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Nefopam Versus Ketorolac for Post-operative Pain Control in Cesarean Section

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نيفوبام و كيتورولاك للتحكم في الالم بعد الولادة القيصرية

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Abstract

More than 230 million people undergo surgery each year worldwide and the number is increasing annually. Surgery causes commonly postoperative pain that should be alleviated as soon and as effective as possible to reduce suffering, to promote the healing process and rehabilitation and to prevent complications. However, clinical pain management after surgery is far from being successful despite dramatically increased scientific evidence in this area. Many patients suffer from severe pain after surgery. Aim: The aim of this study is to compare between ketorolac and nefopam when administered intravenously as post-operative analgesia in cesarean section. Patients and methods: 60 patients, who were candidates for elective & emergency cesarean section, Patients were randomly assigned to receive intravenous infusion of Nefopam (Group A) or an intravenous infusion of Ketorolac (Group B) with induction of anesthesia. All patients received Tramadol ampule 100 mg after delivery of baby as analgesia. The patients were also observed for development of sweating, nausea and vomiting with the vital signs during recovery phase. Results: there are a significant difference between group A (Nefopam) and group B (Ketorolac) regarding Numerical rating scale (NRS) and patient satisfaction. Conclusions: Nefopam is more effective than ketorolac in controlling pain for patients undergoing cesarean section.

Keywords: Ketorolac, Nefopam, Cesarean section, Pain.

المستخلص

يخضع أكثر من 230 مليون شخص للجراحة كل عام في جميع أنحاء العالم ويتزايد العدد سنويًا. تسبب الجراحة ألمًا شائعًا بعد الجراحة يجب تخفيفه بأسرع ما يمكن وبفعالية قدر الإمكان لتقليل المعاناة وتعزيز عملية الشفاء وإعادة التأهيل ومنع المضاعفات. ومع ذلك ، فإن إدارة الألم السريرية بعد الجراحة بعيدة كل البعد عن النجاح على الرغم من الأدلة العلمية المتزايدة بشكل كبير في هذا المجال. يعاني العديد من المرضى من آلام شديدة بعد الجراحة , الهدف من هذه الدراسة هو المقارنة بين كيتورولاك و نيفوبام عند تناولهما عن طريق الوريد كمسكن بعد الجراحة في الولادة القيصرية. عرض 60 مريضًا ، كانوا مرشحين للولادة القيصرية الاختيارية والطارئة و الذين تم تعيينهم عشوائياً لتلقي اما التسريب الوريدي من مادة Nefopam (المجموعة أ) أو التسريب الوريدي من مادة كيتورولاك (المجموعة ب) مع تعريض الى التخدير. تلقى جميع المرضى ترامادول أمبول 100 ملغ بعد ولادة الطفل كمسكن للألم. كما لوحظ على المرضى تطور التعرق والغثيان والقيء مع العلامات الحيوية أثناء مرحلة الشفاء. بينت النتائج وجود فرق كبير بين المجموعة أ (نيفوبام) والمجموعة ب (كيتورولاك) فيما يتعلق بمقياس التصنيف العددي (NRS) ورضا المريض. استنتج من هذه الدراسة ان Nefopam أكثر فعالية من كيتورولاك في السيطرة على الألم المرضى الذين يخضعون لعملية قيصرية.

الكلمات المفتاحية: كيتورولاك ، نيفوبام ، ولادة قيصرية ، ألم.

Introduction

More than 230 million people undergo surgery each year worldwide and the number is increasing annually (Weiser *et al.,* 2008) (Nalini *et al.,* 2017). Surgery causes commonly postoperative pain that should be alleviated as soon and as effective as possible to reduce suffering, to promote the healing process and rehabilitation and to prevent complications. However, clinical pain management after surgery is far from being successful despite dramatically increased scientific evidence in this area. Many patients suffer from severe pain after surgery (Gerbershagen *et al.,* 2014).

