Postoperative analgesia is not different after local vs systemic administration of meloxicam in patients undergoing inguinal hernia repair

[L'analgésie postopératire ne diffère pas après l'administration locale ou intraveineuse de méloxicam pour une herniorraphie inguinale]

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Purpose: To distinguish between local and systemic drug effects, we compared pain scores, analgesic consumption and plasma concentrations after local *vs iv* administration of meloxicam 7.5 mg in patients with inguinal hernia repair.

Methods: In a double-blind, randomized study 56 patients received either local or *iv* meloxicam 7.5 mg. Postoperative pain was assessed with a visual analogue scale (VAS) at rest, on mobilization, and on coughing, the need for supplementary analgesics (fentanyl *iv* and/or acetaminophen-codeine tablets) was recorded, and blood samples were drawn during 24 hr after meloxicam administration.

Results: No significant differences were found between groups with respect to pain scores, or in the consumption of supplementary analgesics. Following local application of meloxicam, the peak plasma concentration (C_{max}) of 0.5 ± 0.2 mg·L^{-1} achieved after 1.8 ± 0.5 hr was much lower than the C_{max} of 2.5 ± 0.9 mg·L^{-1} achieved immediately after *iv* administration ($P < 0.05$). Mean meloxicam plasma concentration after infiltration was significantly lower than after *iv* doses for the first three hours after administration ($P < 0.05$).

Conclusion: We showed no differences in pain scores and analgesic consumption between local and *iv* administration of meloxicam 7.5 mg during the first 24 hr after herniorrhaphy, while plasma concentration of meloxicam was lower after local administration. These results indicate a lack of difference in pain relief after concentrating meloxicam at the hernia wound or after achieving high blood levels rapidly (*iv*). Local administration of meloxicam may confer an advantage over systemic administration by eliciting lower incidences of systemic adverse effects.

Objectif : *Distinguer les effets médicamenteux locaux et systémiques en comparant les scores de douleur, la consommation analgésique et les concentrations plasmatiques après l'administration locale ou iv de 7,5 mg de méloxicam chez des patients qui subissent une herniorraphie inguinale.*

Méthode : *Il s'agit d'une étude randomisée et à double insu auprès de 56 patients qui ont reçu 7,5 mg de méloxicam local ou intraveineux. La douleur postopératoire a été évaluée avec une échelle visuelle analogique (EVA) au repos, pendant le mouvement et la toux. Le besoin d'analgésie complémentaire (fentanyl iv et/ou comprimés d'acétaminophène-codéine) a été enregistré et les échantillons sanguins prélevés pendant 24 h après l'administration de méloxicam.*

Résultats : *Aucune différence intergroupe significative n'a été trouvée quant aux scores de douleur ou à la consommation d'analgésique complémentaire. Après l'infiltration de méloxicam, la concentration plasmatique maximale (Cmax) de 0,5 ± 0,2 mg·L^{-1} atteinte après 1,8 ± 0,5 h a été plus faible que la Cmax de 2,5 ± 0,9 mg·L^{-1} atteinte immédiatement après l'administration iv ($P < 0,05$). Pendant les trois premières heures après l'administration de méloxicam, la concentration plasmatique moyenne était plus basse après l'infiltration qu'après les doses iv ($P < 0,05$).*

Conclusion : *Pendant les 24 premières heures suivant une herniorraphie, les douleurs et la consommation d'analgésique n'ont présenté aucune différence après l'administration locale ou iv de 7,5 mg de méloxicam. Mais, la concentration plasmatique de méloxicam a été plus faible après l'administration locale. La douleur n'est pas mieux soulagée avec le méloxicam concentré au site de la plaie herniaire ou administré par voie iv permettant d'atteindre rapidement des concentrations plasmatiques élevées. Par ailleurs, l'infiltration pourrait réduire davantage l'incidence d'effets secondaires généralisés.*

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THE efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) for postoperative pain relief is well recognized but may be accompanied by undesirable systemic effects.

