

A Comparative Study with Oral Nifedipine, Intravenous Nimodipine, and Magnesium Sulfate in Postoperative Analgesia

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We tested the ability of two L-type calcium channel blockers (nifedipine and nimodipine) and the *N*-methyl *D*-aspartate natural antagonist magnesium to decrease morphine requirements and pain in the postoperative period in 92 patients undergoing elective colorectal surgery. In a randomized, double-blinded study, patients were assigned to one of four groups. The control group received placebo. The nifedipine group received 60 mg of oral nifedipine. The magnesium group received an initial dose of 30 mg/kg followed by 10 mg · kg⁻¹ · h⁻¹ of magnesium sulfate over 20 h. The nimodipine group received 30 μg · kg⁻¹ · h⁻¹ of nimodipine over 20 h. Postoperative morphine consumption was assessed for 48 h. Pain at rest

and pain on movement were assessed up to the fifth day postsurgery. There were no differences among groups in postoperative morphine consumption at 12 and 24 h. The nifedipine group consumed more morphine than the control and nimodipine groups during 24–48 h. Pain at rest scores were higher at 16 and 24 h in the nifedipine group than in the other three groups. Pain on movement scores were lower at 72 h in the nimodipine group than in the control and nifedipine groups. In conclusion, the perioperative application of oral nifedipine, IV nimodipine, or IV magnesium sulfate failed to decrease postoperative morphine requirements after colorectal surgery.

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Voltage-gated calcium channel conductance is essential for the nervous system to signal painful events. The movement of Ca²⁺ into and out of the sensory neurons is involved in a variety of processes, including the release of neurotransmitters. Numerous animal studies indicate a close relationship between the antinociceptive effect of opioids and Ca²⁺ concentrations. Drugs that increase intracellular Ca²⁺ in neurons block opioid analgesia (1) or produce hyperalgesia (2) when injected supraspinally. Conversely, acute opioid exposure decreases intracellular Ca²⁺ levels and Ca²⁺ binding to synaptic membranes and vesicles (3). Calcium chelators and calcium channel blockers (CCB) not only enhance opioid analgesia (2), but may be antinociceptive *per se* (4).

Evidence suggests that the increase of intracellular Ca²⁺ plays a key role in the establishment of central sensitization (5). Noxious stimulation produces an influx of Ca²⁺ through both voltage-sensitive calcium channels that facilitates presynaptic neurotransmitter release and postsynaptic *N*-methyl *D*-aspartate calcium channels (NMDA-CCs), which triggers the sequence of events leading to cellular hyperexcitability. Studies in animal models of persistent pain in which central sensitization is present support this theory (5).

Magnesium is a physiological blocker of the NMDA-CC (6). It may suppress neuropathic pain (7), enhance morphine analgesia, and attenuate morphine tolerance (8) in rats. Magnesium deficiency produces hyperalgesia that can be reversed by NMDA antagonists (9) and has been related to acute medical/surgical conditions in which pain or stress is present (10).

The development of central sensitization may be prevented not only with NMDA antagonists, but also with CCBs and magnesium, which block Ca²⁺ entry into the neurons. We assessed and compared the efficiency of oral nifedipine, IV nimodipine, and magnesium sulfate for postoperative pain relief.

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Methods

We conducted a randomized, doubled-blinded, placebo-controlled study in 92 patients, ASA physical status I-II, scheduled for colorectal surgery from March 1997 to November 1998. The study was approved by the hospital ethical committee and written informed consent was obtained from the participants. Exclusion criteria were an age <30 yr or >75 yr; treatment with analgesics, CCBs, magnesium, or opioids; and a previous history of psychiatric, neurologic, cardiovascular, respiratory, liver, or renal disease. All surgeries were performed by one team of surgeons, with the same surgical technique and suprainfraumbilical incision.

Patients were randomly assigned by the hospital pharmacy to four groups: Group C = control; Group NF = nifedipine gastrointestinal therapeutic system formulation (GITS); Group MG = magnesium; Group NM = nimodipine. The protocol of the administration of studied drugs is shown in Table 1.