Pain which is considered as the most common symptom that brings patients to see a physician is nearly always a manifestation of a pathological process. This symptom may have a wide variety of causes ranging from relatively benign conditions to acute injury, myocardial ischemia, degenerative changes, or malignancy. Pain relief has significant physiological benefits; hence, monitor-ing of pain relief is increasingly becoming an important postoperative quality measure. The goal for postoperative pain management is to reduce or eliminate pain and discomfort with a minimum of side effects (Richard, 2013). 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. Pain needs to be quantified to be treated effectively. The gold standard is the patient's self-assessment done routinely after surgery to measure the efficacy of pain management. Several scoring tools are available but a 10-point pain assessment scale, where 1 is no pain and 10 is the worst possible pain imaginable, has been nationally accepted. The key to adequate pain control is to reassess the patient and determine if he or she is satisfied with the

outcome. A satisfaction score should be obtained together with a pain score so as to minimize the chances that inadequately treated pain goes unnoticed. Responsive analgesia management with good patient communication is the key to a successful program (Garimella & Cellini, 2013 ; Haefeli, 2006).

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 (Alfonsi *et al.*, 2004). It was developed in the early 1970s as an antidepressant and myorelaxant but has been shown to be effective in preventing acute postsurgical hyperalgesia and nonsurgical neuropathic pain. Oral and intravenous forms of Nefopam are used, and the drug has an oral bioavailability of 40% and a plasma half-life of 3-5 h. Plasma peak concentrations are reached 15-20 min after intravenous injection and at 30 min during continuous infusion. Nefopam hydrochloride is a centrally acting antinociceptive 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 glutamatergic receptors and it also has supraspinal and spinal sites of action (Jin *et al.,* 2016). In addition to its analgesic effect, it also reduces postoperative shivering, making it favorable for perioperative use. Given that postoperative pain is acute nociceptive, inflammatory and even neuropathic in nature (Choi , 2016).

Despite the above-mentioned properties favoring Nefopam for perioperative use, adverse effects such as confusion and tachycardia have been

well noted. Furthermore, unexpected side effects including neuropsychiatric (related with abuse), cutaneous, or anaphylactic reactions have been reported. Therefore, extensive use of Nefopam in the perioperative period should wait until further research establishes the safety of the intraoperative use of Nefopam, defines the analgesic mechanisms, and provides good quality strategies for Nefopam in the multimodal analgesic approach (Choi, 2016).

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 has been used safely and effectively in select pediatric populations but at present is not recommended for use in children under the age of 17. Routes of administration include intravenous (IV), IM, oral (PO), ophthalmic, and intranasal (IN). 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. It is metabolized by the liver into hydroxylated and conjugated forms. The primary route of excretion is renal with 92% of the administered dose being found in the urine. Ketorolac crosses the placenta and is also excreted into breast milk in small quantities. The adverse events associated with ketorolac are similar to those of other NSAIDs, which include gastrointestinal (GI) bleeding, renal impairment, liver dysfunction, and possible allergic reactions. Use of ketorolac disrupts platelet aggregation through the inhibition of thromboxane A2.

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.

The aim of this study was to comparison between Ketorolac and Nefopam when administered intravenously with Tramadol during induction of anesthesia as post-operative analgesia over a 12 h period following surgery in patients who had undergone cesarean section.

Materials and Methods

This study is prospective, randomized, double-blinded clinical trial. The study was conducted in operating theatres in Al-Imamaien Al-Kadhumaien Medical City in Baghdad, Iraq, from August 2017 till January 2018. Sixty patients were prepared to cesarean sections; patients were divided into two equal groups. Group A received slow intravenous Nefopam and group B received slow intravenous ketorolac and both group received tramadol intravenously to compare the potency of these analgesic drugs in post-operative measures as a plan for post-operative pain management. Approval were obtained from Iraqi Committee for medical specializations as well as written informed written consent for participation in the study was signed by investigated subjects according to the Helsinki principles.