NSAIDs inhibit the activity of cyclooxygenases (COX). It has been suggested that the well-known adverse effects of NSAIDs are caused by inhibition of COX-1, whereas inhibition of COX-2 is the mechanism by which NSAIDs exert their anti-inflammatory, antipyretic, and analgesic effects.[1] This is the rationale for the development of new, COX-2 selective NSAIDs, because the NSAIDs used so far preferentially inhibit COX-1.[2]

Meloxicam is a relatively new NSAID which has consistently demonstrated selective COX-2 inhibition.[3] It shows similar efficacy to standard NSAIDs but has an improved tolerability profile, consistent with the finding of COX-2 selectivity. Meloxicam is at the moment the only COX-2 selective NSAID developed for parenteral administration. Meloxicam is suitable for once daily administration, because of its elimination half-life ($t_{½}$) of approximately 20 hr and it is well tolerated with respect to local and systemic reactions.[4] The recommended dose of meloxicam is 7.5–15 mg every 24 hr. For postoperative pain, one study has shown a significant analgesic effect following administration of rectal meloxicam 15 mg in patients after abdominal hysterectomy.[5]

Some suggest a peripheral-central synergistic action of NSAIDs that varies depending on the particular NSAID and on the presence or absence of an inflammatory process.[6] NSAIDs inhibit prostaglandin synthesis in peripheral tissues and, therefore, administration of a dose of NSAID locally would be expected to produce more intense analgesia than if the same dose was given systemically.

A small number of studies have investigated the postoperative analgesic effect of wound infiltration (WI) with NSAIDs compared with systemic administration and the results are discordant[7–12] with three studies showing improved pain relief after intra-wound administration[7,11,12] and with another three studies showing no difference between intra-wound infiltration and systemic administration.[8–10]

In an effort to distinguish between local and systemic drug effects, we compared pain scores, consumption of supplementary analgesics and plasma concentrations of meloxicam 7.5 mg after local infiltration and *iv* administration in patients undergoing inguinal hernia repair.

Methods

Fifty-six patients, 18–65 yr of age, scheduled for elective inguinal herniorrhaphy were included in this double-blind, randomized study. Approval was given by the Regional Ethics Committee and the Danish Medicines Agency prior to study commencement and written informed consent was obtained from all patients. Patients were recruited from the Department of Surgical Gastroenterology, Gentofte University Hospital during the period August 1999 to October 2000. Patients were not included if they had a history of drug or alcohol abuse, chronic pain, daily intake of analgesics, known upper gastrointestinal bleeding, renal disease, asthma, hypersensitivity to meloxicam or any other NSAID, any bleeding disorder, or were unable to cooperate.

The study drugs were identical injection fluids of meloxicam 10 $mg \cdot mL^{-1}$, or vehicle without meloxicam. The vehicle control (placebo) was prepared by the hospital pharmacy.

The patients received no premedication. General anesthesia was induced with fentanyl 2 $\mu g \cdot kg^{-1}$ and propofol 2.5 $mg \cdot kg^{-1}$ *iv*. A laryngeal mask airway was inserted and anesthesia was maintained with propofol and oxygen/air.

The surgical techniques were open procedures, with or without extirpation of the hernial sac. Annulorrhaphy or a tension-free herniorrhaphy (Lichtenstein) with insertion of a polypropylene mesh were used for an indirect inguinal hernia. A tension-free herniorrhaphy (Lichtenstein) with insertion of a polypropylene mesh was used for a direct inguinal hernia.

At the end of surgery, prior to skin closure, patients were allocated randomly, on the basis of a computer-generated schedule, in a double-blind manner, to receive *either* surgical WI with 0.75 mL meloxicam 10 $mg \cdot mL^{-1}$ (7.5 mg meloxicam) and 0.75 mL vehicle control *iv or* to receive 0.75 mL meloxicam *iv* and infiltration of the surgical wound with 0.75 mL vehicle control. The surgeon, who was blinded to the content of the study syringe, injected either meloxicam or vehicle in the subfascial layer of the inguinal canal and, simultaneously, the anesthesiologist administered the *iv* injection of either vehicle or meloxicam. All patients were transferred to the same recovery room and observed by nursing staff experienced in postoperative pain treatment. Patients ingested two tablets of a fixed combination of acetaminophen 500 mg plus codeine phosphate 30 mg PRN every six hours for postoperative analgesia during the 24 hr study period. If analgesia provided by the tablets was insufficient, as considered by the patient, fentanyl 1 $\mu g \cdot kg^{-1}$ *iv* was administered on request. The patients received no other analgesics during the study.

Time from meloxicam administration to first analgesic request and the total number of doses required

during the first six hours and 24 hr after meloxicam administration were recorded. Postoperative pain was assessed by the patients using a visual analogue scale (VAS, 0 mm=no pain, 100 mm=worst pain imaginable) at rest, during mobilization from the supine to the sitting position, and during coughing at 1, 1.5, 2, 2.5, 3, 4, 5, 6, 10, and 24 hr after administration of meloxicam. The primary end-point of this study was pain (VAS score) during mobilization at six hours and the secondary end-point was the six hours' consumption of supplementary analgesics.

