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Epidural magnesium reduces postoperative analgesic requirement

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Background. Magnesium has antinociceptive effects in animal and human models of pain. Our hypothesis was that the addition of magnesium to postoperative epidural infusion of fentanyl may decrease the need for fentanyl.

Methods. Fifty patients undergoing hip surgery were enrolled to receive either fentanyl (Group F) or fentanyl plus magnesium sulphate (Group FM) for 24 h for epidural analgesia. All patients were equipped with a patient-controlled epidural analgesia device and the initial settings of a demand bolus dose of fentanyl 25 μg. In Group FM, patients received 50 mg magnesium sulphate epidurally as an initial bolus dose followed by a continuous infusion of 100 mg day^{-1}. Ventilatory frequency, heart rate, blood pressure, pain assessment using a visual analogue scale (VAS), sedation scores and fentanyl consumption were recorded in the postoperative period.

Results. There was no significant difference between groups in the time to first analgesic requirement. Compared with Group F, patients in Group FM received smaller doses of epidural fentanyl ($P<0.05$). The cumulative fentanyl consumption in 24 h was 437 (SD110) μg in Group F and 328 (121) μg in Group FM ($P<0.05$). Patients in Group F showed a higher VAS score in the first hour of the postoperative period ($P<0.05$). The groups were similar with respect to haemodynamic and respiratory variables, sedation, pruritis, and nausea.

Conclusion. Co-administration of magnesium for postoperative epidural analgesia results in a reduction in fentanyl consumption without any side-effects.

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Regional anaesthesia is a safe, inexpensive technique, with the advantage of prolonged postoperative pain relief. Effective treatment of postoperative pain blunts autonomic, somatic, and endocrine responses. It has become common practice to use a polypharmacological approach for the treatment of postoperative pain, because no drug has yet been identified that specifically inhibits nociception without associated side-effects.[1] Research continues concerning different techniques and drugs that could prolong the duration of regional anaesthesia and postoperative pain relief.

Magnesium is the fourth most plentiful cation in the body. It has antinociceptive effects in animal and human models of pain.[2 3] These effects are primarily based on the regulation of calcium influx into the cell, that is natural physiological calcium antagonism and antagonism of *N*-methyl-D-aspartate (NMDA) receptor.[1] It has been reported that intrathecal magnesium enhances opioid antinociception in an acute incisional model.[3] These effects have prompted the investigation of magnesium as an adjuvant for postoperative analgesia. There are studies concerning different routes of magnesium administration such as i.v. or intrathecally, that improve anaesthetic and analgesic quality.[1 4–6] No clinical studies have examined the effect of magnesium administered epidurally with opioids. We therefore conducted a prospective, randomized, controlled clinical trial with a hypothesis that the addition of magnesium to postoperative epidural fentanyl may decrease the requirements for fentanyl and may improve the quality of analgesia.

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Methods

After obtaining institutional Ethics Committee approval and written informed consent, 50 patients were enrolled into the study. Eligible patients were those undergoing elective hip replacement under regional anaesthesia, aged 42–78 years, ASA I–III. Patients for whom a central neuraxial block was contraindicated and those with a history of adverse reaction to any study medication were excluded. Inability to use the patient-controlled analgesia device and communication difficulties that would prevent reliable postoperative assessment were also exclusion criteria. Patients were briefed before operation on visual analogue pain scales (VAS: 0: no pain, 10: worst pain ever) and how to operate the patient-controlled epidural analgesia (PCEA).

After i.v. access had been established and an infusion of crystalloid commenced, all patients had a combined spinal-epidural anaesthetic. The epidural space was identified at L3–4 or L4–5 using a loss-of-resistance technique. Dural puncture was performed by a needle-through-needle technique with a Whitacre 26 G needle; hyperbaric bupivacaine 0.5%, 1.5 ml was injected into the intrathecal space. An epidural catheter was then inserted into the epidural space. Sensory block was assessed bilaterally by using analgesia to pinprick with a short needle. Motor block was evaluated using a modified Bromage scale[7] (0: no motor block, 1: inability to raise extended legs, 2: inability to flex knees, 3: inability to flex ankle joints). During the course of operation, epidural bupivacaine 0.5% was given, if required, to achieve a block above T8 level.

When surgery was complete, patients were randomized, by a sealed envelope technique, into one of the two groups. All patients were equipped with a PCEA device (Abbott Pain Management Provider, Abbott Laboratories, USA) and the initial settings of a demand bolus dose of fentanyl 5 ml (5 $\mu g\,ml^{-1}$) with no background infusion, lockout interval 20 min, and 4 h limit of 30 ml (150 μg fentanyl). In Group F (F) (n=25), patients received epidural saline at a rate of 1 $ml\,h^{-1}$ for 24 h with another infusion pump (Pilote A2IS, Fresenius Vial SA, France). In Group FM (n=25) magnesium sulphate 50 mg (Galen Ilac sanayi, Turkey) in 5 ml volume as a bolus dose was given followed by a continous epidural infusion of 100 mg at a total 24 ml volume for 24 h. The continuous epidural infusion of either saline or magnesium was connected to the epidural catheter hub with a y-set. The analgesic regimen was prepared by the anaesthesiologist managing the patient, who was not subsequently involved in data collection. It was commenced in the recovery room while the block was still effective. Patients and nursing staff were blinded to the group randomization.

