

ORIGINAL ARTICLE

To Evaluate The Efficacy And Safety Of Intra Venous Diclofenac Sodium With Or Without Pre-Emptive Ketamine As A Part Of Multimodal Analgesia For Early Post-Operative Pain Relief In Lower Limb Surgery

Kanta Bhati¹, Sonali Dhawan²

^{1,2}Associate Professor, Department of Anaesthesia, Sardar Patel Medical College, Bikaner, Rajasthan, India

ABSTRACT:

Background and Aim: Multimodal analgesia relates a balanced approach to treat post-operative pain by combining multiple therapeutic agents and regional techniques. This study was conducted to evaluate the post-operative analgesic efficacy and safety of intravenous water based diclofenac sodium with or without pre-emptive intravenous ketamine in lower limb orthopedic surgery under spinal anaesthesia. **Methods:** This was a prospective, randomized, comparative hospital based study. Three groups of 30 patients each, i.e., receiving diclofenac sodium with or without pre-emptive ketamine and control group were enrolled. VAS score, time of first analgesic request, duration of analgesia, total analgesic requirement in first 24h, intra-operative and post-operative hemodynamics, any side effects and complication were recorded. **Results:** The VAS score was significantly lower in Group DK as compared to Group NS and Group D ($P=0.001$) at T30min to T24h. Mean time for first analgesic request was longer in group DK (373 ± 9.39 min), as compared to group NS (179.13 ± 5.95 min) and group D (228.30 ± 7.97 min). Total analgesic consumption in postoperative 24h was lower in group DK (1.27 ± 0.45) as compared to group NS (2.86 ± 0.44) and group D (1.67 ± 0.55). No significant adverse effects were found in any group. **Conclusion:** Pre-emptive use of ketamine with intravenous diclofenac sodium as a part of multimodal analgesia regimen render the patient pain-free in immediate post-operative period and minimize the demand of rescue analgesic.

Keywords: Multimodal analgesia, pre-emptive, ketamine, diclofenac.

Corresponding author: Dr. Sonali Dhawan, Associate Professor, Department of Anaesthesia, Sardar Patel Medical College, Bikaner, Rajasthan, India

This article may be cited as: Bhati K, Dhawan S. To Evaluate The Efficacy And Safety Of Intra Venous Diclofenac Sodium With Or Without Pre-Emptive Ketamine As A Part Of Multimodal Analgesia For Early Post- Operative Pain Relief In Lower Limb Surgery. *J Adv Med Dent Sci Res* 2015;3(1):266-270.

INTRODUCTION

Current techniques for post-operative pain relief use both multimodal and pre-emptive analgesia to improve the outcome of surgery while minimizing the potential adverse effects of the opioid medication.^[1] Pre-emptive analgesia is initiated before surgery in order to prevent the establishment of central sensitization, evoked by the incisional and inflammatory injuries occurring during surgery and in the early post-operative period.^[2] A broader definition of multimodal analgesia relates a balanced approach to treat post-operative pain by combining adjuvants, analgesics, opioids and regional techniques.^[3,4] Diclofenac acts via inhibiting cyclooxygenase enzyme thereby reducing prostaglandin synthesis that sensitizes peripheral nociceptors leading to their down regulation.^[5] Ketamine is a non-selective N-methyl-D-aspartate (NMDA) receptor antagonist which, at sub-anaesthetic doses (≤ 0.5 mg/kg intravenous), possesses centrally mediated analgesic properties with minimal effect on consciousness and cognition.

METHODS

This prospective, randomized, comparative, hospital based study was carried out after approval from institutional review board. Written informed consent was obtained from all the patients before surgery. Ninety patients of ASA-PS grade I/II aged 18-65

years, of both sexes, randomly allocated into three groups ($n=30$), planned for lower limb surgeries were enrolled. The primary objective of the study was to compare the intensity of pain by VAS score. The secondary objectives were to compare the time to first rescue analgesia (duration of analgesia) and to compare the total dose of rescue analgesic in first 24h post- surgery in between the groups.

