Effect of intrathecal magnesium in the presence or absence of local anaesthetic with and without lipophilic opioids: a systematic review and meta-analysis

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Editor’s key points

- The authors have reviewed magnesium as an adjunct to local anaesthetics (LA) in spinal anaesthesia.
- Fifteen randomized controlled trials (980 patients) met the inclusion criteria for the review.
- Importantly, magnesium increased the duration of intrathecal LA and lipophilic opioids.
- This effect was seen in non-obstetric, but not in obstetric, patients.

Summary. Spinal anaesthesia is the primary anaesthetic technique for many types of surgery. Adjuncts to the local anaesthetics (LA) used in spinal anaesthesia can exhibit undesirable side-effects, limiting their use, but magnesium may have advantages in this respect. We sought randomized control trials (RCTs) in patients undergoing all types of surgery and in women in labour to compare the effect of intrathecal magnesium sulphate ± LA ± lipophilic opioid (experimental group) with the use of either intrathecal lipophilic opioids ± LA or LA only (control group). The primary outcome was the duration of spinal anaesthesia. Secondary outcomes were: onset and time to maximal sensory blockade, onset of motor block, and duration of sensory and motor blockade. We found 15 RCTs comprising 980 patients. The duration of spinal anaesthesia was significantly increased in the experimental group [standardized mean difference (SMD) −1.05 (−1.70, −0.41) (P=0.0011)], compared with the control group. This increased duration of spinal anaesthesia was seen in non-obstetric studies, SMD −1.38 (−2.11, −0.66) (P=0.0002), but not in obstetric studies, SMD −0.55 (−1.87, 0.77) (P=0.41). There was no delay in the onset of sensory or motor blockade. The incidence of hypotension and pruritus was similar in both groups. Heterogeneity was high in all outcome measures. The duration of spinal anaesthesia may be increased by the addition of magnesium to lipophilic opioids ± LA.

Keywords: anaesthesia duration; local anaesthetic; magnesium; opioid; spinal

Spinal anaesthesia is often used in orthopaedic, obstetric, and urological surgery. Recent developments have led to greater patient satisfaction and accelerated functional recovery, allowing earlier discharge from hospital. Commonly, intrathecal local anaesthetics (LA) are combined with opioids to prolong analgesia.¹ Opioids do not prolong motor recovery or discharge time, and may attenuate the stress response.² They are associated with a number of undesirable side-effects, including delayed respiratory depression, urinary retention, pruritus, haemodynamic instability, and nausea and vomiting.³

Other drugs that potentiate spinal antinociception in adults have been studied, and all exhibit adverse effects. Epinephrine, clonidine, ketamine, and neostigmine have been added to intrathecal LA in the presence and absence of opioids, in an attempt to prolong analgesia and reduce the side-effects of intrathecal opioids.⁴–⁷

Magnesium is an abundant cation in the body, essential to numerous physiological activities. It is an established i.v. treatment of pre-eclampsia, acute asthma, and tachyarrhythmias. Magnesium is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, and inhibits voltage-gated calcium channels.⁸–¹⁰ There are contradictory reports about the role of i.v. magnesium sulphate in reducing intra- and postoperative analgesic requirements.¹¹–¹³ But even high doses of i.v. magnesium sulphate such as those used in preeclampsia undergo minimal transfer across the blood–brain barrier.¹⁴ Magnesium sulphate is currently unlicensed for intrathecal use in the UK.

Animal studies have demonstrated that intrathecal magnesium suppresses nociceptive impulses in a neuropathic pain setting, and potentiates opioid antinociception.¹⁵–¹⁶ Intrathecal magnesium was first used in humans in 1906. Haubold and Meltzer¹⁷ gave 1000–2000 mg, producing profound motor and sensory block for 3–27 h in orthopaedic, general surgical, and gynaecological procedures with complete recovery. In 1985, Lejuste¹⁸ recorded the effects of intrathecal magnesium sulphate 1000 mg given...
inadvertently in a 22 week pregnant patient requiring insertion of a McDonald suture, producing a dense motor block lasting 90 min before complete resolution. Buvanendran and colleagues conducted the first prospective, human, randomized control trial (RCT) to determine whether intrathecal magnesium and fentanyl without LA compared with fentanyl and saline without LA could prolong the duration of spinal analgesia in labouring parturients. The duration of spinal anaesthesia was significantly prolonged in the magnesium group, with no effect on motor block, sensory block, or incidence of pruritus. However, the results from subsequent studies have been inconsistent. The purpose of this systematic review was to determine whether magnesium is a useful intrathecal adjuvant with or without the use of opioids or LA to relieve postoperative and labour pains. The primary outcome was the duration of spinal anaesthesia. The secondary outcomes included beginning of sensory and motor block, time to maximal sensory block, and duration of sensory and motor block.

Methods
Search strategy
We identified RCTs using MEDLINE from 1950 to March 2012 and EMBASE from 1980 to March 2012, CINAHL, and Google Scholar using the keywords and text words: intrathecal, subarachnoid, spinal, magnesium, and human (Fig. 1). We also searched the bibliographies of relevant reviews, and identified RCTs and published abstracts from relevant anaesthesia meetings that were held from 2000 to 2012 by the American Society of Anesthesiologists, the Society of Obstetric Anaesthesia and Perinatology, the Obstetric Anaesthetists Association, and the European Society of Anaesthesiology. We contacted investigators if the data set was incomplete. The search was completed by all the authors and the results were compared. The final list of qualifying studies was derived by consensus (Table 1). There was no language restriction.

