Placebo controlled comparison of the opioid sparing effect of meloxicam and diclofenac after abdominal hysterectomy

Jamil S. Anwari, MBBS, FFARCS, *Samina Anjum,* MBBS MD, *Saleh Al-Khunain,* MBBS.

ABSTRACT

الهدف: من أجل دراسة الأثر التوفيري (المقتصد) للأفيونات لكل من عقاري الميلوكسيكام والدايكلوفيناك وعقار الغفل (الدواء الوهمي) ، وذلك بعد عمليات استئصال الرحم عن طريق البطن.

الطريقة: أجريت هذه الدراسة في مستشفى القوات المسلحة بالرياض (المملكة العربية السعودية) خلال الفترة من فبراير2004 لغاية نوفمبر 2006 م ، وقد شملت هذه الدراسة مجموعة من النساء تتراوح أعمارهن بين 60–25 سنة ، وما بين الدرجة الأولى إلى الثانية حسب تصنيف الجمعية الأمريكية للتخدير.أما أولئك الذين لديهم أمراض عضوية ملحوظة أو موانع لاستعمال الأفيونات أو لمجموعة أدوية مضادات الالتهابات غير الستيرويدية فقد تم استثنائهم من الدراسة . كل المرضى تعرضوا للتخدير العام وتم إعطائهم عقار المورفين عن طريق الوريد ومن ثم تمت أنبوبتهم رغاميا ووضعوا بعدها على جهاز التهوية خلال العملية. لقد تم توزيع المرضى عشوائيا ثم أعطوا شرجيا إما عقار الميلوكسيكام (15 ملجم) أو الدايكلوفيناك (100 ملجم) أو الغفل (الدواء الوهمي) . ويجدر بالذكر أن المرضى وأطباء التخدير وكذلك الممرضات اللاتي كن يعاين المرضى في مرحلة ما بعد العملية ، كل أولئك تم إغفالهم عن هذه الأدوية وعن ماهية ما أعطي للمريض ، وفي غرفة الإفاقة مباشرة كان المرضى يُشرعون على عقار المورفين وريديا عن طريق نظام التسكين الذاتي للألم .أما المعلومات التي تم استقصائها فقد شملت صفات المريض(كالعمر والوزن) ومدة العملية وكذلك مجموع جرعات عقار المورفين التي تم استهلاكها خلال 24 ساعة .

النتائج: في هذه الدراسة تم إشراك ما مجموعه 75 مريض (25 في كل مجموعة) وخمسة فقط من هؤلاء تم إسقاطهم . لم يكن هناك تباين في العمر وأوزان المرضى وكذلك مدة العملية ، وجميعهن تعرضن إما لاستئصال كلي أو جزئي للرحم . إن المتوسط (الانحراف المعياري) لمعدل استهلاك عقار المورفين خلال 24 ساعة في مرحلة ما بعد العملية كانت 37،7 (11،1) ملجم ، 40،1 (7،8) ملجم ، 45،2(9،8) ملجم لكل من الدايكلوفيناك والميلوكسيكام والغفل (الدواء الوهمي) على التوالي . وبالمقارنة مع الغفل (الدواء الوهمي) فإن متوسط استهلاك المورفين في مجموعة الدايكلوفيناك (وليس في مجموعة الميلوكسيكام) كان قليلا بشكل ملحوظ (وبقيمة احتمالية تقل عن 0،05) .

خاتمة: دراستنا هنا توضح وتثبت أن عقار الدايكلوفيناك له أثر مقتصد (توفيري) واضح على استهلاك الأفيونات أثناء عمليات استئصال الرحم عن طريق البطن ، وفي المقابل لا وجود لهذا الأثر مع عقار الميلوكسيكام .

Objective: To compare the opioid sparing effect of meloxicam, diclofenac, and placebo after abdominal hysterectomy.

