



## COMPARISON OF INTRAVENOUS DICLOFENAC SODIUM WITH OR WITHOUT PRE-EMPTIVE KETAMINE FOR POSTOPERATIVE ANALGESIA IN PATIENTS UNDERGOING TOTAL ABDOMINAL HYSTERECTOMY UNDER SPINAL ANAESTHESIA. A COMPARATIVE MULTIMODAL ANALGESIA APPROACH

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### ABSTRACT

**BACKGROUND AND AIMS:** Pre-emptive analgesia is initiated before surgery in order to prevent the establishment of central sensitization during intra-operative and early post-operative period. 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 patients undergoing total abdominal hysterectomy under spinal anaesthesia.

**METHODS:** This was a prospective, randomized, double blinded controlled comparative tertiary hospital based study. Three groups of 30 patients each, i.e., receiving diclofenac with and without pre-emptive ketamine and control group were enrolled. The time of first analgesic request, total analgesic requirement in first 24h, intra-operative and post-operative vitals, any side effects and complication were recorded.

**RESULTS:** Statistically significant differences were observed in post-operative mean VAS scores between T30m to T24h, mean time of requirement of first dose of rescue analgesia request was longer in patients in group DK ( $373 \pm 9.39$  min.), as compared to group NS ( $179.13 \pm 5.95$  min.) and group D ( $228.30 \pm 7.97$  min.), post-operative requirement of analgesia in first 24h was lower in group DK ( $1.27 \pm 0.45$ ) as compared to group NS ( $2.86 \pm 0.44$ ) and group D ( $1.67 \pm 0.55$ ), and quality of analgesia among the three groups ( $p=0.001$ ).

**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, post-operative pain, ketamine, diclofenac

### INTRODUCTION

Multimodal modality of analgesia is most widely used for post operative pain relief. Multimodal and pre-emptive analgesia these two concepts can be combined together to improve the outcome of surgery while minimizing the potential adverse effects of the opioid medication.<sup>[1]</sup> 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.<sup>[2]</sup> Multimodal analgesia targets multiple nociceptive pathways (both central & peripheral) through several mechanism resulting in additive or synergistic effect of analgesic medication. It includes administration of pharmacological medication of different classes, employing various analgesic agents & techniques thus providing greater pain relief with lower doses of medication & less side effects compared to monomodal therapy.<sup>[3,4]</sup>

Diclofenac, being an NSAID, is thought to act via inhibiting prostaglandin synthesis. Diclofenac sodium is an analgesic, antipyretic, anti-inflammatory drug. Ketamine is a N-methyl-D-aspartate (NMDA) receptor antagonist which, at sub-anaesthetic doses ( $\leq 0.5$  mg/kg intravenous [IV]), ketamine possesses centrally mediated analgesic properties with minimal effects on consciousness and cognition. Numerous clinical studies support the role of sub-anaesthetic ketamine as an analgesic, particularly for acute pain in the perioperative period.<sup>[5]</sup>

This study was designed to evaluate the effectiveness and safety of intravenous diclofenac sodium with or without pre-emptive ketamine for post-operative pain relief without any

complication and side effects in Total abdominal hysterectomy under spinal anaesthesia.

### METHODS:

The present study was conducted during the period from August 2018 to July 2019 on 90 ASA grade I and II female patients, age greater than 40 years undergoing TAH under spinal anaesthesia in Department of Anaesthesia at our tertiary care hospital after taking approval from Institutional Ethical Committee (2019/1554/19-03-2019/06) and valid written informed consent from patients / their close relatives. 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 would be sufficient to detect a difference of 180 minute between study Groups with a significant level of  $< 0.05$  and power of study as 80.00%.

