Postoperative analgesia with *iv* propacetamol and ketoprofen combination after disc surgery

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Purpose: The concept of balanced analgesia suggests that a combination of analgesic drugs may enhance analgesia and reduce side effects after surgery. This study evaluated the effect of the combination of propacetamol (Prodafalgan) and ketoprofen (Profenid) after surgery of a herniated disc of the lumbar spine.

Methods: After randomization, 60 patients received: placebo (group 1); 2 g propacetamol (group 2); 50 mg ketoprofen (group 3); or a combination of 2 g propacetamol and 50 mg ketoprofen (group 4). Drugs were administered every six hours for two days after surgery. The patients used morphine with patient controlled analgesia pumps (bolus 1 mg; lock out time 10 min) and were evaluated with a visual analogue scale (VAS) at rest and movement every six hours for two days. Side effects were noted.

Results: The patient characteristics and surgery were identical for each of the four groups. The VAS scores throughout the study were lower in group 4 than in groups 1, 2 and 3 both at rest ($P < 0.05$) and on movement ($P < 0.01$). The cumulative dose of morphine at 48 hr was lower in group 4 than in group 1 (23.4 ± 5 mg *vs* 58.9 ± 9 mg; $P < 0.01$) or group 2 (23.4 ± 5 mg *vs* 43.4 ± 6.6 mg; $P < 0.05$) and similar to that in group 3 (34.2 ± 4.5 mg). The incidence of side effects was similar in all groups.

Conclusion: The combination of propacetamol and ketoprofen reduced pain scores both at rest and on movement. The drug combination did not reduce the morphine consumption and incidence of side effects.

But: Le concept d'analgésie balancée suggère que l'association de drogues analgésiques en postopératoire peut permettre d'améliorer l'analgésie et réduire les effets secondaires. Cette étude a évalué l'intérêt d'une association de propacetamol (Prodafalgan) et de ketoprofen (Profenid) pour l'analgésie après chirurgie d'une hernie discale lombaire.

Méthodes: Après randomisation 60 patients ont reçu: un placebo (groupe 1); 2 g de propacetamol (groupe 2); 50 mg de ketoprofen (groupe 3); où l'association de 2 g de propacetamol et 50 mg de ketoprofen (groupe 4). Les produits analgésiques ont été administrés toutes les six heures pendant 48 h. Les patients utilisaient de la morphine grâce à une pompe d'analgésie autocontrôlée pendant 48 h (bolus 1 mg; période réfractaire 10 min) et la douleur était évaluée par échelle visuelle analogique toutes les six heures au repos et au mouvement. Les effets secondaires étaient notés toutes les six heures.

Resultats: Les patients et la chirurgie étaient similaires dans les quatre groupes. Les scores d'EVA étaient plus bas pendant les 48 heures de l'étude dans le groupe 4 par rapport à ceux des groupes 1, 2 et 3 au repos ($P < 0.05$) comme au mouvement ($P < 0.01$). Les doses cumulées de morphine étaient significativement plus basses à 48 h dans le groupe 4 par rapport au groupe 1 (23.4 ± 5 mg *vs* 58.9 ± 9 mg; $P < 0.01$), groupe 2 (23.4 ± 5 mg *vs* 43.4 ± 6.6 mg; $P < 0.05$) et pas significativement différentes de celles du groupe 3 (34.2 ± 4.5 mg). L'incidence des effets secondaires était similaire dans tous les groupes.

Conclusion: L'association de propacetamol et ketoprofen a réduit les scores de douleur au repos et au mouvement par rapport aux groupes traités par une seule drogue analgésique. L'association propacetamol-ketoprofen n'a pas significativement réduit la consommation de morphine et les effets secondaires liés à la morphine.

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THE possibility of enhancing postoperative analgesia and reducing the side effects related to analgesic drugs may justify the use of analgesic combinations.[1,2] This concept of balanced analgesia,[3] is used for systemic administration of analgesics such as opioids combined with non steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen.[1,2] Despite the increasing popularity of systemic balanced analgesia among anaesthetists, the usefulness of these drug combinations is still debated since most studies have demonstrated a reduction of opioid consumption with only a limited effect on the quality of analgesia as reflected by the pain scores or the incidence of side effects.[1,4] Different mechanisms and sites of action for the analgesic effect may also justify the combination of non-opioid analgesics as acetaminophen and NSAIDs, but no previous study has evaluated this combination for postoperative analgesia.

