An Evaluation of a Single Dose of Magnesium to Supplement Analgesia After Ambulatory Surgery: Randomized Controlled Trial

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BACKGROUND: Previous studies have suggested that magnesium may be a useful adjuvant to postoperative analgesia.

METHODS: We randomized adults undergoing ambulatory ilioinguinal hernia repair or varicose vein operation under general anesthesia (propofol, fentanyl, isoflurane-N_2O) to receive magnesium sulfate 4 g IV or physiological saline after induction. All patients preoperatively received diclofenac 100 mg rectally and those undergoing hernia repair had a postoperative ilioinguinal-iliohypogastric nerve block done. Pain, analgesic consumption, and adverse effects were recorded in the recovery room and, using a questionnaire, up to 3 days postoperatively.

RESULTS: We randomized 200 patients (101 magnesium, 99 placebo). There were no differences in hemodynamic variables before and immediately after study drug injection. Pain intensity at rest and on movement after 1, 2, and 4 h, time to first rescue analgesic, and cumulative numbers of non-opioid and opioid analgesics were similar among groups. There was no difference in the incidence of postoperative nausea and vomiting, dizziness, headache, or fainting. The incidence of postoperative shivering was significantly lower in the magnesium group (4% vs 13.1%, $P = 0.0232$). Adequately completed questionnaires were returned by 84 placebo and 82 magnesium patients. There was no difference between groups for any of the analyzed outcomes during the first three postoperative days, neither for patients undergoing inguinal hernia repair nor for those undergoing varicose vein stripping.

CONCLUSIONS: In patients undergoing ambulatory ilioinguinal hernia repair or varicose vein operations under general anesthesia supplemented with other analgesic adjuvants, pretreatment with IV magnesium sulfate 4 g has no impact on postoperative pain and analgesic consumption.

(Anesth Analg 2007;104:1374–9)

Magnesium inhibits calcium's entry into the cell via a noncompetitive blockade of the *N*-methyl-D-aspartate (NMDA) receptor (1). Magnesium and the NMDA receptor are thought to be involved in the modulation of pain (2). Magnesium is also a physiological calcium antagonist at different voltage-gated channels (3); these channels may be important in the mechanisms of antinociception (4).

In a rat model, intrathecal magnesium sulfate induced spinal anesthesia (5). In clinical trials, magnesium treatment improved symptoms of primary dysmenorrhea (6) and had a beneficial effect in patients affected by menstrual migraine (7), or headache (8). However, trials testing the effect of perioperative magnesium supplementation on postoperative pain and analgesic consumption reached inconsistent conclusions (9,10).

We report on a clinical trial that tested the effect of a single preoperative IV bolus of magnesium sulfate on postoperative pain and analgesic requirements in patients undergoing outpatient inguinal hernia surgery and vein stripping.

METHODS

Patients

Adults scheduled for ambulatory ilioinguinal hernia repair or varicose vein operations under general anesthesia were asked to participate in a randomized, double-blind, placebo-controlled trial. The study was approved by the local ethics committee. Patients were given written information concerning the nature of the study, and were asked to give written consent when they were willing to take part in the trial. All procedures were performed by one of two anesthesiologists and by one of five surgeons.

Patients did not receive any premedication. Anesthetic induction was with fentanyl 2 μg/kg and propofol

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DOI: 10.1213/01.ane.0000263416.14948.dc

2 mg/kg IV. After loss of eyelid reflex, a laryngeal mask was inserted and patients were allowed to spontaneously breathe isoflurane in N_2O/O_2 (70/30%). The isoflurane concentration was adjusted to keep arterial blood pressure and heart rate within 20% of preoperative values. No supplemental opioids were given. Before start of surgery, patients received diclofenac 100 mg rectally. Those undergoing hernia repair had an ilioinguinal-iliohypogastric nerve block done with 20 mL bupivacaine 0.5% at the end of surgery.

After anesthetic induction, patients received a slow IV bolus injection of either 10 mL magnesium sulfate ($MgSO_4$) 40% (corresponding to 4 g of $MgSO_4$) or 10 mL physiological saline. The hospital pharmacy was responsible for randomization (table of random numbers), stratification (inguinal hernia versus varicose vein), and preparation of the study drugs in indistinguishable and numbered plastic syringes. The randomization code was broken once the study was finished. Perioperative monitoring was with electrocardiogram, end-tidal CO_2, digital pulse oximetry, and noninvasive arterial blood pressure. After surgery, patients were transferred to the recovery room.