Methods: This study was conducted at the Riyadh Military Hospital, Riyadh, Kingdom of Saudi Arabia from February 2004 to November 2006. Women of American Society of Anesthesiologist's classification I or II of ages 25-60 years scheduled for abdominal hysterectomy were included. Those with significant systemic disease or contraindication to opioid or non-steroidal anti-inflammatory drugs were excluded from the study. All patients received general anaesthesia and intravenous (IV) morphine, and were intubated and ventilated for the operation. The patients were randomized and rectally received meloxicam (15 mg), diclofenac (100 mg), or placebo suppository. Patients, anesthetists, and nurses managing the patients postoperatively were blinded to these drugs. In the recovery room, (IV) patient controlled morphine was commenced. The information sought included patient characteristics (age, weight), duration of operation, and doses of morphine consumed in 24 hours.

Results: Seventy-five patients (25 in each group) participated in this study and only 5 patients dropped out. There was no difference in age and body weight of the patients, and duration of the operation. All underwent either total or sub-total hysterectomy. The mean (SD) morphine consumption in the 24-hour postoperative period was 37.7 (11.1) mg for the diclofenac group, 40.1 (7.8) mg for the meloxicam group, and 45.2 (9.8) mg for the placebo group. As compared to placebo, the mean morphine consumption in diclofenac (but not in meloxicam) group was significantly (p<0.05) reduced.

Conclusion: Our study demonstrates a significant opioid sparing effect after abdominal hysterectomy with diclofenac, but not with meloxicam.

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From the Department of Anaesthesia & Intensive Care, Riyadh Military Hospital, Riyadh, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. Jamil S Anwari, C-151, Department of Anaesthesia & Intensive Care, Riyadh Military Hospital, PO Box 7897, Riyadh 11159, Kingdom of Saudi Arabia. Tel. +96 (1) 4777714 Ext. 5288. E-mail: janwari@hotmail.com

Postoperative pain after abdominal hysterectomy is usually controlled with parenteral narcotics. Combining analgesics from different pharmacological classes is a strategy that is frequently used in postoperative pain management with the goal of improving analgesia while minimizing the side effects of each individual drug.[1] This concept of "balanced analgesia", also known as multimodal analgesia, is particularly applicable in the case of a combination of opioid and non-opioid analgesics.[2,3] Addition of non-steroidal anti-inflammatory drugs (NSAIDs) for the control of post operative pain helps in reducing the opioid requirement. They work by inhibiting the cyclo-oxygenase (COX) enzyme system, which catalyses the production of prostaglandins and other inflammatory mediators from arachidonic acid. The COX consists of 2 isoforms, COX-1 and COX-2.[4,5] The COX-1 derived prostaglandins are responsible for physiological function.[6] The COX-1 is produced constitutively throughout the body and is involved in the production of thromboxane A2 in the platelets, prostaglandin E2 in the kidneys, and prostacyclin in the endothelial cell and gastric mucosa. Conversely, COX-2 derived prostaglandins mediate pathophysiological and inflammatory processes including pain. Conventional NSAIDs (such as diclofenac, indomethacin) inhibit both COX-1 and COX-2. As compared to non-selective NSAIDs, selective (COX-2) inhibitors have the analgesic efficacy comparable with that of conventional NSAIDs but have less interference with the physiological function of the stomach, kidneys, and platelets. Theoretically, COX-2 inhibitors are analgesics with minimal potential for adverse effects. Meloxicam manufactured by Boehringer Ingelheim is regarded as a first generation of selective COX 2- cyclooxygenase enzyme inhibitors with up to 77-fold selectivity for COX-2.[7] Two large-scale trials, MELISSA[8] (Meloxicam Large-scale International Study Safety Assessment) and SELECT[9] (Safety and Efficacy Large-scale Evaluation of COX-inhibiting Therapies), which compared meloxicam with traditional NSAIDs, have established superior gastrointestinal tolerability and equivalent analgesic efficacy of meloxicam in osteoarthritis patients. The purpose of our study is to look at the postoperative opioid sparing effects of meloxicam and diclofenac when compared with placebo.

