International Journal of Obstetric Anesthesia (2012) **21**, 212–216
0959-289X/$ - see front matter
http://dx.doi.org/10.1016/j.ijoa.2012.01.006

ELSEVIER
www.obstetanesthesia.com

ORIGINAL ARTICLE

The effect of intravenous magnesium therapy on the duration of intrathecal fentanyl labor analgesia

J.T. Sullivan,[a] N. Higgins,[a] P. Toledo,[a] B.M. Scavone,[b] R.J. McCarthy,[a] C.A. Wong[a]
[a] *Department of Anesthesiology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA*
[b] *Department of Anesthesia and Critical Care, University of Chicago Medical Center, Chicago, IL, USA*

ABSTRACT
Background: Magnesium has been reported to augment the analgesic effects of opioids when co-administered into the cerebrospinal fluid. The purpose of this study was to determine the influence of intravenous magnesium therapy administered for preeclampsia on the duration of intrathecal fentanyl analgesia for labor.
Methods: Thirty-four nulliparous parturients having labor induced for preeclampsia and receiving intravenous magnesium therapy were recruited. Thirty-four nulliparous patients having labor induced for elective or medical reasons were recruited as controls. At request for analgesia, baseline serum magnesium levels were obtained and combined spinal–epidural analgesia was initiated with intrathecal fentanyl 25 μg. Before injection of fentanyl, a sample of cerebrospinal fluid was obtained for magnesium assay. An epidural catheter was sited but no additional medications were administered until the second request for analgesia. The primary outcome was duration of intrathecal fentanyl analgesia.
Results: There was no difference in the median duration of analgesia between the magnesium [79 min (95% CI 76 to 82)] and control groups [69 min (95% CI 56 to 82)] (difference between medians: 10 min (95% CI −4 to 21 min; $P = 0.16$). There was neither a relationship between the serum and cerebrospinal fluid magnesium concentrations nor the cerebrospinal magnesium concentration and duration of intrathecal fentanyl analgesia.
Conclusions: Intravenous magnesium therapy at doses typically used for seizure prophylaxis in preeclampsia did not influence the duration of intrathecal fentanyl labor analgesia. However, this study may have been underpowered to detect a difference and future study is warranted.

Keywords: Labor analgesia; Intrathecal opioid; Fentanyl; Magnesium

Introduction

Magnesium, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, has been shown to potentiate opioid analgesia in many settings. When administered into the intrathecal (IT) or epidural space of both obstetric[1–3] and non-obstetric patients[4–7] as part of a neuraxial technique, it has been reported to prolong the duration of co-administered spinal opioid analgesia or result in improved postoperative analgesia. Intravenous magnesium improves postoperative analgesia and decreases opioid analgesic requirements when used in conjunction with general anesthesia in non-obstetric patients.[8–16] Conversely, in patients receiving bupivacaine-fentanyl patient-controlled epidural analgesia (PCEA) for postoperative analgesia, systemic magnesium therapy did not decrease the volume of self-administered epidural solution.[17] This latter effect has not been studied in obstetric patients.

The exact site and mechanism of action of magnesium's analgesic effect has not been fully elucidated but a central site is likely given the analgesic augmentation seen with magnesium administered directly into the cerebrospinal fluid (CSF).[1–3] The purpose of this study was to determine the influence of intravenous magnesium, administered for eclampsia prophylaxis, on the duration of IT fentanyl labor analgesia. Our hypothesis was that intravenous magnesium therapy would prolong the duration of action of IT fentanyl analgesia as part of a combined spinal-epidural (CSE) technique.

Methods

After Institutional Review Board approval, nulliparous parturients having labor induced at 34 weeks of gestation or greater from June 2005 to December 2006 were

Accepted January 2012
Correspondence to: John T. Sullivan, M.D., Department of Anesthesiology, 251 E. Huron Street, F5-704, Chicago, IL 60611, USA.
E-mail address: sullivan@northwestern.edu

recruited to participate in this prospective observational study. After written informed consent was obtained, parturients receiving intravenous magnesium therapy for preeclampsia (4-g loading dose followed by an infusion of 2 g/h) were compared with control parturients who were not receiving intravenous magnesium therapy. Exclusion criteria included patients with a cervical dilation of <3 cm at the time of neuraxial analgesia request, known contraindications to CSE, or those who had previously received systemic opioid labor analgesia. Maternal age, parity, gestational age and reason for labor induction were recorded. Blood samples for baseline serum magnesium levels were drawn at the time of intravenous catheter placement.

