# Effects of epidural magnesium sulphate on intraoperative sufentanil and postoperative analgesic requirements in thoracic surgery patients

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## Abstract

Introduction. Thoracic surgery is associated with high levels of pain.

Magnesium has antinociceptive effects in animal and human models of pain.

Objectives**.** The aim of this randomized prospective study was to assess the effects of continuous epidural magnesium infusion during thoracic surgery on intraoperative sufentanil consumption and postoperative analgesic requirements during the first 48 hours after surgery.

Materials and methods. Seventy patients were randomized into two groups of 35 patients: Group 1 (magnesium group) received an epidural with 10% magnesium sulfate ($MgSO_4$) along with anesthetic drugs (midazolam, propofol, rocuronium, sufentanil, levobupivacain), and group 2 (control group) received an epidural with 0.9% sodium chloride (NaCl) solution along with anesthetic drugs intraoperatively. Postoperatively, group 1 patients were administered the 10% magnesium sulfate epidural in addition to a local anesthetic and opioid, whereas group 2 patients were administered the local anesthetic and opioid alone. Primary outcomes of the study were to determine the cumulative doses of intraoperatively administered sufentanil and cumulative doses of sufentanil and levobupivacaine administered during the first 48 h postoperatively.

Secondary outcomes were a visual analog scale (VAS) score for rest and movement every 4 hours, level of sedation, cardiovascular, respiratory and neurological complications, incidence of postoperative shivering, nausea and vomiting and global patient satisfaction.

Results. The cumulative sufentanil dose required intraoperatively was significantly lower in the magnesium group: 43.00 µg *vs* 56.3 µg ( $p = 0.001$). VAS scores measured every 4 hours at rest and movement during the first 48 hours postoperatively, cumulative analgesic consumption, incidence of shivering, nausea and vomiting were significantly lower in the magnesium group. The global satisfaction score was significantly higher in the magnesium group (4.3 *vs* 3.7; $p = 0.005$).

Conclusion. The addition of magnesium in the epidural mixture of sufentanil and levobupivacaine led to more efficient intraoperative and postoperative analgesia, lower sufentanil and levobupivacaine consumption, lower incidence of postoperative shivering, nausea and vomiting. Epidural with magnesium appears to be a useful adjunct to anesthetic drugs, which can exert positive effects on the course and outcome of thoracic surgery patients.

**Key words:** thoracic surgery, postthoracotomy pain, perioperative

analgesia, magnesium

# Introduction

Patients undergoing surgical resection of the lungs are generally classified, according to the American Society of Anesthesiology (ASA), as class III, along with preoperatively impaired pulmonary function, mostly coronary comorbidity, and compromised immune status due to malignant and chronic lung diseases. (1)

Thoracic surgery is associated with severe painful stimuli.

Inadequate postoperative pain control leads to dysfunction of the respiratory musculature, diaphragm in particular, causing hypoventilation, hypoxia, atelectasis, pneumonia, coronary stress and increases the rate of deep vein thrombosis and chronic postoperative pain syndrome. (2)

Current treatment of postoperative pain should be prophylactic, i.e. preemptive, based on the mechanisms induced by the operative procedure (somatic and visceral nociceptive pain, neuropathic component of pain, static and dynamic pain). (3)

Thoracic epidural multimodal preventive analgesia with administration of local anesthetic and opioid generally ensures good intra- and postoperative analgesia with minimal depression of the central nervous system (CNS) and respiratory system. However, in thoracic surgery patients, besides the additive effect, the addition of opioid to local anesthetic may exert an array of dose-dependent undesired effects, e.g., impaired intestinal motility, nausea, vomiting, pruritus, decreased coughing reflex and respiratory depression, in patients with impaired pulmonary function in particular. (3)

The antinociceptive effect of magnesium is based on two mechanisms: blockade of calcium entry in the cell (the basic mechanism of action) and noncompetitive antagonizing the *N*-methyl-d-aspartate (NMDA) receptors. Magnesium antagonizes NMDA receptors in the CNS. The other mechanism of magnesium action is reduction of catecholamine release due to sympathetic stimulation, thus decreasing peripheral sensitization of nociceptors in the stress response to operative procedure. (4-6)

Trials with intrathecal and epidural magnesium administration have shown that magnesium is a valuable adjuvant analgesic, but very few data are available on its analgesic effects in lung resection surgery. (7-10)

The aim of the present study was to assess effects of continuous epidural magnesium infusion during thoracic surgery on intraoperative sufentanil consumption and postoperative analgesic requirements during first 48 hours after surgery.