Postoperative monitoring consisted of ventilatory frequency, heart rate, and non-invasive arterial blood pressure measurements at 30 min, and then at 1, 2, 4, 8, 12, and 24 h. Hypotension was defined as systolic blood pressure <80 mm Hg or >30% decrease from baseline, and hypertension was defined as blood pressure >180 mm Hg systolic or 110 mm Hg diastolic. Hypotension was treated with an i.v. fluid bolus of 500 ml of lactated Ringer's solution followed by i.v. ephedrine if required. Tachycardia was defined as heart rate >120 beats min^{-1} and bradycardia was defined as <50 beats min^{-1}. Sedation was assessed on a four-point scale:[8] 0: awake and alert, 1: mildly sedated, easily aroused; 2: moderately sedated, aroused by shaking, 3: deeply sedated, difficult to be aroused by physical stimulation.

Patients' first analgesic requirement times were recorded. The time from the completion of the surgery until the time to first use of rescue medication by PCEA was defined as the time to first requirement for postoperative epidural analgesia. Pain assessments using a standard 10 point VAS were made at 30 min, and then at 1, 2, 4, 8, 12, and 24 h in the postoperative period. A resting pain score of $\leq$3 was considered satisfactory pain relief. If patients had inadequate analgesia, supplementary rescue analgesia with oral tramadol 50 mg was available. Patients were discharged to the ward when all discharge criteria were met; that is with completely resolved motor block, stable vital signs and satisfactory pain relief, and absence of nausea and vomiting. Epidural fentanyl consumption was also recorded at the same time points. Patients were evaluated for the side-effects related to epidural drugs (drowsiness, respiratory depression, nausea, vomiting). Adverse events related with the drugs and epidural catheter were recorded throughout the 24 h study period and followed up to 7 days after patients were discharged from the hospital.

All statistical analyses were performed using SPSS for windows 12.0. Continuous variables were tested for normal distribution by the Kolmogorov–Smirnov test. The statistical evaluation of variables, such as patient characteristics and haemodynamic variables was performed using independent samples t-test because the distributions of these variables were normal. VAS scores and sedation scores of the patients were analysed using Mann–Whitney U-test. Fentanyl consumption of the groups was compared with two-way repeated-measures analysis of variance (ANOVA) followed by a Bonferroni multiple comparison *post hoc* test. A sample size of 20 patients per group was needed to detect a difference of at least 20% in fentanyl consumption (α=0.01, two-sided, power=90%) with two sample t-test.[5 9] A value of P<0.05 was considered statistically significant. The results are expressed as mean (SD).

Results

Fifty patients undergoing hip replacement were studied (25 in each group). There were no differences in age, body weight, or sex ratio between the groups. These groups

Table 1 Patient characteristics and the duration of surgery in the two groups. Data are given as mean (range) or mean (SD)

	Group F (fentanyl) $n=25$	Group FM (fentanyl+ magnesium) $n=25$
Age (yr)	59.9 (43–78)	60.8 (42–75)
Females/males	12/13	14/11
Weight (kg)	69 (17)	72 (12)
Height (cm)	171 (9)	168 (8)
Duration of surgery (min)	118.4 (22.5)	113.6 (23.5)

were similar in the duration of surgery (Table 1). No difference in the quality of sensory and motor block before and during the surgery was noted between groups, and none of the patients required supplemental analgesia during surgery. Systolic, diastolic, mean arterial blood pressures, heart rates, and oxygen saturations remained stable, and there was no significant difference between the groups. There were no cases of postoperative haemodynamic or respiratory instability during the observation period. Mean arterial blood pressures were similar in this period (Fig. 1).

Although the time to first analgesic requirement time was slightly longer when magnesium was co-administered, there was no significant difference between the groups [37.1 (22) *vs* 51.6 (38) min]. In the analysis of fentanyl consumption, significant differences were seen between the groups. Compared with patients in Group F, Group FM received smaller doses of epidurally infused fentanyl at all time points after 30 min (Fig. 2). When we compared cumulative fentanyl consumption at each time point by using independent samples *t*-test, the differences between the groups were statistically significant at 2 and 24 h ($P<0.05$). While the cumulative fentanyl consumption of Group F was 437 (110) μg, patients in Group FM received 328 (121) μg fentanyl in 24 h. None of the patients required supplementary oral tramadol. Patients in Group F showed a higher VAS score in the postoperative period. But the difference between the groups was statistically significant only at 1 h after surgery ($P<0.05$, Fig. 3). There was no significant difference in sedation scores between the two groups.

