Analgesic Effect of Intraarticular Tramadol with Morphine after Arthroscopic Knee Surgery

Hussain Faisal[1], Arjun Lamichhane[1], Deepak Mahara[1].

[1]Department of Orthpaedics and Trauma Surgery. Institute of Medicine Tribhuvan University, Kathmandu, Nepal

ABSTRACT

Introduction: Post-operative improved pain control of patients has made arthroscopy as a day care procedure, reducing patient's expenses and hospital staffs work load. Various analgesic drugs have been administered into the joint following Arthroscopy. Intra-articular injection of morphine has been practiced in many centres all over the world. We aimed to compare the efficacy of intra-articular tramadol and morphine. Tramadol is an opioid drug with similar analgesic properties like morphine. Tramadol unlike morphine is readily available over the counter not being abused and has more favourable side effects.

Methods: It was a prospectively randomized double-blind study in which sixty patients having elective arthroscopic surgery of the knee were randomized into two groups. Group A (Tramadol Group) received intra-articular tramadol 50mg and Group B (Morphine Group) received morphine 5mg in equivalent volumes. Post-operative pain using Visual Analogue Score (VAS) between 0 and 10, (0 no pain to 10 worst pain) requirement of first analgesic, and incidence of side effects were recorded postoperatively at intervals of 3,4,5,6 and 24 hours.

Results: The assessment of VAS score among the two groups in 3,4,5,6 and 24 hours of IA injection showed a *p value* of 0.349, 0.807, 0.676, 0.271 and 0.163 respectively, suggesting non significant difference in two groups. There was statistically significant result *(p=0.005)* for request of first analgesia (Ibuprofen 400mg+ Paracetalmol 500mg) at 6 hours of IA injection with tramadol group, requiring less analgesics. There are no other clinically important differences between the groups, including preoperative duration of symptoms, postoperative pain scores and side effects irrespective of the diagnosis and the procedure performed.

Conclusion: 50 mg IA tramadol provides analgesia equivalent to 5 mg IA morphine.

Key Words: Analgesic; Intra-articular; Morphine; Pain; Postoperative.

INTRODUCTION

Arthroscopic knee surgery is one of the most common surgical procedures done in an outpatient basis. Postoperatively improved pain control of patients has made this surgery as a day care procedure, reducing patient's expenses and hospital staffs work load[1]. Various analgesic drugs have been administered into the joint following this type of surgery. Intra-articular injection of morphine following knee arthroscopy has been practiced in many centres all over the world. Morphine is an opioid agonist drug and it has long been known to relieve severe pain with remarkable efficacy[2]. Tramadol is a synthetic codeine analog that is a weak opioid receptor agonist. Generally opioids also can produce analgesia when administered peripherally, since these receptors are present on peripheral nerves and will respond to peripherally applied opioids and locally released endogenous opioid compounds when up-regulated during inflammatory pain states[3]. Part of tramadols analgesic effect is produced by inhibition of uptake of norepinephrine and serotonin, which are neurotransmitters in neuronal circuit responsible for pain and many other actions.[4] And hence beign having local anaesthetic effect that is not opioid receptor related.[5-6] Tramadol's analgesic effect has been equated with that of morphine, with a more favorable side-effect profile for tramadol including less respiratory depression, nausea and vomitting[7]. Whether opioid and nonopioid actions of tramadol would provide superior peripheral analgesia compared with opioid morphine needs to be explored. The aim of the study was to compare the analgesic effect of intra-articular (IA) tramadol with IA morphine.

Correspondence

Dr. Hussain Faisal

Department of Orthopaedics and Trauma Surgery
Institute of Medicine, Tribhuvan Unversity Teaching Hospital.Kathmandu, Nepal
Email: hussain_phaisal@hotmail.com

METHODS

After ethical committee approval, informed written consent was obtained from 60 patients who fulfill the inclusion criteria to undergo elective knee arthroscopic surgery. Standard general anaesthesia was given to all the cases. A short-acting opioids (fentanyl) was used and general anesthesia was maintained with halothane and oxygen at the beginning of the operation. No non-steroidal anti-inflammatory drugs or additional pain medications were administered. All the arthroscopies were performed under tourniquet application on thigh and by two orthopaedic surgeons trained in arthroscopic surgery in department of orthopaedics and trauma, TUTH. Two standard portals (anteromedial and anterolateral) or more was used.