# Materials and methods

Ethical approval for this study (Ethical Committee N°380-59-1016-13/195/86) was provided by the Ethical Committee of University of Zagreb, School of Medicine,Zagreb, Croatia (Chairperson prof dr Branimir Jakšić ) on 21st March, 2013.

This prospective placebo-controlled randomized study included 70 ASA I-III patients undergoing elective thoracic surgery. Exclusion criteria were patients with major liver or kidney impairment, neuromuscular disease, II-III degree AV block, extreme obesity, and those exposed to opioids and/or calcium channel blockers before surgery.

Seventy patients were randomized into two groups of 35 patients: group 1 (magnesium group) received an epidural with10% magnesium sulphate ($MgSO_4$) along with anesthetic drugs, and group 2 (control group) received an epidural with 0.9% sodium chloride (NaCl) solution along with anesthetic drugs intraoperative. Postoperatively, group 1 patients were administered an epidural with 10% magnesium sulphate in addition to local anesthetic and opioid, whereas group 2 patients were administered local anesthetic and opioid alone.

On preoperative examination, patients included in the study were informed of the methods of pain intensity assessment, which included a visual analog scale (VAS) for rest and movement. All study patients were premedicated with 7.5 mg midazolam *per os* one hour before the operation. In all patients, cardiovascular function was monitored by electrocardiography (Datex-Ohmeda) and invasive blood pressure measurement (Datex-Ohmeda), oxygenation by pulse oximeter (Datex-Ohmeda), ventilation by capnography (Datex-Ohmeda), level of neuromuscular blockade by a Train of Four (TOF) Guard neurostimulator (Organon Tehnika), and level of hypnosis by bispectral index (BIS) determination on a BIS monitor (Datex-Ohmeda).

Group 1 patients were injected 0.2 μg/kg sufentanil, 10 mg 0.5% levobupivacaine and 50 mg 10% $MgSO_4$ *via* epidural catheter (Th 4-Th 6) 15 minutes before induction of general anesthesia. Group 2 patients were injected 0.2 μg/kg sufentanil and 10 mg 0.5% levobupivacaine *via* epidural catheter (Th 4-Th 6) 15 minutes before induction of general anesthesia. Anesthesia was induced with midazolam at a dose of 0.03 mg/kg, sufentanil 0.3 μg/kg and propofol 1 mg/kg. After the induction of anesthesia, group 1 patients were administered continuous epidural infusion of 10% $MgSO_4$ at a dose of 10 mg/h, whereas group 2 patients received the same volume of epidural 0.9% NaCl.

In all patients, neuromuscular blockade was achieved with muscle relaxant rocuronium at a dose of 0.7 mg/kg to facilitate endotracheal intubation. All patients were mechanically ventilated with 1:1 air/oxygen mixture.

Hypnosis was maintained by continuous propofol infusion according to BIS values 40-60, and myorelaxation according to TOF = 1 by continuous rocuronium infusion. Intraoperative elevation of the mean blood pressure and pulse by ≥20% of the initial values was defined as inadequate analgesia. These patients received a sufentanil bolus dose of 0.2 μg/kg. At the end of the operation, propofol was discontinued on skin closure and neuromuscular blockade was antagonized by the administration of 0.01 mg/kg atropine and 0.025 mg/kg neostigmin. The patients were extubated when the BIS values reached 80 and the TOF ratio was > 0.8.

During the first 48 h postoperatively in the intensive care unit, group 1 patients were administered a continuous infusion of sufentanil 1 µg/mL, levobupivacaine 1 mg/mL and 10% $MgSO_4$ 1 mg/mL *via* epidural catheter. In the same period, group 2 patients received a continuous infusion of sufentanil 1 µg/mL and levobupivacaine 1 mg/mL *via* epidural catheter. The value of VAS ≤3 was maintained by adjusting the rate of infusion. The values of VAS score for rest and movement and the level of sedation were determined every 4 hours. Patient's global satisfaction levels regarding comfort and quality of pain control were assessed using a five-point scale.