Pre-anaesthetic check-up including history, physical and general examination and routine laboratory investigations was carried out a day before surgery. The procedure and Visual Analogue Scale (VAS) for pain was explained to every patient at the time of pre-anaesthetic evaluation. All patients were kept nil by mouth for eight hours before the surgery. Using computer generated random numbers, the patients were randomly allocated into three groups ($n=30$). (Figure 1)

On the day of surgery after confirmation of fasting status, patient was shifted to OT and multipara monitors were attached. Baseline SBP, DBP, SpO₂ and Pulse rate were recorded (T₀) and the patient was preloaded with 10 ml/kg ringer lactate intravenously over 15-20 min. All patients received inj. Ranitidine 50mg I.V. and inj. Metaclopramide 10mg I.V. for aspiration prophylaxis 15min. before surgery.

According to patient convenience, either in sitting or lateral decubitus position, lumbar puncture was

performed at L3-L4 interspace through midline approach using a disposable 25G Quincke's spinal needle after full aseptic precautions. 0.3mg/kg of (0.5% Heavy) bupivacaine and 25µg fentanyl given in the subarachnoid space after confirmation of free flow of CSF and patient was made supine immediately. Continuous monitoring of vital parameters was done throughout intra-operative period. All patients (T0) and at 30min, 1, 3, 6, 12, 24h post-surgery. Duration of analgesia was defined as the time duration from completion of surgery to the time patient requested for first analgesic medication or VAS≥4. Intra venous Tramadol 100 mg in 500 ml NS or 75 mg diclofenac sodium deep intra muscular was given as rescue analgesic. The time to first analgesic request and total analgesic requirement for first 24 h was noted. Any side effects and complications were also recorded. For data analysis Microsoft Excel 2007 was used and data was analyzed with the help of percentage, mean

received oxygen via nasal prongs with a flow of 3-4 L/min.

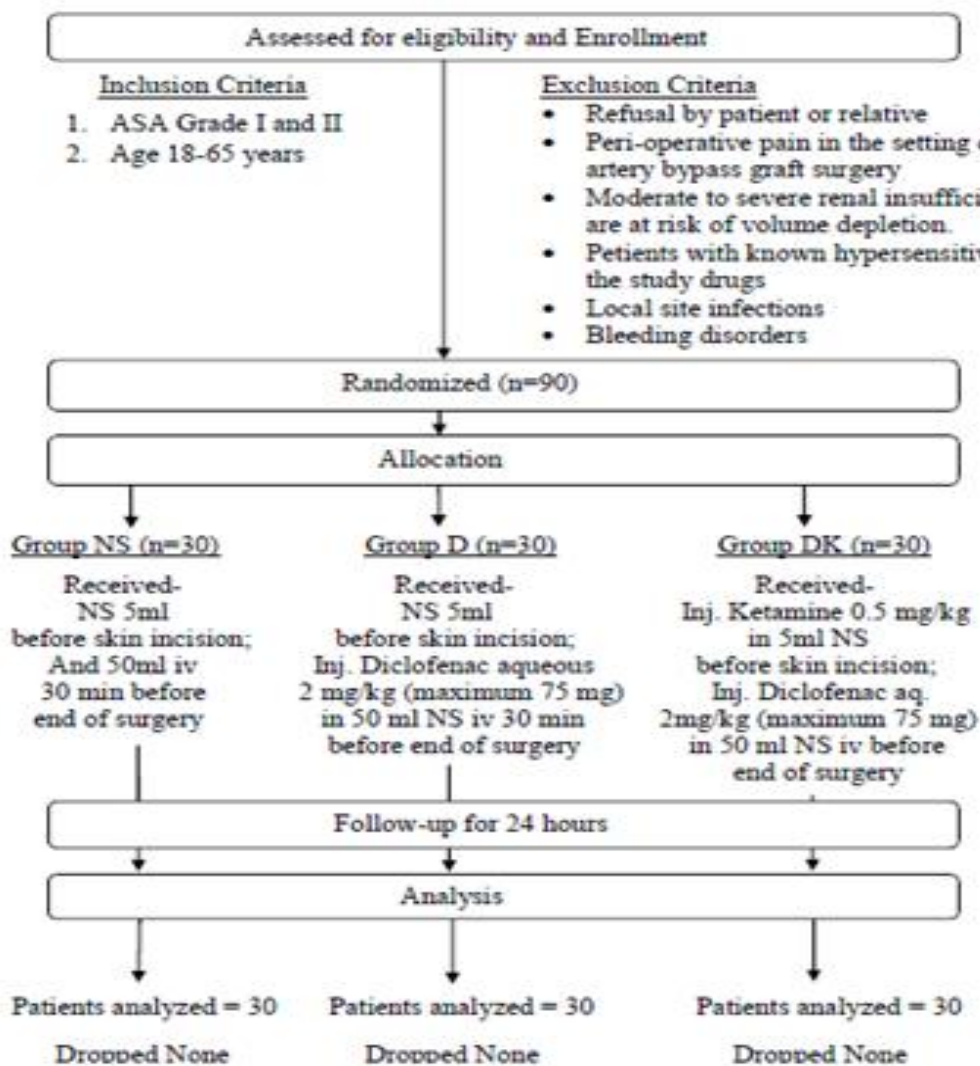
Study drugs were given as per group allocation to each patient. (Figure 1)

