

Preincisional Treatment to Prevent Pain After Ambulatory Hernia Surgery

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We designed this study as a randomized comparison of postoperative pain after inguinal hernia repair in patients treated with triple preincisional analgesic therapy versus standard care. Triple therapy consisted of a nonsteroidal antiinflammatory, a local anesthetic field block, and an *N*-methyl-*D*-aspartate inhibitor before incision. The treatment group ($n = 17$) received rofecoxib, 50 mg PO, a field block with 0.25% bupivacaine/0.5% lidocaine, and ketamine 0.2 mg/kg IV before incision; controls ($n = 17$) received a placebo PO before surgery. The anesthetic protocol was standardized. Postoperative pain was treated by fentanyl IV and oxycodone 5 mg/acetaminophen 325 mg PO as required for pain.

Pain scores (0–10) and analgesic were recorded for the first 7 days after surgery. Pain scores were 47% lower in the treatment group before discharge (3.1 ± 0.6 versus 5.9 ± 0.6 , $P = 0.0026$) (mean \pm SE) and 18% less in the first 24 h after discharge (5.6 ± 0.4 versus 6.8 ± 0.5 , $P = 0.05$); oral analgesic use was 34% less in the treatment group (4.6 ± 0.8 doses versus 7.1 ± 0.7 doses, $P = 0.02$) in the first 24 h after surgery. We conclude that triple preincisional therapy diminishes pain and analgesic use after outpatient hernia repair, and encourage further evaluation of this technique.

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Inguinal hernia repair is an operation frequently performed on an outpatient basis under general, spinal, or local anesthesia (1). It is frequently associated with moderate-to-severe pain after operation (2,3) that can delay discharge and cause persistent distress (4). Generally, recovery and discharge are expedited, with fewer complications, when hernia repair is performed under local anesthesia (5). However, many surgeons and patients prefer the procedure be done with general/spinal anesthesia. Regardless of the type of anesthesia used, prevention and treatment of postoperative pain must be addressed, and theoretically the same modalities of therapy should be available to all.

Typically, postherniorrhaphy pain is treated by opioids combined with acetaminophen or a nonsteroidal antiinflammatory (NSAID). If surgery is performed under general anesthesia, local anesthetic is often administered at the end of surgery, either as an ilioinguinal nerve block or injected or deposited directly into the wound (2). However, there is evidence that

treatment designed to prevent pain in advance of surgical trauma may be more effective than simply instituting analgesic therapy in response to pain after surgery (6). It is hypothesized that such "preemptive analgesia" prevents central sensitization and hyperexcitability of neurones ("windup"). Central sensitization is thought to be dependent on painful stimuli acting on *N*-methyl-*D*-aspartic acid (NMDA) receptors located within the central neuraxis (7). Preemptive treatment with local anesthetics, antiinflammatories, or NMDA inhibitors have all been proposed as methods of inhibiting transmission of noxious stimuli thereby preventing stimulation of NMDA receptors and central sensitization (6,7). Clinical studies, however, have often failed to demonstrate a preemptive analgesic effect with single modes of therapy (8). Kissin (9) suggested that a combination of preemptive therapies might be more effective than any single modality, which alone might be incomplete in its preemptive effect. Preoperative therapy may also simply ensure that therapeutic levels of drug are attained at completion of surgery.

Accordingly, the purpose of this study was to determine whether combined preoperative use of an NSAID, an NMDA inhibitor, and a local anesthetic field block would reduce pain after hernia surgery when compared with a standard technique of injecting local anesthetic into the wound at the end of surgery. The null hypothesis tested was that pain scores would

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not differ between the treatment and control groups. Oral rofecoxib (50 mg PO) was used as an antiinflammatory drug, and ketamine was used as an NMDA inhibitor. A cyclo-oxygenase-2 inhibitor (Cox-2 inhibitor) (rofecoxib) was chosen as the NSAID in this study to avoid inhibition of platelet function and increased bleeding time, as may occur with traditional NSAIDs (10).

Methods

This study was approved by the IRB at the University of Washington and all patients consented to participate. The study was a prospective, pseudo-double-blinded comparison of triple, preincisional analgesic therapy versus standard therapy in patients having open hernia repair under general anesthesia. Standard therapy was defined by a preliminary observational study (11). Consecutive patients aged 18–75 yr having general anesthesia for hernia surgery were solicited for study. Patients with a known history of drug or alcohol abuse in the past 6 mo were excluded from the study.