Hemodynamic parameters (central venous pressure, non-invasive systolic and diastolic blood pressure, heart rate) urine output and respiratory rate were recorded 48 hours postoperatively. In addition episodes of shivering and postoperative nausea and vomiting (PONV) were recorded during the study period.

Primary outcomes of the study were to determine cumulative doses of intraoperative administered sufentanil and cumulative doses of sufentanil and levobupivacaine administered during 48 h postoperatively.

Secondary outcomes were VAS score for rest and movement every 4 hours, level of sedation, cardiovascular, respiratory and neurological complications, incidence of postoperative shivering, nausea and vomiting and global patient satisfaction.

### Statistics

Prior to statistical processing, continuous variables were tested for normality of distribution by Kolmogorov-Smirnov test. Descriptive values of continuous variables were expressed as arithmetic mean and standard deviation or median and interquartile range, as appropriate. Values of categorical variables are shown as absolute and relative frequencies.

The t-test for independent samples or its nonparametric alternative, Mann-Whitney U test was employed to compare continuous variables between the two study groups. Differences in categorical variables were analysed by means of the $\chi^2$-test. The level of significance in all procedures was set at $p<0.05$. Complete data processing was performed using SPSS 17 for Windows statistical software (SPSS Inc., Chicago, IL, USA).

# Results

A total of 70 patients were enrolled in this study. The magnesium group included 35 patients, 11 (31.4%) of them female and the control group 35 patients, 13 (37.1%) of them female.

The magnesium and control group were comparable for age, weight, gender and duration of surgery (table 1).

The induction doses of sufentanil were similar and comparable in both groups with p=0.228. Mean added sufentanil dose required intraoperative was significantly lower in the magnesium group, compared to controls (17.1 μg versus 31.9 μg; p< 0.001). The mean cumulative dose of sufentanil was 43.00 μg in magnesium group and 56.3 μg in control group (p = 0.001) (figure 1).

VAS scores measured every 4 hours at rest and movement during the first 48 hours postoperatively were significantly lower at all measured intervals in the magnesium group (figures 2, 3).

Cumulative epidural dose of sufentanil during 48 h postoperatively was significantly lower in magnesium group (208.2 +/- 41.19 μg), compared to 341.25 +/- 48.43 μg in the control group I (p < 0.001). Same was true for cumulative epidural dose of levobupivacain with mean dose of 202.5

+/- 43.74 mg in magnesium group versus 331.26 +/- 70.46 mg in the control group ($p < 0.001$).

Global satisfaction score was significantly higher in group 1 (4.3 versus 3.7, p = 0,005).

The two groups were similar in respect to hemodynamic parameters during surgery.

Shivering was significantly less in group 1:4 patients versus 24 in group 2. The incidence of nausea and vomiting was also significantly less in group 1, 6 patients versus 15 in group 2. Respiratory depression or neurologic deficit was not observed in any patient. Hemodynamic instability or any other cardiac problem possibly connected with magnesium was not observed.

# Discussion

The aim of this prospective double-blind placebo-controlled randomized study was to assess the effect of epidural magnesium sulphate on intraoperative and postoperative analgesia requirements, incidence of postoperative nausea, vomiting and shivering, and postoperative level of sedation in patients undergoing thoracic surgery . The large operative wound after thoracotomy induces significant stimulation of the mechanical high-threshold nociceptors, i.e. endings of the primary afferent A-delta high-conductivity fibers in the skin and subcutaneous tissue, leading to the occurrence of ‘pinching’ or ‘squeezing’ pain (epicritic pain). This pain sensation is almost unbearable for patients on deep breathing, when the skin in the incision area is tightened (dynamic pain). Thoracotomy incision causes injury of the skin, soft tissue, muscle, costovertebral and costotransverse ligaments, thus inducing strong and prolonged stimulation of polymodal receptors. At thoracotomy, parietal, visceral, mediastinal and diaphragmatic pleura is a considerable source of strong nociception, which is classified as visceral nociceptive pain. (1,2) The purpose of efficient postoperative pain management is to ensure optimal analgesic effect without development of respiratory depression, pruritus, nausea and vomiting; therefore, adding to the epidural mixture a drug that can reduce the analgesic dose of opioid is highly welcome. In elderly patients and in those with chronic obstructive pulmonary disease higher doses of opioid analgesic may increase the rate of serious side effects. (3)

Our study showed that the cumulative dose of opioid administered intraoperatively is significantly lower in group M patients as compared with group C, either comparing the total dosage or dose *per* kg body weight.