Oral tablets of placebo were prepared by the hospital pharmacy. These tablets and nifedipine GITS were distributed by a nurse blinded to the allocated group. The tablets were given 3 h before surgery because plasma levels of nifedipine GITS are not detectable for at least 3 h after its administration. We chose oral nifedipine GITS because of the simplicity of its administration and advantageous pharmacokinetic properties. This osmotic system tablet presents a zero order delivery, a relatively constant plasma concentration over at least an 18-h interval, and its absorption is unaffected by changes in gastrointestinal motility and pH.

The studied IV drugs were prepared and labeled by a nurse not involved in the perioperative care of the patient. A saline solution of 500 mL was wrapped with an opaque cover and connected to an opaque system because nimodipine is sensitive to the light. We used nimodipine in the customary dose for the treatment of cerebral hemorrhage.

The IV initial dose of magnesium sulfate was calculated according to weight and is similar to the customary dose in the treatment of dysrhythmias (2 g/70 kg). The maintenance dose was slightly smaller than that used in the referred setting (0.7 g/70 kg). These doses are also smaller than those used in the treatment of preeclampsia (4 g initial dose and 2 g/h for maintenance). In a previous trial (11), the initial dose was larger (3 g) and the maintenance dose was similar (0.5 g). Because of the variability of patient weight we preferred to design a mg/kg dose.

The night before surgery patients received 1.5 mg of oral bromazepam. During the preoperative visit, we explained the use of a patient-controlled analgesia (PCA) device, and a standard horizontal 100-mm pain visual analog scale (VAS).

Patients received an oral tablet (studied drugs) approximately 3 h before surgery, and 0.01 mg/kg atropine, 0.05 mg/kg diazepam, and 1.25 mg droperidol as premedication 30 min before anesthetic induction. Standard anesthetic induction was done with thiopental, atracurium, and 4 $\mu\text{g}/\text{kg}$ IV fentanyl, and maintained with isoflurane, nitrous oxide in oxygen, and a continuous infusion of fentanyl at 1 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ until the closing of the peritoneum. An initial dose of the studied IV drug was given in a period of time of 20 min after anesthetic induction, followed by an IV drip over 20 h. A bolus dose of 0.05 mg/kg morphine was injected 15 min after stopping the fentanyl infusion. Antagonism of neuromuscular blockade was achieved with 0.01 mg/kg atropine and 0.02 mg/kg neostigmine IV.

After surgery, patients stayed in the postanesthesia care unit for 24 h. On arrival, 2 mg IV morphine was given at 5 min intervals if the patient reported pain (VAS ≥ 5). When VAS was <5, a PCA device (Provider; Abbott Laboratories, North Chicago, IL) containing 1 mg/dose morphine with 10 min lockout interval and no continuous infusion, was connected to the patient. Benzodiazepines were avoided during the first 48 h. The administration of nonsteroidal antiinflammatory drugs (NSAIDs) was restricted to patients whose morphine requirements were more than 0.3 mg/kg during the first 6 h and had persisting pain (VAS ≥ 5). They received 2 g of IV propacetamol and, if necessary, 2 g of IV metamizole.

On arrival at the holding area, the level of anxiety was assessed by the anesthesiologist according to the following scale: 1 = patient calm; 2 = patient nervous; 3 = patient very nervous. Morphine requirements were assessed 12, 24, and 48 h after surgery. VAS at rest was assessed at 30, 60 min, 2, 6, 16, 24, 48, 72 h and on the fifth day postsurgery. VAS on movement (when patient sat up 45° from the supine position) was assessed at 16, 24, 48, 72 h and fifth day after surgery. The requirements of NSAIDs were assessed according to the following score: 0 = no NSAIDs; 1 = propacetamol; 2 = metamizole.