Patients in the treatment group received rofecoxib, 50 mg PO, in a gelatin capsule 30 min before surgery, ketamine, 0.2 mg/kg IV, 5 min before incision, and local anesthetic infiltration by the technique of Lichtenstein (12) (40 mL of lidocaine 0.5% and bupivacaine 0.25%, final concentration, administered as a field block by the surgeon). Ten mL of the same solution was instilled under the repaired external oblique aponeurosis before skin closure. To ensure standardization of technique for the local anesthetic block, a stepwise diagram was used in the operating room for each patient. Rofecoxib in gelatin capsules was continued for 48 h in the treatment group after surgery to inhibit production of inflammatory mediators of pain (50 mg PO in the AM).

Patients in the control group received placebo capsules instead of rofecoxib before and after surgery, fentanyl, 1.0 $\mu\text{g}/\text{kg}$ IV, before incision instead of ketamine, and 10 mL of local anesthetic solution (as above) instilled under the repaired external oblique aponeurosis before skin closure.

The anesthetic technique was standardized as propofol induction and sevoflurane/60% nitrous oxide for maintenance. Sevoflurane concentration was adjusted to maintain a bispectral index of approximately 45–50; increases of blood pressure 10% more than baseline or heart rate 20% more than baseline were treated by fentanyl, 0.4 $\mu\text{g}/\text{kg}$ IV. If necessary, endotracheal intubation was facilitated by succinylcholine (1.5 mg/kg) and surgical relaxation was facilitated by vecuronium, 0.05 mg/kg (reversed by neostigmine with glycopyrrolate). All patients received ondansetron, 4 mg IV, approximately 20 min before the end of surgery for antiemetic prophylaxis.

In the recovery unit, pain was treated with fentanyl in 25- μg increments, and oxycodone 5 mg/acetaminophen 325 mg (Percocet[®]) 1–2 tablets PO when able to take oral medication. Patients who required more than 75 μg of fentanyl IV were permitted a single dose of ketorolac, 30 mg IV. Pain was assessed at 15-min intervals using an 11-point numeric pain scale (zero equals no pain, 10 equals the worst pain imaginable). Maximum pain, duration of time with pain >3, total analgesic dose, duration of analgesic therapy (first to last analgesic plus 20 min), and duration of recovery were recorded before discharge. Rescue antiemetics included droperidol, 0.625 mg IV, followed by metoclopramide, 10 mg IV. Meperidine, 12.5 mg IV, was permitted for shivering. Patients were discharged with Percocet[®] and instructed to take 1–2 tablets every 4–6 h as necessary for pain.

Recovery data after discharge were obtained by phone at 24 h, 48 h, and 7 days after surgery. Data included maximum and minimum pain scores, pain in response to rising to a standing position and to walking, analgesic use in the preceding 24 h, and the occurrence of pain that prevented or interrupted sleep. Symptoms possibly related to analgesic use were recorded. A global assessment of activity (0–100, expressed as a percentage of normal) was obtained at each time interval, and reasons for disability elicited (“Why <100% of normal?”). Finally, patients evaluated satisfaction with analgesia on a scale of 1–10 (where 1 = as dissatisfied as could possibly be imagined and 10 = as satisfied as they could possibly be) and, if dissatisfied, provided reasons for their dissatisfaction. At least three attempts were made to contact each patient at each time interval after discharge. Patients, recovery room nurses, and the research study coordinator remained blinded as to group assignment.

Group means for continuous variables were compared by Student's *t*-test for unpaired data. For non-continuous data, comparisons were made by the Mann-Whitney *U*-test. Tests of association for binary variables were made by χ^2 . An overall α of 0.05 was considered significant for primary outcome variables. Nominal *P* values are shown in the tables.

Based on a previous observational study, we predicted approximately 26 patients would be required to detect a 2.0-point reduction in maximum pain score (approximately 40% change), which we considered would be the minimum response of clinical interest (80% power, $\alpha = 0.05$). An additional eight patients were included to ensure an adequate number of subjects. Accordingly, a total of 34 patients were studied (17 patients/group).

Results

The groups were comparable with respect to demographic characteristics and anesthetic care (Table 1).