Total doses of levobupivacaine and sufentanil administered over 48 h postoperatively were significantly lower in group M patients that received magnesium in addition to sufentanil and levobupivacaine. The patients administered magnesium sulphate had lower VAS values for pain at rest and on coughing and movement throughout the 48-h period. All these differences were statistically significant.

The presence of severe pain in the perioperative period is explained by the activation of NMDA receptors on the dorsal horn with excitatory transmitters (glutamate), which leads to the entry of $Ca^{2+}$ ions in the cell by initiating the cascade of central sensitization that is now believed to cause the severe and prolonged postoperative pain. The NMDA receptor is an amino acid receptor responsible for the excitatory synaptic transmission and possessing the d+binding sites positive for the excitatory amino acid glutamate and negative for ketamine or magnesium. (4,5)

Magnesium blocks the entry of Ca ions in the cell and non-competitively antagonizes NMDA receptor channels. As an NMDA antagonist, magnesium leads to the voltage dependent blockade of NMDA receptor, thus playing a major role in the prevention and treatment of the intensive postoperative pain. (6)

Although the mechanism of interaction between NMDA receptors and opioid antinociception has not yet been fully clarified, magnesium is considered to enhance the analgesic effect of opioids and reduce the development of tolerance. (6)

One of the possible mechanisms for the analgesic action of epidural magnesium is its diffusion through the dura. In the CNS, magnesium reaches a concentration that is high enough to attenuate the function of NMDA ionophores. It is magnesium bioavailability in the CNS that is considered crucial for its action, since the intrathecal administration of magnesium along with fentanyl significantly prolonged the duration of analgesia *versus* fentanyl alone in the studies conducted by Buvanedran et al. , Ozalevli et al. and Ulungenc et al. (8-10) In the study by Bilir et al., the addition of magnesium to the epidural mixture of fentanyl and local anaesthetic significantly reduced total postoperative utilization of fentanyl. (7)

The epidural doses of magnesium administered to our patients could be presumed to have increased its cerebrospinal fluid (CSF) concentrations, thus attenuating the electrophysiological sequels of NMDA receptor activation. Another possible mechanism would imply the supraspinal action of magnesium as a consequence of its systemic absorption. (11-13)

Numerous authors have investigated the effect of epidural and intrathecal administration of magnesium on the use of opiates and opioids and other analgesics in patients undergoing minor surgical procedures associated with perioperative nociception of lower intensity (gynaecologic, orthopaedic, ophthalmologic and daily surgery procedures). (14-20) All these studies confirmed the efficacy of magnesium in reducing postoperative pain intensity and opioid requirements, while prolonging the duration of postoperative analgesia. Gupta et al. investigated the impact of intravenous magnesium on postoperative pain intensity and epidural analgesics fentanyl and bupivacaine requirements in thoracic surgery patients undergoing lung volume reduction surgery. Study results showed a significantly longer duration of analgesia and reduced fentanyl and bupivacaine utilization in the group of patients administered magnesium intravenously. (21)

Kim et al. evaluated the effects of epidural magnesium on the cumulative dose of ropivacain in patients, with patient controlled epidural analgesia after thoracotomy, and concluded that magnesium showed no beneficial effect in the early period after surgery. (22)

A study conducted by Kogler J. revealed the intravenous bolus doses of fentanyl and the total dose of intravenous and epidural fentanyl, administered intraoperative to thoracic surgery patients, to be statistically significantly lower in the group of patients receiving continuous intravenous infusion of magnesium. Pain intensity, as determined by VAS did not differ significantly between the groups during 48 h, in particular during the first 24 h ($p=0.409$) postoperatively. The lower absolute scale values on coughing and movement in patients administered magnesium postoperatively pointed to the more efficient control of dynamic pain, which can be influenced by magnesium *via* NMDA receptor blockade. (23)

A search of the literature yielded only the study by Lee et al., who investigated the effect of perioperative epidural magnesium on the rate of chronic postoperative pain in thoracic surgery patients undergoing a video-assisted thoracic surgery procedure. Study results failed to show a lower incidence of chronic pain in this group of patients. (24)

In thoracotomy patients, the positive effects of reduced doses of local anesthetics administered postoperatively contribute to better hemodynamic stability, fast recovery of physiologic diaphragm movements, increase the functional residual capacity and lung volume, while maintaining the intercostal musculature strength necessary for efficient expectoration. (22)

Therefore, we believe that the low doses of total levobupivacaine administered postoperatively in our group of thoracic surgery patients, who received magnesium in addition to sufentanil and levobupivacaine, could had a favourable effect.