For the measurement of meloxicam plasma concentrations blood samples (4 mL) were drawn before and 1, 3, 5, 10, 30, 45, 60 min and 1½, 2, 2½, 3, 4, 6, and 24 hr after drug administration. The blood was centrifuged and the plasma was frozen at -20°C until assay.

Meloxicam concentrations were measured by means of a high-performance liquid chromatography method (details available upon request). The calibration curve was linear in the range up to 10 $mg \cdot L^{-1}$, with a limit of detection of 0.1 $mg \cdot L^{-1}$. Intra-assay variations were 4.5% for 0.3 $mg \cdot L^{-1}$ and 2.3% for 1.5 $mg \cdot L^{-1}$. Inter-assay variations were 6.0% and 2.4% for concentrations 0.3 $mg \cdot L^{-1}$ and 1.5 $mg \cdot L^{-1}$, respectively.

Plasma concentration-time profiles were constructed. A 1-compartment model was used to analyze data (WinNonlin, Pharsight Corp., Cary, NC, 1998). The quality of fit of the pharmacokinetic model to the data was judged by visual examination of plots of observed *vs* predicted concentrations.

Time to reach maximum concentration (T_{max}), and maximum plasma concentrations (C_{max}) were determined directly from the individual plasma concentration-time profiles. The area under the plasma drug concentration-time curve $(AUC)_{0\text{-}t}$ was estimated by the trapezoidal rule. The terminal elimination half-life ($t_{½}$) was calculated using the equation: $t_{½}=\ln 2/k_e$. The elimination rate constant (k_e) is the slope of the terminal portion of the plasma concentration-time curve. Clearance (CL) after *iv* and clearance related to bioavailability (CL/F) after local administration, and volume of distribution (V) after *iv* administration and volume of distribution related to bioavailability (V/F) after local application were obtained from the 1-compartment analysis.

We set the acceptable risk of type 1 error at 5% and that of type 2 error at 20%. With the smallest difference between mean values not to be overlooked=2.5, the necessary fixed sample size was calculated to be 22 patients in each group. Based on these values we decided to include 25 patients in each group. Excluded patients were replaced until 50 data sets were available for analysis.

Data are presented as mean values with their standard deviations and when appropriate as median values and ranges. Analysis of demographic data was performed by Chi-square test. Kruskal-Wallis nonparametric one-way analysis of variance was used to evaluate the differences in pain score. If multiple testing was performed, significant *P* values were corrected with a Bonferroni factor for multiple comparisons. Duration of surgical procedure, time to first analgesic requirement, total six hours and 24 hr analgesic requirements, and pharmacokinetic estimates, were analyzed by using one-way analysis of variance (ANOVA). The Fisher's exact test was used to compare the number of fentanyl doses. Statistical significance was defined as $P < 0.05$.

Results

Sixty patients were considered for inclusion in the study but four did not want to participate. Of the 56 patients included, 27 patients were randomized to receive local infiltration of meloxicam and 29 patients received meloxicam as an *iv* injection. Six patients were excluded during the 24 hr study period leaving 25 patients in each study group: two immediately after surgery (one patient in the local group because herniorrhaphy was not necessary, and one patient in the *iv* group because an analgesic other than prescribed in the study protocol was administered during surgery); two at three hours and one at four hours in the *iv* group, and one at five hours in the local group due to alcohol intake or intake of an analgesic other than prescribed, respectively. There were no significant differences in patient characteristics and perioperative data between the two groups (Table I).

There were no statistically significant differences between groups for VAS pain scores at rest, during mobilization from the supine to the sitting position or during coughing at any time, although there was a trend towards reduced pain scores during mobilization and coughing after 2.5 hr in the *iv* group (Figure 1).