Table 1. Patient Demographic Characteristics and Details of Anesthetic Management

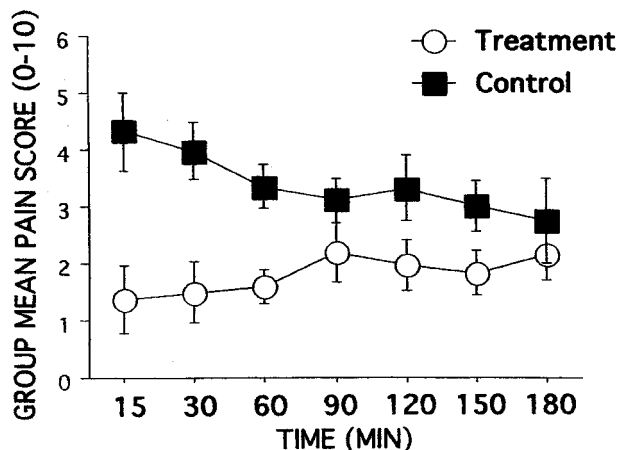
	Treatment Group (n = 17)	Control Group (n = 17)
Age (yr)	41 (3.4)	40 (3.7)
Height (cm)	180 (1.7)	180 (0.3)
Weight (kg)	82 (0.3)	83 (3.4)
Duration of surgery (min)	84 (6.4)	85 (7.8)
Duration of anesthesia (min)	104 (7.4)	101 (8.3)
Airway management		
% intubated	63	44
% LMA	38	56
Mean end-tidal sevoflurane conc (%)	1.2 (0.1)	1.3 (0.1)
Mean BIS level	44 (1)	44 (1.2)
Mean fentanyl dose (µg/kg)	0.7 (0.5)*	1.8 (0.2)

All values are mean (SE) or percentage.
LMA = laryngeal mask airway; BIS = bispectral index.
* *P* < 0.01 for differences between groups.

The intraoperative fentanyl dose was less in the treatment group. The majority of patients (15 in each group) had a tension-free repair with mesh. Two patients in the treatment group and one in the control group had a sutured repair. One patient in the control group was found to have a cord lipoma and did not actually have a hernia repaired. Group mean pain scores were lower in the treatment group in the first 60 min of recovery (Fig. 1). Pain scores after discharge are shown in Figure 2, and statistical comparisons of pain and analgesic use in Table 2. Patients in the treatment group had less severe pain in the recovery room (47% reduction in maximum pain scores before discharge) and less severe pain in the first 24 h at home after discharge. The treatment group also used less analgesic (Percocet) in the first 24 h after discharge (Table 2). Excluding the four patients who did not have tension-free mesh repairs did not alter the significance of comparisons between groups; however, the pain reported by the two patients having sutured repair in the treatment group was more intense than the mean for the other 15 patients in the same group; i.e., they reported maximum pain in the postanesthesia care unit (PACU) of 7.5 versus 2.5 for the remainder of the treatment group.

The effects of treatment on recovery duration, activity levels, and satisfaction with analgesia are shown in Table 3. Overall, discharge times were comparable in the two groups, but the time expended for treatment of pain was less in the treatment group before discharge. The incidence of emetic symptoms tended to be more frequent in the treatment arm (treatment group 66% versus control group 33%; *P* = 0.13). If patients with emetic symptoms were excluded from

