The Professional Medical Journal
www.theprofesional.com

DOI: 10.17957/TPMJ/17.3766

ORIGINAL PROF-3766

INTRA ARTICULAR ADMINISTRATION;

TO DETERMINE THE ANALGESIC EFFICACY OF BUPIVACAINE AND COMPARE IT WITH LEVOBUPIVACAINE, DURING SURGICAL PROCEDURES OF THE KNEE JOINT

Hamid Raza[1], Bashir Ahmed[2], Kamlaish[3]

1. MBBS, FCPS
Assistant Professor Anesthesiology & ICU,
Liaquat University of Medical and Health Sciences Jamshoro.
2. MBBS FCPS
Assistant Professor Anesthesiology and ICU,
Dow University of Health Sciences, Civil Hospital Karachi.
3. MBBS, MRCP
Consultant Anesthetist,
Dow University of Health Sciences, Civil Hospital Karachi.

Corresponding Author:
Dr. Hamid Raza
B 15 Samanabad Bhitai Town
Qasimabad Hyderabad, Pakistan.
drhamidraza1@gmail.com

Article received on:
07/12/2016
Accepted for publication:
20/04/2017
Received after proof reading:
05/06/2017

ABSTRACT... Objectives: The aim of our study is to provide a comparison between levobupivacaine and bupivacaine administered intra articulary in the knee joint during arthroplasty procedures, and compare the postoperative analgesic effects. **Method: Study Design:** Randomized control trial. **Period:** One year duration from March 2015 to March 2016. **Setting:** Tertiary care centre in Karachi, Pakistan. The study population consisted of n= 50 patients belonging to ASA class II and III, who were scheduled to undergo TKA (total knee arthroplasty). The patient population was divided into two groups, group A consisted of all the patients who received bupivacaine, and group B consisted of all the patients who received levobupivacaine. All the patients were between the ages of 18 and 70 years, and had normal joint mobility. After explaining the procedure and taking due informed consent, the patients were informed about the use of the visual analog scale for pain and the patients controlled epidural anesthesia (PCEA). Readings of echocardiograph, blood pressure and pulse oximetry, sensory and motor characteristics of the established block, side effects, number of boluses and doses of PCEA, total amount of pain relief medications utilized over the period, VAS scores and time of mobilization and discharge from the hospital were also noted in a pre-designed. Statistical analysis was done using SPSS version 23. **Results:** The study population consisted of n= 50 patients. The VAS scores at were found to be lower in the bupivacaine group at 4,8,12 and 24 hours and VAS scores at 48 hour were lower in levobupivacaine group having a p value of less than 0.05, but the VAS scores were similar at the 0,2 and 72 hours in both the groups. The post-operative analgesic requirement was similar for both groups. The sensation of pain at the time of post-operative physiotherapy measure with the VAS score, was also similar in the two groups having a p value of less than 0.05. Similar results were found between the time of discharge and time of mobility, having a p value of less than 0.05**. Conclusion:** The use of multimodal analgesia with the administration of intra articular local anesthetics combined with PCEA is a very effective method to provide post-operative pain relief in patients undergoing total knee arthroplasty.

Key words: Intra articular administration, knee arthroplasty, levobupivacaine, bupivacaine, post-operative analgesia, patient controlled epidural analgesia.

Article Citation: Raza H, Ahmad B, Kamlaish. Intra articular administration; to determine the analgesic efficacy of bupivacaine and compare it with levobupivacaine, during surgical procedures of the knee joint. Professional Med J 2017;24(6):924-929. **DOI:** 10.17957/TPMJ/17.3766

INTRODUCTION

The complex surgical procedure of total knee arthroplasty can be performed under either regional or general anesthesia and both methods have their own pros and cons. The regional anesthesia provides less hemorrhage and less central nervous system side effects, while the general anesthesia provides a good muscular relaxation, reduces DVT (deep venous thrombosis) and provides good postoperative pain relief (regional anesthesia includes spinal, epidural, combined spinal and epidural anesthesia). Management of pain in total knee arthroplasties is a major concern for both the orthopedic surgeon and the anesthetist.[1,2]

A patient undergoing total knee arthroplasty may suffer from edema, spasms and knee pain post operatively, hence requiring the administration of analgesic medications which also improve outcome by affecting the mobility of the knee joint, increases the muscular strength and allowing

early mobilization and rehabilitation. Various techniques have been utilized for the maintenance of post-operative pain such as opioids, local anesthetics, peripheral nerve blocks and epidural analgesia. The properties such as short time of onset, long duration of analgesia and minimal side effects are the optimal characteristics of a post-operative analgesic.[3]

The drug levobupivacaine is a long acting local anesthetic and is preferred over bupivacaine. In comparison with bupivacaine, levobupivacaine has more margin of safety in terms of side effects when used in big doses.[4] Intravenous analgesics fail is to provide analgesia at rest, relief from motion related pain and the spasms of the musculature, hence intra articular drugs are preferred.[5] The aim of our study is to provide a comparison between levobupivacaine and bupivacaine administered intra articulary in the knee joint during arthroplasty procedures, and compare the postoperative analgesic effect using the VAS score.

