Nefopam versus Ketorolac for Post-operative Pain Control after Cesarean Section: A Prospective Randomized Clinical Study

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Received:

Accepted:

Abstract

Background: Cesarean delivery is the most common inpatient surgical procedure performed worldwide; improving the peri-operative care of parturient has significant global implications. **This study aimed to** compare Ketorolac versus Nefopam when administered intravenously with Tramadol during induction of anesthesia as post-operative analgesia over a 24 hours period following surgery in patients who undergo cesarean section. **Methods:** This prospective randomized study was conducted on 100 female patients with American Society of Anesthesiolbogists (ASA) classification II. Patients were randomly allocated into two equal groups: group N: received slow intravenous administration of Nefopam. Group K: received slow intravenous administration of Ketorolac. **Results**: The time of the 1st rescue analgesic requirement was significantly delayed in group N compared to Group K (P<0.001). Bradycardia and hypotension did not occur in any of the studied groups. Incidence of nausea & vomiting was significantly higher in group N compared to Group K (P=0.015). The patients' satisfaction was significantly different between both groups, showing that group N was significantly satisfied compared to Group K (P<0.001). Nefopam was associated with significantly lower pain scores, lower heart rate, lower mean arterial pressure, delayed first rescue analgesic requirement, and lower total opioid consumption compared to Ketorolac. However, the incidence of nausea and vomiting was significantly higher in the Nefopam group.

Keywords: Ketorolac; Nefopam; Tramadol; Cesarean Section.

Introduction

Cesarean delivery is the most common inpatient surgical procedure performed worldwide; improving the peri-operative care of parturient has significant global implications (1).

Acute postpartum pain is a key determinant of maternal satisfaction; may lead to persistent postoperative pain. It is a predictor of postpartum depression; and can reduce early breast-feeding success (2).

The goal for postoperative pain management is to reduce or eliminate pain and discomfort with a minimum of side effects. Various agents (opioid vs. non-opioid), routes (oral, intravenous, neuraxial, regional) and modes (patient controlled vs. "as needed") for the treatment of postoperative pain exist. The gold standard is the patient's self-assessment done routinely after surgery to measure the efficacy of pain management. Responsive analgesia management with good patient communication is the key to a successful program (3).

Nefopam is a benzoxazocine compound that is structurally related to orphenadrine and diphenhydramine. It is a centrally acting analgesic with both supra-spinal and spinal sites of action. Nefopam is neither an opiate nor a non-steroidal non-inflammatory drug. Nefopam does not induce respiratory depression, even in postoperative patients (4).

Nefopam hydrochloride is a centrally acting ant nociceptive compound that inhibits the reuptake of serotonin, norepinephrine and dopamine, the three most important substances in the transmission of pain resulting in reduced glutaminergic transmission by decreasing the activation of postsynaptic glutaminergic receptors and it also has supraspinal and spinal sites of action. Given that postoperative pain is acute nociceptive, inflammatory and even neuropathic in nature (5).

Ketorolac (tromethamine) is the first NSAID approved for parenteral use. It is used for a variety of clinical indications but is mainly administered for the management of postoperative pain. It can also be used for treatment of cancer related pain, for pain after cesarean delivery, and in the emergency department for treatment of migraine headaches, renal colic, musculoskeletal pain, and sickle cell crisis. Ketorolac primarily exerts its effects through inhibition of the cyclooxygenase (COX) -1 and -2 isozymes, with a greater affinity for COX-1. All forms of Ketorolac are rapidly absorbed with a mean half-life for absorption of 3.8 minutes, and duration of action of approximately 6 to 8 hours. The adverse events associated with ketorolac are similar to those of other NSAIDs (6).

The use of ketorolac is associated with a small increased risk of GI and possibly operative site bleeding, and it is

advisable to always communicate with the surgeon before administering this drug preoperatively (7).

The purpose of this study was to compare Ketorolac versus Nefopam when administered intravenously with Tramadol during induction of anesthesia as post-operative analgesia over a 24 hours period following surgery in patients who undergo cesarean section.

Patients and methods

This prospective randomized cross-sectional study, was done in the period from January 2024 until June 2024, at Benha University Hospitals on 50 patients

An approval from the Research Ethics Committee of Benha Faculty of Medicine was obtained (MS 42-11-2023)

An informed written consent from all patients or first-degree relatives before participation was obtained.

The study aimed to compare the efficacy of intravenous Nefopam and Ketorolac, administered with Tramadol during the induction of anesthesia, for post-operative analgesia over a 12-hour period following cesarean section.