Sedation was assessed 0, 2, 6, 16, 24, and 48 h postsurgery according to the following score: 1 = fully awake; 2 = somnolent, responds to verbal commands; 3 = somnolent, responds to tactile stimulation; 4 = asleep, responds to painful stimulation. Noninvasive systolic arterial blood pressure, diastolic arterial blood pressure, mean arterial blood pressure, heart rate, respiratory rate, and pulse oximetry oxygen saturation were recorded at intervals of 4 h during the first 24 h. Time for return to normal bowel function (bowel sounds, withdrawal of nasogastric tube, oral fluids intake, flatus passed, and evacuation of bowels) was assessed according to the following score: 1 = <24 h; 2 = >24 h and <48 h; 3 = >48 h and <72 h; 4 = >72 h and <96 h; 5 = >96 h and <120 h; 6 = >120 h. Blood

Table 1. Medication for the Four Groups

	3 h Presurgery oral tablet	Postanesthetic induction initial dose	During 20 h (25 mL/h) maintenance dose
Group C	Placebo	100 mL of saline	500 mL of saline
Group NF	Nifedipine GITS 60 mg	100 mL of saline	500 mL of saline
Group MG	Placebo	Magnesium sulfate 30 mg · kg ⁻¹ · h ⁻¹ (in 100 mL of saline)	Magnesium sulfate 10 mg · kg ⁻¹ · h ⁻¹ (in 500 mL of saline)
Group NM	Placebo	100 mL of saline	Nimodipine 30 μg · kg ⁻¹ · h ⁻¹ (in 500 mL of saline)

C = control, NF = nifedipine, MG = magnesium, NM = nimodipine.

samples for determination of serum magnesium concentrations were obtained before anesthetic induction (basal), and at 0, 12, 24, and 48 h after surgery.

Analysis of variance and the χ^2 test were performed to compare demographic data and preoperative clinical variables. The Kruskal-Wallis test and the Mann-Whitney *U*-test with Bonferroni correction were used to compare ordinal data (VAS at rest, VAS on movement, preoperative anxiety, sedation, and the variables related to bowel function) and to compare preoperative anxiety with morphine requirements. Analysis of variance was used to compare postoperative morphine consumption among groups. The χ^2 test was also used to analyze dichotomous variables. A $P < 0.05$ was considered statistically significant. A sample size of 17 patients per group was needed to detect a difference in morphine consumption between treatments of one SD at a two-sided 5% significance level with a power of 80% (11a).

Results

Ninety-six patients were enrolled in the study. Data from four patients were not included in the analysis (one in Group C, two in Group NF, and one in Group MG). One patient received a mistaken dose of fentanyl during surgery, another one experienced intense low back pain in the postoperative period, another presented with an anxiety condition that contributed to large morphine consumption, and another one was reoperated 48 h postsurgery (for bleeding).

The four groups were not significantly different with regard to age, weight, sex, type, or duration of surgery and intraoperative doses of fentanyl (Table 2). There were no differences in preoperative level of anxiety among groups.

Mean morphine doses at different periods and cumulative morphine doses at 24 and 48 h are shown in Fig 1. There were no significant differences among groups in postoperative morphine consumption during 0–12 and 12–24 h. Group NF had significantly large morphine consumption compared with Groups C and NM at 24–48 h.

No relationship was found between the level of anxiety and total morphine requirements in the control

group. Pain at rest was significantly more in Group NF than in the other three groups at 16 and 24 h after surgery (Fig. 2). Pain on movement was significantly less in Group NM than in Groups C and NF at 72 h (Fig. 3).

Twenty patients required NSAIDs in the first 48 h (three of Group C, 10 of Group NF, three of Group MG, and four of Group NM). Three of Group C, five of Group NF, one of Group MG, and two of Group NM required metamizole.

There were no significant differences among groups in sedation scores at 0, 2, 6, 16, 24, and 48 h postsurgery. There were no significant differences among groups in systolic, diastolic and mean arterial pressures, heart rate, respiratory rate, and pulse oximetry (with oxygen mask at F_{iO_2}) of 40% during the first 24 h. Only three patients who had hypotension during surgery, required ephedrine. Only one patient had bradycardia, both during surgery and in the postoperative period, that did not require treatment. There were no significant differences among groups in time for bowel sound return, withdrawal of the nasogastric tube, intake of fluids, flatus passed, and evacuation of the bowel.

The incidence of nausea, vomiting, and other side effects was similar in all groups (Table 3). A total of 28 patients experienced at least one episode of nausea during the first 48 h related to head position changes in 20 patients (probably because of nasogastric tube). Only four patients required treatment (1.25 mg droperidol in two and 8 mg ondansetron in addition to droperidol in the other two) because they presented with more than one episode. Persistent ileus was considered when time for bowel sound return was longer than 72 h after surgery.