MATERIALS AND METHODS

The type of study is a randomized control trial, conducted for a period of one year duration from March 2015 to March 2016, at a tertiary care centre in Karachi, Pakistan. The study population consisted of n= 50 patients belonging to ASA class II and III, who were scheduled to undergo TKA (total knee arthroplasty) according to standard procedure.

The patient population was divided into two groups using a random number generator (the software operator was the person in charged with allocation of the patients to respective groups according to the number that came up, during procedure the anesthetist was blinded to the drugs administered as they were prepared by a different anesthetist who himself was blinded to the patients identity, thus a double blind study design), group A consisted of all the patients who received bupivacaine, and group B consisted of all the patients who received levobupivacaine.

All the patients included in the study were between the ages of 18 and 70 years, who agreed to participate in the study, gave full informed consent and having normal joint mobility pre operatively without any significant co morbidities. The patients who were excluded from the study were those who refused to participate in the study, had severe co morbidities such as hepatic, renal, neurological or cardiovascular diseases or were unfit for surgery.

After explaining the procedure and taking due informed consent, the patients were informed about the use of the visual analog scale for pain (divided from 0 to 10, 0 being no perception of pain and 10 being the most extreme painful sensation possible) and the patients controlled epidural analgesia (PCEA). VAS was used to determine the outcome. All the patients were monitored intra operatively using standardized equipment. Readings of echocardiograph, blood pressure and pulse oximetry at regular time intervals (at 5,15,30,60 and 90 mins or till end of procedure) as well as sensory and motor characteristics of the established block at various intervals (2,4,8,12,24,48 and 72 hours postoperatively) side effects, number of boluses and doses of PCEA, total amount of pain relief medications utilized over the period was observed, VAS scores and time of mobilization and discharge from the hospital were also noted in a pre-designed proforma.

All the patients received low molecular weight heparin as prophylaxis for thromboembolism and also antibiotics for prophylaxis from infections. The patients were infused with Ringers lactate solution at 10ml per kg an hour before the procedure, pre-operative values were noted then the patients were given 0.03mg per kg of intravenous midazolam for sedation pre operatively. The patients were positioned for surgery, lidocain 2% was administered sub cutaneously for local anesthesia as 2 to 3ml per requirement. The epidural anesthesia was established by inserting 18 gauge spinal needle in the L3-L4 disc space and levobupivacaine 0.5% 15mg was administered over half a minute. The epidural needle was replaced by epidural catheter, the procedure was started after noting that appropriate spinal block has been

established, and patients were given oxygen at a rate of 3 liters per min during the procedure.

Various side effects were also recorded such as nausea, vomiting, bradycardia (heart rate of less than 60 beats per minute), hypotension, urinary retention and pruritis etc in the proforma. These conditions were treated accordingly using drugs such as metoclopromide, atropine, ephedrine and naloxone at appropriate doses if any side effects were noted. Near the end of procedure local anesthetics were administered, bupivacaine 0.5% in group A and levobupivacaine 0.5% in group B respectively. Postoperative pain management was carried out by the use of patient controlled epidural analgesia using a mixture of drugs such as levobupivacaine 0.125% with fentanyl 2mcg per ml, with a dose of 5 ml followed by a 30min interval where the drug administration was blocked out (so that the patient cannot overdose on these drugs, the drugs were administered without a loading dose and without a 4 hourly maximum dose limit). Also the patients received 1gm paracetamol orally after every 6 hours for post-operative analgesia. The epidural catheters were removed on the 72nd hour postoperatively, and after 12 hours the last dose of low molecular weight heparin was administered.

Physiotherapy was started on first postoperative day (isometric quadriceps exercises) and any pain present was duly noted. After removal of the drains placed at 2nd post-operative day, isotonic quadriceps exercises were also initiated under the guidance of a trained physiotherapist. Statistical analysis was done using SPSS version 23, mean and standard deviation as well as frequencies and percentages were used to analyze the quantitative data. A p value of less than 0.05 was considered to be statistically significant. Chi square test was used to analyze categorical variables. ANOVA and dependent t test were using to analyze data when necessary.

