Effects of magnesium sulphate on intraoperative neuromuscular blocking agent requirements and postoperative analgesia in children with cerebral palsy

H.-S. Na\textsuperscript{1}, J.-H. Lee\textsuperscript{2}, J.-Y. Hwang\textsuperscript{1}, J.-H. Ryu\textsuperscript{1}, S.-H. Han\textsuperscript{1}, Y.-T. Jeon\textsuperscript{1} and S.-H. Do\textsuperscript{1*}

\textsuperscript{1}Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, Seongnam, Gyeonggi-do, Republic of Korea. \textsuperscript{2}Department of Anesthesiology and Pain Medicine, Seoul National University Hospital, Seoul, Republic of Korea

\*Corresponding author. E-mail: shdo@snu.ac.kr

\textbf{Background.} In this double-blind, randomized, placebo-controlled study, we evaluated the effects of magnesium sulphate on neuromuscular blocking agent requirements and analgesia in children with cerebral palsy (CP).

\textbf{Methods.} We randomly divided 61 children with CP undergoing orthopaedic surgery into two groups. The magnesium group (Group M) received magnesium sulphate 50 mg kg\textsuperscript{-1} i.v. as a bolus and 15 mg kg\textsuperscript{-1} h\textsuperscript{-1} by continuous infusion during the operation. The control group (Group S) received the same amount of isotonic saline. Rocuronium was administered 0.6 mg kg\textsuperscript{-1} before intubation and 0.1 mg kg\textsuperscript{-1} additionally when train-of-four counts were 2 or more. I.V. fentanyl and ketorolac were used to control postoperative pain. Total infused analgesic volumes and pain scores were evaluated at postoperative 30 min, and at 6, 24, and 48 h.

\textbf{Results.} The rocuronium requirement of Group M was significantly less than that of Group S [0.29 (0.12) vs 0.42 (0.16) mg kg\textsuperscript{-1} h\textsuperscript{-1}, \textit{P}<0.05]. Cumulative analgesic consumption in Group M was significantly less after operation at 24 and 48 h (\textit{P}<0.05), and pain scores in Group M were lower than in Group S during the entire postoperative period (\textit{P}<0.05). Serum magnesium concentrations in Group M were higher until 24 h after operation (\textit{P}<0.05). The incidence of postoperative nausea and vomiting and rescue drug injections was similar in the two groups. No shivering or adverse effects related to hypermagnesaemia were encountered.

\textbf{Conclusions.} I.V. magnesium sulphate reduces rocuronium requirements and postoperative analgesic consumption in children with CP.

\textit{Br J Anaesth} 2010; \textbf{104}: 344–50

\textbf{Keywords:} anaesthesia, paediatric; analgesia, postoperative; ions, magnesium; neuromuscular block, rocuronium

Accepted for publication: December 1, 2009

Cerebral palsy (CP) is a non-progressive motor disorder caused by injury to the developing brain during the perinatal period.\textsuperscript{1} Children with CP are vulnerable to hypothermia, nausea, vomiting, muscle spasm, and ensuing pain during the perioperative period, and thus require careful management.\textsuperscript{2} \textsuperscript{3} Furthermore, it has been demonstrated that they are resistant to non-depolarizing neuromuscular blocking agents.\textsuperscript{4}

The perioperative use of magnesium sulphate was first reported to decrease analgesic requirements during the postoperative period by Tramer and colleagues,\textsuperscript{5} and has since been investigated as an effective adjuvant during anaesthesia and postoperative analgesia.\textsuperscript{6}–\textsuperscript{9} Although the mechanism underlying the analgesic effect of magnesium is unclear, magnesium acts as an antagonist of \textit{N}-methyl-\textit{D}-aspartate (NMDA) type glutamate receptors, the block of which is known to inhibit the induction and maintenance of central sensitization to nociceptive stimuli.\textsuperscript{10} \textsuperscript{11} Therefore, magnesium seems to alleviate postoperative pain. Furthermore, magnesium has been suggested as a possible
means of resolving muscle rigidity and spasm in tetanus. High magnesium concentrations inhibit release of acetylcholine from the presynaptic nerve terminal and enhance the effect of non-depolarizing neuromuscular blocking agents. These effects are due to the competition of magnesium ion with calcium ion. Patients with CP suffer from a distinctive pain resulting from muscle spasm; this is known to be related to the stimulation of alpha motor neurones by excessive excitatory neurotransmitters, especially glutamate, together with inadequate release of gamma-aminobutyric acid (GABA). Thus, baclofen, an agonist at GABAB receptors, has been used as the drug of choice to reduce the pain associated with muscle spasm. In view of the fact that magnesium acts as an NMDA receptor antagonist (a major subtype of the ionotropic glutamate receptor family) and inhibitor of acetylcholine release, we hypothesized that the perioperative administration of magnesium sulphate might alleviate postoperative pain and reduce muscle spasms in CP patients. In this study, we investigated the effect of magnesium sulphate on intraoperative neuromuscular blocking agent requirements and postoperative analgesia in children with CP.