The site of action of NSAIDs is controversial: peripheral[5–8] and central effects have been suggested.[9,10] Similarly, central,[6,11] and peripheral actions have been described for acetaminophen.[5,12] Ketoprofen (Profenid, Specia Laboratory, Paris France), is frequently used for *iv* postoperative analgesia in combination with propacetamol (Prodafalgan, UPSA Laboratory Rueil Malmaison, France), an acetaminophen pro-drug that is available for *iv* injection in France but not, presently, in North America.[13] Propacetamol (Prodafalgan) is hydrolyzed by plasma esterases and 50% of the injected drug is converted into acetaminophen.

This study was designed to evaluate the benefit of the combination of two non-opioid analgesic drugs, ketoprofen (Profenid) and propacetamol (Prodafalgan) for *iv* postoperative analgesia after surgery of a herniated lumbar disc.

Methods

Patient selection and randomization procedure

Following Institutional Ethics Committee approval and written informed consent, 64 adults scheduled for first time for surgery of one herniated lumbar disc participated in the study. Exclusion criteria were: contraindications to NSAIDs (i.e., peptic ulcer, renal insufficiency, allergy to NSAIDs), surgery performed under regional anaesthesia, age <18 yr or >85 yr, ASA physical status >3, and herniated disc with neurological deficit or intense pain justifying emergency surgery. Patients with contraindications to the self-administration of opioids were not included (i.e., difficulty in understanding the PCA device, past history of drug abuse, severe respiratory insufficiency). The location (back, leg or combination of the two locations), the intensity of preoperative pain and the consumption of analgesics were noted. Postoperative exclusion criteria included severe respiratory depression requiring administration of naloxone to antagonize the opioids; difficulty with the use of the PCA device (i.e., venous access impossible, non-comprehension by the patient); and the postoperative prescription of other analgesic drugs than PCA morphine.

Before the study began, a random number table was used to generate a randomized schedule specifying the group to which each patient would be assigned upon entry into the trial. In case of exclusion, the next patient took the spot on the randomized schedule.

Anaesthesia

All patients received 2 $mg \cdot kg^{-1}$ hydroxyzine *po* 120 min before surgery. General anaesthesia was induced with 3–5 $mg \cdot kg^{-1}$ thiopentone, 0.1 $mg \cdot kg^{-1}$ vecuronium and 1–2 $\mu g \cdot kg^{-1}$ fentanyl. The trachea was intubated and anaesthesia was maintained with O_2/N_2O and isoflurane. Injections of fentanyl were allowed at the discretion of the anaesthetist responsible for the patient.

Administration of the analgesic drugs

The patients were randomly allocated to four groups: patients in group 1 received placebo; those in group 2 were treated with 2 g propacetamol diluted in specific solvent; in group 3 with 50 mg ketoprofen; and in group 4 with the combination of 2 g propacetamol and 50 mg ketoprofen given in two separate injections to avoid precipitation of propacetamol (UPSA laboratory, unpublished data). Patients in all groups received two injections to assure blinding. All drugs were administered *iv* after dilution in 125 ml dextrose 5% labelled with the randomization number of the patient. Drug administration was begun at the time of skin closure and repeated thereafter every six hours for 48 hr. All patients and staff involved in data collection were unaware of the group to which the patient had been assigned. In case of emergency the anaesthetist who was responsible for the patient had ready access to the nature of the drugs administered to the patient.

After arrival in the recovery room, when the patient was amenable to VAS evaluation (H0), pain was controlled by a titration of morphine *iv* administered by a nurse (3 mg morphine every 10 min until pain VAS score <30). The titration was stopped in the case of a sedation score=3. Subsequently, all patients were given access to a PCA pump for 48 hr after surgery (PCA; Abbott Laboratory, France). This pump used morphine with a bolus of 1 mg and a lock out time of 10 min with neither continuous infusion nor a four hour limit.