There were no significant differences between the local and the *iv* groups in the number of patients requesting supplementary fentanyl or in cumulative postoperative fentanyl requirements (zero to three hours). In the local infiltration group seven patients required fentanyl and the mean dose was 70 μg. In the *iv* group five patients required fentanyl and the mean dose was 80 μg. Also, there was no difference between groups for the time from administration of meloxicam to the first request for fentanyl (Table II). There were no differences between the local and the *iv* groups in the number of patients requesting supplementary acetaminophen-codeine or for the cumulative aceta-

TABLE I Demographic and perioperative data (number or median (range)). No significant differences between groups

	Groups	
	Local administration of meloxicam 7.5 mg	*iv injection of meloxicam 7.5 mg*
No. of patients included	27	29
No. of patients at the end of surgery	26	28
No. of patients 24 hr after surgery	25	25
Sex (M/F)	25/1	27/1
Age (yr)	51 (25–65)	52.5 (19–65)
Weight (kg)	78.5 (61–97)	73.5 (60–100)
Indirect/direct herniorrhaphy	17/9	21/7
Open procedures		
Annulorrhaphy	7	7
Lichtenstein with polypropylene mesh	19	21
Duration of surgery (min)	40 (23–78)	45 (27–77)

TABLE II Postoperative analgesic requirements from 0 to 24 hr after meloxicam administration (number or median (range)). No significant differences between groups

	Groups	
	Local administration of meloxicam 7.5 mg	*iv injection of meloxicam 7.5 mg*
Fentanyl iv		
0–3 hr		
No. of patients requesting	7/26	5/28
No. of doses requested	9	6
Time to first request (min)	42 (20–125)	55 (11–180)
Acetaminophen-codeine tablets		
0–6 hr		
No. of patients requesting	21/25	22/25
Doses requested	1 (0–3)	1 (0–2)
0– 24 hr		
No. of patients requesting	24/25	24/25
Doses requested	3 (0–5)	3 (0–5)
Time to first request (min)	115 (50–623)	95 (35–545)

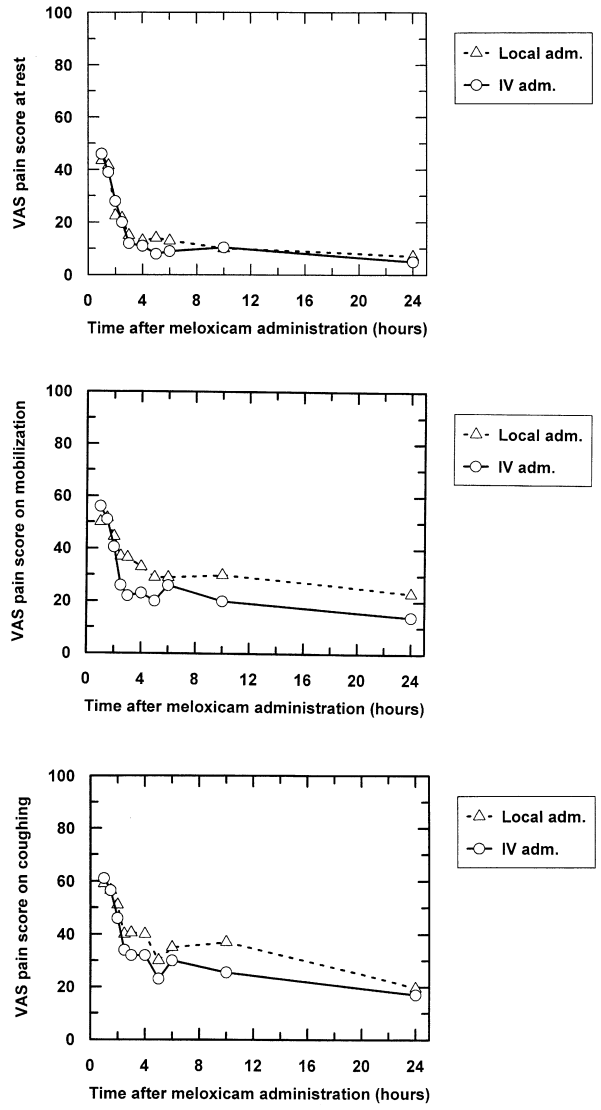

FIGURE 1 Postoperative visual analogue scale (VAS) pain scores following local and *iv* administration of meloxicam. Pain scores were assessed at rest, on mobilization from the supine to the sitting position and on coughing. No significant differences between groups.

minophen-codeine requirements from zero to six hours and zero to 24 hr after meloxicam administration. Also, there was no difference between the local and the *iv* group for the time from administration of meloxicam to the first request for acetaminophen-codeine (Table II).

The 1-compartment model described the data better than other compartmental models as evaluated by Akaike/Schwarts Information Criteria, residual plots, predicted concentrations vs observed concentrations and with different methods of weighting.