The inclusion criteria:

1. Elective or emergency cesarean sections under general anesthesia.
2. ASA class two.
3. Weight between 70-110 Kg
4. Age between 20-40 years old.

The exclusion criteria:

1. Patient refusal.
2. Patient with history of renal impairment.
3. Diabetic patients.
4. Patient with history of hypertension.
5. Patients in which her wound infiltrated by local anaesthesia.
6. Cases with allergy to medications used in the study.
7. Patient already on analgesics treatment.

Study procedure

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

The blinded technique was ensured by preparing the medication by my colleague, so he was handling as 10 ml syringe of either Nefopam diluted or ketorolac diluted solution. We both do not know which one was Nefopam or Ketorolac. 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 emergence phase 100 percent oxygen was administered and the patients were extubated when they met the standardized extubation criteria.

On recovery, observer starts 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 evaluated for the presence of Nausea, vomiting and sweating. Then we documented data after 1 hr., 6hr. and 12 hr. Post-operative which include Numerical Rating Scale (figure1), Nausea and vomiting and finally patient satisfaction by the following parameters:

Very satisfied 5

Somewhat satisfied 4

Neither satisfied nor dissatisfied 3

Somewhat dissatisfied 2

Very dissatisfied 1

Data analysis

The statistical analysis of this prospective study performed with the statistical package for social sciences (SPSS) 20.0 and Microsoft Excel 2013. Numerical data described as mean and standard deviation, Analysis of variance (ANOVA) used for comparison among study groups. Categorical data were described as count and percentage. Chi-square test or fisher exact test used to estimate the association between variables. The lower level of accepted statistical significant difference is bellow or equal to 0.05.

Results

This study included 60 patients; divided into two groups, 30 for each group all of them met the entry criteria of the study. Patients were able to complete the entire study and their data were included in the final analysis.

There are no statistical differences between Ages, weight; Dose of Pitocin, blood loss and heart rate with p values are 0.703, 0.334, 0.325, 0.810 and 0.371 respectively. There is decrease in mean arterial blood pressure in group B (86.97 mmhg) more than group A (97.10 mmhg). With a significant p value less than 0.001. (Figure 3-1)

Table 1: Patient Characteristics

	Group		P value
	Nefopam	Ketorolac	
Age	27.90±4.69	28.37±4.76	0.703
Weight	83.10±7.82	85.47±10.78	0.334
Pitocin	23.00±5.96	26.00±7.70	0.325
Blood loss	860.00±310.84	841.67±275.46	0.810
MAP	97.10±8.17	86.97±10.34	<0.001
HR	88.53±12.80	91.50±12.67	0.371