Postoperative management and evaluation

A 10 cm visual analogue scale (VAS) (with endpoints labelled "no pain" and "worst possible pain") was used to assess pain intensity at rest and on non standardized movement (e.g., mobilisation in the bed, sitting, coughing), in the recovery room (H 0) before morphine titration and then every six hours for 48 hr after the completion of surgery. Evaluation was performed before administration of analgesic drugs. The site of pain was also noted (back, leg or combination of the two locations)

Side effects (nausea, vomiting, pruritus, urinary retention, sedation, respiratory depression) were noted every six hours if present. Sedation was monitored using the following scale : 0: patient fully alert; 1: intermittent sedation; 2: patient sedated but responsive to verbal stimuli; 3: patient unresponsive to verbal stimuli. Sedation was considered to be present when sedation score was ≥2 at least once during the 48 hr of the study. Respiratory depression was defined as the combination of SpO_2 <95 % and sedation score = 3 in the recovery room and respiratory rate <10 min^{-1} and sedation score = 3 on the surgical ward. Urinary retention was considered to be present when bladder catheterization had to be performed at least once during the 48 hr of the study. Nausea and vomiting were considered to be present when at least one episode was noted during the 48 hr of the study.

Statistical analysis

Demographic data were compared using factorial analysis of variance (ANOVA) and post-hoc comparisons using Fisher's protected least squares difference test (PLSD Fisher's test). The chi square test was used to compare frequency of side effects, sex distribution and type of pain. The VAS scores at rest or on movement and hourly doses of morphine were analysed with two-way repeated-measures ANOVA and post-hoc comparisons with the PLSD Fisher's test. The cumulative morphine doses were analysed by ANOVA factorial and post-hoc comparisons with PLSD Fisher's test. A value of $P < 0.05$ was considered significant. Data are expressed as mean ± SEM.

Results

Demographic and clinical variables

Four patients were excluded during the study: one due to prescription of another analgesic by the surgeon (group 4), one due to patient decision (group 4); one due to difficult venous access (group 3) and another due to occurrence of delirium tremens (group 2). Therefore, 60 patients were studied prospectively during the 48 hr of the trial (15 in each group). The intensity and location of preoperative pain were similar (Table I). In all groups, the patients were using various combinations of NSAIDs, acetaminophen or codeïne before surgery. They stopped the use of any antiinflammatory drug eight days before surgery to avoid increased perioperative bleeding and used on demand analgesia with a combination of acetaminophen and dextropropoxyphène (Diantalvic). The groups were similar with respect to demographic variables, duration of surgery and peroperative opioid consumption (Table I).

Postoperative pain and analgesic consumption

1) PAIN INTENSITY AT REST

The location of postoperative pain was similar in all groups (Table I). It was located mainly in the back (67–87 %) or, less frequently, both in the leg and the

TABLE I Demographic data and anaesthetic procedure

	Group 1 (n=15)	*Group 2 (n=15)*	*Group 3 (n=15)*	*Group 4 (n=15)*
Age (yr)	41.8 ± 2. 4	41.8 ± 2. 7	49.7 ± 2. 9	40.2 ± 2 .7
Weight (kg)	71.5 ± 3	70.2 ± 3. 5	70.7 ± 3. 8	66 ± 2.6
Sex male (n)	9	8	8	6
Preoperative VAS score	43.6 ± 6. 8	48.1 ± 2. 9	50.8 ± 5. 9	42.5 ± 7 .7
Preoperative leg and back pain (n)	8	9	10	10
Preoperative leg pain (n)	3	4	3	2
Preoperative back pain (n)	4	2	2	3
Peroperative fentanyl (mg)	213 ± 17	208 ± 17	220 ± 20	207 ± 12
Duration of surgery (min)	89 ± 9	74 ± 8	76 ± 6	71 ± 6
Postoperative back pain (n)	11	13	11	10
Postoperative leg and back pain (n)	4	2	4	5

Values are expressed as mean ± SEM or number of patients (n).

No significant differences among groups (ANOVA factorial, PLSD Fisher's test)

Group 1: patients treated with placebo; group 2 patients treated with propacetamol 2 g every six hours; group 3: patients treated with ketoprofen 50 mg every six hours; group 4: patients treated with propacetamol 2 g and ketoprofen 50 mg every six hours.

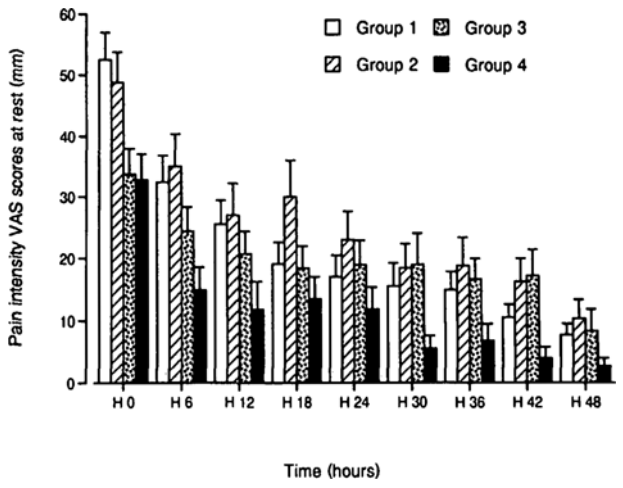

FIGURE 1 Time course of the VAS pain scores in the four groups at rest.