RESULTS

The study population consisted of n= 50 patients, divided into two groups A and B using a random number generator, in regards with the age, height, weight, gender, ASA classification status and duration of the surgery, both the groups were found to be very similar. Refer to Table-I. Similarly no statistically significant difference was found in the patients of two groups regarding the heart rate, blood pressure and oxygen saturation values, also similar situation was found when assessing the patients for side effects or complications such as pruritis, respiratory depression, nausea, vomiting and urinary retention in the post-operative period, having p values of greater than 0.05. n= 1 patient developed hypotension in the first hour post operatively in group B (levobupivacaine group) and n=1 patient developed hypotension in the second hour post operatively in group A (bupivacaine group). The required motor block was very well established in both the groups at 0 hour, at 2 hour postoperatively 10 patients from bupivacaine group and 5 patients from levobupivacaine group still experienced motor block, while at 4 hour post operatively 1 patient from each group suffered motor block, and no patients suffered motor block at 8 hour post operatively.

The VAS scores at were found to be lower in the bupivacaine group at 4,8,12 and 24 hours and VAS scores at 48 hour were lower in levobupivacaine group having a p value of less than 0.05, but the VAS scores were similar at the 0,2 and 72 hours in both the groups. Refer to Figure-1. The post-operative analgesic requirement was similar for both groups. Refer to Table-II. The sensation of pain at the time of post-operative physiotherapy measure with the VAS score, was also similar in the two groups having a p value of less than 0.05. Similar results were found between the time of discharge and time of mobility, having a p value of less than 0.05

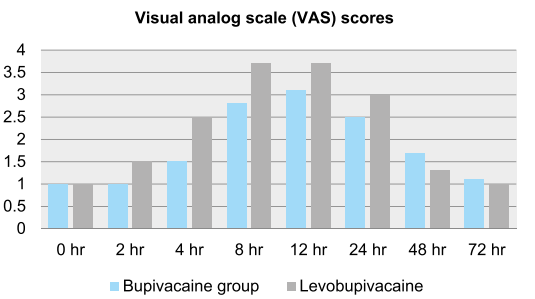

Figure-1. The visual analog scale (VAS) scores in both groups.

Characteristics	Group A	Group B	P value
Age in years	65 +/- 6.67	64.5 +/- 7.2	0.716
Gender			0.488
Male	21 (84%)	19 (76%)	
Female	4 (16%)	6 (24%)	
Weight in kg	81.02 +/- 10.5	82.1 +/- 9.43	0.732
Height in cm	160.4 +/- 5.75	159.9 +/- 4.32	0.669
ASA classification			0.432
Class II	13 (52%)	16 (64%)	
Class III	12 (48%)	9 (36%)	
Duration of procedure in mins	100.17 +/- 20.5	99.32 +/- 21.36	0.327

Table-I. Demographic and other characteristics of the patients in two groups.

Characteristics	Groups	1st post op day	2nd post op day	3rd post op day	P value
Required number of boluses per day					0.084
	Group A	31.46 +/- 24.40	24.07 +/- 19.88	19.3 +/- 14.59	
	Group B	38.86 +/- 28.33	21.15 +/- 17.01	17. 76 +/- 12.41	
Delivered number of boluses per day					0.348
	Group A	15.86 +/- 6.77	9.96 +/- 4.80	8.94 +/- 3.96	
	Group B	16.38 +/- 8.40	9.69 +/- 5.41	8.49 +/- 4.19	
Total consumption of analgesia in ml					0.371
	Group A	79.18 +/- 33.46	49.67 +/- 23.82	44.77 +/- 19.80	
	Group B	81.68 +/- 41.64	48.5 +/- 27.14	42.6 +/- 21.01	

Table-II. Characteristics of the patient controlled anesthesia.

DISCUSSION

According to the results of our study the VAS scores were found to be lower in the bupivacaine group in the initial few hours postoperatively (4,8,12,24 hours), but they were lower for the levobupivacaine group at the 48th hour, virtually everything else such as the requirement for PCEA (boluses and dosage), physiotherapy associated pain, discharge and mobilization times were identical. We had utilized in our study intra articular injections of the two drugs, paracetamol and PCEA as modalities to relieve the post-operative pain.