Postoperative analgesia was with co-proxamol tablets (dextropropoxyphene hydrochloride 32.5 mg, acetaminophen 325 mg), maximum two tablets every 4 h. When analgesia was deemed inadequate [visual analog scale (VAS) >40/100 mm with 0 = least possible pain and 100 = worst possible pain] or when the patient was asking for supplemental analgesia, an oral or rectal nonsteroidal antiinflammatory drug (NSAID) (diclofenac 50–100 mg, ibuprofen 400 mg) or an IV or IM opioid (morphine, meperidine, tramal, fentanyl) was given.

End-Points

During surgery, episodes of bradycardia (heart rate <50 bpm) and arterial hypotension (systolic blood pressure <90 mm Hg) were recorded.

In the recovery room, pain, analgesic consumption, and adverse effects were recorded at 1, 2, and 4 hours. Pain intensity (VAS) was measured at rest and on movement (coughing for inguinal hernia repair patients, leg raising for varicose vein patients). The delay for the first request for and the average amount of rescue analgesia (oral or rectal NSAIDs, IV or IM opioids) were recorded. Before patients left the recovery room, they and the caring nurse were asked to globally assess the overall quality of postoperative recovery on a 5-point verbal scale (1 = excellent, 2 = very good, 3 = good, 4 = fair, 5 = poor). Presence or absence of adverse effects (headache, dizziness, nausea, vomiting, shivering) was recorded. We regarded the typical postoperative muscle vibrations as shivering. Intensity and duration of adverse effects were not considered. We also noted the delay until the first oral intake. Finally, we recorded reasons for prolonged stay in the recovery room (defined as ≥4 h) and unanticipated admission.

Patients were asked to fill-in a questionnaire twice daily (morning and evening) for 3 days and to mail it back in a stamped envelope. They recorded the number of co-proxamol tablets they had taken, and rated pain intensity at rest and on standing on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). They were also asked to rate quality of sleep during the first three nights on a five-point verbal scale, and to report on any adverse effects.

Analyses

There was a *pre hoc* decision to analyze all data according to intention-to-treat. Reasons for withdrawals and drop-outs were recorded but drop-outs were not replaced. A previous similar two-arm study included 25 patients per group and had enough power to show significantly decreased postoperative pain intensity scores in patients who had received magnesium (9). In the present project, however, we had to deal with two uncertainties. First, instead of testing an IV bolus and subsequent continuous infusion of magnesium, we intended to test the effect of a single IV bolus dose only; thus the cumulative dose of magnesium would be smaller than in the previous study. Second, instead of including patients undergoing major surgery, we planned to test the analgesic efficacy of magnesium in patients undergoing minor surgeries with potentially lower baseline pain. We therefore decided to randomize 100 patients in each group. This large number additionally allowed for drop-outs and for studying potential adverse events with more confidence. Stratification of the patients according to the type of surgery (ilioinguinal hernia repair versus varicose vein operations) enabled us to analyze these surgical subgroups separately and to evaluate the impact of the type of surgery on the potential analgesic effect of magnesium.

Continuous variables were analyzed using Student *t*-test. Scores were analyzed using the Mann–Whitney *U*-test for independent samples and the Wilcoxon ranked sum test for dependent samples. Differences among group means were compared using one-way analysis of variance. Dichotomous data were analyzed using χ^2 test. A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

We randomized 200 patients; 101 received magnesium sulfate and 99 placebo. All patients were followed-up until they left the recovery room. Seventy-seven men and three women had a hernia repair; 30 men and 90 women underwent a varicose vein operation. Surgical techniques were comparable among groups (Table 1).