Upon request for analgesia, the following data were recorded: pain (assessed on a 100-mm unmarked visual analog scale (VAS) with the left end labeled "no pain" and the right end labeled "worst imaginable pain"), cervical dilation and intravenous magnesium bolus time and duration of infusion. A second blood sample was drawn from a vein remote from the intravenous line for another serum magnesium level. After identifying the epidural space using a 17-gauge Tuohy needle with a loss-of-resistance to air technique, a 27-gauge Whitacre spinal needle was used to puncture the dura and approximately 0.3–0.5 mL of CSF was collected for a CSF magnesium concentration assay. Fentanyl 25 μg was injected through the spinal needle, the spinal needle was removed, and a catheter was sited in the epidural space. No additional medications were administered until the second request for analgesia. Interval pain scores were assessed using the VAS at 15-min intervals until the second request for analgesia. At this time an epidural test dose (lidocaine 45 mg with epinephrine 15 μg) was injected and 0.125% bupivacaine 10–15 mL was administered in 5-mL increments until adequate analgesia was obtained. The peak cephalad sensory level to ice was recorded. Analgesia was maintained with our institution's PCEA protocol (bupivacaine 0.06%, fentanyl 2 μg/mL). Labor outcome data were recorded including mode of delivery and neonatal weight.

The primary outcome variable was the duration of analgesia as defined by the time interval between the IT injection of fentanyl and the second request for analgesia. Kaplan Meier survival curves were constructed for the primary outcome. Pain burden, defined as the area under the VAS pain score-time curve (AUC_{0-60}), was calculated for 60 min following IT injection by adding the products of four interval pain scores multiplied by 15 min.

Statistical analysis

A total sample size of 68 (34 per group) was estimated to achieve 80% power to detect a hazard rate of 0.33 when the proportions surviving in each group are 0.5 and 0.8 at α of 0.05 using a two-sided log rank test. These results assume that two sequential tests are made using the O'Brien-Fleming spending function. The estimated median duration of IT fentanyl analgesia was 60 min based on data from a previously published study.[1] The Shapiro–Wilk and Kolmogorov–Smirnov tests were used to test the hypothesis of normal distribution. Kaplan Meier survival curves were constructed for the primary outcome (duration of analgesia) and differences in median values evaluated using the log rank test. The exact Wilcoxon rank sum test was used to determine the difference in the median duration of analgesia and calculate the 95% confidence interval of the difference. Pearson correlation was used to assess the association between serum and CSF magnesium concentrations and the primary outcome. Confidence intervals for the *r*-value were calculated at 95% using a 10 000 bootstrap sample. Continuous data were compared between groups using the two-sample t test and reported as mean ± SD. Interval data that did not meet the criteria of a normal distribution were compared between groups using the exact Wilcoxon rank sum test and reported as median [interquartile range]. Categorical data (spontaneous vaginal, instrumental vaginal, cesarean) were compared using Fisher's exact test and reported as counts. Analysis was by intent-to-treat and all *P* values were 2-sided. A *P* value <0.05 was required to reject the null hypothesis. Statistical analysis was performed using R version 2.13.0, (The R Foundation for Statistical Computing).

Results

Sixty-eight patients were recruited to participate in this study (34 preeclamptics receiving magnesium and 34 controls). The following protocol violations were recorded: two patients in the magnesium group and one in the control group received an epidural test dose immediately following the IT injection; one subject in the control group received fentanyl 20 μg; two patients in the treatment group received systemic opioid analgesia (one received a single dose of nalbuphine 2.5 mg for pruritus in the interval between IT injection and second request for analgesia, and one received three doses of hydrocodone/acetaminophen 2, 4, and 11 h preceding IT injection). One patient in the control group was redefined as parous (previous 33 week loss) following enrollment. All patients completed the protocol and were included in the analysis.

There were differences between the treatment and control groups in the indication for induction of labor and gestational age (Table 1). Both groups requested analgesia at similar stages of labor as defined by cervical dilation and pain scores. There were no differences between groups in baseline serum magnesium levels (Table 2). The median [range] total magnesium dose before study drug administration was 14 [5–39] g and patients received magnesium equal to 60 [66–372] mg/kg of body weight.