Inclusion criteria were female patients aged between 20 to 40 years old, weight ranged between 70 and 110 Kg and American Society of Anesthesiologists (ASA) classification I and II.

Exclusion criteria were patient refusal, who are taking analgesics for chronic illness or have a history of substance abuse, who are unable to describe their postoperative pain (e.g., language barrier or neuropsychiatric disorder), with known allergy to Nefopam, Ketorolac and opioid, with infection at the site of the needle puncture, and with major respiratory, cardiac, renal or hepatic disorders.

Grouping: Patients were randomly allocated into two equal groups: **Group N:** Received slow intravenous administration of Nefopam. **Group K**: Received slow intravenous administration of Ketorolac.

Nefopam Dosing: Patients in this group received a slow intravenous infusion of Nefopam. The dose of Nefopam was typically initiated at 20 mg, diluted in 100 mL of 0.9% saline, and administered over 15-20 minutes. This dosing regimen was chosen based on the standard analgesic protocol for Nefopam in postoperative pain management. The infusion was started just before the induction of anesthesia to ensure adequate plasma levels by the time of surgical incision.

Tramadol Adjunct: In addition to Nefopam, patients in Group N also received Tramadol as part of their analgesic regimen. The dose of Tramadol was 100 mg, administered intravenously, to complement the analgesic effect of Nefopam and provide

a multimodal approach to pain management.

Group K (Ketorolac Group):

Ketorolac Dosing: Patients in this group received a slow intravenous infusion of Ketorolac. The standard dose for Ketorolac in this setting was 30 mg, diluted in 100 mL of 0.9% saline, and administered over 15-20 minutes. This dosage is in line with the recommended dose for postoperative analgesia in adults undergoing surgical procedures.

Tramadol Adjunct: Similar to Group N, patients in Group K also received tramadol as an adjunct analgesic. The dose was the same as in Group N, 100 mg intravenously, to ensure consistency in the analgesic protocol between the two groups.

Additional Medications:

Anesthetic Agents: All patients in both groups received standard anesthetic agents for induction and maintenance of anesthesia. Sevoflurane was used for maintenance, and neuromuscular blockade was reversed with neostigmine and atropine at the end of the surgery.

Pitocin: After the delivery of the fetus, all patients received 20 to 40 IU of Pitocin (oxytocin) to facilitate uterine contraction and reduce the risk of postpartum hemorrhage.

Monitoring and Adjustments:

Patients were closely monitored during and after the administration of Nefopam and Ketorolac for any signs of adverse reactions or inadequate pain control. The doses were chosen based on standard practice and the specific needs of the patient population undergoing cesarean section.

If necessary, adjustments to the analgesic regimen were made based on the patient's response and the clinical judgment of the attending anesthesiologist.

Anesthetic and Analgesic Protocol:

Before induction of anesthesia name, age, patient identification number, weight, ASA class, and initial vital signs all were recorded. Anesthesia was induced with medications mentioned above, and then endotracheal intubation was performed by direct laryngoscopy. Then slow intravenous administration of Nefopam was given to (group N) and slow intravenous administration of Ketorolac was given to (Group K). Sevoflurane was used. Both groups received Tramadol to ensure analgesia.

The technique was ensured by preparing the medication. 10 ml syringe of either Nefopam diluted or ketorolac diluted solution. All patients received from 20 IU to 40 IU of Pitocin after delivery of fetus. After skin closure, Sevoflurane was turned off; neuromuscular blockade was reversed with neostigmine and atropine. Oral suction was done before

extubation. During the emergency phase 100 percent oxygen was administered and the patients were extubated when they meet the standardized extubation criteria.

Postoperative Monitoring and Data Collection:

On recovery, observer started to record the mean arterial blood pressure (MAP), heart rate (HR), O2 saturation and estimate the blood loss at the end of operation. Also, patient was evaluated for the presence of nausea, vomiting and sweating. Then the data were documented after 1 hr., 6 hr. and 12 hr. The post-operative measurements which include Numerical Rating Scale, nausea and vomiting and finally patient satisfaction were recorded.

Statistical analysis

Statistical analysis was done by SPSS v27 (IBM©, Armonk, NY, USA). The Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analyzed by unpaired student t-test. Quantitative non-parametric data were presented as the median and interquartile range (IQR) and were analyzed by Mann Whitney-test. Qualitative variables were presented as frequency and percentage (%) and analyzed using the Chi-square test or Fisher's exact test when appropriate. A two-tailed P value < 0.05 was considered statistically significant.