Values are expressed as mean ± SEM.

Group 1: patients treated with placebo; group 2 patients treated with propacetamol 2 g every six hours; group 3: patients treated with ketoprofen 50 mg every six hours; group 4: patients treated with propacetamol 2 g and ketoprofen 50 mg every six hours.

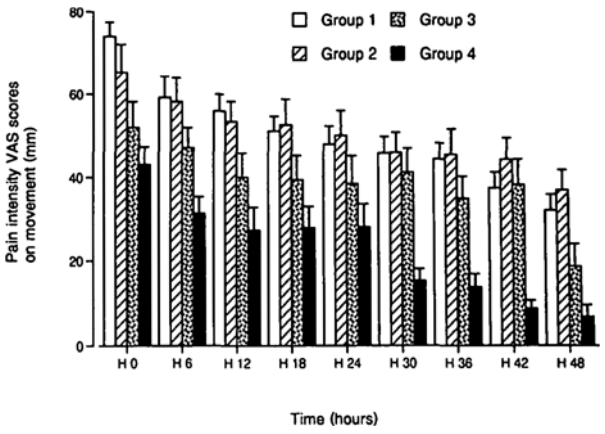

FIGURE 2 Time course of the VAS pain scores in the four groups on movement.

Values are expressed as mean ± SEM.

Group 1: patients treated with placebo; group 2 patients treated with propacetamol 2 g every six hours; group 3: patients treated with ketoprofen 50 mg every six hours; group 4: patients treated with propacetamol 2 g and ketoprofen 50 mg every six hours.

back (13–33 %). The evolution of the pain intensity scores at rest during the study is shown in Figure 1. The scores were reduced throughout the 48 hr of the study in group 4 patients receiving the drug combination compared with groups 1, 2 and 3 ($P = 0.01$ *vs* group 1, $P = 0.001$ *vs* group 2, $P = 0.04$ *vs* group 3). In contrast, the VAS pain intensity scores at rest in the patients in groups 2 and 3 receiving propacetamol and ketoprofen respectively were not reduced throughout the study compared with group 1 ($P = 0.3$ group 2 *vs* group 1, $P = 0.6$ group 3 *vs* group 1).

II) PAIN INTENSITY ON MOVEMENT

Evolution of the VAS pain intensity scores on movement is presented in Figure 2. The VAS pain intensity scores on movement for patients in group 4 receiving the drug combination, was reduced compared with the other groups for the duration of the study ($P = 0.0001$ *vs* group 1, $P = 0.0001$ *vs* group 2, $P = 0.003$ *vs* group 3). The VAS pain intensity scores of group 2 receiving propacetamol were not different from group 1 ($P = 0.72$). In group 3 patients receiving ketoprofen the VAS pain intensity scores were reduced compared with groups 1 and 2 ($P = 0.04$ *vs* group 1, $P = 0.04$ *vs* group 2).

III) CUMULATIVE DOSES OF MORPHINE

Figure 3 represents the cumulative doses of morphine (CDM) for the four groups over the entire study. Morphine titration in the recovery room in group 4 (3 ± 1.1 mg) was reduced compared with group 1

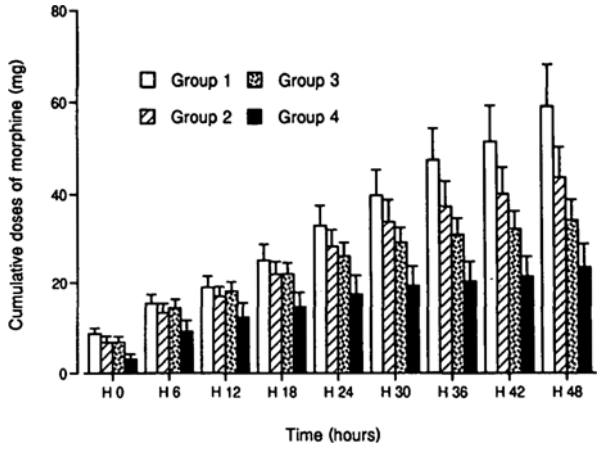

FIGURE 3 Time course of the cumulative doses of morphine in the four groups.