There were no differences in hemodynamic variables before and immediately after study drug injection (Table 2). The slowest heart rate was 48 bpm in the placebo group and 49 bpm in the magnesium group. There was no statistically significant difference in the number of patients with heart rates <50 bpm

Table 1. Patients Characteristics, Intraoperative Analgesia, and Surgical Technique

	Placebo		Magnesium	
	Inguinal hernia	Varicose vein	Inguinal hernia	Varicose vein
Number of patients	99		101	
Gender, m/f	38/1	15/45	39/2	15/45
Age (yr)	48.8 ± 12.0	42.8 ± 12.9	48.2 ± 14.2	42.1 ± 11.0
Weight (kg)	78.3 ± 12.0	68.7 ± 10.6	77.5 ± 10.1	67.8 ± 11.1
Fentanyl 2 μg/kg IV, at induction	+	+	+	+
Diclofenac 100 mg pr, before start of surgery	+	+	+	+
Ilioinguinal bupivacaine 0.5% 20 mL, at end of surgery	+		+	
Direct hernia	19		19	
Mesh	36		37	
Varicose vein unilateral		45		43
Varicose vein stripping		27		27
Groin incision		50		54

Data are means ± SD or numbers.

There were no significant differences between magnesium and placebo.

Table 2. Hemodynamic Parameters

	Placebo (n = 99)		Magnesium (n = 101)	
	Inguinal hernia (n = 39)	Varicose vein (n = 60)	Inguinal hernia (n = 41)	Varicose vein (n = 60)
Heart rate before injection	80.6 ± 14.0		83.7 ± 12.7	
Heart rate after injection	72.8 ± 14.3		76.5 ± 13.6	
No. patients with at least one episode of heart rate <50/min	13 (13.1)		22 (21.8)	
Diastolic blood pressure before injection	68.4 ± 12.3		70.6 ± 13.4	
Diastolic blood pressure after injection	59.9 ± 11.8		57.2 ± 10.3	
Systolic blood pressure before injection	118.5 ± 16.0		122.1 ± 16.3	
Systolic blood pressure after injection	108.2 ± 17.4		107.9 ± 13.3	
No. patients with at least one episode of systolic blood pressure <90 mm Hg	8 (8.1)		13 (12.9)	

Data are means ± SD , or numbers (%).

There were no significant differences between magnesium and placebo.

immediately after the injection of magnesium (21.8% with magnesium versus 13.1% with placebo; P = 0.1366). In both groups, arterial blood pressure significantly decreased after anesthetic induction and study drug injection. However, there was no difference in pre- and postinjection values between the two groups.

In the recovery room, pain intensity at rest and on movement after 1, 2, and 4 h, time to first rescue analgesic, time to first oral intake, cumulative number of co-proxamol tablets and the number of patients needing extra doses of any supplemental NSAIDs or opioid analgesic were similar among magnesium and placebo groups (Table 3). Also, there were no differences in these outcomes when surgical subgroups were analyzed separately.

In both surgical subgroups, inguinal hernia repair and varicose vein stripping, average pain intensity values consistently decreased over time, from 50–60 mm on the 100 mm VAS at 1 h to 20–30 mm at 4 h. In both surgical subgroups and at all timepoints, pain intensity on movement was consistently more pronounced than pain intensity at rest. Finally, patients undergoing inguinal hernia repair had higher pain intensity values at each timepoint compared with those undergoing varicose vein stripping. These differences were most pronounced when pain on movement was measured; for instance, at 2 and 4 h, average pain intensity values of patients undergoing inguinal hernia repair were twice as high as in patients undergoing varicose vein stripping (Table 3).

There was no difference in the incidence of postoperative nausea and vomiting, dizziness, headache, or fainting in the recovery room (Table 4). The incidence of nausea and vomiting was more frequent in patients undergoing varicose vein operations; this was most likely due to the higher number of females in that