Surgery was performed after achieving adequate levels of sensory and motor block. VAS scores, post-operative vitals were noted immediately after transfer to post anaesthesia care unit and SD in the form of tables and charts. ANOVA (one factor) was applied for all quantitative parameters. Chi-square test was applied for all qualitative parameters and "p" values calculated using statistical software Primer of Biostatistics version 6.0. P value less than 0.05 was considered statistically significant. The sample size was calculated according to the time to initiation of pain and it was estimated that a group sample size of 30 patients for each group to detect a difference of 180 minute with power of study as 80.00%.

RESULTS

The methodology of the study is shown as a consort flow diagram (Figure 1):

Fig 1: Consort flow diagram



Demographic data were comparable in all three groups. The inter group difference of peri-operative haemodynamics was also statistically insignificant. The mean duration of surgery in all the three groups was found to be comparable (p value 0.550), (Table 1). Post-operative VAS score was statistically significant (p=0.001) between T30 min to T24 h with lower VAS scores in Group DK as compared to Group NS and Group D (Table 2).

Duration to first rescue analgesic was significantly higher (p=0.001) in Group DK (~6hrs) as compared to Group NS (~3hrs) and Group D (~4hrs), as depicted in Graph 1. Analgesic dose requirement in first 24 hours was significantly lower in Group DK (1.27±0.45) as compared to Group NS (2.86±0.44) and Group D (1.67±0.55); p value=0.001 (Graph 2)

Any fall in systolic blood pressure of more than 30% of baseline or MAP < 60 mmHg was considered as hypotension and was managed by intravenous fluids and inj. Mephentermine 6mg I.V. if required. Inj. Ondansetron (0.1mg/kg) intravenous was administered to treat nausea. However, no significant anaesthesia related complication was observed in any group.