Values are expressed as mean ± SEM.

Group 1: patients treated with placebo; group 2 patients treated with propacetamol 2 g every six hours; group 3: patients treated with ketoprofen 50 mg every six hours; group 4: patients treated with propacetamol 2 g and ketoprofen 50 mg every six hours.

(8.7 ± 1.2 mg; $P = 0.001$), group 2 (6.8 ± 1.3 mg; $P = 0.03$) or group 3 (6.8 ± 1.2 mg; $P = 0.03$). The CDM at 48 hr was lower for group 4 than for group 1 (23.4 ± 5 mg *vs* 58.9 ± 9 mg; $P < 0.01$) and group 2 (23.4 ± 5 mg *vs* 43.4 ± 6.6 mg; $P < 0.05$) and similar to group 3 (34.2 ± 4.5 mg). The CDM in group 3 was reduced compared with group 1 (34.2 ± 4.5 mg *vs* 58.9 ± 9 mg; $P < 0.01$).

IV) MORPHINE CONSUMPTION PER HOUR

The morphine consumption per hour (MCH) in group 4 receiving the drug combination was reduced compared with groups 1 and 2 ($P = 0.0003$ *vs* group 1; $P = 0.04$ *vs* group 2) and similar in group 3. The MCH throughout the study in the group 3 treated with ketoprofen was different from the MCH in the group 1 ($P = 0.01$) (Figure 4).

Side effects

Side effects are listed in Table II. No differences appeared among the four groups. One case of respiratory depression occurred in the recovery room in group 1. The patient recovered without administration of an opioid antagonist within one hour and was maintained in the study. No patient complained of stomach pain suggesting a gastrotoxicity of ketoprofen.

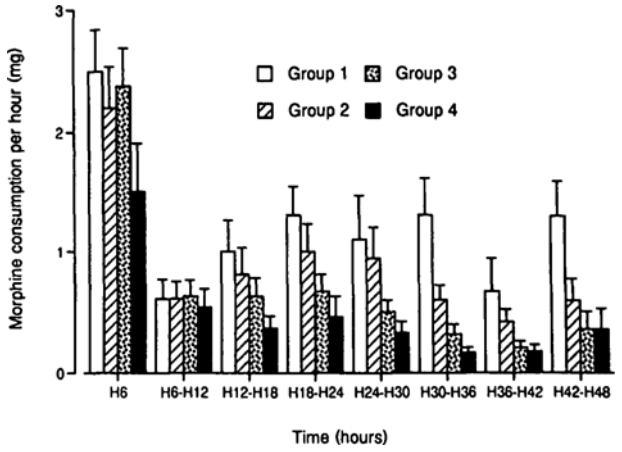

FIGURE 4 Time course of the consumption of morphine per hour in the four groups.

Values are expressed as mean ± SEM.

The morphine consumption on the y-axis represents the average consumption per hour for a six hour interval.

Group 1: patients treated with placebo; group 2 patients treated with propacetamol 2 g every six hours; group 3: patients treated with ketoprofen 50 mg every six hours; group 4: patients treated with propacetamol 2 g and ketoprofen 50 mg every six hours.

TABLE II Side effects

	Group 1 (n=15)	*Group 2 (n=15)*	*Group 3 (n=15)*	*Group 4 (n=15)*
Nausea, vomiting (n)	3	4	4	2
Urinary retention (n)	3	4	3	2
Sedation (n)	2	4	0	1
Respiratory depression (n)	1	0	0	0

Values are expressed as number of patients (n)

No significant differences among groups (Chi 2)

Group 1: patients treated with placebo; group 2 patients treated with propacetamol 2 g every six hours; group 3: patients treated with ketoprofen 50 mg every six hours; group 4: patients treated with propacetamol 2 g and ketoprofen 50 mg every six hours.

Discussion

This study is the first to demonstrate the benefit of combining propacetamol and ketoprofen to treat postoperative pain. This benefit is revealed by a reduction, throughout the 48 hr of the study, of pain both at rest and on movement compared with groups treated with either propacetamol or ketoprofen alone. However, the observed reduction in opioid consumption in the group receiving the drug combination did not differ from that in the ketoprofen only group and did not reduce the occurrence of side effects.