The study design was a prospective, randomized, double blinded controlled comparative, tertiary hospital based study; using computer generated random numbers, the patients were randomly allocated into three groups of 30 patients in each. Fig (1)

Pre-anaesthetic evaluation including history, physical and general examination was carried out a day before surgery. The procedure was explained to each patient. All patients were kept nil by mouth for six hours before the surgery. Visual Analogue Scale (VAS) for pain was explained to every patient at the time of pre-anaesthetic evaluation. Routine laboratory investigations like haemogram, bleeding time, clotting time, blood sugar, blood urea, serum creatinine, serum bilirubin (direct, indirect and total), urine examination, serum total protein, serum alkaline phosphate, SGOT, SGPT, chest x-ray

and ECG were done for every patient.

After confirmation of fasting status patient was shifted to OT & baseline parameters was noted after applying multipara monitors i.e. NIBP, ECG, SPO2 & pulse rate. Intravenous line secured with 18 G cannula & inj RL was started at 10 ml/kg/hour. Taking all antiseptic precaution spinal anaesthesia was given at L2-L3 or L3-L4 space using inj bupivacaine 0.5% H (0.25 mg/kg) with inj fentanyl 25 µg either in sitting or lateral decubitus position depending upon patient convenience. Surgery was allowed when sensory loss at T6 & Bromage motor scale was grade 1 or 2. Patient was monitored through out the surgery. After completion of surgery patient was shifted to recovery area with stable hemodynamic. Intra-operative and post-operative vitals, any side effects and complication were recorded.

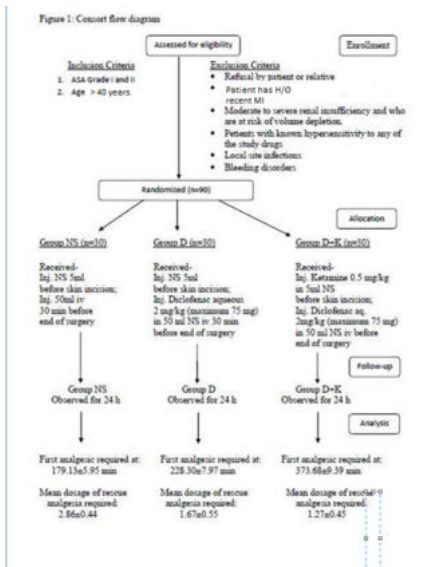
VAS scores, post-operative vitals were noted immediately after transfer to post anaesthesia care unit (T0) and at 30min, 1, 3, 6, 12, 24h post-surgery. Ondansetron 4 mg IV was given if patients complained of nausea or vomiting. 75 mg Diclofenac Sodium deep intra muscular as per hospital schedule was given when VAS > 4 or when the patient demanded analgesia. The time to first analgesic request and total analgesic requirement for first 24 h was noted.

Data was collected from eligible patients with the help of a pre-structured pre-tested proforma. For data analysis Microsoft Excel 2007 was used and data was analyzed with the help of percentage, mean and SD in the form of tables and charts. Appropriate tests of significance were applied wherever required. 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.

**RESULTS:**

Demographic data and peri-operative haemodynamic parameters were comparable in all three groups. All the three groups were comparable regarding mean age and mean weight (p value 0.814 and 0.872 respectively). The mean duration of surgery in all the three groups was found to be comparable (p value 0.550), as shown in Table 1.

Table 2 shows statistical analysis of post-operative VAS Scores at different time intervals. Post-operative VAS score was seen statistically significant (p=0.001) between T30 min to T24 hours with lower VAS scores in Group DK as compared to Group NS and Group D.



