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Aziza Mohammad Hussain

Aga Khan University

Fauzia A Khan

Aga Khan University

Lumaan Sheikh

Aga Khan University

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Effect of Diclofenac Suppository on Tramadol Consumption in Posthysterectomy Pain

Aziza Mohammad Hussain, Fauzia A. Khan and Lumaan Sheikh*

ABSTRACT

Objective: To determine reduction in dose of tramadol and side effects in posthysterectomy patients on addition of diclofenac on rectal suppository.

Study Design: Randomized double blinded placebo controlled study.

Place and Duration of Study: The Aga Khan University Hospital, Karachi, Pakistan, from August 2004 to January 2006.

Methodology: Seventy ASA I and II females, aged 20 and above, who underwent elective abdominal hysterectomy, were included in this study. Patients received identical looking suppository of either 100 mg diclofenac sodium or placebo after induction of anaesthesia and then 12 hourly for 24 hours. General anaesthesia was standardized and tramadol was given by patient controlled intravenous analgesia delivery system in the recovery.

Results: The mean dose \pm SD of tramadol used in first 24 hours was found to be 317 ± 153 mg in the placebo-tramadol group compared to 258 ± 192 mg in the diclofenac-tramadol group ($p = 0.15$, 95% CI = 1.24 to -1.34, 6.63). Seventeen (49 %) patients in the placebo-tramadol group and 14 (40%) in the diclofenac-tramadol group used rescue analgesia ($p=0.47$). Sedation score was similar in both the groups and there was no difference in the incidence of nausea and vomiting and use of antiemetics between the groups.

Conclusion: This study did not show any reduction in tramadol consumption, given via patient controlled intravenous analgesia when rectal suppository of 100 mg diclofenac was added.

Key words: Postoperative pain management. Tramadol. Diclofenac sodium.

INTRODUCTION

Opioids are commonly used for the management of intraoperative and postoperative pain. Systemic administration of high doses of opioids is associated with a variety of adverse reactions such as pruritis, sedation, nausea, vomiting, respiratory depression and constipation.¹ The development of multimodal or balanced analgesia techniques for postoperative analgesia, involving the use of combinations of drugs, has helped to improve quality of analgesia with reduction in incidence and severity of these side effects.² Opioid consumption can be significantly reduced by combining them with non-opioid analgesic in pain therapy. Non-steroidal anti-inflammatory drugs (NSAIDs) effectively reduce opioid consumption by 20-30% to improve analgesia and reduce side effects.^{3,4} A combined therapy of opioids and NSAIDs could result in synergistic analgesia by acting through different mechanisms.⁵

In postoperative pain management, tramadol is an alternative agent to morphine for Patient Controlled Intravenous Analgesia (PCIA) treatment. Tramadol is a centrally acting analgesic with opioid and non-opioid modes of action. It is a weak μ receptors agonist and its analgesic activity is mostly via inhibition of re-uptake of neurotransmitters like norepinephrine and serotonin in the central nervous system.⁶ The advantage of tramadol over traditional opioids is minimal potential for tolerance and respiratory depression but also has nausea and vomiting as side effects which affect physician and patients' satisfaction.⁷

NSAIDs are mainly used as co-analgesics for the treatment of postoperative pain in moderate to major surgery. They block the synthesis of prostaglandins by inhibiting Cyclooxygenase (COX), thereby reducing production of mediators of the acute inflammatory response. By decreasing the inflammatory response to surgical trauma, NSAIDs have been supposed to reduce peripheral nociception. More recent studies also suggest that the central response to painful stimuli may be modulated by NSAIDs-induced inhibition of prostaglandin synthesis in the spinal cord.¹

There has been little published work on the synergism of tramadol (opioid) and diclofenac (NSAIDs). The purpose of this study was to determine whether addition of diclofenac suppository reduced tramadol consumption and side effects in posthysterectomy patients.

Department of Anaesthesia, The Aga Khan University Hospital, Karachi.

* Department of Gynaecology and Obstetrics, The Aga Khan University Hospital, Karachi.

Correspondence: Dr. Aziza M. Hussain, Flat No. 306, Mustafa Arcade, Block-A, Sindhi Muslim Society, Karachi.
E-mail: aziza.mohammad@aku.edu

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METHODOLOGY

The study was conducted in the Aga Khan University Hospital, Karachi, from August 2004 to January 2006. After obtaining institutional ethical committee approval and written informed consent from patients, 70 ASA I and II female patients, aged 20 and above, undergoing elective abdominal hysterectomy under Pfannenstiel incision technique, were recruited in this randomized double blind placebo controlled trial. Exclusion criteria were hysterectomy under midline incision technique, emergency surgery, surgery for malignancy, history of chronic pain, peptic ulceration, bleeding disorders, impaired renal or hepatic function, sensitivity to NSAID or opioids, and patients' inability to use Patient-Controlled Analgesia (PCA).