Methods. After approval from the local research and ethical committee and informed patient consent, a randomized double blind placebo controlled clinical trial design was employed. The study population was female patients admitted to the Riyadh Military Hospital, Riyadh, Kingdom of Saudi Arabia for abdominal hysterectomy. The patients who were included in this study were all American Society of Anesthesiologists (ASA) classification I or II, aged between 25-60 years and agreed to use intravenous morphine patient controlled analgesia (PCA) after abdominal hysterectomy. Patients excluded from the study were those who were ASA ≥ III and with a history of bronchial asthma, hypertension, renal disorder, coagulation disorders, and thrombocytopenia. Patients who had gastrointestinal bleeding, or duodenal ulceration within 30 days before receipt of study medication, who had received any analgesic (including neuroleptic or antiepileptic), antipsychotic, or corticosteroid drugs, other than those required for surgery, within 24 hours before surgery, who have a history of allergy to morphine or NSAIDs, who could not understand or use PCA were not included in this study. Patients with planned hysterectomy combined with salpingectomy or indicated for malignant condition, were not included in the study. The sample size is based on a previous study by Tang et al.[10] Thus, a sample size of 25 patients per treatment group will be required to detect a difference of at least 7 mg in 24 hours at α=0.05, power of 80%, and SD estimate of 20. The patients were randomized to the treatment (analgesia) group by opening a sealed envelop containing a piece of paper on which "M" (meloxicam) or "D" (diclofenac) or "X" (placebo-glycerin) was written. Envelopes were randomly picked up and opened by the scrub nurse before the start of the operation. She administered either meloxicam or diclofenac or glycerin suppository to the patient. Patients, anesthetists, and nurses managing the patients postoperatively were blinded to these drugs. The data were collected using a standardized form. The information sought included patient characteristics (age, weight), duration of operation, and doses of morphine consumed in theater, post anaesthesia care unit (PACU) and during a 24-hour post-operative period. Patients received temazepam 20 mg and metoclopramide 10 mg orally one and a half hours before the operation. Prior to the induction of general anesthesia, intravenous line, and standard monitoring (noninvasive blood pressure monitoring, ECG, and pulse oximetry) was established. The patient was induced with fentanyl 2 μg/kg, propofol 2 mg/kg, and cisatracurium 0.1 mg/kg. After 2 minutes, the patient was intubated and ventilated with oxygen, nitrous oxide, and sevoflurane. Intravenous morphine (0.1 mg/kg) was incrementally given over a period of 10 minutes. Hypotension (systolic BP <25% preoperative value) was treated with either ephedrine 10

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Table 1 - Mean (SD) age and body weight of women, duration of surgery, and intra operative morphine given to patients until the commencement of PCA.

Parameter	Diclofenac	Meloxicam	Placebo
Age (years)	46.5 (6)	43.8 (9.7)	47.8 (5.7)
Body weight (kg)	75.2 (9)	77.3 (3.4)	78.2 (15.5)
Duration of surgery (minutes)	85 (23)	94 (18)	88 (20)
Intraoperative and PACU morphine (mg)	15.5 (3.1)	14.7 (2.8)	15.0 (3.0)

PACU -post anesthesia care unit, SD - standard deviation, PCA - patient controlled analgesia

Table 2 - Mean (SD) pain and sedation score, and number (n) of patients who felt PONV during the 24 hour post operative period in the diclofenac, meloxicam, and placebo group.

	Diclofenac	Meloxicam	Placebo	*P-value*
Mean pain score	1.3 (0.5)	1.4 (0.6)	1.4 (0.8)	ns
Mean sedation score	1.3 (0.5)	1.3 (0.7)	1.4 (0.5)	ns
PONV (n/N)	4/24	4/23	4/23	ns

PONV - post operative nausea and vomiting, N - number of patients who completed the study

Table 3 - Comparison of mean consumption of PCA morphine with diclofenac, meloxicam, and placebo.