Discussion

We found no statistically significant differences among groups for postoperative morphine consumption after colorectal surgery, except during the 24- to 48-hour time interval, where, surprisingly, Group NF had significantly larger morphine consumption than Groups C and NM. There is no clear reason for the observed more intense pain at rest scores in Group NF at 16 and 24 hours postsurgery, nor the larger morphine consumption in this group during 24–48 hours. Although total

Table 2. Demographic and Intraoperative Data for the Four Treatment Groups

	Group C	Group NF	Group MG	Group NM
Number (n)	24	22	23	23
Age (yr)	58.6 ± 11.3	55.9 ± 10.6	60.6 ± 9.1	59 ± 9.1
Weight (kg)	75.2 ± 13.8	74.4 ± 14.8	71.1 ± 12.1	74.5 ± 10.5
Sex (n)				
Male	16	15	16	15
Female	8	7	7	8
Intraoperative fentanyl (µg)	520.7 ± 72.1	541 ± 160.7	465 ± 83.4	493 ± 104.4
Surgical procedure (n)				
Proctectomy	15	12	13	12
Sigmoidectomy	7	7	5	9
Colectomy	2	3	5	2
Duration of surgery (min)	158 ± 44	166 ± 65	151 ± 32	157 ± 62

Values are mean ± SD or n.
C = control, NF = nifedipine, MG = magnesium, NM = nimodipine.

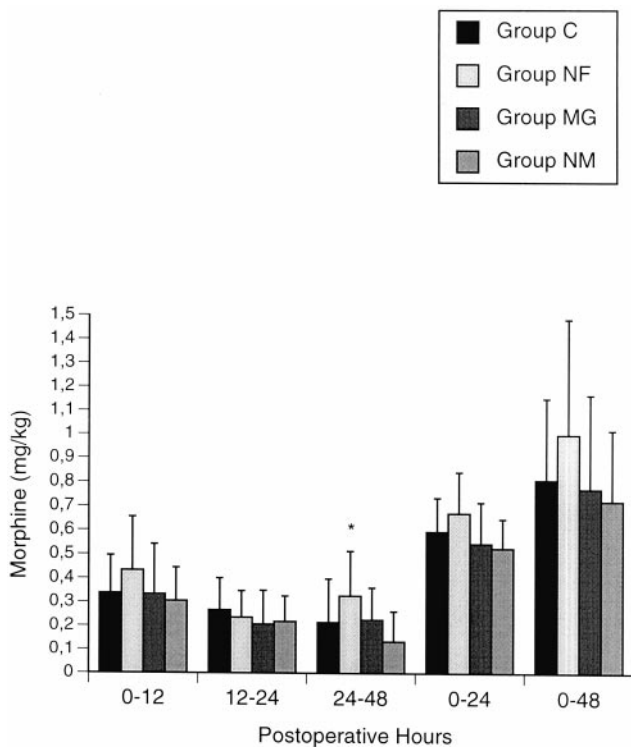


Figure 1. Postoperative morphine consumption. Mean and SD are shown. Group C = control; Group NF = nifedipine; Group MG = magnesium; Group NM = nimodipine. *Different from Group C and NM ($P < 0.05$).

morphine consumption was similar in the four groups, Group NF had the largest total and partial mean doses (except at 12- to 24-hour interval). The lower efficacy profile of this group is also shown in that more patients required NSAIDs than the other groups. Neither is a clear reason for lower pain on movement scores in Group NM at only 72 hours. This group also had the smallest total mean morphine consumption. If nimodipine could exert a preemptive analgesic effect, VAS scores both at rest and on movement should be less before 48 hours and thereafter.