PAIN SCORES BEFORE DISCHARGE



ANALGESIC USE BEFORE DISCHARGE

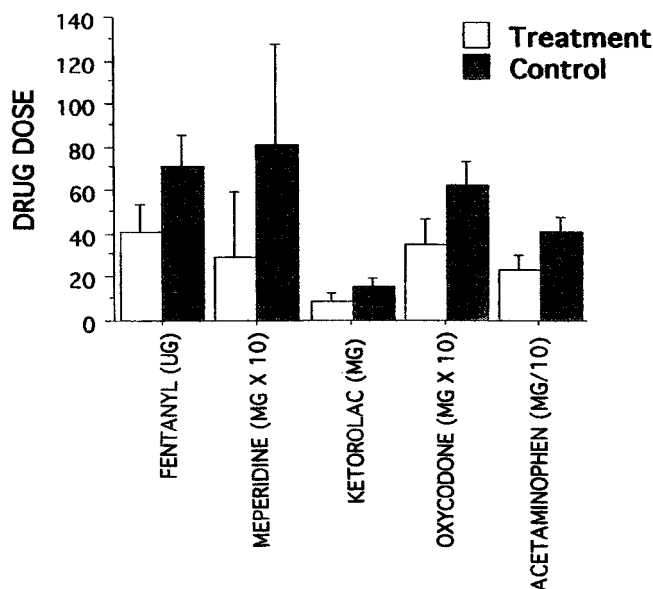


Figure 1. Upper panel: mean pain scores (0–10) for the first 180 min of recovery in treatment (open circles) and control groups (closed squares). Differences between groups were significant at 30 and 60 min (*P* ≤ 0.001). Lower panel: mean dose of analgesics received in the recovery unit before discharge. Fentanyl was administered in 25-µg increments. Meperidine was administered to treat shivering. Oxycodone 5 mg and acetaminophen 325 mg were administered as a fixed dose combination (Percocet®). Open bars = treatment group; filled bars = controls. Differences between groups were not statistically significant.

the analysis, recovery duration up to the time of discharge was 55 min less in the treatment group (117 min versus 173 min in treatment and controls respectively; *P* = 0.0025). Pain preventing patients from falling asleep at night was less common in the treatment group at 48 h (7% versus 44% in treatment and controls respectively; *P* = 0.03). There were no

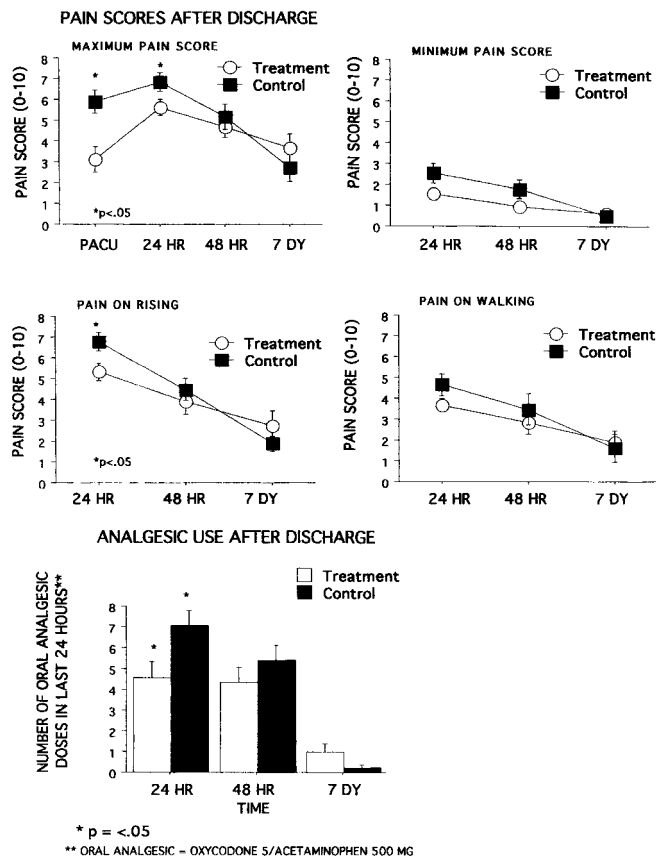


Figure 2. Upper four panels: group mean pain scores reported by patients after discharge to home. Maximum pain, minimum pain, pain on rising to a standing position, and pain on walking were elicited. Open circles = treatment group; closed squares = controls. Statistical comparisons are shown in Table 2. Lower panel: group mean analgesic use after discharge. Rescue analgesic was oxycodone 5 mg/acetaminophen 325 mg in a fixed dose combination (Percocet®). Statistical comparisons are shown in Table 2.

differences between groups in activity level or satisfaction with analgesia. The incidence of side effects was not different in the two groups. The most common side effects at 24 h in all patients were drowsiness (61%), dry mouth (58%), light-headedness (42%), and difficulty concentrating (35%); constipation was the most frequent at 48 h (67%).

Discussion

In this study, pain severity and analgesic use were diminished in the first 24 h after surgery by multimodal preincisional treatment. Maximum pain score was 47% less before discharge and 18% less in the first 24 h after discharge in the triple therapy group.