The post-operative pain, is a notorious side effect caused due to surgical trauma and causes havoc by delaying mobility and recovery time. It is a major concern for the orthopedic surgeons especially during total knee arthroplasty surgery. The surgeons are pro active in controlling the pain, and use various modalities simultaneously for pain relief.[6,7] But they are successful in controlling the post-operative pain in only half the cases.[8] The intra articular administration is beneficial in total knee arthroplasty procedures as it increases mobility, range of motion and reduces the time of hospital stay, by inhibiting the inflammatory and neuroendocrine stress response. [9]

Various factors determine the post-operative pain level such as quality and type of intra articular analgesic utilized, pre-operative status of pain, type of anesthesia and type of surgical procedure done, duration of the procedure and experience of the surgeon.[10] Before a comparison is made with other studies it is imperative that standardization is made sure before a question about efficacy of analgesics can be raised.[11]

Some studies assessed pain during rest, and some during mobility,[12] we preferred to measure the pain score at both during the resting condition and during physiotherapy, for up to 72 hours postoperatively. There is some established benefit of intra articular administration of the analgesic medication as compared with other modalities, such as local anesthetics provide an immediate effect, but lasts for a short duration. But with other systemic administration the side effects of toxicity, due to absorption restricts its use and a constant

infusion might cause infection.[9,12] Various studies also promote the use of local analgesics as to curb the pain at site of origin with minimal side effects.[13] The two drugs levobupivacaine and bupivacaine (which is used classically as local analgesic) are found to be very similar in there anesthetic and analgesic properties, however some studies in rodents report less side effects with levobupivacaine.[14] But data is lacking in its use as an intra articular analgesic. Some studies report damage to the cartilaginous tissue with use of local anesthetics in arthroscopic procedures.[15] But that is supposed to be due to a high dose of anesthetic combined with administration of corticosteroids for a prolonged period of time.[16,17] In our study we only administered a single intra articular dose without any adjuvant, to avoid the damage to cartilaginous tissues. According to a study by Stein et al they found a direct relation between length of procedure and postoperative pain when it comes to arthroscopic surgeries of the knee joint.[18] In our study there was no difference is length of procedure in the two groups. In our study the highest values of pain scores were noted in the 8th and 12th hour post operatively. The use of levobupivacaine in the PCEA might have decreased the VAS scores in the intra articular levobupivacaine group after the 12 hour mark. The PCEA application might also have had an effect of the lower levels of pain experienced at the start of mobility exercises after 24 hour mark.

The two drug combination of fentanyl (4mcg/ml) and levobupivacaine (0.125%) have been shown to be effective in combination as compared to their separate use by Kopacz et al in their study.[19] We used a lower dose of the fentanyl (2mcg per ml) and levobupivacaine (0.125%) in our study, and observed low VAS scores which might be due to the synergistic effect of concomitant intra articular analgesic and PCEA. Most other studies[20] only followed the patients till 24 or 48 hours, and in our study we followed the patients till 72 hours, hence a comparison is difficult in this respect. Various studies show that the use of PCA (epidural PCA is more efficacious than intravenous PCA) with concomitant use of intra articular or sub cutaneous analgesic is superior to PCA alone.[2,4,10] In conclusion we recommend further studies to be done in order to assess the cartilaginous damage of intra articular administration of analgesics and also the plasma concentrations of the drugs and other long term side effects.

CONCLUSION

The use of multimodal analgesia with the administration of intra articular local anesthetics combined with PCEA is a very effective method to provide post-operative pain relief in patients undergoing total knee arthroplasty.

REFERENCES

1. Sitsen E, Van Poorten F, Van Alphen W, Rose L, Dahan A, Stienstra R. **Postoperative epidural analgesia after total knee arthroplasty with sufentanil 1 microg/ml combined with ropivacaine 0.2%, ropivacaine 0.125%, or levobupivacaine 0.125%: a randomized, double-blind comparison.** Anesth Pain Med. 2007; 32:475-480.

2. Bozkurt M, Yilmazlar A, Bilgen OF. **Comparing the effects of analgesia techniques with controlled intravenous and epidural on postoperative pain and knee rehabilitation after total knee arthroplasty.** Joint Diseases and Related Surgery. 2009; 20:64-70.

3. Baskan S, Taspinar V, Ozdogan L, Gulsoy KY, Erk G, Dikmen B, et al. **Comparison of 0.25% levobupivacaine and 0.25% bupivacaine for posterior approach interscalene brachial plexus block.** J Anesth. 2010; 24(1):38-42. doi: 10.1007/s00540-009-0846-0.