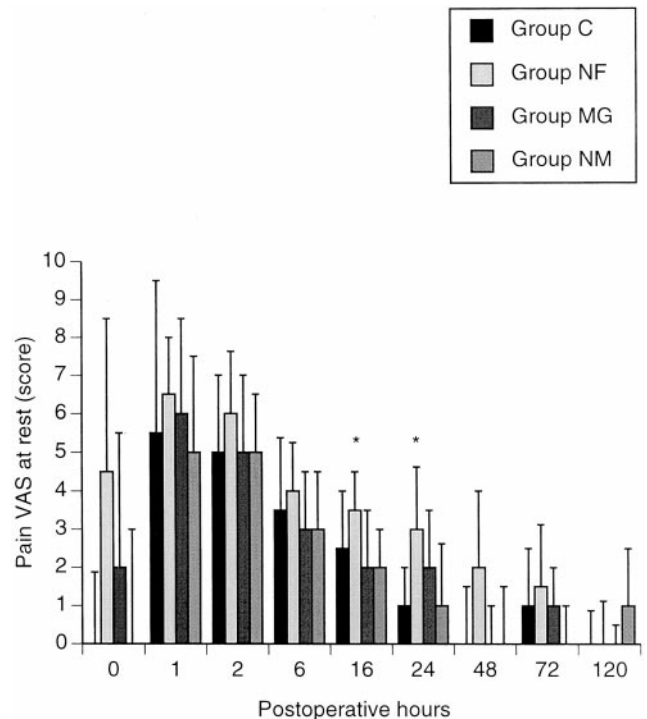


Figure 2. Pain visual analog scale at rest. Median and interquartile range are shown. Group C = control; Group NF = nifedipine; Group MG = magnesium; Group NM = nimodipine. *Different from other three groups ($P < 0.05$).

There are few randomized, placebo-controlled double-blinded clinical studies that test the role of L-type calcium channel blockers (L-CCBs) or magnesium sulfate in postoperative analgesia. The trials that test the effect of L-CCBs found positive (12-14) and negative results in relation to analgesic consumption (15). Only two trials (14,15) have an adequate number of patients, a similar type of surgery, and a time of assessment of at least 12 hours with the use of a PCA device. Lehmann et al (15) found no statistically significant differences in postoperative fentanyl consumption with IV nimodipine at the same dose that was used in our study; however,

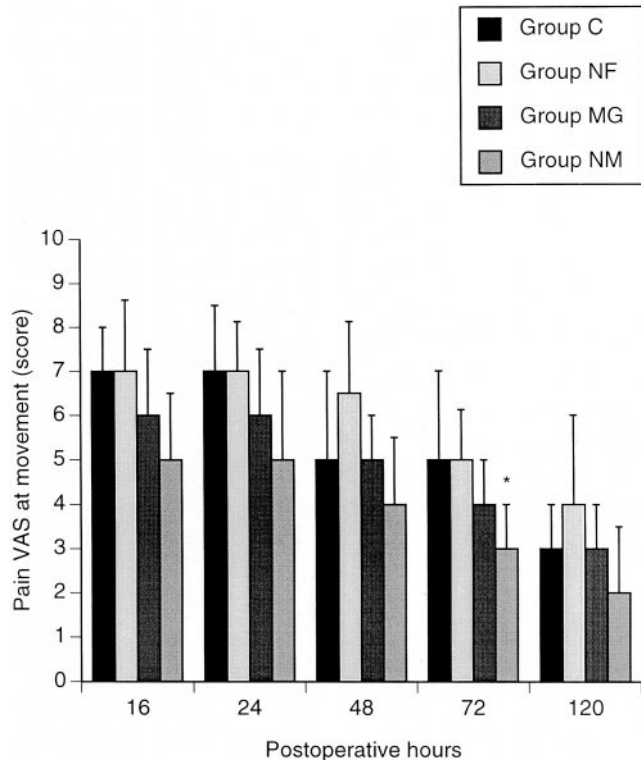


Figure 3. Pain visual analog scale on movement. Median and interquartile range are shown. Group C = control; Group NF = nifedipine; Group MG = magnesium; Group NM = nimodipine. *Different from Groups C and NF ($P < 0.01$).

Choe et al. (14) found less postoperative analgesic consumption (mixture of morphine-ketorolac-droperidol) with epidural verapamil.

The role of nimodipine in cancer pain is conflicting. Santillán et al. (16) found positive results; however, Roca et al (17) obtained negative results similar to ours. Hasegawa et al. (18) also obtained negative results by evaluating the effect of different L-CCBs in pain induced by a cold-pressor test.