The results of our study indicate that satisfactory hemodynamic stability was maintained in both patient groups, while systolic and diastolic pressure and pulse values were comparable on all measurements and differences did not reach statistical significance.

In our study, the rate of postoperative nausea, vomiting, pruritus and postoperative shivering was lower in the group of patients administered magnesium. The difference pointed to the antiemetic action of magnesium, or to an indirect effect because of the lower need of opioids in the group of patients administered magnesium.

Shivering is an involuntary, oscillating muscular activity that stimulates metabolic activity by the increased oxygen consumption and the formation of carbon dioxide of up to 800% basal values. Postoperative hypertension increases the intensity of sympathetic activity, peripheral vascular resistance and the risk of myocardial ischemia, along with the occurrence of dysrhythmias, in particular threatening patients with existing ischemic heart disease and reduced respiratory reserve.

The sedation score did not differ significantly between the two groups. There was no excessive drowsiness or respiratory depression in the group of patients administered magnesium, which is consistent with the reports by Bilir et al. and El Kerdawy et al. (7,14) We recorded no neurologic complications that could be associated with epidural magnesium.

The magnesium safety profile relative to the CNS was evaluated in experimental dog and rat models. Results showed the use of magnesium to have prevented spinal injury in spite of severe ischemia, and did not cause any histopathological lesions of neural structures.

Literature data show that accidental epidural administration of high doses of magnesium (8.7-9.6 g) and intrathecal administration of 1000 mg caused no neurologic lesion except for transient motor blockade (Goodman et al., Lejuste et al.). (25,26)

The present study limitation was the use of only one dose – response evaluation, and lack of determination of cerebrospinal fluid magnesium concentration as this was considered to be invasive.

# Conclusion

Results of the present study indicate that the addition of magnesium in the epidural mixture of sufentanil and bupivacaine led to more efficient intraoperative and postoperative analgesia and to lower utilization of sufentanil and bupivacaine.

We observed a lower rate of nausea, vomiting, pruritus and postoperative shivering.

The magnesium dosage used in the study was associated with normal hemodynamic and respiratory status of patients.

We can conclude, that, based on the favorable effects recorded, epidural magnesium appears to be a useful adjunct to anesthesiologic drugs, which can exert positive effects on the course and outcome of thoracic surgery procedures.

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**Table 1.** Demographic characteristics.

| Parameter | Mg | Control | p |
|---|---|---|---|
| **Age** (years; mean +/- SD) | 58,7 +/- 10,89 | 60,3 +/- 12,34 | 0,553* |
| **Gender** (N and % female) | 11; 31,4% | 13; 37,1% | 0,615† |
| **Body mass** (kg; mean +/- SD) | 74,3 +/- 6,47 | 73,9 +/- 5,88 | 0,282* |

| | | | |
|---|---|---|---|
| **Procedure duration** (min; mean +/- SD) | 114,1 +/- 12,61 | 113,9 +/- 11,43 | 0,069* |