Patients were randomly divided into two groups to either receive diclofenac suppository or a placebo after induction of anaesthesia. The randomization was done by the pharmacy department. Patients were allocated randomly according to a list of random numbers into two groups in sealed opaque envelopes. The suppositories were provided by the pharmacy and an appropriate code number (case 1, case 2 and so on) was assigned. The investigators were unaware of the group. During pre-operative assessment, the patient were instructed regarding Verbal Rating Score (VRS) of pain (0 = no pain, 1 = mild pain, 2 = moderate pain and 3 = severe pain)⁸ and were also familiarized with the use of PCA pump to minimize pain (obtaining a score less than 2).

The number of patients recruited was based on detecting a difference of 30% in total tramadol consumption between the two groups in 24 hours, an alpha (α) error of 5% and β error of 20% at a standard deviation of 166. All the patients were then premedicated with 7.5 mg midazolam tablet half to one hour prior to surgery.

On arrival in the operating room, routine monitoring i.e. electrocardiogram, non-invasive blood pressure and pulse oximetry was instituted. A baseline reading of systolic, diastolic and mean blood pressure, heart rate and oxygen saturation was obtained after a resting period of 5 minutes.

Anaesthesia was induced with intravenous tramadol 2 mg kg⁻¹, thiopentone 4-5 mg kg⁻¹ and atracurium 0.5 mg kg⁻¹. After tracheal intubation, patients lungs were mechanically ventilated and anaesthesia maintained with 60% nitrous oxide, oxygen and isoflurane (MAC 1). A rectal suppository, either diclofenac 100 mg or placebo, was inserted before start of surgery. Heart rate systolic, diastolic, and mean blood pressure and oxygen saturation were monitored throughout the maintenance period and documented at 10 minutes interval.

At the end of the surgery, residual neuromuscular blockade was antagonized with neostigmine 2.5 mg and

glycopyrrolate 0.5 mg. In the recovery, a PCA pump was connected to the patients, which contained 10mg ml⁻¹ tramadol. The bolus dose was set at 10 mg (1ml) with a lock out interval of 10 minutes. There was no background infusion. Patients had been previously instructed to use PCA to minimize pain (i.e. maintain pain score of less than 2).

Any side effects like nausea, vomiting and respiratory depression were monitored. The level of sedation was assessed by using the sedation score described by Chernik *et al.* (0 = awake, 1 = sleeping comfortably and responding to vocal commands, 2 = somnolence, deep sleep but responding to vocal commands, 3 = not arousable, deep sleep).⁹ Persistent nausea (defined as feeling of nausea for more than 30 minutes) and vomiting more than twice was treated with intravenous metoclopramide 10 mg bolus. If patient was unable to obtain adequate analgesia with two consecutive dose of tramadol, 10 mg boluses of pethidine were administered intravenously as rescue analgesia, to minimize pain.

Postoperatively, similar rectal suppository as given intraoperatively (whether it was diclofenac or placebo) was inserted 12 hourly for next 24 hours. Patients were assessed at 6, 12 and 24 hours, postoperatively for blood pressure, heart rate, respiratory rate, side effects (nausea and vomiting and sedation) and for rescue medication received. Blindness during the study period was ensured by blinding the anaesthetist and the nurse recording the parameters to the patient group. PCIA pump used by the patient is called attempts. Good attempts are those in which the drug is delivered to the patient. Number of attempts (which include total attempts and good attempts) and total tramadol dose consumed (to minimize pain) was retrieved from the PCA computer memory after 24 hours postoperatively. Neither the pain score, nor the number of attempts at different time intervals were assessed.

Using EpiData (version 3.1), frequencies, mean and standard deviation of all quantitative variables were generated. Independent samples t-test for quantitative variable between the two groups (placebo and diclofenac) were calculated. Repeated measures of ANOVA were conducted to see the association within group at different times and between groups (placebo and diclofenac) for heart rate, systolic and diastolic blood pressures. Association between placebo and diclofenac group for nausea, vomiting and antiemetic and rescue analgesia use were looked at by using Chi-square test. Independent sample 't' test was also used to observe mean difference between groups (placebo and diclofenac) for number of attempts and total consumption of tramadol during 24 hours postoperatively. A p-value of <0.05 was considered statistically significant.