Results

There was no significant difference between both groups regarding the baseline characteristics (age, weight, height, BMI and ASA), duration of surgery, the baseline HR and MAP. **Table 1**

NRS at all-time measurements (2, 4, 6, 8, 12 and 18h) was significantly lower in group N compared to Group K (P<0.05), except at T0 and 24h was insignificantly different between both groups. The postoperative HR at all-time measurements (2, 4, 6, 8, 12 and 18h) was significantly lower in group N compared to Group K (P<0.05), except at T0 and 24h was insignificantly different between both groups. **Table 2**

The postoperative MAP at all-time measurements (2, 4, 6, 8, 12 and 18h) was significantly lower in group N compared to Group K (P<0.05), except at T0 and 24h was insignificantly different between both groups. The time of the 1st rescue analgesic requirement was significantly delayed in group N compared to Group K (P<0.001), and the total opioid consumption was significantly lower in group N compared to Group K (P=0.039). **Table 3**

There was no significant difference between both groups regarding the blood loss. Regarding the adverse events, nausea & vomiting occurred in 11 (22%) patients in group N and 2 (4%) patients in Group K. Bradycardia and hypotension did not occur in any of the

studied groups. Incidence of nausea & vomiting was significantly higher in group N compared to Group K (P=0.015). **Table 4**

The patients' satisfaction was significantly different between both groups, showing that group N was significantly satisfied compared to Group K (P<0.001). **Table 5**

Table 1: Baseline characteristics and vital signs of the studied groups

		Group N (n=50)	Group K (n=50)	P value
Age (days)		28.2 ± 4.04	28.7 ± 5	0.554
Weight (Kg)		89.8 ± 12.71	85.6 ± 11.76	0.094
Height (m)		1.63 ± 0.03	1.6 ± 0.03	0.349
BMI (Kg/m^2)		33.8 ± 5.13	32.4 ± 4.4	0.152
ASA	**ASA I**	36 (72%)	30 (60%)	0.205
	ASA II	14 (28%)	20 (40%)	
Duration of surgery (min)		50.1 ± 6.14	50.5 ± 6.07	0.732
HR (beats/min)		86.2 ± 8.46	84.8 ± 8.5	0.398
MAP (mmHg)		82.1 ± 7.9	84 ± 7.24	0.199

BMI: body mass index, ASA: American Society of Anesthesiologists, HR: heart rate, MAP: mean arterial pressure.

Table 2: Postoperative pain assessment by numerical rating scale (NRS) & Postoperative heart rate (beats/min) of the studied groups

	Group N (n=50)	Group K (n=50)	P value
T0	2 (1-3)	2 (1-3)	0.801
2h	2 (1-2)	3 (2-4)	<0.001*
4h	2 (2-3)	4 (3-5)	<0.001*
6h	2 (2-3)	3 (2-4)	0.025*
8h	3 (2-3)	3 (2-5)	0.021*
12h	3 (2-4)	4 (3-5)	<0.001*
18h	3 (3-4)	4 (3-5)	0.002*
24h	2 (1-3)	2 (1-2.75)	0.922
Postoperative heart rate			
T0	81.7 ± 7.05	83.3 ± 7.88	0.275
2h	89.3 ± 7.43	95.1 ± 9.6	0.001*
4h	89.2 ± 6.95	94.8 ± 9.55	0.001*
6h	89.5 ± 7.6	95.1 ± 11.86	0.006*
8h	89.7 ± 8.05	93.6 ± 10.65	0.042*
12h	94.5 ± 8.99	100.1 ± 10.3	0.004*
18h	92.9 ± 10.02	101.5 ± 9.89	<0.001*
24h	92.6 ± 9.65	93.3 ± 9.91	0.737

Table 3: Postoperative mean arterial pressure (mmHg) and rescue analgesic requirements of the studied groups

	Group N (n=50)	Group K (n=50)	P value
T0	84.96 ± 8.17	85.4 ± 8.21	0.770
2h	93.3 ± 8.85	98.8 ± 11.7	0.009*
4h	93.6 ± 9.26	102.6 ± 10.34	<0.001*
6h	95.8 ± 10.1	99.9 ± 8.32	0.029*
8h	93.2 ± 11.29	97.5 ± 9.14	0.037*
12h	95.9 ± 8.99	103.5 ± 10.98	<0.001*
18h	93.4 ± 8.45	103.9 ± 9.23	<0.001*
24h	93.1 ± 8.73	95.96± 9.51	0.120
Time of 1st rescue analgesic requirement (hr)	18.9 ± 7.44	9.8 ± 8.56	<0.001*
Total opioid consumption (mg)	23.1 ± 7.64	26.4 ± 8.27	0.039*

Data presented as Mean±SD, *: statistically significant as p value <0.05.