Methods
With IRB approval and informed parental consent, children with CP undergoing orthopaedic osteotomy were enrolled in this double-blind, randomized, prospective study. Patients were included from June 2008 to February 2009. Children aged between 5 and 15 yr with spastic and paraplegic type CP were eligible for inclusion. The motor disorder of the subjects was slight to moderate and ranged from 1 to 3 using the Gross Motor Function Classification System-Expanded and Revised. Children with major cardiovascular, respiratory, hepatic or renal dysfunction, mental retardation, hyper- or renal dysfunction, mental retardation, hypersensitivity to magnesium, regular analgesic medication, and heart rate (HR) within 20% of preoperative values. Muscle relaxation was maintained with intermittent rocuronium (0.1 mg kg⁻¹, i.v.) whenever the twitch response of TOF stimulation at the wrist was ≥2 every 15 min after checking the TOF response every 5 min. When there were clinical signs of recovery from muscle relaxation (notch of end tidal CO₂ curve, body movement, hiccup), additional rocuronium was administered, even though TOF count was 0 or 1 (rocuronium 0.1 mg kg⁻¹, i.v. and then once more or not after checking the TOF response again in 5 min). No additional rocuronium was administered from ~30 min before the end of the surgery and total rocuronium doses were recorded. During operations, mean arterial pressure (MAP) and HR were measured at the following time points: before induction, before intubation, after intubation, at operation start, at 15, 30, 60, 90, 120, 150 min after operation start, at the end of surgery, and at arrival in the post-anaesthetic care unit (PACU). Sevoflurane and study drugs were discontinued after skin closure and an i.v. postoperative analgesic infusion device (AutoMed® 3200, ACE Medical Corp., Ltd, Seoul, Korea) was started. Fentanyl 20 µg kg⁻¹ and ketorolac 2 mg kg⁻¹ were made up to 100 ml in normal saline and the infusion rate, bolus dose, and lock time interval were set at 1 ml h⁻¹, 1 ml, and 15 min, respectively. Parents were trained how to use the device in advance. After checking the return of the third twitch in the TOF response, glycopyrrolate 0.01 mg kg⁻¹ and neostigmine 0.05 mg kg⁻¹ were administered to reverse residual neuromuscular block, and subjects were extubated. Subjects were observed for signs of hypermagnesaemia, including CNS depression, respiratory depression, cardiac arrhythmia, and any other adverse events.

Study outcomes were recorded by one anaesthesiologist unaware of group allocations at 30 min after PACU arrival and at 6, 24, and 48 h after leaving the operating theatre. Postoperative pain scores were assessed using the 10-point Faces Pain Scale-Revised (FPS-R) (Fig. 1). In addition, sedation was monitored using a three-point rating scale; 0, no response; 1, arousable on calling; and 2, awake. When subjects complained of pain, the FPS-R was checked and if necessary, rescue analgesic drug (ketorolac 0.5 mg kg⁻¹) was administered. Postoperative analgesic consumption volume, rescue drug administration, and adverse effects (shivering, nausea, and vomiting) were recorded. Blood samples for serum Mg²⁺ concentration determination were...
obtained before and immediately after surgery, and 6 and 24 h after operation.

According to power analysis, at least 30 subjects were required in each group to show a difference of 5 ml in postoperative analgesic consumption with a statistical power of 80% and a type 1 error of 5%. We assumed a standard deviation (SD) of 6.3 ml based on pilot data and a dropout rate of 15%. Data were expressed as mean (SD). Subject characteristics and total rocuronium dose were analysed using Student’s t-test. Serum Mg$^{2+}$ concentrations, haemodynamic variables, analgesic consumption volumes, and postoperative FPS-R scores were analysed by repeated-measures ANOVA, and when a significant intergroup difference was found, the Mann–Whitney U-test was used to compare the groups at individual time points. The $\chi^2$ test was used to determine the significance of differences with respect to operation type, consciousness scores, and dichotomous data (presence of postoperative adverse effects and rescue drug medication). Statistical analyses were performed using SPSS 15.0 version (SPSS Inc., Chicago, IL, USA) on Microsoft Windows XP. P-values of $<0.05$ were considered statistically significant.