Patients aged between 15 to 70 years, who under went diagnostic arthroscopies, Arthroscopic meniscal excision or repair, Arthroscopic removal of loose bodies, Arthroscopic debridement or combination of these procedure were included in the study. Those who required Epidural or spinal anaesthesia, Allergies to local anaesthetic or opioids, Ligament reconstruction and articular cartilage procedures, Cases of extensive arthroscopic synovectomy, Severe cardiovascular, respiratory, metabolic or neurological diseases, Postoperative splinting and pregnant were excluded from this study.

At the conclusion of surgery, patients were randomized to a particular group, Group A (Tramadol Group -30 patients) and Group B (Morphine Group - 30 patients) and the appropriate study drug was injected into the knee by the surgeon, who was blinded to its contents. The study drug prepared by the scrub nurse, who keeps the record of injection, was injected before the release of tourniquet. All cases were observed by the author who was also blinded and recorded pain, supplemental analgesic requirements, and incidence of side effects at 3,4,5,6 and 24 hours post-operatively. Post-operative pain was assessed using Visual Analogue Score (VAS) between 0 and 10, (0 no pain to 10 worst pain). Pain score was assessed in the recovery room for 6 hours. In case of need of supplementary analgesics, Ibuprofen 400 mg plus 500mg paracetamol was administered orally. In the event that there was no pain relief, 75 mg diclofenac was injected intramuscular. The time to the first request for analgesia and the total analgesic consumption was recorded for 24 hours duration at intervals of 3,4,5,6, and 24 hours. At the time of discharge the patients were instructed to take oral analgesic combination of Ibuprofen 400mg + paracetamol 500mg, as required for a maximum of 8 hourly intervals. The patients were discharged from the recovery room after 6 hours with a copy of VAS to record pain at home at 24 hours of intra-articular injection. The final VAS recording was taken when the patient returns to OPD on the 4th or 5th day of surgery.

Demographic data, distribution of sex, preoperative symptoms and post-operative analgesic consumption in two groups were analyzed by analysis of variance and compared by applying chi-square test. Comparison of mean VAS in two groups was done by applying independent t-test. The Fisher's Exact test was used to compare analgesic requirements and side effects. A probability of $P < .05$ was considered statistically significant.

RESULT

There were no significant differences among the two groups with respect to age, sex, duration of pre-operative, VAS score for pain at the specified intervals, Table1.

Table1. Demographic Variables

Characteristics	Tramadol	Morphine	p
Age	30.30 ± 12.69	30.63 ± 9.23	0.908
Sex (M/F)	21/9	20/10	0.780
Side (Right/ Left)	17/13	15/15	0.605
Duration of pre-operative symptoms*	9.47 ± 6.87	18.83 ± 30.30	0.576

***Duration of pre-operative symptoms in months**

Post-operative VAS for both groups at 3,4,5 and 6 hours of intra-articular injection range from 3.00 to 4.13 (moderate pain) and their p values were statistically not significant. The post-operative VAS for both groups at 24 hours range from 2.07 to 2.67 (mild pain). This is also not significant statistically for both groups, Table 2

Two patients (6.7%) required first oral analgesic (Ibuprofen400mg + paracetamol 500mg) in Group A (Tramadol) at six hours of intra-articular injection while eleven patients (36.7%) requested from Group B (Morphine) during the same interval, Table 3. These results are statistically significant. P=0.005. All other intervals of analgesic consumption are not significant including oral and injectible analgesic.

When postoperative VAS at interval of 3,4,5,6 and 24 hours of intra-articular injection was correlated with duration of pre-operative symptoms within the two groups all the results were not significant among the groups. This shows that there is no significant difference of analgesia with tramadol or morphine at these hours of intra-articular injection irrespective of preoperative symptom.