The trials that test the role of magnesium sulfate (11,19) found positive and negative results, respectively, in relation to morphine consumption, although the period of maintenance infusion was longer in the study of Tramer et al (11) (20 hours) than in the study of Wilder-Smith et al (19) (only intraoperative).

There are several possible reasons for our negative results in postoperative morphine consumption. First, the individual variability in morphine consumption that predicts the need of a bigger sample size (47 patients per group) to detect a variation between treatments for at least 25%, if the SD is equal to 40% of the mean.

Second, despite several previous animal studies showing that CCBs enhance the analgesic effect of systemically administered opioids, it is probable that CCBs are more effective by intrathecal and epidural routes, as it was demonstrated in the study of Choe et al. (14). Systemic CCBs may also enhance the analgesic

Table 3. Incidence of Side Effects and Complications

	Group C	Group NF	Group MG	Group NM
Nausea	8	7	5	7
Vomiting	2	0	0	1
Pruritus	0	1	0	0
Respiratory Rate <10 breaths/min	0	0	0	0
Hiccups	2	0	4	0
Sweating (first 48 h)	2	0	2	2
Dizziness (at standing up)	2	2	2	2
Bad dreams	1	0	1	2
Delirium	0	0	0	1
Ileus	1	0	5	0
Intake intolerance	5	4	3	2
Hypotension	2	1	1	2
Bradycardia	0	0	0	1

C = control, NF = nifedipine, MG = magnesium, NM = nimodipine.

effect of epidural morphine (13). One may question whether the route of the administration of nifedipine is the most appropriate. Although, theoretically, surgery should not affect nifedipine GITS absorption (there are no data from literature on this question), the lack of plasma level determination prevents us from definitive conclusions about any coanalgesic effect.

Third, although the influx of Ca^{2+} through both CCs and NMDA-CCs may be involved in the establishment of central sensitization, Ca^{2+} influx through NMDA-CC appears to be more important. Ca^{2+} chelators, which reduce all available extracellular Ca^{2+} (not just that entering through CCs) and noncompetitive NMDA antagonists are more efficient than CCBs in suppressing persistent pain (5). Although magnesium can suppress neuropathic pain in rats (7), ketamine (an NMDA antagonist) has been more effective than magnesium both in chronic neuropathic (20) and postoperative pain in which central sensitization is present (19).

Fourth, it is possible that L-CCs are less important than other types of CCs in pain pathways. Three main types of calcium channels (L, T, and N) have been identified in sensory neurons of the spinal cord. Although both L-CCs and N-CCs have been involved in the release of neurotransmitters and neuromodulators in sensory neurons, N-CCs may be more important than L-CCs in spinal pain transmission. L-CCBs enhance the antinociceptive effect of morphine, but are not antinociceptive *per se* at the spinal cord level (21). However, the antinociceptive effect of N-CCBs alone has been demonstrated in different animal models of pain (22). Nimodipine could not prevent the inhibitory effects of Ca^{2+} in morphine analgesia, whereas ω -conotoxin GVIA (an N-CCB) completely prevented it (23), which indicates that N-CCs may be even more important than L-CCs in morphine analgesia.

Fifth, L-CCBs, and perhaps magnesium, may be less important in acute than in chronic pain. Chronic pain and opioid tolerance are associated with changes in neuronal intracellular calcium levels, and L-CCs appear to be involved in the establishment of opioid

tolerance (24). There is a significant difference between the acute and the tolerant condition in CCB enhancement of opioid analgesia (25). Perhaps this is the reason for finding different results in clinical trials of cancer patients with morphine tolerance (16) and in acute (15,18) or chronic settings without tolerance (17). In one study, intrathecal infusion of magnesium with morphine attenuated morphine tolerance (8).

In conclusion, the use of oral nifedipine, IV nimodipine, or magnesium sulfate at normal clinical doses failed to decrease postoperative morphine requirements in patients undergoing colorectal surgery. Therefore, their clinical use specifically for postoperative pain management may not be justified. It is possible that the use of L-CCBs or magnesium sulfate by other routes of the administration (intrathecal/epidural), with or without opioids, may offer clinical advantages. Studies of these drugs by these routes must await proper preclinical toxicity screening.

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