Each of the three treatment modalities had individually been reported to decrease postoperative pain (13). Each is believed to act by a different mechanism. We expected that combining all three would provide an indication of the maximum benefit attainable using

Table 2. Statistical Comparison of Pain Scores and Analgesic Use

	Treatment Group	Control Group
Pain Scores (0-10)		
PACU		
Maximum pain	3.1 (0.6)†	5.9 (0.6)
Pain at discharge	1.4 (0.2)‡	2.5 (0.2)
Duration of pain	17 (8)†	55.9 (10)
0-24 h		
Maximum	5.6 (0.4)*	6.8 (0.5)
Minimum	1.6 (0.3)	2.5 (0.5)
Pain on walking	3.7 (0.3)	4.6 (0.5)
Pain on rising	5.3 (0.4)*	6.8 (0.4)
24-48 h		
Maximum	4.6 (0.5)	5.2 (0.6)
Minimum	0.9 (0.2)	1.8 (0.5)
Pain on walking	2.8 (0.5)	3.5 (0.8)
Pain on rising	3.9 (0.6)	4.4 (0.5)
6-7 days		
Maximum	3.7 (0.7)	2.7 (0.6)
Minimum	0.6 (0.3)	0.5 (0.3)
Pain on walking	1.9 (0.6)	1.6 (0.7)
Pain on rising	2.8 (0.7)	1.9 (0.4)
Analgesic Use		
PACU Fentanyl (µg)	41 (13)	71 (15)
PACU Percocet (doses)	0.7 (0.2)	1.3 (21)
0-24 h Percocet (doses)	4.6 (0.8)*	7.1 (0.7)
24-48 h Percocet (doses)	4.3 (0.7)	5.4 (0.7)
6-7 days Percocet (doses)	1.0 (0.4)	0.2 (0.2)

All values are mean (SE).

PACU = postanesthesia care unit.

* P ≤ .05; † P < .01; ‡ P < .001 for significance of difference between treatment and control.

these three mechanisms of preemptive analgesia that are readily available to most practitioners. The study design did not, however, permit ascertaining which of the three modalities were most important to any benefits observed, nor did it permit assigning blame to any one drug for adverse effects.

The benefit of local anesthetic field block before hernia surgery has previously been investigated by Tverskoy et al. (14). In that study, "constant" pain and incident pain were less severe for 48 h after surgery in patients who received a preoperative field block with bupivacaine compared with patients who received no local anesthetic at all. The lesser duration of effect in our study (24 h) may be related to differences in study design. In the Tverskoy et al. study, the treatment group received meperidine at regular intervals strictly regulated by protocol in addition to a local anesthetic block, whereas the control group received only meperidine with no local anesthetic. The lack of local anesthesia in their control group may have enhanced the intergroup differences compared with the present study, in which control patients did receive a local anesthetic block at the end of surgery and all patients were permitted to medicate themselves to their level of comfort. The reduction in pain scores in our study

Table 3. Relationship of Treatment to Activity and Satisfaction with Analgesia

	Treatment Group	Control Group
Before discharge		
Recovery time (min)		
Phase 1	79 (13)	77 (7)
Phase 2	98 (20)	111 (12)
Total recovery duration	170 (1)	181 (10)
Duration pain therapy (min)	55 (7)*	75 (7)
Total recovery duration excluding patients with nausea or vomiting (min)	117 (10)	173 (11)
% Incidence of nausea or vomiting	67	33
After discharge		
Difficulty going to sleep (%)		
0-24 h	19	24
24-48 h	7*	44
Awakened by pain (%)		
0-24 h	50	53
24-48 h	29	31
Fraction of normal activity (%)		
0-24 h	17	25
24-48 h	28	38
Primary reason cited by patients for limitation of activity (%)		
Pain	69	65
Surgeon orders	0	6
Common sense	25	24
Fatigue	6	6
Satisfaction with analgesia (0-10)		
In PACU	9.3 (0.2)	9.4 (0.2)
0-24 h postdischarge	9.1 (0.3)	8.1 (0.6)

All values are mean (SE) or percentage.
PUACU = postanesthesia care unit.
* $P < 0.05$.

occurred despite a reduction in rescue analgesic use (Percocet) in the treatment group and despite local anesthetic infiltration at the end of surgery in the control group. The latter may have tended to minimize intergroup differences when compared to the Tverskoy et al. study. However, we chose to evaluate our treatment group relative to what normally occurs in our institution to determine whether the triple therapy contributed to improving existing care. Previous studies comparing pre- versus postoperative administration of local anesthetic (lidocaine) in the wound have yielded contradictory results (15,16). In a review of this topic, Callesen (2) concluded that local anesthetic infiltration was effective in reducing postoperative pain, that subfascial infiltration of local anesthetic appeared to be more effective than simple

subcutaneous infiltration, and that the time of injection of local anesthetic was relatively unimportant.