Table 2. Visual Analogue Score at different time period

VAS	Tramadol	Morphine	P
VAS at 3 hours	4.13±1.78	3.67±2.04	0.349
VAS at 4 hours	3.63±1.56	3.73±1.60	0.807
VAS at 5 hours	3.27±1.46	3.43±1.61	0.676
VAS at 6 hours	3.00±1.51	3.47±1.74	0.271
VAS at 24 hours	2.07±1.36	2.67±1.88	0.163

VAS (Visual Analogue Score) at rest

Table 3. Comparative characteristics of Both the Groups.

Characteristics	Tramadol	Morphine	P
Patients not requiring any extra analgesics	15(60%)	10(40%)	0.69
Patients required extra analgesics	15(43%)	20(57%)	0.190
Oral analgesics at 3 hours of post-op	3(10%)	3(10%)	1.00
Oral analgesics at 4 hours of post-op	3(10%)	3(10%)	1.00
Oral analgesics at 5 hours of post-op	2(6.7%)	0	0.47
Oral analgesics at 6 hours of post-op	2(6.7%)	11(36.7%)	0.005
Oral analgesics at 24 hours of post-op	13(43.3%)	16(53.3%)	0.43
I.M Diclofenac 75mg injection	3(10%)	3(10%)	1.00
Side effects (Nausea/Vomiting)	1(3.3%)	0	0.50

DISCUSSION

Post operative pain management with intra-articular analgesic injection following knee arthroscopy has been practiced many centeres.[7-10] Analgesics with different doses and different combinations have been applied to provide optimum analgesia to patients undergoing knee arthroscopy.[7,11] Out of those combinations an ideal drug with properties of good analgesic control, less systemic side effect is to be identified. Further more, requirement of additional analgesic is to be explored. Morphine has good analgesic control when injected intra-articularly following knee arthroscopy.[8,11] However nausea vomiting and respiratory depression are common side effects of morphine. Tramadol is an opioid drug with similar properties of morphine but causes less side effects like nausea, vomiting and respiratory depression.[12] Intra-articular local anaesthetics are often used for the management and prevention of pain after arthroscopic knee surgery, with bupivacaine most commonly used.[13,14] However, because of their high systemic absorption, short duration of effect, their uses are of limited bennefit.[7,13,15] Stein et al.[9] reported the intra-articular morphine-induced analgesia in patients after arthroscopic knee surgery. Since then many workers established that intra-articular opioids produce a profound anti-nociceptive effect and it has been widely used intra-articularly with or without local anaesthetics for the management of pain after arthroscopic knee surgery.[6,8,15] Opioid receptors have long been recognized in the brain and central nervous system, but have only recently been demonstrated in the periphery on nerve endings.[16-20] Stein and his colleagues[9] provided the first clinical evidence of the peripheral action of opioids, showing that anti-nociceptive effect of intra-articular morphine was blocked by intra-articular naloxone. The peripheral opioid action involves a number of mechanisms, including inhibition of action potentials in pain fibres[16,21] and inhibition of the release of excitatory substance P.[16,22] Action on Post-ganglionic nerve terminals blocks the release of several sensitizing prostanoids, which may be important in sympathetically maintained pain syndrome.[23]

We did not use control case because tramdol is an opioid drug with similar actions like morphine and several studies has shown analgesic effect of morphine when injected intra-articularly. Mahara DP et al[10] concluded that low dose (2mg) intra-articular morphine injection is a good alternative to other pain management modalities especially for day care patients following arthroscopic knee surgery. In a similar study like our study by S. B. Akinci et al[11], conclude that tramadol 50mg and morphine 5mg provide similar analgesia when given intra-articularly.