RESULTS

There were no dropouts during the study period. The demographic data of both groups is given in Table I. Both groups were comparable with respect to age, body weight, ASA physical status and duration of surgery.

There was no difference in the systolic (SBP), diastolic (DBP) mean arterial pressure (MAP) and heart rate measured at corresponding time intervals (Table II), and difference between the two groups (placebo and diclofenac) at all times was found to be insignificant.

Table I: Demographic characteristics and duration of surgery. Mean (SD).

Variable	Tramadol and placebo (n=35)	Tramadol and diclofenac sodium group (n=35)	95% confidence for the difference SD. (upper and range)
Age (years)	43.2 (5.19)	44.3 (5.22)	1.24 (-1.34, 6.63)
Weight (kg)	67.0 (12.22)	69.7 (10.92)	2.7 (-2.83, 8.23)
Duration of anaesthesia (minutes)	122.6 (40.33)	122.2 (41.20)	-9.8 (-19.98, 19.19)
ASA physical status (I:II)	21:14	17:18	

Table II: Systolic (SBP), diastolic (DBP) mean arterial pressure (MAP) and heart rate (HR), mean (SD).

Variable	Hours after operation	Tramadol and placebo (n=35)	Tramadol and diclofenac sodium (n=35)
HR (beat/ min)	0	80.74 ± 13.4	82.60 ± 14.6
	6	83.11 ± 7.8	81.57 ± 9.3
	12	84.83 ± 6.8	80.71 ± 9.4
	24	84.89 ± 7.8	81.06 ± 8.9
SBP (mm Hg)	0	126.74 ± 14.9	128.83 ± 16.1
	6	122.40 ± 11.2	125.31 ± 10.3
	12	122.60 ± 9.9	122.34 ± 9.6
	24	123.31 ± 9.8	122.14 ± 8.8
DBP (mm Hg)	0	72.69 ± 10.7	76.77 ± 10.0
	6	77.71 ± 7.7	78.31 ± 8.2
	12	76.80 ± 7.4	78.71 ± 7.0
	24	78.54 ± 7.48	77.83 ± 7.4
MAP (mm Hg)	0	94.09 ± 11.0	95.06 ± 12.0
	6	92.63 ± 6.6	93.69 ± 7.9
	12	91.60 ± 7.7	93.11 ± 6.3
	24	93.46 ± 7.3	92.66 ± 6.4

The mean ± SD dose of tramadol used in the first 24 hours postoperatively in the placebo-tramadol group was 317 ± 153 mg and 258 ± 192 mg in the diclofenac-tramadol group to relieve pain (Table III). Though clinically, the dose was less in the diclofenac-tramadol group, the difference was not statistically significant ($p=0.159$). When use of rescue analgesia was compared in both the groups, 17 (49%) patients used rescue analgesia in the placebo-tramadol group

compared to 14 (40%) patients in the diclofenac-tramadol group, but this difference was not significant ($p=0.47$). Rescue analgesia was needed in both groups on arrival in recovery but the requirements decreased subsequently and after 12 hours no rescue analgesia was required in either of the groups. The average number of attempts in the diclofenac - tramadol group was greater (184.94 ± 257) than in the placebo-tramadol group (153.86 ± 177) but this was not significant ($p=0.557$, Table III).

Table III: Dosing pattern and use of rescue analgesia. Mean (SD or percentage).

Variable	Tramadol and placebo (n=35)	Tramadol and diclofenac sodium group (n=35)	95% confidence interval for the difference. SD (upper and lower range)
Mean dose (mg)	317 (153)	258 (192)	1.24 (-1.34, 6.63)
Median dose (mg)	320 (153)	210 (192)	
Rescue			
Analgesia used	17 (49 %)	14 (40%)	
Average attempts	153.86 (176.5)	184.94 (256.8)	52.68 (-74.04, 136.21)

Occurrence of nausea and/or vomiting was similar in both placebo-tramadol and diclofenac-tramadol groups. Twelve (34%) patients had nausea in both the groups. Vomiting occurred in 4 (11%) patients in placebo-tramadol group and 5 (14%) in diclofenac-tramadol group. These differences were not statistically significant. Nineteen (54%) patients in the placebo-tramadol group and 16 (46%) in the diclofenac group were given antiemetic but the use was not statistically significant. ($\chi^2 = 0.514$, $df=1$, $p=0.473$).

In the recovery room, none of the patient had respiratory rate less than 10 breaths per minute. Eleven (31%) of patients were somnolent but rousable (score of 2) in the placebo-tramadol group compared to 14 (40%) in the diclofenac - tramadol group. Six hours postoperatively, only 2 patients (6%) in the placebo-tramadol group compared to 01 (3%) in the diclofenac-tramadol group had a score of 2. None of the patients had a score of 3 at any time during the study period.