Previous research on the effects of pretreatment with ketamine on postoperative pain scores and analgesic use has yielded positive as well as negative outcomes (17-19). We chose a modest dose of ketamine (0.2 mg/kg) to avoid the undesirable side effects that have been reported with larger doses of ketamine (20). We observed occasional patients who seemed to be mildly "dissociated" (staring aimlessly about the room) on arrival in the PACU, but no patient was observed to be obviously hallucinating and no patients described hallucinations or unpleasant dreams after discharge.

NSAIDs diminish pain after inguinal herniorrhaphy either alone (21) or in combination with a local anesthetic field block (22). Rofecoxib, in our study, was administered preoperatively and in the morning at 24 h and 48 h after surgery to diminish production of inflammatory mediators of pain. In a study of ambulatory patients having otologic surgery, Issioui et al. (23) reported decreased pain and opioid use and increased satisfaction with analgesia when rofecoxib, instead of acetaminophen or placebo, was given before and for 48 h after surgery. A single preoperative dose of rofecoxib (50 mg PO) has been reported to decrease pain for up to 16 h and opioid use for 24 h after spine surgery (24). In our patients, significant decreases in pain scores and opioid use were only demonstrable in the first 24 h after surgery despite patients continuing to take rofecoxib for 48 h after surgery. Because the serum half-life of rofecoxib is approximately 17 h (25), it is possible that drug concentrations at effect sites decreased to less than therapeutic levels in the evening (after morning dosing). This might explain why patients in the treatment group had less difficulty than the control group initially falling asleep at 48 h (when the effects of other anesthetic drugs had resolved) but had an equivalent incidence of nighttime awakening by pain. Although all patients received acetaminophen as well as oxycodone (as Percocet), acetaminophen is not considered to be an antiinflammatory and should not have prevented demonstrating an antiinflammatory effect of rofecoxib (26). It has also been reported that there is no additional analgesic benefit gained by adding acetaminophen to rofecoxib for pain relief.

The definition of preemptive analgesia is somewhat controversial (9), and the effects are often difficult to demonstrate clinically (8). It is debatable whether our patients truly manifested "preemptive analgesia" or simply obtained benefits from drugs administered preoperatively that inhibited pain at therapeutically adequate concentrations. The reduction in effect after 24 h suggests that if a preemptive effect occurred, its duration was relatively short.

Interestingly, although opioid use was less in the treatment group, there was no reduction in the incidence of side effects typically attributed to opioids. This may reflect our relatively small sample size, or it could be related to the occurrence of equally bothersome side effects in response to drugs in the treatment arm of the study. In particular, there was a tendency towards increased postoperative nausea and vomiting (PONV) in the treatment group (66% versus 33% in the treatment and control groups, respectively) that, although not statistically significant, may have affected patients adversely in the treatment limb of the study. A larger patient population would be required to evaluate whether there is an association between the small doses of ketamine used in the treatment group and postoperative emetic symptoms. Ketamine has been associated with PONV when administered at larger doses (17). Rofecoxib infrequently causes nausea or vomiting, and its use has actually been associated with a reduction in emetic symptoms in some human studies (13,27).

This study may be criticized because it was not truly double-blinded. Although the patients, the nurses caring for them, and the study coordinator who recorded all of the data were blinded to group assignment, the surgeons and anesthesiologists caring for the patients were not. However, the conduct of anesthesia and the analgesic regimen were strictly controlled by protocol to minimize any effects that might result from bias of the surgeon or anesthesiologist. The sample size in this study was also relatively small. Thus, there was inadequate power to make reliable comparisons between groups for some of the secondary variables measured, in particular, the incidence of PONV.

In conclusion, we have demonstrated that trimodal therapy with rofecoxib, 50 mg PO, ketamine, 0.2 mg/kg IV, and a local anesthetic field block administered before open hernia repair is associated with reduced pain scores and analgesic use in the first 24 h after surgery. We conclude that further studies are warranted to determine whether all three components of therapy are equally beneficial, and conversely, whether elimination of one or more components would diminish the incidence of undesirable side effects, particularly PONV. Overall, the combination therapy reduced pain and analgesic requirements for at least 24 h but did not alter the duration of recovery.

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