Results

Figure 2 details the flow of participants screened for the trial. Subject characteristics (age, weight, height, and gender) and surgical data (operation types, duration of anaesthesia and operation, and recovery data) are shown in Tables 1 and 2.

The amounts of rocuronium used during anaesthesia were 0.24 (0.12) mg kg$^{-1}$ h$^{-1}$ in Group M and 0.42 (0.16) mg kg$^{-1}$ h$^{-1}$ in Group S ($P<0.001$). Mg$^{2+}$ concentrations were similar in the two groups before magnesium infusion, but mean serum Mg$^{2+}$ concentrations 6 and 24 h after operation were significantly higher in Group M ($P<0.001$) (Table 3).

The two groups were significantly different in terms of cumulative analgesic consumption ($P=0.035$) and FPS-R
scores ($P<0.001$). In particular, analgesic consumption in Group M was less at 24 and 48 h after operation ($P=0.017$ and 0.001, respectively) (Fig. 3), and postoperative FPS-R scores were significantly lower in Group M over the entire observation period ($P<0.05$) (Fig. 4). Rescue analgesic was needed after operation in 12 patients (40%) in Group S and in nine patients (30%) in Group M, but this difference was not significant ($P=0.367$). Although MAP and HR were generally lower in Group M, this was not statistically significantly different by repeated-measures ANOVA (Figs 5 and 6). However, MAP values before and after intubation ($P=0.004$) were significantly lower in Group M compared by the Mann–Whitney U-test (Fig. 5).

Incidence of PONV was not significantly different in the two groups (6 subjects (20%) in Group S and 5 (16.7%) in Group M, $P=0.694$), and no shivering was detected in either group. During the observation period, the two groups had similar consciousness scores in the PACU ($P=0.731$), and no signs of hypermagnesaemia or of any other adverse events were observed.

### Discussion

The principal finding of this study is that the intraoperative administration of magnesium sulphate reduced neuromuscular blocking agent requirements and postoperative analgesic consumption in children with spastic type CP. Furthermore, it also improved the quality of postoperative analgesia.

The usual operations performed on patients with CP are lower limb orthopaedic procedures, which range from minor soft tissue releases, such as tenotomy and tendon transfer, to major osteotomy on one or both lower limbs. Such operations are generally performed between the ages of 5 and 12 yr, and patients with CP who undergo extensive lower limb orthopaedic surgery are prone to frequent and severe pain after operation. Regional techniques and various drugs have been applied to reduce muscle spasticity and postoperative pain.²³

Magnesium sulphate has been studied as an adjuvant drug for anaesthesia and analgesia by numerous investigators. Although the majority of studies have concluded that magnesium sulphate has a positive analgesic effect, some have produced negative results.²⁰ ²¹ For example, Bhatia and colleagues²² found that magnesium sulphate did not decrease morphine requirements after operation after open cholecystectomy.

In the present study, our results are similar to those obtained during our previous study⁸ in which magnesium sulphate was found to be a useful analgesic adjuvant in
adult gynaecological patients. Bolus infusion of the analgesia infusion device was controlled by parents, which could well have affected the mean volume of analgesics administered. However, the lower pain scores of Group M despite similar analgesic consumption during the immediate and early postoperative periods suggest that magnesium reduces muscle spasm in addition to inhibiting nociception associated with central sensitization, and that this contributes to the quality of postoperative analgesia.

Special regard should be paid to the optimal bolus and maintenance doses of magnesium sulphate required. The magnesium sulphate regimen used in this study (50 mg kg\(^{-1}\) bolus followed by 15 mg kg\(^{-1}\) h\(^{-1}\) infusion) is less than half of the dose for the treatment of pre-eclampsia,\(^ {10}\) and the immediate postoperative serum Mg\(^{2+}\) concentration [1.34 (0.13) mmol litre\(^{-1}\)] in Group M was substantially lower than its toxic level (2.5 mmol litre\(^{-1}\)). A similar regimen was studied by Seyhan and colleagues\(^ {6}\) who concluded that the minimum dose required for a significant reduction in anaesthetic and analgesic consumption was 40 mg kg\(^{-1}\) bolus followed by a 10 mg kg\(^{-1}\) h\(^{-1}\) infusion. On the basis of these findings, our trial dose appears to be sufficient to reduce postoperative analgesic requirements. In other studies, serum Mg\(^{2+}\) concentrations did not reach toxic levels even after continuous infusion for 24 h (50 mg kg\(^{-1}\) bolus followed by 2 g h\(^{-1}\) infusion) or 48 h (30 mg kg\(^{-1}\) bolus followed by 10 mg kg\(^{-1}\) h\(^{-1}\) infusion).\(^ {9,23}\) However, Mg\(^{2+}\)-related side-effects should always be considered and careful management should be taken when administering magnesium sulphate to patients with diminished renal function.\(^ {10}\)