We did not observe significant differences in results between intra-articular tramadol 50mg and 5 mg morphine with respect to pain using VAS system, and side effects. There was less analgesic requirement in tramadol group with significant result for patients who required first analgesic (Ibuprofen 400mg + Paracetamol 500mg) at 6 hours postoperatively, $P = 0.005$, Table 3. This may be due to longer half life of the tramadol, more potent efficacy of

metabolites and multiple mechanism of analgesic effect.[24]

The average duration of symptoms was 14.15 months. Most symptomatic knees, 48 (80%) were within one year of duration. Within this duration we expected patients to have increased opioid receptors as well as inflammation significantly. We observed that all patients in both groups had VAS range 3 - 4.13 (moderate pain), till six hours of post operatively and at 24 hours mean VAS range was 2.07 – 2.67 (mild pain). This persisting pain could be due to chronic inflammatory mediators which have built up within the knee joint.

Injury to the sensitive structures in the knee joint and inflammation cause C and A-δ fibers to undergo changes such as sensitization, increased activity in normally silent nociceptors.[2] Likar et al[25] mentioned increasing duration of symptoms increases the number of receptors in the inflamed tissues. Several workers[26.27] have demonstrated that increased duration increase number of receptors in the synovium. Most severe acute pain can usually be well controlled with significant but tolerable adverse effects with currently available opioid analgesics. However, chronic pain is not very satisfactorily managed with opioids.[2] The moderate pain which persisted till 6 hours in both groups and the mild pain which persisted at 24 hours in both groups could be due to pain from the inflammatory mediators.

Three patients in each group had severe pain at three hours of intra-articular injection and received first analgesic i.m diclofenac 75mg injection, P= 1, and it was statistically not significant. Out of these six patients, three patients did not take any other analgesic during the 24 hours. One patient consumed further three doses of oral analgesic during the 24 hours duration. This could be due to the inflammatory pain which either persisted from the preoperative symptoms or after the arthroscopic procedure, in which the opioid drugs has limited action.

Despite the combination of different analgesic mechanism of tramadol, we could not find any superiority between intra-articular tramadol and intra-articular morphine with respect to VAS score, preoperative symptoms and side effects. However tramadol, unlike morphine is readily available over the counter, not being abused and have more favourable side effects. In future further studies, with larger number of patients are needed to compare the side effects of intra-articular administered morphine and tramadol. We believe that intra-articular tramadol can be an alternative to intra-articular morphine for post-operative analgesia after arthroscopic knee surgery.

CONCLUSION

We conclude that 50 mg intra-articular tramadol provides analgesia equivalent to 5 mg intra-articular morphine.