The mean time-concentration profiles zero to six hours and zero to 24 hr after local and *iv* administration of 7.5 mg doses of meloxicam are presented in Figure 2, and the pharmacokinetic parameters of meloxicam are shown in Table III. Following local administration of meloxicam the drug was absorbed into the systemic circulation after approximately three minutes and a mean C_{max} value of 0.5 ± 0.2 mg·L^{-1} was achieved after 1.8 ± 0.5 hr (t_{max}). A drug plasma

TABLE III The pharmacokinetic parameters of meloxicam 7.5 mg after local and *iv* administration (mean ± SD)

	T_{lag} (h)	T_{max} (h)	C_{max} (mg·L^{-1})	$t_{1/2}$ (h)	AUC (mg·hr^{-1}·L^{-1})	CL/F[a)] (L·hr^{-1}kg^{-1})	V/F[a)] (L·kg^{-1})
Local group	0.06 ± 0.04	1.8 ± 0.5	0.5 ± 0.2	53.1 ± 19.8	13.3 ± 6.8	0.1 ± 0.03	2.2 ± 1.9
iv group	—	—	2.5 ± 0.9	19.2 ± 6.4	30.2 ± 7.9	0.4 ± 0.2	4.2 ± 0.7

T_{lag}=absorption lag time; T_{max}=time to maximum concentration; C_{max}=maximum plasma concentration; $t_{½}$=terminal elimination half-life; AUC=area under plasma concentration-time curve; V=volume of distribution; CL=clearance; F=bioavailability; a)=CL and V in the case of *iv* administration.

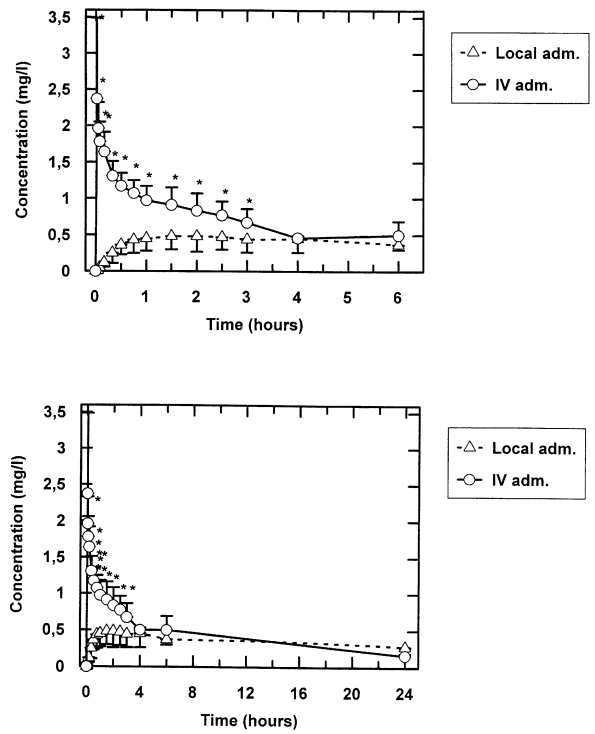

FIGURE 2 The mean time-concentration profiles zero to six hours and zero to 24 hr after local and *iv* administration of meloxicam. *P <0.05.

concentration plateau of approximately 0.4 mg·L^{-1} was then maintained up to 24 hr after administration. Following *iv* administration of meloxicam drug plasma concentrations declined after a rapid distribution phase mean C_{max} was 2.5 ± 0.9 mg·L^{-1}. A relatively constant drug plasma concentration plateau of about 0.5 mg·L^{-1} was achieved after four hours declining to about 0.2 mg·L^{-1} at 24 hr. During the first three hours the mean plasma drug concentration was significantly lower after local than after *iv* administration (P <0.05) but after four hours plasma concentration profiles were almost identical (Figure 2).

All patients were observed for postoperative bleeding secondary to the use of meloxicam.

Only one patient in the *iv* group had the dressing changed twice during the study period due to minor bleeding.

Discussion

This study showed no significant differences in pain scores and consumption of supplementary analgesics between local application and *iv* administration of a single dose of meloxicam 7.5 mg during the first 24 hr after inguinal herniorrhaphy while mean plasma meloxicam concentration was significantly lower after local compared with *iv* administration during the first three hours.

Several placebo-controlled studies have shown that systemic NSAIDs reduce post herniorrhaphy pain and use of additional analgesics.[7,10,13,14] Local NSAIDs may have several advantages over their systemically administered counterparts, as they deliver high drug concentrations locally into affected tissues, while producing limited systemic absorption.