Table 3. Pain Intensity and Analgesic Consumption in the Recovery Room

	Placebo (n = 99)		Magnesium (n = 101)	
	Inguinal hernia (n = 39)	Varicose vein (n = 60)	Inguinal hernia (n = 41)	Varicose vein (n = 60)
Pain intensity at rest 1 h	57.6 ± 23.0	51.6 ± 26.6	57.9 ± 25.8	49.2 ± 22.5
Pain intensity at rest 2 h	36.8 ± 21.0	33.2 ± 22.9	38.9 ± 25.6	27.0 ± 18.5
Pain intensity at rest 4 h	24.7 ± 17.0	18.3 ± 14.5	30.1 ± 25.4	18.7 ± 15.8
Pain intensity on movement 1 h	69.8 ± 24.0	46.0 ± 26.1	63.0 ± 27.3	50.1 ± 26.3
Pain intensity on movement 2 h	56.1 ± 28.0	24.3 ± 16.8	58.0 ± 27.1	24.4 ± 19.4
Pain intensity on movement 4 h	47.1 ± 25.0	22.9 ± 20.1	45.5 ± 28.2	19.8 ± 16.7
Time to 1st rescue analgesic (min)	57.8 ± 48.0	49.4 ± 42.7	63.7 ± 59.0	60.0 ± 54.3
Time to 1st oral intake (min)	63.0 ± 32.0	66.7 ± 41.2	70.9 ± 44.1	54.9 ± 32.5
No. co-proxamol tablets	2 (0–6)	2 (0–4)	2 (0–4)	2 (0–4)
No. patients receiving any rescue analgesic	7 (17.9)	10 (16.6)	8 (19.5)	12 (20)
No. patients receiving an NSAID	4 (10.3)	9 (15)	6 (14.6)	12 (20)
No. patients receiving an opioid	3 (7.7)	3 (5)	3 (7.3)	1 (1.7)

Data are means ± SD, numbers (%), or medians (range).

Pain intensity was evaluated using a visual analogue scale (0 = least possible to 100 = worst possible pain). There were no significant differences between magnesium and placebo. NSAIDs were diclofenac or ibuprofen. Opioids were morphine, meperidine, tramal, or fentanyl.

Table 4. Adverse Effects and Global Assessment

	Placebo (n = 99)		Magnesium (n = 101)	
	Inguinal hernia (n = 39)	Varicose vein (n = 60)	Inguinal hernia (n = 41)	Varicose vein (n = 60)
Nausea and/or vomiting	19 (19.2)		25 (24.8)	
	5 (12.8)	14 (23.3)	7 (17.1)	18 (30)
Dizzyness	12 (12.1)		10 (9.9)	
Headache	24 (24.3)		23 (22.8)	
Shivering	13 (13.1)*		4 (4.0)*	
Fainting	7 (7.1)		7 (6.9)	
Global assessment from patient's view	2 (1–4)	2 (1–5)	2 (1–5)	2 (1–5)
Global assessment from nurse's view	3 (1–5)	2 (1–5)	2 (1–5)	2 (1–5)

Data are means ± SD, numbers (%), or medians (range).

There were no significant differences between magnesium and placebo except for the *incidence of shivering (P = 0.0232). Global assessment was evaluated on a 5-point scale before the patients left the recovery room.

subgroup. Differences between magnesium and placebo, however, were not different in the surgical subgroups. The incidence of postoperative shivering was significantly lower in the magnesium group (4% vs 13.1%, P = 0.0232). Twenty-two patients (11%; 13 placebo, 9 magnesium) needed an overnight admission due to dizziness with or without fainting (n = 10 patients), pain (n = 6), postoperative nausea and vomiting (n = 2), or bleeding (n = 4). There were no differences between groups. When the patients left the recovery room, global assessment scores from the patients' or the nurses' points of view were comparable between the groups (Table 4).

Adequately filled-in questionnaires were returned by 166 patients (83%; 84 placebo, 82 magnesium). There was no significant difference between magnesium and placebo patients for any of the analyzed end-points, neither for patients undergoing inguinal hernia repair nor for those undergoing varicose vein stripping (Table 5). Compared with patients who had undergone varicose vein surgery, those who had undergone inguinal hernia repair had higher median pain scores at rest on Days 2 and 3, and had higher median pain scores on movement on Days 1 and 2. Inguinal hernia patients also consumed more co-proxamol tablets and had lower median scores for quality of sleep during the second and the third postoperative night.

DISCUSSION

We were unable to show any beneficial effect of a single preoperative IV bolus dose of magnesium sulfate on pain intensity and analgesic requirements in patients undergoing outpatient inguinal hernia repair or varicose vein surgery under general anesthesia supplemented by local anesthesia blocks (inguinal hernia repair) and NSAIDs.

There may be several reasons for this negative result. The dose of magnesium that we tested may have been too small. However, previous studies tested similar regimens and found statistically significant beneficial effects on both postoperative opioid consumption and pain intensity (11,12). Levaux et al.

