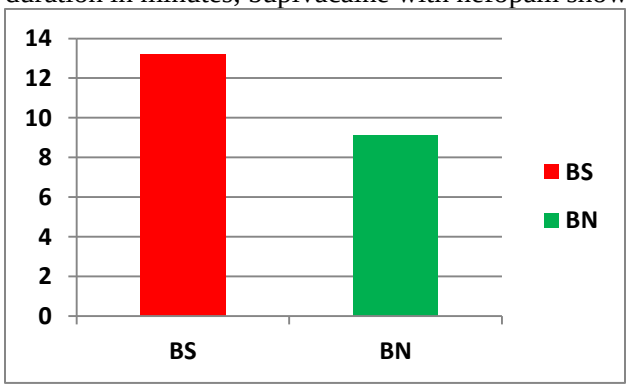
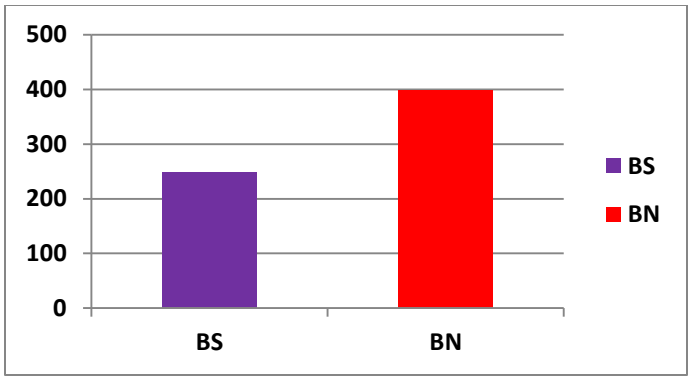


Figure (7) Bupivacaine with normal saline versus bupivacaine with nefopam in term of motor block onset in minutes, bupivacaine with nefopam show significant statistical difference ($p<0.001$).



Figure(8) Bupivacaine with normal saline versus bupivacaine with nefopam in term of motor block duration in minutes, bupivacaine with nefopam show significant statistical difference (p<0.001).

Discussion:

As we mentioned that The duration of action of bupivacaine when used in any peripheral nerve block is 2-4 hours, which sometime do not cover the duration of surgical operation, in addition to that bupivacaine do not give proper surgical anesthesia , proper muscles relaxation and postoperative analgesia. .So many trials have been done throughout the world to mix bupivacaine with any drug to prolong it duration of action and intensify its block.

According to my knowledge this trial is a rare trial in which we mix bupivacaine with nefopam, so I will depend in our disscussion on other trials in which they add other additive drug (like dexamethasone, clonidine, magnesium sulphate …etc) to prolong the sensory and motor block duration of bupivacaine.

In our study, the mean of sensory block duration was 274.8+-20.12 min in Group BS and 448.8 ± 23.61 min in Group BN. This difference was highly statistically significant with P < 0.0001. The mean duration of motor block was 247.88 ± 18.85 min in Group BS and 398.00 ± 22.94 min in Group BN. This too was found to be highly statistically significant with P < 0.0001.

I and my colleagues did controlled double blind study in which we add dexamethasone to bupivacaine in USG brachial plexus block, supraclavicular approach, in patients underwent upper limb surgeries. We found that dexamethasone prolong the duration of both sensory and motor block. We found dexamethasone prolong the duration of sensory block from 289.5 minutes in control group to1160 minutes in dexamethasone group and increase the motor block duration from 216.27 minutes in control group to 870.87 minutes in dexamethasone group.(16(

The result was similar to study done by Shwetank Rai and his colleagues who did their trial on 60 patients , 30 patients received bupivacaine alone and 30 patients received bupivacaine with dexamethasone. They found that dexamethasone increase the duration ofsensory block ftom 289 to1160minutes and that of motor block from216 to870.8 minutes and shorten the onset of sensory block from 8.4 to 6.4 minutes and that of motor block from 17 to14 minutes.(17(

The hemodynamic parameters such as heart rate (HR), systolic BP, and diastolic BP were stable in both groups in our study. This was similar to the results of the study conducted by El-Abrade and Elshmaa.(2(,who also found that all parameters (PR,BP,SPO2) are similar in both groups.