Characteristics	Group NS (n=30)	Group D (n=30)	Group D+K (n=30)	P value
Age (Years)	45.3±12.01	44.61±20.54	44.46±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 1: Distribution of patients as per age, weight and duration of surgery**

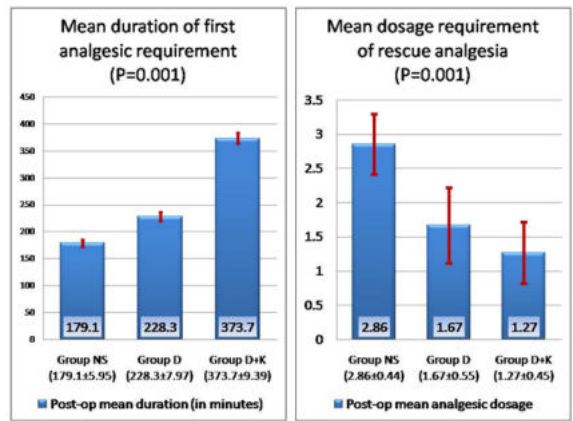
Time	Group NS		Group D		Group D+K		P value
	Mean	SD	Mean	SD	Mean	SD	
T0	0.44	0.50	0.43	0	0.23	0.43	0.521
T30	1.4	0.62	0.93	0.25	0.53	0.50	0.001*
T1	1.93	0.58	1.33	0.50	0.86	0.56	0.001*
T3	4.40	1.43	3.36	0.60	1.8	0.48	0.001*
T6	3.63	0.99	4.36	0.91	4.26	1.28	0.001*
T12	4.56	0.76	4.13	1.26	4.0	0.98	0.001*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

**Table 2: Statistical analysis of post-operative mean VAS score at different time intervals**

Quality of analgesia	Group NS	Group D	Group D+K	P value
Poor	23	1	0	0.001
Good	7	19	10	
Excellent	0	10	20	

**Table 3: Comparison of quality of analgesia in all the three groups**

Table 3 depicts comparison of quality of analgesia in all the three groups. The difference was statistically significant (p<0.05) in Group NS showing poor quality analgesia as compared to Group D and Group DK.



**Graph 1 (A): Post-operative mean duration of first analgesic requirement and (B): Post-operative mean dosage requirement of rescue analgesia in first 24hrs**

Post-operative mean duration of first analgesic demand was found to have statistically significant difference (p=0.001) among the three groups. Duration of analgesia was significantly higher among Group DK (~6hrs) as compared to Group NS (~2hrs) and Group D (~3hrs). graph 1 (A).

Statistical analysis of post-operative mean dosage requirement of rescue analgesia in first 24 hours among all the three groups has been depicted in Graph 1 (B). A highly significant difference was observed with p value 0.001, analgesic dose requirement being significantly higher among Group NS (2.86±0.44) when compared with Group D (1.67±0.55) and Group DK (1.27±0.45).

Complications: There were no complications observed in group DK while two patients in group D and three patients in group NS experienced hypotension and two patients in group NS had nausea.

#### DISCUSSION:

Adequate control of acute post-operative pain remains a challenge despite the improved understanding of pain mechanisms and implementation of a wide array of analgesic techniques. No single analgesic technique provides 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 and decreasing opioid-associated adverse effects such as nausea, vomiting, pruritis, sedation and respiratory depression.<sup>[6]</sup>

This study compared the efficacy and safety of intravenous diclofenac sodium with or without pre-emptive ketamine for post-operative pain relief in TAH under spinal anaesthesia.

Post-operative mean VAS score was found to be lower in Group DK as compared to Group NS and Group D. The difference between the groups statistically significant (p values <0.001) in early post-operative period at 30 minutes ( $1.4 \pm 0.62$ ,  $0.93 \pm 0.25$ ,  $0.53 \pm 0.50$ ), at first hour ( $1.93 \pm 0.58$ ,  $1.33 \pm 0.50$ ,  $0.86 \pm 0.56$ ), at 3 hours ( $4.40 \pm 1.43$ ,  $3.36 \pm 0.60$ ,  $1.8 \pm 0.48$ ), at 6 hours ( $3.63 \pm 0.99$ ,  $4.36 \pm 0.91$ ,  $4.26 \pm 1.28$ ) at 12 hours ( $4.56 \pm 0.76$ ,  $4.13 \pm 1.26$ ,  $4.00 \pm 0.98$ ), and at 24 hours ( $5.03 \pm 0.93$ ,  $4.96 \pm 1.42$ ,  $3.06 \pm 1.01$ ) respectively in Group NS, Group D and Group DK.