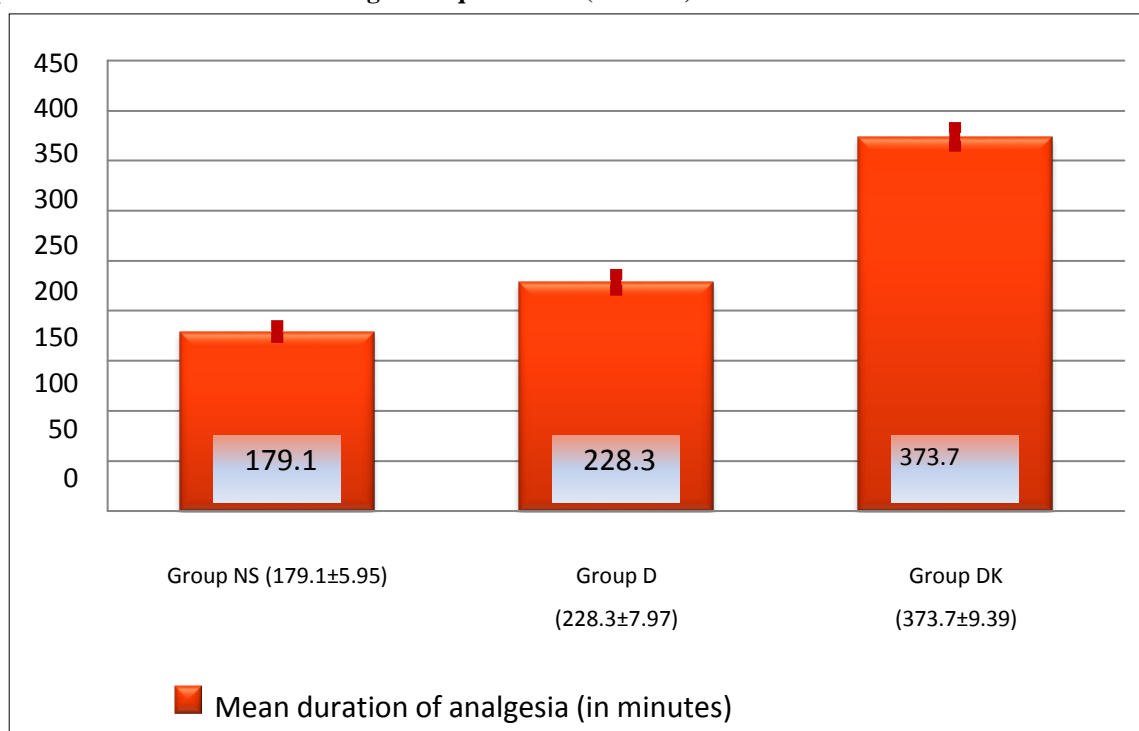
Table 1: Demographic data and duration of surgery

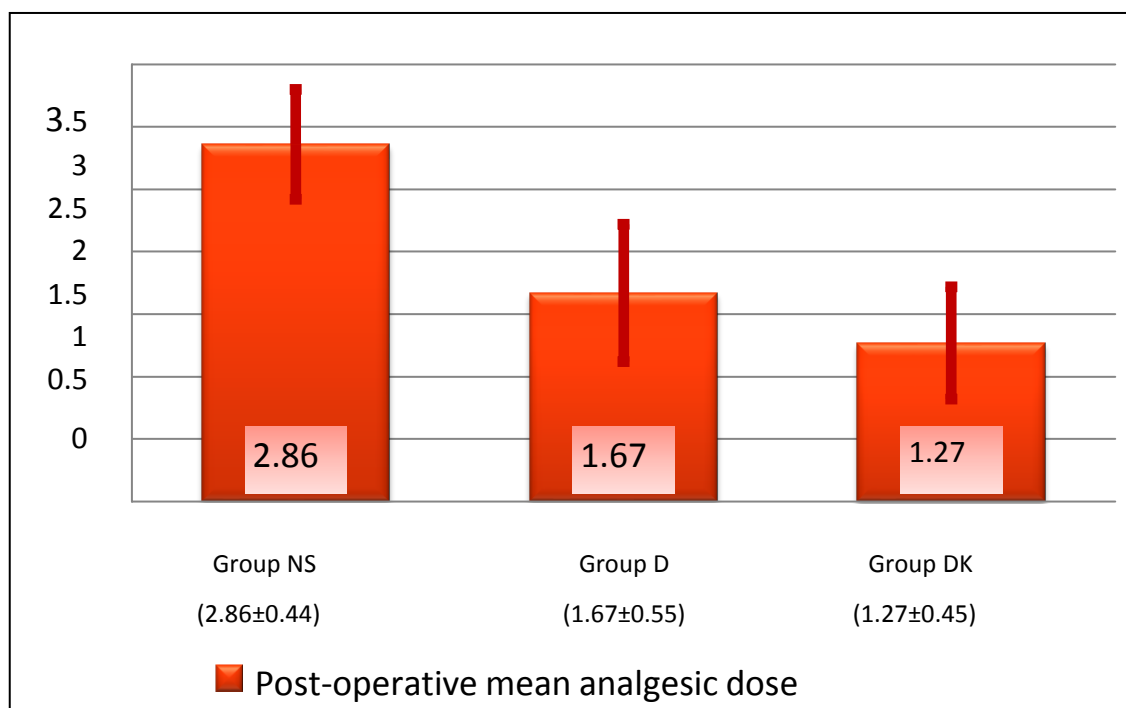
Characteristics	Group NS (n=30)	Group D (n=30)	Group D+K (n=30)	P value
M:F	23:7	27:3	28:2	0.302
Age (Years)	39.3±12.01	38.61±20.54	38.46±13.60	0.814
Weight (kg)	61.96±10.78	58.81±10.81	61.90±10.82	0.872
Duration of surgery	86.44±35.41	80.30±28.85	88.16±33.00	0.550