Similar results were also seen in a study by Vieira et al. (2008)(5(who in a randomized study evaluated the effect of dexamethasone on analgesia with 0.5% bupivacaine with epinephrine and clonidine. The median sensory block duration was 1457 in dexamethasone group and that of control group was 833 min and the p value (P < 0.0001) while motor block duration was 1374 in dexamethasone group versus 827 min (P < 0.0001) when compared with the control. These results though similar are slightly higher than ours. This difference

could be due to the added vasoconstrictive effects of epinephrine and also due to the addition of clonidine.

The results of our trial are contrary to results of study conducted by Moffat AC, Kenny GN, Prentice JW

They did comparison study on 48 patients who underwent upper abdominal surgery with ASA of 2-3.They compared the morphine sparing effect of both nefopam and diclofenac (voltarine) when used singly or in combination on postoperative pain. They divided the patients into three groups , group A who received nefopam injection 20 mg every 6 hours ,group B who received diclofenac injection 75 mg every 12 hours and normal saline as placebo every 12 hours and group c who received both nefopam 6 hourly and diclofenac every 12 hours . They did post-operative pain assessment every 6 hours using VAS scale and gave morphine when VAS>3 by patient –controlled analgesia system which give morphine intravenously.

They found that group B who received diclofenac alone needs less morphine than group C who received both nefopam and diclofenac and this group needed less morphine than group A who received nefopam alone.

They also found that pain scores post-operatively was higher in group A (take nefopam alone) than group B (received diclofenac alone) and group C(received combination of nefopam &and diclofenac,($P<0.05$) .

K AL-Refaey and his colleagues did their trial on 90 patients, all these patients underwent laparoscopic cholecystectomy, they did bilateral transverse abdominus plane block with bupivacaine 0.5% and magnesium sulphate. They divided the patients into 2 groups, group B received bupivacaine alone and the second group received bupivacaine and magnesium sulphate 150 mg (group M) they found VAS in B groupwas2.1+-0.5 and in M group was 1.2+-0.5, the duration of analgesia was 16+-2.5 in B group and 19+-2.2 in M group and lower morphine consumption in M group 0.9+-0.1 in B group, 0.5+-0.1 mg In M group so they conclude that magnesium reduce the pain scores, increase duration of analgesia and decrease the analgesic requirement in the first postoperative day. {19}

As we mentioned before that one of the mechanisms of action of nefopam is blocking of voltage sensitive sodium channels in nerve fibers which is similar to mechanism of action of any local anesthetic drug, together they have additive effects (8((9(in addition to that when we put nefopam very near to any peripheral nerve, we increase the bio viability of nefopam to its site of action (1(.

Conclusion:

Addition of nefopam to bupivacaine in sciatic N block and femoral N block in below knee surgical operations causes rapid onset of both sensory and motor block with prolongation of sensory and motor block with excellent intraoperative and postoperative analgesia in comparison with bupivacaine alone with good hemodynamic stabilization and without side effects.

Recommendation:

We advise all our colleagues to do other supportive similar studies (bupivacaine with nefopam in regional anesthesia) and we prefer to take larger sample size and multicenteric study then if they are similar to our results then we will recommend to add nefopam to bupivacaine to increase the duration of both sensory and motor block and shorten the onset of action.