Nesek-Adam V et al<sup>[7]</sup> reported significant difference in VAS score between patients receiving combination of diclofenac and ketamine compared to placebo at 1 (p<0.001), 2(p<0.001), 4(p=0.03) and 6h (p<0.01). Their results are comparable to our study. Our study also has similar results to Mahmoud M Amer et al<sup>[8]</sup> 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 time of first analgesia request was longer in patients in Group D+K ( $373.68 \pm 9.39$ ) as compared to Group NS ( $179.13 \pm 5.95$ ) and Group D ( $228.30 \pm 7.97$ ) (p value 0.001). Total number of mean doses of rescue analgesia required within first 24 hrs was lower in Group D+K ( $1.27 \pm 0.45$ ) as compared to Group NS ( $2.86 \pm 0.44$ ) and Group D ( $1.67 \pm 0.55$ ) which was found to be statistically significant (p value 0.001).

Nesek-Adam et al<sup>[7]</sup> in their study also found that the duration for requirement of first rescue analgesia was longer in patients receiving a combination of diclofenac and ketamine ( $6.4 \pm 4.0$ h) as compared to patients receiving placebo ( $1.3 \pm 1.0$ h) and diclofenac alone ( $3.8 \pm 3.9$ h). Their results were comparable to our study. In contrast to our results, OzgurCanbayetal<sup>[9]</sup> reported that the pre-emptive use of diclofenac sodium in combination with ketamine and remifentanyl did not enhance post-operative analgesia after laparoscopic gynecological procedures. The results of study conducted by Heydari SM et al<sup>[10]</sup> were similar to our study who compared the preventive analgesic effect of ketamine, paracetamol and magnesium sulfate on post-operative pain control in patients undergoing lower limb surgery. They found that total opioid use was lower and the time for the first request for post-operative analgesia was longer for ketamine group. Post-operative pain score was significantly lower in ketamine group than others at 2 and 6 hours post-operatively.

Although diclofenac and ketamine have been individually reported to decrease post-operative pain, it is considered that possibly due to different mechanisms and sites of action, this drug combination is more effective than either drug alone. The administration of analgesic drug before nociceptive input can prevent peripheral and central sensitization and improve post-operative analgesia.<sup>[11]</sup>

#### CONCLUSION:

Pre-emptive intravenous ketamine and intravenous diclofenac sodium as a part of multimodal analgesic regimen decreases pain score and postoperative analgesic requirement and also delays the time to first analgesic request and provides better satisfaction with pain relief as compared to the standard regimen alone.

Therefore we recommend this multimodal analgesic regimen in TAH under spinal anaesthesia to enhance the recovery 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. *AnesthAnalg* 1993; 77:362-79.
2. Kissin I. Pre-emptive analgesia. *Anaesthesiol* 2000; 93:1138-43.
3. Moucha CS, Weiser MC, Levin EJ. Current strategies in anaesthesia and analgesia for total knee arthroplasty. *J Am Acad Orthop Surg* 2016; 24(2):60-73.
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. Himmelseher S, Durieux ME. Ketamine for perioperative pain management. *Anesthesiology* 2005; 102:211-20.
6. Rewari V, Ramachandra R. Continuous wound infiltration of local anaesthetics for acute post-operative pain – A revisit. *Indian J Anaesth* 2019; 63(6):425-7.
7. Nesek-Adam V, Grizelj-Stojicic 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.
8. 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.
9. 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.
10. Heydari SM, Hashemi SJ, Pourali S. The comparison of preventive Analgesic effect of ketamine, Paracetamol and magnesium sulfate on post-operative pain control in patients undergoing lower limb surgery. *Adv Biomed Res* 2017; 6:134.
11. White PF. The role of non-opioid analgesic techniques in the management of pain after ambulatory surgery. *Anasthanalg.* 2002; 94:577-585.