Mean (SD) consumption of PCA morphine (mg)		*P*-value
Diclofenac 37.7 (11.1)	Placebo 45.2 (9.8)	< 0.05
Meloxicam 40.1 (7.8)	Placebo 45.2 (9.8)	ns
Meloxicam 40.1 (7.8)	Diclofenac 37.7 (11.1)	ns

PCA - Patient controlled analgesia, SD - standard deviation, NS - not significant

mg intravenous bolus or fluids (crystalloids, colloids, or blood). Hypertension (systolic blood pressure>25%) was treated with fentanyl 0.5 µg/kg or by increasing the sevoflurane, or both. After the operation was completed, the scrub nurse gave either meloxicam 15 mg or diclofenac 100 mg or glycerin suppository to the patient as indicated by the randomization process. General anesthesia was discontinued, and the patient was extubated and transferred to the PACU for standard care. Upon regaining consciousness, the patient received boluses of intravenous morphine until the pain was adequately controlled and then, intravenous PCA morphine was commenced. The PCA was set at 1.5 mg per press of the button by the patient, the lockout interval was 10 minutes and the basal infusion rate was at 1.0 mg/hour. In the ward, the patient was monitored hourly for pain. A 4-point verbal rating scale was used to evaluate the pain intensity. Post-operative pain and sedation were monitored as none, mild, moderate, and severe and recorded as zero, one, 2, and 3. The vital signs (blood pressure, heart rate, and respiratory rate) were monitored 4 hourly. Twenty-four hours after the commencement of the PCA, the total morphine consumed by the patient was recorded.

The data were analyzed by the computer using Epi Info 2000 software and using repeated measures-analysis of variance and Tukey/Scheffe studentized range tests. Patient demographics were tested using X^2 analysis. A value of $p<0.05$ was considered significant.

Results. Seventy-five patients (all Saudi women) participated in this study and only 5 patients dropped out (2 from control, 2 from meloxicam, and one from diclofenac group.) Three (one from each group) suffered severe post operative nausea and vomiting (PONV) and requested to stop PCA, while in the other 2 patients, technical problems resulted in premature termination of the study. There was no difference in the age and body weight of the patients, duration of the surgery and morphine given to patients until the commencement of PCA (**Table 1**). All under went either total or sub-total hysterectomy. There was no difference in the mean pain and sedation score and in patients who felt PONV in the 24-hour postoperative period (**Table 2**). There was no patient with a respiratory rate of ≤12/min. The mean (SD) morphine consumption (mg) in the 24 hours post hysterectomy period with diclofenac, meloxicam, and placebo, and their statistical comparison is shown in **Table 3**.

Discussion. For the post abdominal hysterectomy pain, the opioid sparing effect of non-specific COX inhibitors such as diclofenac,[11] indomethcin,[12] and ketorolac[13] have been established. Recently, a new generation of NSAIDs, cyclooxgenase-2 preferential inhibitors have been introduced in clinical practice. Studies have also shown the opioid-sparing effect of COX-2 inhibitors such as celecoxib,[14] rofecoxib,[15] parecoxib,[16] and valdecoxib.[17] Our study compared the postoperative opioid sparing effect of meloxicam and diclofenac with placebo, and demonstrated that when meloxicam was compared with diclofenac, the morphine requirements in the meloxicam group were higher than diclofenac group, however, this difference was not statistically significant. However, when compared with placebo, diclofenac (but not meloxicam) caused a significant reduction in opioid requirement following abdominal hysterectomy. A previous study using rectal meloxicam 15 mg (verses placebo) after abdominal

hysterectomy also demonstrated a lack of significant opioid sparing effect.[18] Our study showed that in comparison with placebo, morphine consumption was reduced by 16.6% with diclofenac and 11.3% with meloxicam.