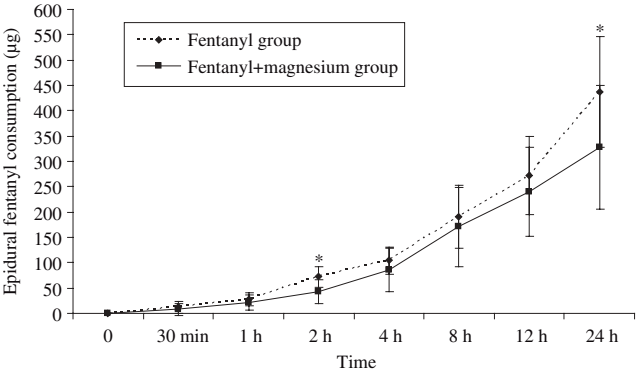


Fig 2 Patient-controlled epidural fentanyl consumption of patients after surgery. The fentanyl consumption was significantly less on co-administration of magnesium. The difference in cumulative fentanyl consumption between groups was statistically significant at 2 and 24 h (*$P<0.05$) by using independent samples *t*-test. Data are given as mean (SD).

No side-effects including nausea, vomiting, hypotension, drowsiness, and respiratory depression were reported. Two patients in each group complained of pruritis. No complications from the combined spinal-epidural block were noted.

Discussion

The results of this study showed that the addition of epidural magnesium, a competitive NMDA antagonist, reduces epidural fentanyl use in postoperative PCEA.

Because of its greater liphophilic nature, fentanyl offers some advantages for epidural analgesia. Fentanyl undergoes rapid vascular absorption from the epidural space, and it spreads less rostrally than other commonly used opioids.[10] Although some investigators have suggested that the predominant mechanism of the analgesic effect of

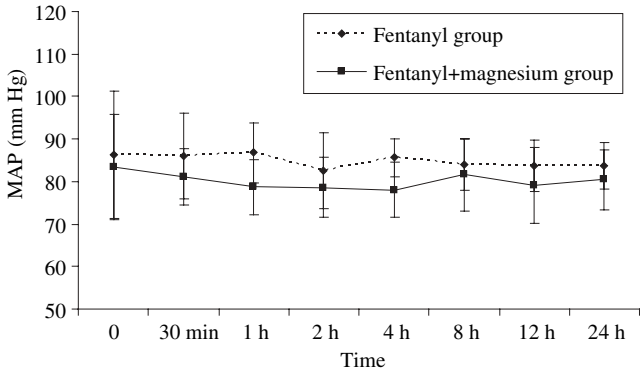


Fig 1 Mean arterial blood pressures (MAP) in the postoperative period. There were no significant differences between groups. Data are given as mean (SD).

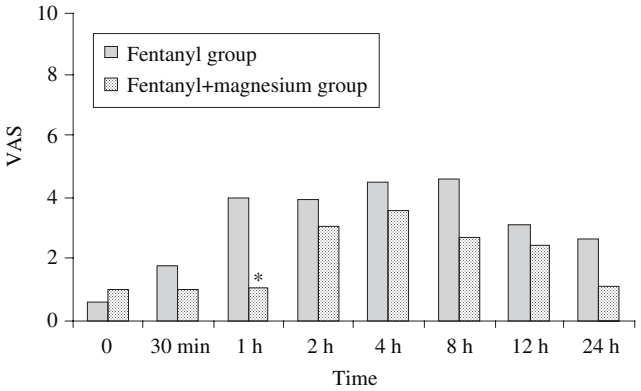


Fig 3 Intensity of postoperative pain as measured using a VAS. *$P<0.05$ between groups.

epidural fentanyl is systemic in nature, it is postulated that the epidural route is more effective than an i.v. infusion when the epidural catheter was inserted near the vertebral level of surgery.[10–12] The rapidity of analgesic effect of epidural fentanyl administration and the relatively short duration of action makes it the drug of choice for postoperative acute pain.[13] Liphophilic nature of fentanyl limits its cephalad migration and this results in a lower incidence of side-effects such as respiratory depression, urinary retention, nausea, and vomiting.[10] In our study, the average dose of epidural fentanyl in both groups was less than the recommended doses. Larger doses of opioids may increase the incidence of side-effects, especially in elderly patients. The aim of postoperative analgesic management must be to provide adequate analgesia without major respiratory depression or other side-effects. The co-administration of opioids with drugs that would reduce analgesic consumption will be beneficial for postoperative pain management.