* Student t-test

† Chi-square test

**Figure 1.** Intraoperative sufentanil doses required.

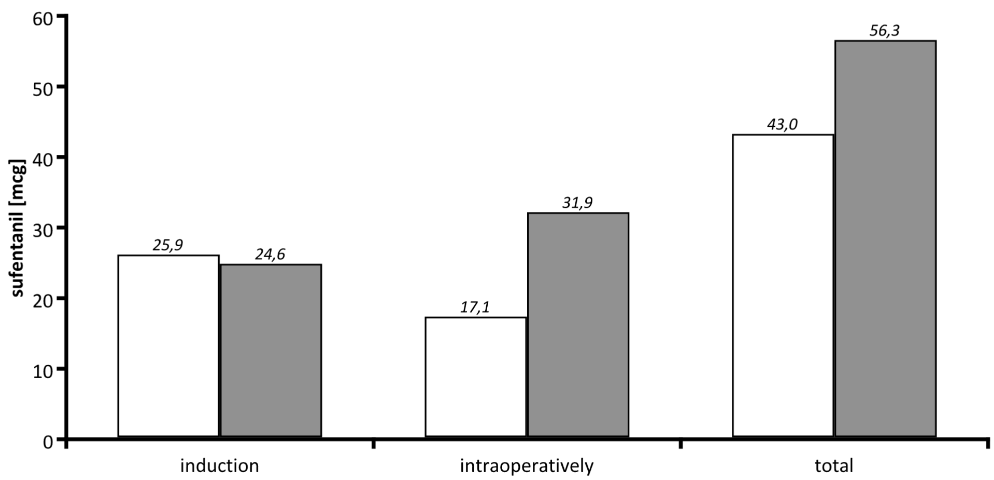


Figure legend: white = Mg group; grey = control group

**Figure 2.** VAS score at rest during 48 h postoperatively.

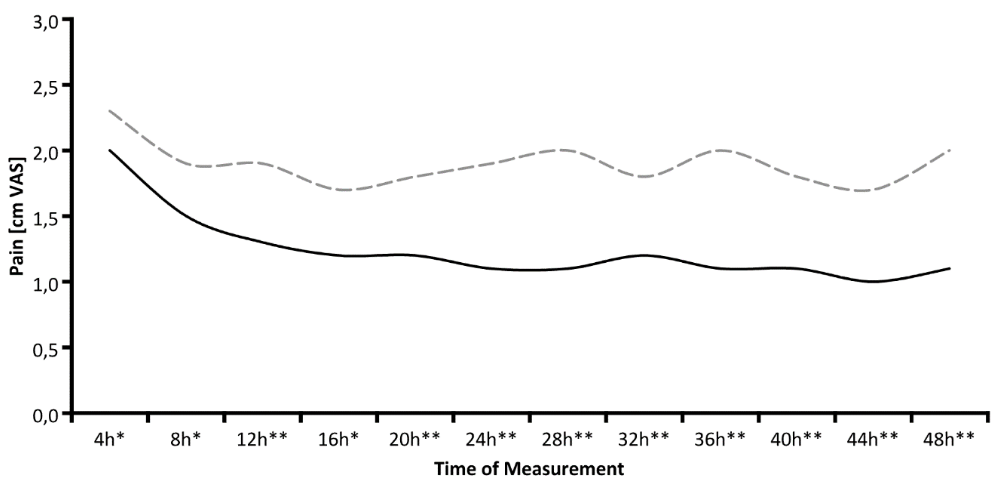


Figure legend: black line = Mg group; grey dashed line = control group; * p<0,05; ** p<0,001

**Figure 3.** VAS score at movement during 48 h postoperatively.

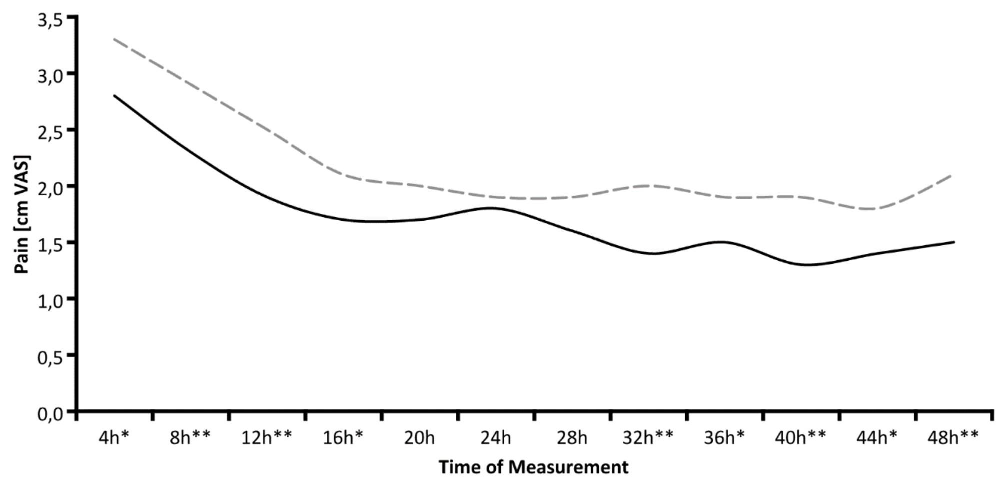


Figure legend: black line = Mg group; grey dashed line = control group; * p<0,05; ** p<0,001

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