DISCUSSION

This study has demonstrated that in patients undergoing abdominal hysterectomy, diclofenac 100 mg rectally, at the time of induction, did not significantly reduce PCA tramadol consumption to obtain VAS of less than 2, in the first 24 hours after surgery.

Tramadol has a similar efficacy to morphine when used as an analgesic in abdominal surgery.¹⁰ It is a weak μ agonist with a multimodal mechanism of action. The μ agonist effect enhances the function of spinal descending inhibitory pathway by inhibition of re-uptake of both 5 Hydroxytryptamine (5HT) and nor epinephrine together with pre-synaptic stimulation of 5HT release.¹¹

It has emerged as an alternative drug to morphine for I.V. PCA¹² and has shown good efficacy after major orthopaedic surgery.^{12,13} Its particular advantage is its lesser potential of respiratory depression.¹⁴ One of the limitations of its use in PCA is the incidence of its side effects specially nausea and vomiting.¹⁵ One of the ways to tackle this issue by using combination of tramadol with other non-narcotic analgesic drugs and thus decreases the opioid requirements and lessening the incidence of side effects. Combinations that have been investigated with variable results are intravenous (I.V.) tramadol and ketorolac infusion for major abdominal surgery, I.V. tramadol and metamizol, I.V. tramadol and ketoprofen, I.V. tramadol and lysine acetyl salicylate, an injectable aspirin, and tramadol piroxican combination.¹⁶⁻²⁰

Diclofenac is an NSAID that reduces morphine consumption after total abdominal hysterectomy.²¹ Most but not all studies with narcotic NSAID combination have shown a decrease in opioid requirement.²² Rectal NSAID is a cost-effective method in the management of surgical pain and has been shown to decrease morphine consumption by 50 % in patients undergoing abdominal hysterectomy.^{23,24} Not much literature is available on the combination of these two i.e. tramadol and diclofenac. The total morphine dosage administered I.V. by PCA over a particular period of time has been used as a measure of efficacy of postoperative analgesia by several studies as used in this methodology.²⁵ We used an intravenous bolus dose of tramadol of 10 mg with a lockout interval of 10 minutes for a period of 24 hours. Background infusion as the method would not be appropriate to evaluate a decrease in narcotic demand.²⁶ The routine institutional practice is to discontinue PCA after 24 hours in order to encourage patients to ambulate. The present results demonstrated a slight decrease in total tramadol requests in the diclofenac group but this did not achieve statistical significance.

The most commonly reported side effect was nausea (34% in each group) and vomiting (11% placebo vs. 14% in diclofenac group). Excessive sedation was not seen in either group. Evidence supporting increased bleeding with NSAIDs is equivocal,²⁷ but excessive bleeding was not reported in any of our patients. Diarrhea, a rarely reported side effects of diclofenac suppository was also not seen.²⁴ This study, therefore, did not demonstrate any significant effect of diclofenac suppository in reducing side effects due to tramadol. Ng *et al.* all demonstrated a reduction in morphine consumption with diclofenac suppository given after induction of anaesthesia in total abdominal hysterectomy but side effects were not decreased.^{28,29} This fact has also been commented upon by other authors with other drug combinations.^{21,24} It is hypothesized that only if addition of diclofenac decreases morphine consumption by 50%, only then a reduction in side effects is seen.²¹

Negative findings have also been reported in several other studies, with either diclofenac morphine combination or other narcotic and non opioid combinations of postoperative pain.^{29,30} In the present study, reasons could be several. Firstly, surgery was performed by different surgeons. Variations in dissection and surgical techniques can lead to a difference in postoperative analgesic requirements. The timing of administration of analgesic drug has also been implicated in lack of opioid sparing effect.³⁰ Vandermeulen *et al.* suggested that lack of opioid sparing effects with NSAIDs after certain operations may have resulted because of its postoperative use only.³¹ Certain pharmacokinetic characteristics, such as low lipid solubility and high protein binding, may also prevent the central effect.³² This has been reported with tenoxicam.

Individual variations in pain perception and scores may also not show a significant effect.³² As the number of boluses requested/delivered by the PCA pump at each hour were not assessed, therefore, the differences between the immediate and late postoperative periods could not be observed. Other patient factors like patient suffering from pain but not demanding analgesia are also a possibility.

CONCLUSION

The addition of diclofenac suppository 100 mg (inserted after induction) to PCA with tramadol offered no advantage in pain relief or opioid consumption for the first 24 hours after total abdominal hysterectomy.

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