Table 5. Pain Intensity at Rest and on Movement, Number of Pain Killers Taken, and Quality of Sleep, Day 1–3

	Placebo (n = 84)		Magnesium (n = 82)	
	Inguinal hernia (n = 33)	Varicose vein (n = 51)	Inguinal hernia (n = 33)	Varicose vein (n = 49)
Pain intensity at rest				
Day 1 AM	1 (0–3)	1 (0–2)	1 (0–2)	1 (0–3)
Day 1 PM	1 (0–3)	1 (0–2)	1 (0–3)	1 (0–3)
Day 2 AM	1 (0–2)	0 (0–2)	1 (0–3)	0 (0–2)
Day 2 PM	1 (0–2)	0 (0–3)	1 (0–3)	0 (0–2)
Day 3 AM	1 (0–2)	0 (0–2)	1 (0–3)	0 (0–2)
Day 3 PM	1 (0–2)	0 (0–2)	0 (0–3)	0 (0–2)
Pain intensity on movement				
Day 1 AM	2 (0–3)	1 (0–3)	2 (0–3)	1 (0–3)
Day 1 PM	2 (0–3)	1 (0–3)	2 (0–3)	1 (0–3)
Day 2 AM	2 (0–3)	1 (0–3)	2 (0–3)	1 (0–2)
Day 2 PM	1 (0–3)	1 (0–3)	2 (0–3)	1 (0–2)
Day 3 AM	1 (0–3)	1 (0–2)	1 (0–3)	1 (0–2)
Day 3 PM	1 (0–3)	1 (0–3)	1 (0–3)	1 (0–3)
Cumulative no. of co-proxamol tablets				
Day 1	6.2 ± 3	3.9 ± 3.5	6.3 ± 2.8	4.3 ± 3.3
Day 2	10.5 ± 5	5.2 ± 5.2	10.4 ± 4.7	5.3 ± 4.5
Day 3	13.5 ± 8	6.0 ± 6.5	13.4 ± 6.3	6.2 ± 5.8
Quality of sleep				
1st night	2 (0–4)	2 (0–4)	2 (0–4)	2 (0–4)
2nd night	2 (0–4)	3 (0–4)	2 (0–4)	3 (0–4)
3rd night	2 (0–4)	3 (0–4)	2 (0–4)	3 (0–4)

Data are means ± SD or medians (range). Data are from patients who sent back adequately filled in questionnaires.

Pain intensity at rest and movement (on standing up) was rated on a 4-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe. Quality of sleep: 1 = very poor to 5 = excellent. There were no significant differences between magnesium and placebo groups.

randomized patients undergoing major orthopedic surgery to an IV bolus of magnesium sulfate 50 $mg \cdot kg^{-1}$ (approximately 3.6 g) and placebo (11). They reported significantly reduced cumulative consumption of piritramide after 12 and 24 h and significantly lower pain intensity in magnesium-treated patients. Seyhan et al. randomized patients undergoing abdominal hysterectomy in a placebo-controlled 4-arm trial; one group received an IV bolus of magnesium sulfate 40 $mg \cdot kg^{-1}$ (approximately 3 g) (12). They reported significantly reduced cumulative 24-h morphine consumption in patients who had received the magnesium bolus compared with placebo. It may further be argued that our study population was too heterogeneous, that all patients received supplemental NSAIDs and that those undergoing inguinal hernia repair additionally received a locoregional anesthetic block; thus, baseline pain may have been too low to evaluate the potential analgesic efficacy of magnesium. Indeed, if there is not enough pain without an analgesic, there is no effective way to test the efficacy of that analgesic intervention (13). In placebo patients, average pain intensity at rest was about 50 mm on the 100 mm VAS scale at 1 h, and was about 30 mm at 2 h. There is both a methodological and an ethical issue here. What pain scores would we be prepared to tolerate only to be able to show that a marginally analgesic intervention is really analgesic? Our trial provides strong evidence that under daily clinical practice conditions, in patients undergoing ambulatory surgery with standard anesthesia and analgesia techniques, 4 g of IV magnesium has no impact on postoperative pain and analgesic consumption. Perhaps more importantly, there was evidence that our study was internally sensitive. For instance, from the first to the fourth postoperative hour, average pain scores decreased consistently. Also, for both types of surgeries, average pain intensity on movement was consistently higher than average pain intensity at rest. Patients undergoing inguinal hernia repair had consistently higher pain scores than those undergoing varicose vein operations. However, despite adequate baseline pain in control patients, and internal sensitivity of our study, there was no evidence of any beneficial effect with magnesium pretreatment, even in the subgroup of patients who had the highest pain scores, i.e., patients after inguinal hernia repair reporting pain intensity on coughing. Finally, we exclude that our study was under-powered, although this is the largest published trial testing the potential analgesic effect of magnesium on postoperative pain. Using data from the most promising result in favor of magnesium, i.e., time to first request of analgesia (Table 3), we may perform a *post hoc* power analysis as to what an adequate number of subjects would be to determine significance. Assuming that a relevant reduction in time to first request of analgesia was 10 min and that the standard deviation was about 40 min as suggested by our data, more than 250 patients would be needed per group to show a statistically significant difference ($\alpha = 0.05$, $\beta = 0.20$).