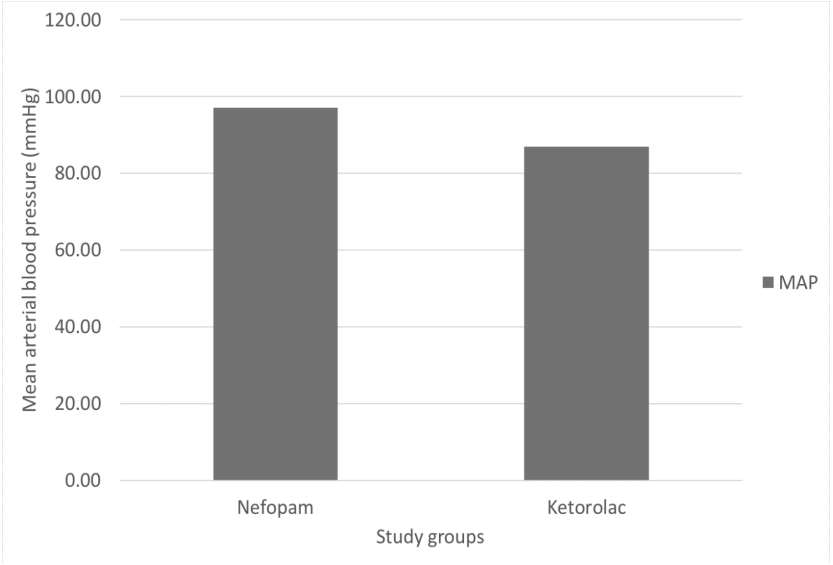

Figure 1: Difference in mean arterial pressure between two groups

The incidence of pain according to the numerical rating scale After 1 hr. post-operative for group A was 0 % no pain, 3.33 % mild pain, 76.67 % moderate pain and 20 % was severe pain, while in group B was 0% no pain, 0 % mild pain, 50 % moderate pain and 50 % was severe pain. With p value less than 0.001. After 6 hrs. The incidence of pain according to numerical pain scale for group A was 0 % no pain, 20 % mild pain ,76.67 % moderate pain and 3.33 % was severe pain, while in group B was 0% no pain, 3.33 % mild pain, 93.3 moderate pain and 3.33 % was severe pain with p value less than 0.001. After 12 hrs. The incidence of pain according to numerical pain scale for group A was 3.33 % no pain, 40 % mild pain, 56.67 % moderate pain and 0% severe pain, while in group B was 3.33 % no pain, 26.67 % mild pain, 70 % moderate pain and 0 % severe pain.

The incidence of nausea and vomiting After 1 hr. post operatively was higher in group A 36.67 % rather than group B 23.33 % with p value less than 0.001. After 6 hr. The incidence of nausea and vomiting was 6.67 % in group A and 0 % in group B. with p value less than 0.001. After 12 hr. The incidence of nausea and vomiting was 0 % in both groups with p value less than 0.001.

Table 2: Numerical rating scale post operatively

Numerical rating scale		Nefopam	Ketorolac	P value
After 1 hr.	0	0 (0)	0 (0)	<0.001
	2	1 (3.33)	0 (0)	<0.001
	4	9 (30)	4 (13.33)	<0.001
	6	14 (46.67)	11 (36.67)	<0.001
	8	4 (13.33)	12 (40)	<0.001
	10	2 (6.67)	3 (10)	<0.001

Numerical rating scale		Nefopam	Ketorolac	P value
After 6 hrs.	0	0 (0)	0 (0)	<0.001
	2	6 (20)	1 (3.33)	<0.001
	4	20 (66.67)	18 (60)	<0.001
	6	3 (10)	10(33.3)	<0.001
	8	1 (3.33)	1 (3.33)	<0.001
	10	0 (0)	0 (0)	<0.001
After 12 hrs.	0	1 (3.33)	1 (3.33)	<0.001
	2	12 (40)	8 (26.67)	<0.001
	4	17 (56.67)	17 (56.67)	<0.001
	6	0 (0)	4 (13.33)	<0.001
	8	0 (0)	0 (0)	<0.001
	10	0 (0)	0 (0)	<0.001

Table 3: Incidence of nausea and vomiting

Nausea & vomiting		Nefopam	Ketorolac	P value
After 1 hr.	No	19 (63.33)	23 (76.67)	<0.001
	Yes	11 (36.67)	7 (23.33)	<0.001
After 6 hrs.	No	28 (93.33)	30 (100)	<0.001
	Yes	2 (6.67)	0 (0)	<0.001
After 12 hrs.	No	30 (100)	30 (100)	<0.001
	Yes	0 (0)	0 (0)	<0.001