4. Bengisun ZK, Salviz EA, Darcin K, Suer H, Ates Y. **Intraarticular levobupivacaine or bupivacaine administration decreases pain scores and provides a better recovery after total knee arthroplasty.** J Anesth. 2010; 24:694- 699. doi: 10.1007/s00540-010-0970-x.

5. Bonica J. Painful disorders of the thigh and knee. In: Bonica J, ed. **The Management of Pain.** 2nd ed. Philadelphia, Lea & Febiger, 1990:1557-1584.

6. Erdine S. Agri, 3. **Baski, Nobel Tip Kitabevleri,** 2007, 3-188.

7. Sizlan A, Atim A, Yurttas Y, Ozkan H, Bilge M, Kuyumcu M, et al. **A comparison of the efficacy of bupivacaine and levobupivacaine in patient-controlled epidural analgesia for postoperative pain in patients undergoing knee arthroplasty.** Joint Diseases and

Related Surgery. 2012; 23:134-139.

8. Ashik M, Shi-Lu C, Jin YS, Hong TM, Nung LN. **Comparison of the different modalities of post-operative analgesia in unilateral total knee arthroplasty patients.** J Orthopaedics. 2010; 7(1)e11.

9. Rasmussen S, Kramhøft MU, Sperling KP, Pedersen JH. **Increased flexion and reduced hospital stay with continuous intraarticular morphine and ropivacaine after primary total knee replacement: open intervention study of efficacy and safety in 154 patients.** Acta Orthop Scand. 2004; 75(5):606-609.

10. Ong JCA, Lin PC, Fook-Chong SMC, Tang A, Ying YK, Keng TB. **Continuous infiltration of local anaesthetic following total knee arthroplasty.** J Orthop Surg. 2010; 18:203-207.

11. Kehlet H, Andersen LO. **Local infiltration analgesia in joint replacement: the evidence and recommendations for clinical practice.** Acta Anaesthesiol Scand. 2011; 55:778-784. doi: 10.1111/j.1399-6576.2011.02429.x.

12. Gentili M, Houssel P, Osman M, Henel D, Juhel A, Bonnet F. **Intra-articular morphine and clonidine produce comparable analgesia but the combination is not more effective.** Br J Anaesth. 1997; 79:660–661.

13. Cook TM, Tuckey JP, Nolan JP. **Analgesia after day-case knee arthroscopy: double-blind study of intraarticular tenoxicam, intraarticular bupivacaine and placebo.** Br J Anaesth. 1997; 78:163-168.

14. Ivani G, Borghi B, Van Oven H. **Levobupivacaine.** Minerva Anestesiol. 2001; 67:20-23.

15. Grishko V, Xu M, Wilson G, Pearsall AW. **Apoptosis and mitochondrial dysfunction in human chondrocytes following exposure to lidocaine, bupivacaine, and ropivacaine.** J Bone Joint Surg Am. 2010; 92:609-618. doi: 10.2106/JBJS.H.01847.

16. Atik OS. **Is single-dose local anesthetic chondrotoxic?** Joint Diseases and Related Surgery. 2012; 23:111-112.

17. Farkas B, Kvell K, Czompoly T, Illes T, Bardos T. **Increased chondrocyte death after steroid and local anesthetic combination.** Clin Orthop Relat Res. 2010; 468:3112-3120. doi: 10.1007/s11999-010-1443-0.

18. Stein C, Comisel K, Haimerl E, Yassouridis A, Lehrberger K, Herz A, et al. **Analgesic effect of intraarticular morphine after arthroscopic knee surgery.** N Engl J Med. 1991; 325:1123-1126.

19. Kopacz DJ, Sharrock NE, Allen HW. **A comparison of levobupivacaine 0.125%, fentanyl 4mcg/ml, or their combination for patient-controlled epidural analgesia after major orthopedic surgery.** Anesth Analg. 1999; 89:1497-1503.

20. Koltka K, Koknel-Talu G, Asik M, Ozyalcin S. **Comparison of efficacy of intraarticular application of magnesium, levobupivacaine and lornoxicam with placebo in arthroscopic surgery.** Knee Surg Sports Traumatol Arthrosc. 2011; 19(11):1884-1889. doi: 10.1007/s00167-011-1497-x.

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Dr. Hamid Raza	Write-up, Statistical analysis, drafting, corresponding author	
2	Dr. Bashir Ahmed	Data collection, Write up, Analysis, Proof Reading	
3	Dr. Kamlaish	Data collection, Write up, Analysis, Literature review