We were using a variety of rescue analgesics. This may be perceived as a limitation of our study. However, intraoperatively, analgesia techniques were well controlled. Postoperatively, we preferred to allow for a certain variety of analgesics to treat pain on request, since our aim was to design a pragmatic and large trial that represented daily clinical practice. The aim was to achieve acceptable pain relief using effective NSAID and opioid regimens. Since there was no evidence for a pharmacological interaction between magnesium and, for instance, morphine or meperidin, there was no reason to believe that the variety of analgesic rescue medications may have had an impact on our results.

It may be hypothesized that magnesium substitution was beneficial only in patients who had hypomagnesemia. Patients undergoing major surgery without magnesium supplementation were shown to be at risk of developing hypomagnesemia in the first 24 postoperative hours (14). This decrease was probably due to the large loss of fluids and fluid movement between body compartments. Magnesium is a noncompetitive blocker of the NMDA receptor (1). It was shown *in vitro* that in magnesium-free solutions, the excitatory amino acids L-glutamate and L-aspartate opened the NMDA cation channels, and in the presence of magnesium, the probability of opening of the channels was reduced (15). Thus, substitution of magnesium in surgical patients at risk of developing hypomagnesemia should prevent hypomagnesemia-related opening of the NMDA receptors. We did not measure magnesium blood concentrations in our patients. It may well be that these relatively young and healthy patients, who were undergoing ambulatory surgeries with minor loss of fluids and subsequent fluid movement between body compartments, were unable to profit from the magnesium substitution, since they were never at risk of developing hypomagnesemia. Also, the dose of magnesium required to manipulate the NMDA receptor in surgical patients remains unknown.

What needs to be done? Published studies have shown a beneficial effect on postoperative pain outcomes with a variety of magnesium pretreatments ranging from IV single boluses (11,12) to IV infusions lasting several hours (9). It may well be that the dose and regimen of magnesium (bolus versus continuous infusion), the kind of surgery (minor versus major), and magnesium homeostasis (normo- versus hypomagnesemia) play a role in the analgesic efficacy of magnesium. In a recently published editorial, it was claimed that "a typical systemic analgesic dose [of magnesium] would be 2 g for a 70 kg patient" (16). Our trial suggests that even a systemic dose of 4 g is unlikely to be analgesic in healthy patients undergoing minor surgeries. Seyhan et al., in their study, were unable to show a benefit with a magnesium bolus followed by a 20 $mg \cdot kg^{-1}$ infusion over 4 h compared with the same bolus followed by a 10 $mg \cdot kg^{-1}$ infusion over 4 h (12). Future research needs to address these questions. Finally, since NMDA receptor antagonists may potentially decrease chronic postsurgical pain, and the incidence of chronic pain after inguinal hernia repair may be high, it would be interesting to examine the potential long-term benefits of magnesium.

In conclusion, within our study model (i.e., patients undergoing outpatient inguinal hernia repair or varicose vein surgery under general anesthesia supplemented by local anesthesia block and NSAIDs) we were unable to show any benefit of a prophylactic, single IV bolus dose of magnesium. Our study does not exclude the possibility that magnesium may provide an opiate-sparing effect in other pain models, or in the absence of other analgesic adjuvants.

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