The incidence of patient satisfaction After 1 hr. post operatively in group A was 0 % very dissatisfied, 16.67 % was somewhat dissatisfied, 66.67 % was neither satisfied nor dissatisfied, 16.67 % was somewhat satisfied and 0 % was very satisfied while in group B was 13.33 % very dissatisfied, 40 % was somewhat dissatisfied, 33.33 % was neither satisfied nor dissatisfied, 13.33 % was somewhat satisfied and 0 % was very satisfied. With p value less than 0.001. After 6 hr. The incidence of patient satisfaction in group A was 0 % very dissatisfied, 3.33 % was

somewhat dissatisfied, 40 % was neither satisfied nor dissatisfied, 53.33 % was somewhat satisfied and 3.33 % was very satisfied while in group B was 3.33 % very dissatisfied, 32.33 % was somewhat dissatisfied, 56.67 % was neither satisfied nor dissatisfied, 13.33 % was somewhat satisfied and 3.33 % was very satisfied. With p value less than 0.001. After 12 hr. The incidence of patient satisfaction in group A was 0 % very dissatisfied, 0 % was somewhat dissatisfied, 26.67 % was neither satisfied nor dissatisfied, 56.67 % was somewhat satisfied and 16.67 % was very satisfied while in group B was 0 % very dissatisfied, 6.67 % was somewhat dissatisfied, 43.33 % was neither satisfied nor dissatisfied, 40 % was somewhat satisfied and 10 % was very satisfied with p value less than 0.001.

Table 4: Incidence of patient satisfaction

Patients satisfaction		Nefopam	Ketorolac	P value
After 1 hr.	1	0 (0)	4 (13.33)	<0.001
	2	5 (16.67)	12 (40)	<0.001
	3	20 (66.67)	10 (33.33)	<0.001
	4	5 (16.67)	4 (13.33)	<0.001
	5	0 (0)	0 (0)	<0.001
After 6 hrs.	1	0 (0)	1 (3.33)	<0.002
	2	1 (3.33)	7 (23.33)	<0.002
	3	12 (40)	17 (56.67)	<0.002
	4	16 (53.33)	4 (13.33)	<0.002
	5	1 (3.33)	1 (3.33)	<0.002
After 12 hrs.	1	0 (0)	0 (0)	<0.001
	2	0 (0)	2 (6.67)	<0.001
	3	8 (26.67)	13 (43.33)	<0.001
	4	17 (56.67)	12 (40)	<0.001
	5	5 (16.67)	3 (10)	<0.001

Discussion

This study examined the analgesic efficacy of Ketorolac and Nefopam that was co-administered with tramadol via IV rout for analgesia in patients undergoing cesarean section (Son *et al.,* 2017) . Patient characteristic (age, weight, dose of Pitocin, blood loss and heart rate) showing no significant differences between the two treatment groups as seen in table 1, P – value for age, weight, dose of Pitocin, blood loss and heart rate were 0.703, 0.334, 0.325, 0.810and 0.371 respectively and all of them more than 0.05. Numerical rating scale After 1 hr., 6 hr., and 12 hrs. Post operatively for group A show less pain than group B, with p value less than 0.001. This makes Nefopam better than ketorolac in controlling pain according to Numerical rating scale (NRS). Ji-Seon *et al.*, One hundred and sixty patients scheduled for laparoscopic cholecystectomy were randomly assigned to ketorolac (Group K) or Nefopam (Group N) groups. The anesthetic regimen was standardized for all patients. The analgesic solution contained fentanyl 600 μg and ketorolac 180 mg in Group K, and fentanyl 600 μg and Nefopam 120 mg in Group N, showing there were no significant differences in postoperative analgesics consumption and pain intensity between the Ketorolac-fentanyl and Nefopam-fentanyl combinations, this due to ketorolac and Nefopam have been used in high doses with high dose of Fentanyl.