Greater than normal doses of non-depolarizing neuromuscular blockers are required in patients with spastic type CP, and their durations of action are shorter than in normal patients. This is due to up-regulation of extrasympathetic acetylcholine receptors.\(^ {3}\) It is well known that magnesium sulphate increases the speed of onset and potentiates the action of non-depolarizing neuromuscular blockers.\(^ {15,24}\) In one study, rocuronium-induced neuromuscular block was prolonged by the prior administration of magnesium sulphate, although it did not increase the speed of onset.\(^ {16}\) The onset or duration of rocuronium was not the aim of this study; however, we observed a significant reduction in rocuronium requirements in the magnesium group.

Although the incidence of PONV was similar in the two study groups, previous reports have produced disparate results in this context.\(^ {8,20}\) Little is known about the antemetic properties of magnesium, but it is conceivable that reduced opioid consumption in Group M reduced the incidence of PONV. Patients with CP are reported to experience PONV more frequently, particularly when opioids are used,\(^ {2}\) but the incidence of PONV in our study might have been underestimated because nausea is difficult to diagnose and vomiting alone is usually observed in young children.\(^ {25}\) Magnesium has been reported to reduce shivering threshold in healthy volunteers,\(^ {26}\) and in a previous study, we found that postoperative shivering in gynaecological patients is markedly reduced by magnesium.\(^ {8}\) However, in the present study, shivering was not encountered. The incidence of postoperative shivering has been reported to vary from 6.3% to 66%.\(^ {27}\) However, much lower incidences (3.5%) have been reported in paediatric patients,\(^ {28}\) and one study, like the present study, reported no shivering among paediatric patients.\(^ {29}\)

This study has some limitations that should be considered. First, we could not objectively investigate muscle spasms. Our subjects were 5–15 yr old, so some young children could not well distinguish spasms from surgical pain. Preliminary preoperative education about the postoperative
with CP under general anaesthesia. We conclude that i.v. magnesium sulphate, a proved analgesic, does not reduce postoperative analgesic requirements. Randomized trials have reported that magnesium reduces propofol and opioid requirements with reference to bispectral index (BIS). We did not investigate sevoflurane requirements because BIS has yet to be calibrated accurately in children.

Thirdly, we used the TOF Watch®® in this study, which has a special algorithm to calculate the TOF ratio. If the value of T2 is higher than that of T1, the TOF value is calculated as T4/T2, and if this ratio is also above 1.0, it shows that the TOF count is not TOF ratio for intraoperative neuromuscular monitoring. This study is neither a dose–response nor a randomised trial for children, so we think that this approach was appropriate for this study.

To the best of our knowledge, this report is the first on the perioperative effects of magnesium sulphate in paediatric patients with CP. In this study, magnesium sulphate (50 mg kg⁻¹ bolus injection and 15 mg kg⁻¹ h⁻¹ infusion during anaesthesia) reduced intraoperative rocuronium requirements and decreased analgesic consumption and pain scores during the first 48 h after operation without any adverse effects. We conclude that i.v. magnesium sulphate should be considered a useful adjuvant in children with CP under general anaesthesia.

References
7 Gupta K, Vohra V, Sood J. The role of magnesium as an adjuvant during general anaesthesia. Anaesthesia 2006; 61: 1058–63
11 Wooff CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. Pain 1991; 44: 293–9
18 Kita M, Goodkin DE. Drugs used to treat spasticity. Drugs 2000; 59: 487–95
21 Ko SH, Lim HR, Kim DC, Han YJ, Choe H, Song HS. Magnesium sulfate does not reduce postoperative analgesic requirements. Anesthesiology 2001; 95: 640–6
27 Alfonsi P. Postanaesthetic shivering: epidemiology, pathophysiology, and approaches to prevention and management. Drugs 2001; 61: 2193–205
29 Wappler F, Frings DP, Scholz J, Mann V, Koch C, Schulte am Esch J. Inhalational induction of anaesthesia with 8% sevoflurane in
children: conditions for endotracheal intubation and side-effects.

30 Wallenborn J, Kluba K, Olthoff D. Comparative evaluation of Bispectral Index and Narcotrend Index in children below 5 years of age. Paediatr Anaesth 2007; 17: 140–7