REFERENCES

1. *Miller, Cole. Textbook of Arthroscopy. 1st ed. 2004 Elsevier; 2004 p 5 – 20.*
2. *Mark A, Schumacher, Allan I, Basbaum, Walter L, Wang. Opioid analgesics & Antagonists. In: Bertram G Katzung, editor. Basic and Clinical Paharmacology. 10th ed. McGraw-Hill; 2007. Chapter 31, p 489 – 500.*
3. *Stein C. Peripheral mechanisms of opioid analgesia Anesth Analg 1993;76:152-191.*
4. *Guyton A C, John E H. Textbook of medical physiology. 11th ed. Elsevier Saunders; 2006. Ch 45, p 556 – 570.*
5. *Tsai Y, Chang P, Jou I. Direct tramadol application on sciatic nerve inhibits spinal somatosensory evoked potentials in rats. Anesth Analg 2001;92:1547-1551.*
6. *Kapral S, Gollmann G Walt B, et al. Tramadol added to mepivacaine prolongs the duration of an axillary brachial plexus blockade. Anesth Analg 1999;88:853-856.*
7. *A Alagol, O U Calpur, G Kaya, Z Pamukcu, F N Turan. The use of intraarticular tramadol for postoperative analgesia after arthroscopic knee surgery: a comparison of different intraarticular and intravenous doses. Knee Surg Sports Traumatol Arthrosc 2004; 12 : 184–188.*
8. *Kanbak M, Akpolat N, Ocal T, Doral MN, Ercan M, Erdem K. Intraarticular morphine administration provides pain relief after knee arthroscopy. Eur J Anaesthesiol 1997; 14:153–156.*
9. *Stein C, Comisel K, Haimerl, Yassouridis A, Lehrberger K, Herz A, Peter K. Analgesic effects of intraarticular morphine after arthroscopic knee surgery. N Engl J Med 1991; 325:1123–1126.*
10. *Mahara D P, Lamichhane A P. Intraarticular Morphine for Post Operative Knee Arthroscopy Analgesia. Journal of Nepal Medical Association 2004; 43: 191-194.*
11. *Seda B, Fatma S, Ozgur A, Mahmut N, Meral K. Analgesic Effect of Intra-articular Tramadol Compared With Morphine After Arthroscopic Knee Surgery. The Journal of Arthroscopic and Related Surgery, Vol 21, No 9 (September), 2005: pp 1060-1065.*
12. *Howard , Gutstein, Huda Akil. Opioid analgesics. In: Goodman Gilman's, editor. The Pharmacological Basis Of Therapeutics - 11th Ed. McGraw-Hill; 2006. P 569 – 609.*
13. *Chirwa SS, McLeod A, Day B Intraarticular bupivacaine (marcaine) after arthroscopic meniscectomy. Arthroscopy 1989; 5:33–35.*
14. *Dahl MR, Dasta JF, Zuelzer W, McSweeney TD Lidocaine local anesthesia for arthroscopic knee surgery. Anesth Analg 1990; 71:670–674.*
15. *Khoury GF, Chen ACN, Garland DE, Stein C. Intra-articular morphine, bupivacaine and morphine/bupivacaine for pain control after knee video arthroscopy. Anesthesiology 1992;77:263-266.*
16. *Joris JL, Dubner R, Hargreaves KM. Opioid analgesia at peripheral sites: A target for opioids released during stress and inflammation. Anesth Analg 1987; 66:1277-1281.*

17. *Stein C, Hassan AHS, Przewloski R, Gramash C, Peter K, Herz A. Opioids from immunocytes interact with receptors on sensory nerves to inhibit nociception in inflammation. Proc Natl Acadi Sci USA 1990; 87:5935-5939.*

18. *Stein C, Millan MJ, Shippenberg TS, Peter K, Herz A. Peripheral opioid receptors mediating antinociception inflammation:Evidence for involvement of mu, delta, and kappa receptors. J Pharmacol Exp Ther 1989; 248: 1269-1275.*

19. *Levine JD, Taiwo YO. Involvement of the mu-opiate receptor in peripheral analgesia. Neuroscience 1989; 32:571-575.*

20. *Stein C. Peripheral mechanisms of opioid analgesia Anesth Analg 1993;76:152-191.*

21. *Basbaum AI, Levine JD. Opiate Analgesia: How central is a peripheral target? N Engl J Med 1991; 325:1168-1169.*

22. *Yaksh TL. Substance P release from knee joint afferent terminals: Modulation by opioids. Brain Res 1988; 458:319-324.*

23. *Taiwo YO, Levine JD. Kappa and delta-opioids block sympathetically dependent hyperalgesia. J Neurosci 1991; 11:928-932.*

24. *L Broomley. Opioids and codein. In: S I Jaggar, A Holdcroft, editors. Core topics in pain.1st ed. Cambridge University Press; 2005. Chapter 40, The action of opioid drugs; p. 274.*

25. *Likar R, Schafer M, Paulak F et al. Intraarticular morphine analgesia in chronic pain patients with osteoarthritis. Anesth Analg 1997;84:1313-1317.*

26. *Stein C, Pflüger M, Yassouridis A, et al. No tolerance to peripheral morphine analgesia in presence of opioid expression in inflamed synovia. J Clin Invest 1996;98:793-799.*

27. *Dionne RA, Lepinski AM, Gordon SM, Jaber L, Brahim JS,Hargreaves KM. Analgesic effects of peripherally administered opioids in clinical models of acute and chronic inflammation. Clin Pharmacol Ther 2001;70:66-73.*