Table 4: Blood loss and adverse events of the studied groups

	Group N (n=50)	Group K (n=50)	P value
Blood loss (ml)	856.0 ± 192.9	862.0 ± 188.3	0.875
Adverse events			
Nausea & Vomiting	11 (22%)	2 (4%)	0.015*
Bradycardia	0 (0%)	0 (0%)	---
Hypotension	0 (0%)	0 (0%)	---

Data presented as Mean±SD,

Table 5: Patients' satisfaction of the studied groups

	Group N (n=50)	Group K (n=50)	P value
Poor	5 (10%)	16 (32%)	<0.001*
Fair	9 (18%)	20 (40%)	
Good	16 (32%)	14 (28%)	
Excellent	20 (40%)	0 (0%)	

*: statistically significant as p value <0.05.

Discussion

In terms of patients' characteristics and clinical data, there was no significant difference between both groups (group N and group K) regarding the baseline characteristics (age, weight, height, BMI and ASA), duration of surgery, and blood loss. There was no significant difference between both groups regarding the baseline HR and MAP.

In agreement with the present work, comparing Ketorolac and Nefopam when administered intravenously as postoperative analgesia in cesarean section, sixty patients, who were candidates for elective & emergency cesarean section, patients were randomly assigned to receive intravenous infusion of Nefopam or an intravenous infusion of Ketorolac with induction of

anesthesia. All patients received Tramadol ampule 100 mg after delivery of baby as analgesia. They reported that there are no statistical differences between ages, weight; blood loss and heart rate with p values are 0.703, 0.334, 0.325, 0.810 and 0.371 respectively (8). However, they found that there is a decrease in mean arterial blood pressure in the Ketorolac group (86.97 mmHg) more than Nefopam group (97.10 mmHg), with a significant p value less than 0.001 (8).

Regarding pain score in the current study, NRS at all-time measurements (2, 4, 6, 8, 12 and 18h) was significantly lower in group N compared to Group K (P<0.05), except at T0 and 24h was insignificantly different between both groups.

In harmony with our findings, reported postoperative pain using the numerical rating scale for Nefopam and Ketorolac. At 1 hour postoperative, Nefopam showed 0% no pain, 3.33% mild, 76.67% moderate, and 20% severe pain, while Ketorolac showed 0% no pain, 0% mild, 50% moderate, and 50% severe pain, with a significant difference (p < 0.001). At 6 hours, Nefopam had 0% no pain, 20% mild, 76.67% moderate, and 3.33% severe pain, whereas Ketorolac had 0% no pain, 3.33% mild, 93.3% moderate, and 3.33% severe pain (p < 0.001). At 12 hours, Nefopam had 3.33% no pain, 40% mild, 56.67% moderate, and 0% severe pain, while Ketorolac had 3.33% no pain, 26.67%

mild, 70% moderate, and 0% severe pain (8).

However, demonstrated postoperative pain intensities measured by the Numerical Rating Scale for two groups, ketorolac and Nefopam groups, at various time points post-surgery. At 2 hours, both groups had a median pain intensity of 4, with no significant difference between them (P = 0.917). This pattern continued at 6 hours (median pain intensity of 3, P = 0.403), 24 hours (median pain intensity of 2, P = 0.273), and 48 hours (median pain intensity of 1, P = 0.976), indicating no significant differences in postoperative pain intensities between the two groups at any of the measured time points (9). This variation may be due to the different studied population involved patients undergoing laparoscopic cholecystectomy, while our study focused on patients undergoing cesarean section.

In the current study, the postoperative HR at all-time measurements (2, 4, 6, 8, 12 and 18h) was significantly lower in group N compared to Group K (P<0.05), except at T0 and 24h was insignificantly different between both groups. The postoperative MAP at all-time measurements (2, 4, 6, 8, 12 and 18h) was significantly lower in group N compared to Group K (P<0.05), except at T0 and 24h was insignificantly different between both groups.

The observed lower postoperative heart rate (HR) and mean arterial pressure

(MAP) in Group N compared to Group K at various time points can be explained by the pharmacological effects of Nefopam. Nefopam's analgesic action leads to better pain control, which in turn can reduce the sympathetic nervous system activation that typically occurs in response to pain. This reduction in sympathetic activity can manifest as lower HR and MAP. Furthermore, Nefopam's potential for reducing anxiety and stress associated with postoperative pain may also contribute to a more stable cardiovascular response (10, 11). In contrast, the effects of Ketorolac, used in Group K, are primarily limited to inhibition of prostaglandin synthesis, which may not provide the same extent of modulation of the sympathetic response, resulting in relatively higher HR and MAP. The lack of significant difference at T0 and 24h may be attributed to the residual effects of anesthesia at T0 and the diminishing effects of the analgesics by 24h postoperatively.