Our study evaluated postoperative pain after surgery of one herniated lumbar disc since this procedure is frequent and well standardized in our hospital. Preoperative pain intensity, location and consumption of analgesic were not different among the four groups. To limit the variation, patients with severe preoperative pain or neurological deficits requiring emergency surgery were not included. Postoperative pain might have resulted from a combination of both somatic pain at the site of surgery and, less frequently, some radicular leg pain but this association was represented equally in each group.

The first result is the reduction in the cumulative opioid consumption over 48 hr due to the concurrent use of propacetamol and ketoprofen. Opioid consumption in the combination group was 46% less than in the propacetamol alone group and 60% less than in the placebo group. However, this reduction was only 22% less than in the ketoprofen alone group. This difference did not reach statistical significance and may have been related to the limited number of patients per group. Similar benefit has been demonstrated previously for the combination of NSAIDs with opioids where the addition of NSAIDs reduced the consumption of opioids by 25–70%.[2] This opioid sparing effect related to the use of the analgesic drug combinations is a worthy goal if it also results in a reduction of side effects. However, this was not the case in our study as in many of the studies evaluating analgesic drug combinations.[1] This may be due to the limited number of patients in this and other studies. Larger studies should logically demonstrate the reduction of dose dependent side effects of opioids such as sedation, respiratory depression, urinary retention or nausea. The large reduction in opioid consumption observed between the groups 1 and 4 (60 %) should be sufficient to reduce side effects.

The second important result is the influence of the drug combination on pain scores at rest and on movement. Our study was not able, as did previous reports, to observe an influence on pain score related to the combination of opioids and propacetamol.[13,14] Although the benefit in postoperative pain score has been identified with the combination of systemic morphine and NSAIDs,[15,16] many studies in which NSAIDs and opioids have been used in combination demonstrated reduction only of opioid consumption with similar or slightly improved pain relief.[1] As previously described for the combination of ketorolac and morphine,[16] the differential analgesic effect on pain at rest and during movement is seen in our study with ketoprofen. Interestingly, the combination of propacetamol and ketoprofen offered a reduction of pain score both at rest and on movement. This reduction was more important than in the group treated with ketoprofen throughout the 48 hr of the study. This effect on pain scores is clinically more important than the opioid sparing effect and may be useful in allowing rapid mobilization or physical therapy during the postoperative period. In fact, recent studies have emphasized the importance of analgesia on movement to obtain rapid recovery and facilitate postoperative rehabilitation.[17,18] Such a sustained effect of analgesic drug combinations on pain with movement as observed with propacetamol and ketoprofen may be helpful in this perspective.

Another advantage of the combination of non-opioid analgesic drugs may be related to the accurate observance of non-opioid analgesic prescription for postoperative pain. In fact, reports in France,[19] and recently in our institution,[20] have described inadequate postoperative opioid analgesia. Due to the fear of side effects and lack of knowledge about postoperative pain treatment, nurses may modify the doses or the interval of the prescribed opioid drugs.[19] This limitation is not observed with non-opioid analgesics such as NSAIDs or propacetamol. Therefore, the powerful analgesia obtained in our study with the combination of propacetamol and ketoprofen may be valuable as a first step for postoperative analgesia. On demand or time contingent analgesia with low doses of opioids may complete this combination if necessary.

Our study demonstrates an additional effect of propacetamol and ketoprofen on postoperative analgesia. These drugs have different sites of action in the nervous system. Propacetamol is a pro-drug hydrolyzed by plasma esterases to acetaminophen and the site of action is mainly central with different hypotheses concerning the precise mechanisms involved: inhibition of prostaglandins,[11] and activation of descending serotoninergic inhibitory pathways.[21] A limited number of studies, in humans[12] and in animals,[5] have suggested a peripheral anti-inflammatory action of acetaminophen. On the other hand, ketoprofen is a member of the NSAID family with a mainly peripheral site of action on the cyclooxygenase enzyme.[5,7,8] Recently, a possible central site of action of NSAIDs was suggested,[9] and specifically observed for ketoprofen.[10] Therefore, these two drugs have complementary analgesic actions probably both at the periphery and in the central nervous system but our study cannot clarify the mechanisms involved. Due to the design of the study with a fixed dose of each drug and no dose response study, we cannot state whether the interaction of the two analgesic drugs is additive or supra-additive.

In conclusion, our study demonstrated the usefulness of combining propacetamol and ketoprofen when treating postoperative pain after surgery of a herniated lumbar disc. The clinically beneficial effects of this combination of non-opioid analgesics on both opioid consumption and pain on movement and at rest are valuable in the treatment of postoperative pain.

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