There are many factors such as patients, nurses, pharmacology of drugs, and so forth, which might have affected the result of our study. Postoperative opioid consumption depends on PCA utilization by the patient. Activation of PCA is an expression of pain by the patient. Variations in pain expression and pain tolerance have been observed across different racial, religious, and ethnic groups.[19,20] In addition, the patient's knowledge is important in the utilization of PCA. In this context, patients in our study were similar in their background and they were all taught utilization of the PCA device. The Australian National Health and Medical Research Council have identified patients' difficulties in communicating their need for analgesia.[21] Such communication problems in our hospital do exist because of language and cultural differences between patients, who are mostly Arabs, and nurses, who are mostly from the Philippines. Opioid sparing differences in the present study may have several explanations based on pharmacodynamic and pharmacokinetic differences. Post abdominal hysterectomy pain has somatic and visceral components. Intrinsic analgesic efficacy and its effectiveness against somatic and visceral components of postoperative pain may vary among COX inhibitors. Diclofenac as compared with meloxicam probably has a wider spectrum of activity against inflammatory and pain mediators. In addition to peripheral COX 1 and 2 inhibition, the antinociceptive effect of diclofenac may result from central mechanism, activation of several types of K(+) channels and by reducing the formation of products of the lipo-oxygenase pathway (5-hydroxyeicosatetraenoic acid, leukotrienes).[22-24] Furthermore, inflammatory mediators such as histamine and platelet activating factors are more strongly antagonized by diclofenac than by other COX inhibitors such as ibuprofen or naproxen.[25] Interestingly, in a placebo controlled study, Dahl et al[26] found no opioid sparing effect of ibuprofen after abdominal hysterectomy.

In simple hysterectomy (without salpingectomy), drugs with an anti spasmolytic property could contribute to analgesia by reducing salphingial pain. In a previous study, metoclopramide appeared to reduce peristalsis and spasms associated with tubal and ureteral surgery and demonstrated an opioid sparing effect in patients undergoing second trimester abortion.[27] Human endosalpinx possesses both COX-1 and 2 and synthesize abundant prostaglandins[28] in response to various stimuli, for example, surgery and inflammation. Prostaglandins increase tubal smooth muscle motility, thereby producing painful contractions.[29] Tubal spasm is effectively relieved by diclofenac, which inhibits not only prostaglandins but also other myo-salphingiotonic mediators. In this regard, diclofenac has been found to be more effective than other COX inhibitors.[25] Moreover, there is level-2 evidence of effectiveness of diclofenac in renal and ureteral colic pain.[30] Thus, it is reasonable to hypothesize that diclofenac is more effective than meloxicam in reducing visceral pain after abdominal hysterectomy and produces more opioid sparing effect. Pharmacokinetic factors such as dose, route of administration, first-pass metabolism, may be important in explaining the differences in the opioid sparing effect of various COX-inhibitors. Nolli et al[31] described inadequate dosing and inappropriate (such as per rectal) route of analgesic drug as a cause of inadequate postoperative pain relief. Moreover, the rate and extent of rectal drug absorption depend on many other factors such as the surface area available for drug uptake, partial avoidance of hepatic first-pass metabolism and co administration of absorption-promoting agents.[32] Paracetamol has been found to be ineffective in providing postoperative analgesia.[33] Both low dose and the rectal route were blamed for the misuse of paracetamol.[33] Doses of meloxicam used in our study might have been too small and/or rectal absorption might have been too slow to achieve a therapeutic plasma concentration during the 24 hours postoperative period. We speculate that an increased dosage or parenteral route would have detected a bigger opioid sparing effect, which probably in the case of meloxicam versus placebo in our study would have achieved statistical significance. In a study, Scott and Jenning[11] found a 50% reduction in morphine consumption in patients undergoing abdominal hysterectomy that had received rectal diclofenac 100 mg at the end of surgery and repeated at 12 hours interval for 3 days.[11] Thus, the apparently more effective reduction of postoperative opioid with diclofenac could have been a dose-dependent phenomenon. In addition to dose, timing of administration of cox inhibitors may be important in their postoperative analgesic and opioid sparing effect.[34] In animals, the production of prostaglandin in the fallopian tube is significantly reduced by pretreatment with indomethacin.[35] In a study, preemptive meloxicam 15 mg (orally) provided better post abdominal hysterectomy analgesia than placebo.[36]

Our study has put the opioid sparing effect of meloxicam in doubt as statistically, it was found neither significantly superior than placebo nor inferior than diclofenac. Further studies with bigger, frequent, or preemptive doses of meloxicam are required, which may explore its statistically significant opioid sparing effect.

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