The first rescue analgesic requirement was significantly delayed in group N compared to Group K (P<0.001), and the total opioid consumption was significantly lower in group N compared to Group K (P=0.039).

The delayed requirement for the first rescue analgesic and lower total opioid consumption observed in Group N compared to Group K can be attributed to the pharmacological properties of Nefopam. Nefopam, a non-opioid centrally acting analgesic, has a unique mechanism of action that involves inhibition of reuptake of serotonin, norepinephrine, and dopamine, as well as modulation of calcium channels and sodium channels, which contributes to its analgesic efficacy (12). This multifaceted action not only provides effective pain relief but also reduces the reliance on additional opioid analgesics, which is reflected in the delayed need for rescue medication and decreased overall opioid consumption in patients receiving Nefopam compared to those receiving Ketorolac, an NSAID that primarily works by inhibiting prostaglandin synthesis and has a more limited mechanism of action in pain control (8).

On the other hand, it was documented that the analgesic consumptions at postoperative 2, 6, 24, and 48 h were similar between the groups. Also, cumulative postoperative analgesic consumptions at postoperative 48 h were similar between the groups (Group K: 93.4 ± 24.0 ml vs. Group N: 92.9 ± 26.1 ml, P = 0.906) (9). This difference may be due to co-administered analgesics used. In this study, both Nefopam and Ketorolac were co-administered with fentanyl, whereas in our study, they were used in conjunction with Tramadol. The choice of co-administered analgesics could affect the overall analgesic efficacy and side effect profile; also the assessed outcomes were up to 48 hours postoperatively, while our study focused on a 12-hour postoperative period.

Regarding the adverse events, nausea & vomiting occurred in 11 (22%) patients

in group N and 2 (4%) patients in Group K. Bradycardia and hypotension did not occur in any of the studied groups. Incidence of nausea & vomiting was significantly higher in group N compared to Group K (P=0.015).

Our results are compatible, also reported the incidence of nausea and vomiting postoperatively. At 1 hour, Nefopam had a higher incidence of 36.67% compared to 23.33% for Ketorolac (p < 0.001). At 6 hours, the incidence was 6.67% for Nefopam and 0% for Ketorolac (p < 0.001). At 12 hours, both groups had a 0% incidence (p < 0.001) (8).

In a retrospective study compare the analgesic effects and adverse drug reactions (ADRs) of fentanyl intravenous patient-controlled analgesia (ivPCA) with Nefopam, a centrally acting analgesic agent with demonstrated opioid sparing activity, as compared to Ketorolac in a tertiary teaching hospital. A retrospective evaluation of electronic medical records was conducted on patient records including either Nefopam or Ketorolac with opioid ivPCA for post-operative pain management in general surgery department from January to December 2014. The status of pain control and ADRs were collected. Out of 6,330 general surgery cases, Nefopam was given in 153 prescriptions (6.9%) and ketorolac in 81 prescriptions (3.6%). The level of pain control was not different between two groups (70.9% vs. 75.3%; p = 0.51), but ADRs were more frequently reported in Nefopam group (9.8% vs. 2.5%; p < 0.05). New ADRs

of hot flushes (n = 1) and paresthesia in hands (n = 1) were reported in Nefopam group and they were unlisted in the approved package insert. No serious ADRs were reported in both groups (13).

In present work, the patients' satisfaction was significantly different between both groups, showing that group N was significantly satisfied compared to Group K (P<0.001).

The reported overall patient satisfaction with Nefopam and Ketorolac was as follows: For Nefopam, 3.33% of patients were very satisfied, 53.33% were somewhat satisfied, 40% were neither satisfied nor dissatisfied, 3.33% were somewhat dissatisfied, and 0% was very dissatisfied. For Ketorolac, 3.33% were very satisfied, 22.33% were somewhat satisfied, 44.44% were neither satisfied nor dissatisfied, 26.67% were somewhat dissatisfied, and 3.33% were very dissatisfied (p < 0.001) (8).

Conclusion

Nefopam was associated with significantly lower pain scores, lower heart rate, lower mean arterial pressure, delayed first rescue analgesic requirement, and lower total opioid consumption compared to Ketorolac. However, the incidence of nausea and vomiting was significantly higher in the Nefopam group.

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