References:

1. SangaM, BanachJ, LedvenaA, ModiNB, Matura. pharmacokienetic,metabolism and excretion of nefopam. the fate of foreign substances in biological system. 2016 Nov;1001-16.
2. Wl-Brady GF,Elshama NS. The Efficacy of mixing dexamethasone,midazolome,epinephrine to bupivacaine 0.5% in Brachial plexus Block, Supraclavicular approach. Saudi Journal of Anesthesia.2014;8:578-83.
3, Duma A,Urbanek B,Sitzwohl C, Kreiger A, Zimpfer M, Kapral S. Clonidine added to local anesthetic agents in Brachial Plexus Block, axillary approach " a randomized controlled study RCT. British Journal of anesthesia 2005;94:112-16.
4. Biradar P A, Kaimer P, Gopalknishna K . Effect of dexamethasone added to Lignocaine in Brachial Plexus Block, Supraclavicular approach "A

prospective randomized double blind study. Indian Journal Of Anesthesia 2013;57:180-4.

5. Vieira PA, Pulai I, Tsao GC, Manikantan P, Keller B, Connelly NR, et al . Dexamethasone added to Bupivacaine 0.5% increase duration of analgesia in ultrasound guided Brachial Plexus Block Interscalene approach. European Journal of Anesthesia. 2010;27:285-8.

6. Wermuth CG, Aldous D, Raboisson P, Rognan D. The practice of Medical Chemistry Elseveir sciences 4th edition. 2015;4:250-51.

7. Kubinyi H, Muller G. Chemo genomics in drugs discovery. A medical Chemistry perspective. SAGE journal, 2012;841:351-81.

8 GirardP, ChauvinM, Verleye M. Nefopam analgesia and its role in multimodel analgesia Review of preclinical and clinical studie.. Clin Exp pharmacol physiol Journal. 2016 Jan;43(1):3-12.

9. Kim KH, Abid S. Rediscovery of nefopam for the treatment of neuropathic pain. The Korean Journal of pain. 2014Apr;27(2):103-11.

10 Kang P,Park SK, Yoo S, Hur M,Kim JT,Bahk JH .comparative effectiveness of pharmacological intervention to prevent shivering after surgery (Network meta analysis). Minerva anesthesiology Journal. 2019 Jan;85(1):60-70. .Alfonsi p, Adam f, Passard A, Guignard B, Sessler DI, Chauvin M. Nefopam a non sedative analgesic selectively reduce shivering threshold in unanasthetised subject. Anaesthesiology Journal.2004 Jan;100(1):37-43.

12 Billota F, Rosa G. Nefopam for severe hiccup. The New England Journal of Medicine. 2000 Dec;343(26):1973-4.

13 Bismuth C, Fourmier PE, Bavoux E, Husson O, Lafon D. chronic abuse of the analgecic nefopam.Journal de Toxicologie Clinique et Experimental(in French). 1987Sep;7(5):343-6.

14 Tracqui A, Berthelon L, Ludes F. Fatal overdosage with nefopam. Journal of Analytical Toxicology. 2002May;26(4):239-43

. 15 Kapfer B, Alfonsi P, Guigard B, Sessler DI, Chauvin M. Nefopam and ketamine comparably enhance postoperative analgesia. Anesthesia and analgesia Journal. 2005 Jan;100(1):169-74.

16 Khaleel K A, Al-attar Z.The efficacy of bupivacaine versus bupivacaine with dexamethasone in supraclavicular brachial plexus block in patients undergoing upper limb surgery. Sch Acad J Pharm. 2020 Jan;9(1):46-50.

17 Rai S, Kedareshvara KS. To compare the effacicy of bupivacaine and bupivacaine with dexamethasone in supraclavicular brachial plexus block in patients undergoing upper limb surgeries. Indian Journal of health sciences and biomedical researches KLEU. 2018;11(1):65-9.

18. Moffat AC, Kenny GN, Prentice JW.. Postoperative evaluation of morphine sparing effect of nefopam and diclofenac after upper abdominal surgery. Anesthesia. 1990 April;45(4):302-5.

19- K AL-Refaey., EM Usama, E AL-Hefnawey. Adding magnesium sulphate to bupivacaine in transverse abdominus plane block in post laparoscopic cholecystectomy. Saudi J of anesthesia. 2016;10(2): p187-91.