We found no statistically significant differences in pain scores at rest, during mobilization, and coughing between the local and the *iv* groups at six hours (primary end point) or at any time during the study period. Also, there were no differences between groups for the time from administration of meloxicam to first analgesic request or in the cumulative postoperative analgesic requirements at six hours or during the first 24 hr after surgery.

There are five published studies examining the effect of WI with NSAIDs on postoperative pain after inguinal herniorrhaphy.[7,8,10–12] In two of the studies, no differences were observed in postoperative pain scores and analgesic requirements between WI and *im* administration of tenoxicam 7.5 mg[8] and between WI and *iv* administration of ketorolac 30 mg,[10] respectively. In contrast to these studies, superior analgesia after locally applied NSAIDs have been reported in three studies.

Significantly lower pain scores and analgesic use were found in the WI groups when comparing WI ketorolac 30 mg and *im* ketorolac 60 mg,[7] WI and *iv* ketorolac 60 mg,[11] and WI and *iv* tenoxicam 10 mg.[12]

We also examined plasma concentrations of meloxicam after local and *iv* administration in order to establish whether the demonstrated efficacy of local application could be accounted for by systemic absorption of the drug or was more likely to be caused by local effect of the drug. We found that the maximum plasma concentration (C_{max}) of meloxicam 7.5 mg was much lower following local application than *iv* administration (0.5 ± 0.2 mg·L^{-1} and 2.5 ± 0.9 mg·L^{-1}, respectively,) and the plasma concentration profile was significantly lower following local application up to three hours after dosing.

The pharmacokinetic parameters of meloxicam after *iv* administration in hernia patients are comparable to previous results in healthy volunteers.[4,15,16] Meloxicam is bound to plasma proteins by more than 99.5%. This agrees with our findings of a small volume of distribution of 4.2 ± 0.7 L·kg^{-1} and a low clearance of 0.4 ± 0.2 L hr^{-1}·kg^{-1}. The terminal elimination half-life was 19.2 ± 6.4 hr. With respect to local application of meloxicam, pharmacokinetic parameters have not been investigated previously. Clearance and volume of distribution related to bioavailability were lower compared to *iv* administration. The mean elimination half-life of 53.1 hr *vs* 19.2 h after *iv* administration may indicate that meloxicam was "stored" in the subfascial layer and slowly released in the systemic circulation.

Our results indicate a lack of any benefit in postoperative pain relief to concentrating the NSAID at the wound or to achieving high blood levels rapidly (*iv*). In daily clinical work local administration of meloxicam may, theoretically, confer an advantage over systemic administration by eliciting lower incidences of systemic adverse effects normally related to higher drug plasma concentrations.

In our study the method of local administration of meloxicam was different from studies of WI with NSAIDs in inguinal herniorrhaphy.[7,8,10–12] In the studies showing superior analgesia following WI with NSAIDs volumes of 10–20 mL were used for perfusion of the surgical wound.[7,11,12] In the negative studies volumes of 40–50 mL were used.[8,10] One study has shown that perfusion of the traumatized area in itself diminishes pain, whether the fluid used for perfusion is saline or a local anesthetic.[17] Therefore, to avoid any possible therapeutic effect due to perfusion of the surgical wound, meloxicam 0.75 mL was applied directly along the entire length of the hernia wound, thus releasing the compound directly into affected tissues. Meloxicam was administered in the subfascial layer since a study in hernia patients by Yndgaard *et al.*[18] has shown that postoperative pain treatment with local lidocaine had a better effect when applied in the subfascial, rather than the subcutaneous, layer.

The study was considered adequately sensitive as the median VAS pain score in both groups at one hour after medication was between 50 mm and 60 mm during mobilization and coughing. Adequate sensitivity in trials of analgesics for acute pain is only achieved in patients experiencing at least moderate pain (VAS >30 mm), since improvement in pain is difficult to detect if pain is absent or of low intensity.[19,20] We did not include a placebo group because it has already been established that systemic NSAIDs reduce pain and analgesic requirements after herniorrhaphy.[7,10,13,14] As well, meloxicam has demonstrated a significant reduction in postoperative pain scores compared with placebo after surgery.[5] We wanted to distinguish between local and systemic drug effects.

In conclusion, following local application and *iv* administration of meloxicam 7.5 mg no differences in pain scores and consumption of supplementary analgesics were found between groups, while plasma concentrations from local doses were significantly lower than from *iv* doses within the first three hours. These results lend no support to any significant difference in postoperative pain relief following administration of meloxicam directly in the hernia wound compared with achieving high blood levels rapidly after *iv* administration.

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