Table 2: Postoperative mean VAS score

Time	Group NS		Group D		Group D+K		P value
	Mean	SD	Mean	SD	Mean	SD	
T0	0.44	0.50	0.43	0	0.23	0.43	0.521
T30	1.4	0.62	0.93	0.25	0.53	0.50	0.001*
T1	1.93	0.58	1.33	0.50	0.86	0.56	0.001*
T3	4.40	1.43	3.36	0.60	1.8	0.48	0.001*
T6	3.63	0.99	4.36	0.91	4.26	1.28	0.001*
T12	4.56	0.76	4.13	1.26	4.0	0.98	0.001*
T24	5.03	0.93	4.96	1.42	3.06	1.01	0.001*

Graph 1: Mean duration of first analgesic requirement (P=0.001)



Graph 2: Mean dosage requirement of rescue analgesia (P=0.001)

DISCUSSION

Adequate control of acute post-operative pain remains a challenge despite the availability of a variety of analgesia none of individual techniques as provide a complete package of good analgesia combined with minimal adverse effects, ease of administration, low cost and patient satisfaction. The concept of multimodal analgesia is, therefore, becoming increasingly popular as it consists of a combination of analgesia techniques aimed at achieving good pain control with reduced opioid-associated adverse effects such as nausea, vomiting, pruritis, sedation and respiratory depression.^[6]

Present study compared the efficacy and safety of intravenous diclofenac sodium with or without pre-emptive ketamine for early post-operative pain relief in lower limb surgery under spinal anaesthesia. The rationale for using combination of ketamine and diclofenac is that they have different mechanisms and sites of action in the pain pathway. Pre-emptive ketamine before nociceptor input can prevent peripheral & central sensitization and diclofenac has been reported to accumulate in inflamed tissue for hours at much higher concentration, thereby decreasing sensitization of peripheral nociceptors.^[7,8]

Administration of a combination of diclofenac sodium and ketamine was observed to provide superior analgesia as compared to administration of diclofenac alone and control (p values <0.001) in post-operative period at 30 minutes, 1, 3, 6, 12 and 24 h. **Nesek-Adam V et al^[9]** did a similar study and reported significant difference in VAS score between patients receiving combination of diclofenac with ketamine and placebo at 1 (p<0.001), 2 (p<0.001), 4 (p=0.03)

and 6h (p<0.01). Their results are comparable to present study. Our results were also comparable to study conducted by **Mahmoud M Amer et al^[10]** who reported significantly lower VAS score in patients receiving combination of IV 1g acetaminophen and 0.5 mg/kg ketamine (P<0.05) as compared to placebo and acetaminophen and ketamine alone.

Patients from all the three study groups required post-operative analgesia, however, the requirement of first time rescue analgesic was significantly earlier in Group NS as compared to Group DK and Group D (p value 0.001). Total number of mean doses of rescue analgesia required within first 24h was lower in Group DK (1.27±0.45) as compared to Group NS (2.86±0.44) and Group D (1.67±0.55) and the difference was statistically significant (p value 0.001). Similar to our study, **Nesek-Adam et al^[9]** also observed that the duration for requirement of first rescue analgesic was longer in patients receiving a combination of diclofenac and ketamine (6.4±4.0h) as compared to patients receiving placebo (1.3±1.0h) and diclofenac alone (3.8±3.9h).