Noxious stimulation leads to the release of neurotransmitters, which bind to various subclasses of excitatory amino acid receptors, including NMDA receptors. Activation of these receptors leads to calcium entry into the cell and initiates a series of central sensitization such as wind-up and long-term potentiation in the spinal cord in the response of cells to prolonged stimuli.[14] Central sensitization has an important role in pain perception and is considered to be one of the mechanisms implicated in the persistence of postoperative pain.[15] NMDA receptor signaling may be important in determining the duration of acute pain.[16] Therefore, NMDA receptor antagonists may play a role in the prevention and treatment of post-injury pain. Ketamine, a better known NMDA antagonist, not only abolishes peripheral afferent noxious stimulation, but can also prevent the central sensitization of nociceptors.[17] It has been demonstrated that adding ketamine to PCEA regimen provides better postoperative analgesia.[17 18] However, it has been reported that ketamine and magnesium inhibit the NMDA system differently.[19] Magnesium blocks calcium influx and non-competitively antagonizes NMDA receptor channels.[20] Non-competitive NMDA receptor antagonists can have an effect on pain when used alone, but it has also been shown that they can reveal the analgesic properties of opioids.[2 21] In this manner, the coadministration of magnesium and an opioid is expected to allow a significant reduction in opioid administration for postoperative pain alleviation.

Many authors have studied the role of magnesium for postoperative analgesia. Most of these studies showed that systemic administration of magnesium is associated with smaller analgesic requirement and less discomfort in the postoperative period.[1 5 6] Although the exact mechanism of the interaction between the NMDA receptor complex and opioid antinociception has not been fully elucidated, it has been reported that magnesium supplement enhances the analgesic effect of opioids and delays the development of tolerance.[3 22] In recent years, intrathecal administration of magnesium has been reported as an effective analgesic and as an adjunct to intrathecal opioid analgesia. It is possible that magnesium analgesic effect occurred at the supra-spinal level and might be related to its systemic absorption. But Ko and colleagues[22] failed to observe postoperative analgesic effect with 50 mg kg^{-1} i.v. magnesium sulphate and they reported that perioperative administration of magnesium did not increase CSF magnesium concentration. So, when compared with these doses, our epidural dose is too low for the systemic effect. Although there is no study about the physicochemical properties of magnesium in relation to its penetration to spinal meninges, another probable mechanism for epidural usage may be related to the diffusion of magnesium from the dura. Buvanendran and colleagues[4] demonstrated in pregnant women that, if magnesium 50 mg and fentanyl 25 μg were given intrathecally, the median duration of analgesia was significantly prolonged compared with plain intrathecal fentanyl. Similarly, in another study by Ozalevli and colleagues,[23] it is reported that the addition of intrathecal magnesium 50 mg to spinal anaesthesia prolongs the period of anaesthesia without additional side-effects. In our study, epidural administration of magnesium reduced postoperative epidural fentanyl consumption in comparison with the saline group. This effect was initially observed 1 h after the start of the infusion and it was more significant after 2 h. The bolus dose of epidural magnesium sulphate may have been the cause of this early reduction in fentanyl consumption.

This is the first randomized human study of epidural magnesium as an antinociceptive modulator. Our study has the limitation of only one dose–response evaluation. We preferred to use a smaller dose of magnesium that would not cause any side-effects. In two cases reported by Goodman and colleagues,[24] larger doses (8.7 g, 9.6 g) of magnesium inadvertently administered into the epidural space did not cause any neurologic injury. Also another report described an inadvertent intrathecal injection of 1000 mg of magnesium producing a transient motor block followed by a complete resolution and no neurological deficit at long-term follow-up.[25] If larger doses are administered epidurally, does postoperative analgesic demand decrease or the analgesic effect enhance? Currently, the answer to this question is unknown. The safety of magnesium in the central nervous system has been evaluated. In a canine model of spinal cord ischaemia, it has been demonstrated that intrathecal magnesium can prevent spinal cord injury despite markedly negative spinal cord perfusion pressure during thoracic aortic cross-clamping. None of the dogs that received intrathecal magnesium had neurological injury and histopathological changes in their study.[26] Chanimov and colleagues[27] showed that repeated intrathecal injections of magnesium sulphate in a rat model indicate a lack of neurotoxicity in histological examination. Only a study in rabbits by Saeki and

colleagues[28] reported toxicity with intrathecal magnesium in larger doses, and in their study the authors stated that the hyperosmolar solutions of magnesium sulphate may have caused neurotoxicity. One of the main differences of this study from ours is the route of administration. And the second difference is the higher doses of magnesium they used.

In conclusion, co-administration of epidural magnesium for postoperative epidural analgesia provided a pronounced reduction in patient-controlled epidural fentanyl consumption without any side-effects. Further studies should address different dosages of magnesium and different surgical settings. The results of the present investigation suggest that magnesium may be a useful alternative as an adjuvant to opioids for PCEA.

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