Boo-Young *et al.*, 120 patients undergoing gynecologic surgery were divided randomly into two groups: Nefopam group treated with oxycodone 1 mg and Nefopam 1 mg bolus; and Ketorolac group treated with oxycodone 1 mg and ketorolac 1.5 mg bolus. After the operation, a blinded observer assessed the pain with a numeric rating scale (NRS) showing there were no

significant differences in NRS between both groups (Hwang *et al.,* 2015). This difference from our study may be due to the use of a different combination with low doses of Nefopam / Oxycodone, Ketorolac / Oxycodone while in our study we used Nefopam / Tramadol, Ketorolac / Tramadol. Kumar *et al*. (1996) prospective double blind randomized clinical trial was conducted in 181 patients after single intravenous (I.V.) bolus dose of these two drugs for relieving acute post-operative pain following upper abdominal surgery. 100 patients received 30 mg Ketorolac (group A) while 81 patients received 20 mg Nefopam (group B). Both the groups were comparable in terms of age and sex. Showing 30 mg Ketorolac provides progressively increasing and lasting pain relief compared to 20 mg Nefopam when used as single I.V. bolus dose in immediate post-operative period following upper abdominal surgery.

(Oh YN *et al., 2018)* Ninety-two patients were randomly divided into two groups to receive intravenous PCA. Patients were assigned to either the Nefopam group (Nefopam 120 mg and Fentanyl 20 μg/kg) or the Ketorolac group (Ketorolac 2 mg/kg and fentanyl 20 μg/kg). Pain was assessed on a visual analogue scale (VAS) and a numeric rating scale (NRS). Additionally, patient satisfaction, adverse events, and vital signs were monitored showing There were no significant differences in VAS score (P = 0.48) or NRS score (P = 0.15) between the two groups. Similarly, patient satisfaction did not differ between the two groups [8.5(0.8) vs. 8.2(1.0), P = 0.14]. There were no statistically significant differences in the incidence of nausea (P = 0.72), vomiting (P = 0.46).in conclusion Nefopam is an appropriate alternative for co-administration with Fentanyl-based PCA in patients who have difficulty using non-steroidal anti-inflammatory drugs.

Incidence of nausea and vomiting after 1 hr., 6 hrs. and 12 hrs. was higher in group A than group B with p value less than 0.001. (Yoon *et al.,* 2015) Sixty patients undergoing laparoscopic gynecologic surgery received IV-PCA. Group A (n = 30) received IV-PCA with a combination of morphine 60 mg and Ketorolac 180 mg, while group B (n = 30) received Nefopam 200 mg (basal rate 1 ml/h, bolus 1 ml, and lockout time 15 min for both). The primary outcome evaluated was analgesic efficacy using the visual analogue scale (VAS).

Other evaluated outcomes included the incidence rate of postoperative nausea and vomiting (PONV) showing the incidence rate of vomiting was not statistically different between the two groups in contrast to our study which showing a statistical significant difference regarding the incidence of nausea and vomiting , this may be due to correlated to the side effects of Nefopam (Lu *et al.,* 2013). Chung *et al.* Patients undergoing gynecological laparoscopic surgery were randomly allocated to receive either Nefopam- (non-opioid; N group) or Fentanyl-based (F group) PCA. PONV and postoperative pain were assessed during the 72 hours following discharge from the post-anesthetic care unit (PACU). The adverse effects of Nefopam were also evaluated. Show the PONV incidence was significantly lower in the N group than the F group at all measured times.

The incidence of patient satisfaction in group A was higher than group B at all times of measures with p value less than 0.001. Boo-Young *et al.* (Hwang *et al*., 2015). 120 patients undergoing gynecologic surgery were divided randomly into two groups: Nefopam group treated with oxycodone 1 mg and Nefopam 1 mg bolus; and Ketorolac group treated with oxycodone 1 mg and Ketorolac 1.5 mg bolus. After the operation, a blinded observer

assessed the pain with a numeric rating scale (NRS), infused PCA dose and sedation score at 1, 4, 24, and 48 h, nausea, vomiting, headache, shivering, pruritus and delirium at 6, 24 and 48 h, and satisfaction at 48 h after the operation. Show there is no significant difference in the patient satisfaction between both groups; this may be due to the use of oxycodone as adjuvant in this study rather than tramadol in our study.

Conclusion

The use of Nefopam as analgesic drug for post-operative analgesia is significantly more effective than Ketorolac.

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