However, in contrast to our results, **Ozgur Canbayet al.^[11]** reported that the pre-emptive use of diclofenac sodium in combination with ketamine and remifentanyl did not significantly enhance post-operative analgesia after laparoscopic gynecological procedures.

Ketamine and diclofenac act on different receptors and also their mechanism of action is very different from each other. Thus, even though use of diclofenac and ketamine alone have been reported to reduce post-operative pain, administration of their combination provides a superior analgesic effect due to synergism

of these drugs. The administration of ketamine before nociceptive input can prevent central sensitization and improve post-operative analgesia.^[13]

Present study had a few limitations. Pain is a subjective sensation, quantification and objective observation was difficult as pain threshold has a great inter patient variability. We could not maintain uniformity in terms of incision length, type of fracture, duration of surgery and type of surgery in our subjects which may have led variability in severity of pain.

CONCLUSION

Use of pre-emptive ketamine and intravenous diclofenac sodium as a part of multimodal analgesic regimen reduces immediate post-operative pain and analgesic requirements with minimal associated adverse effects as compared to the standard regimen alone. Hence, were commending its use in lower limb orthopedic surgery under spinal anaesthesia to enhance therecovery and the render patient pain free.

REFERENCES

1. Woolf CJ, Chong MS. Pre-emptive analgesia-treating post-operative pain by preventing the establishment of central sensitization. *Anesth Analg* 1993; 77:362-79.
2. Kissin I. Pre-emptive analgesia. *Anaesthesiol* 2000; 93:1138-43.
3. Gottschalk A, Gottschalk A. Continuous wound infusion of local anesthetics: importance in postoperative pain therapy. *Anaesthesist*. 2010;59(12):1076–1082.
4. Gritsenko K, Khelemsky Y, Kaye AD, et al. Multimodal therapy in peri-operative analgesia. *Best Pract Res Clin Anaesthesiol* 2014;28(1):59-79.
5. Tonussi CR, Ferreira SH. Mechanism of diclofenac analgesia: direct blockade of inflammatory sensitization. *Eur J Pharmacol*.1994;251:173-179.
6. Liu SS, Richman JM, Thirlby RC, Wu CL. Efficacy of continuous wound catheters delivering local anesthetic for postoperative analgesia: a quantitative and qualitative systematic review of randomized controlled trials. *J Am Coll Surg*. 2006;203(6):914–932.
7. Fowler PD, Shadforth MF, Crook PR, et al. Plasma and synovial fluid concentrations of diclofenac sodium and its major hydroxylated metabolites during long-term treatment of rheumatoid arthritis. *Eur J Clin Pharmacol*. 1983;25:389-394.
8. Schweitzer A, Hasler-Nguyen N, Zijlstra J. Preferential uptake of the non steroid anti-inflammatory drug diclofenac into inflamed tissues after a single oral dose in rats. *BMC Pharmacol*.2009;9:5.
9. Nesek-Adam V, Grizelj-Stojcic E, Masic V, Rasic Z, Schwarz D. Pre-emptive use of diclofenac in combination with ketamine in patients undergoing laparoscopic cholecystectomy: a randomized, double-blind, placebo-controlled study. *Surg Laparosc Endosc Percutan Tech* 2012;22(3):232-8.
10. Amer MM, Rashwan DA, Sayem DM. Pre-emptive Use of Intravenous Acetaminophen, Ketamine or Their Combination in Patients Undergoing Elective Open Abdominal and Urological Surgeries: Effects on Intraoperative and Post-operative Analgesic Requirements. *Med. J. Cairo Univ*. 2013;81(1):975-81.
11. Canbay O, Karakas O, Celebi N, Peker L, Coskun F, Aypar U. The pre-emptive use of diclofenac sodium in combination with ketamine and remifentanyl does not enhance post-operative analgesia after laparoscopic gynaecological procedures. *Saudi Med J* 2006;27(5):642-5.
12. White PF. The role of non-opioid analgesic techniques in the management of pain after ambulatory surgery. *Anasthanalg*.2002;94;577-585.