Selection of included studies
Two authors (A.P.M. and A.B.) scanned the articles retrieved by the initial search to exclude obvious irrelevant studies. Study eligibility was determined by reading the title and abstracts and irrelevant trials were excluded at this stage. Inclusion and exclusion criteria were established before the study was conducted.

Inclusion and exclusion criteria
We sought RCTs in patients undergoing all types of surgery. All the subjects received intrathecal LA apart from two studies, where intrathecal fentanyl and either magnesium or saline was administered. RCTs comparing administration of intrathecal magnesium sulphate + LA ± lipophilic opioid (experimental group) with either intrathecal lipophilic opioid + LA or LA only (control group) were included. We excluded those groups in the included studies which had only magnesium administered intrathecally or epidurally as part of a combined spinal–epidural or epidural technique, respectively. We excluded RCTs that compared intrathecal hydrophilic opioids, for example, morphine with intrathecal magnesium as intrathecal hydrophilic opioids have a prolonged duration of action. The data on all patients irrespective of their age and type of surgery were considered.

Quality of the trials
Two of the authors (A.P.M., A.B.) scored each trial independently using a five-point validated quality index, the Jadad scale. This index consists of 2 points for appropriate reporting of randomization, 2 points for appropriate reporting of blinding, and 1 point for reporting the outcome of all recruited patients. The two authors reviewed the articles and assigned a final score by consensus when initial scores differed. In addition, they noted studies where there was blinding to the randomization. A score of 3 or greater indicates a higher quality paper.

Publication bias
A funnel plot was used for assessing publication bias. This plot is a graph with effect size on the x-axis and a measure of sample size (in this case, the standard error of the effect size) on the y-axis. If small trials are inappropriately represented, the plot will appear to be asymmetrical. In addition, we inspected the Clinical Trials Registry website (http://clinicaltrials.gov; last accessed March 15, 2012) for unpublished data using a broad search strategy (intrathecal and magnesium).

Outcome measurements
The primary outcome was the duration of spinal anaesthesia, defined as the time from intrathecal injection to the onset of pain as defined by the authors. This was either time of first complaint of pain, first request for analgesia, or a reported pain score >3, according to the visual analogue scale. Secondary outcomes were onset of sensory block, time to onset of maximal sensory and motor block, duration of sensory and motor block, and time to complete motor recovery. The onset of sensory block was defined as time between intrathecal injection and absence of pain at the level of T10, assessed by pinprick. The maximal level of sensory block was determined by pinprick every 5 min for 25 min. The duration of sensory block was defined as time to regression of two segments from the maximum block height evaluated by pinprick. Studies varied in evaluating the onset of motor block. All studies used the modified Bromage score (0, no motor loss; 1, inability to flex the hip; 2, inability to flex the knee; 3, inability to flex the ankle). The onset of sensory block varied between a score of 1 and 3 between studies, whereas motor recovery was defined as a Bromage score of zero in all studies. Estimation of postoperative analgesic consumption varied between 24 and 48 h between studies. Morphine consumption was used as the standard postoperative analgesic for analysis. All other opioids used in the studies were converted to equi-analgesic i.v. morphine.
equivalent doses based on the following conversion scale (morphine: opioid): 100:1 for fentanyl, 1:10 for meperidine, and 1:10 for i.v. tramadol. Oral tramadol was converted to oral morphine at both 1:4 and 1:10, in accordance with the variable pharmacokinetics of tramadol, followed by conversion to i.v. morphine at 1:3.23 24

Data management

Data were recorded independently by two of the authors (A.P.M. and A.B.) to avoid transcription errors, with any discrepancies resolved by reinspecktion of the original articles. The data were then entered into the statistical program Revman 5.1.025 (by A.P.M.) and rechecked (by A.B.).

Analysis

The study characteristics are presented in Table 1. Meta-analytic techniques were used where possible to combine the results.25 For dichotomous variables, the odds ratio (OR) and 95% confidence interval (CI) were calculated and combined using a random effects model. A statistically significant difference occurred when the 95% CI did not include 1.0. For continuous variables, the standardized mean difference (SMD) and 95% CI were calculated using random effects modelling. A statistically significant difference occurred when the 95% CI did not include 0. If continuous data were only reported as the median or range, the mean was estimated as equivalent to the median and the standard deviation was computed to be approximately one-quarter of the typical ranges of data values.25 Sensitivity analysis was undertaken with respect to control groups using saline or opioids vs the experimental group using intrathecal magnesium, and according to the methodological quality of the included trials [studies with low quality (Jadad score ≤3) vs studies with high quality (Jadad score >3)]. A sensitivity analysis excluding outliers or studies not using LA in the injected mixture was also undertaken for the primary outcome. In the presence of a multiple intervention group such as variable doses of intrathecal magnesium or the use of fentanyl,20 26 we split the shared group into two equal groups with smaller sample sizes to prevent double-counting of participants in the shared intervention group and to avoid a unit-of-analysis error.27

Heterogeneity was assessed using the $I^2$ statistic. The $I^2$ statistic describes the percentage of total variation in study findings that is due to between study differences rather than due to chance.28 As significant heterogeneity was detected, it was assumed that there was no single ‘true’ effect underlying the data which were constant across different populations, and a random effects model was used.27
<table>
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<th>Authors</th>
<th>Jadad score</th>
<th>Blinding of allocation</th>
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<th>Number of patients</th>
<th>Conc. of magnesium (%)</th>
<th>Volume of drugs (ml)</th>
<th>Dose of LA (mg)</th>
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<th>Experimental group</th>
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Continued
Subgroup analysis

A subgroup analysis was performed for the primary outcome between the non-obstetric and obstetric RCTs. A second subgroup analysis was undertaken comparing the effect of intrathecal magnesium vs LA. A third subgroup analysis compared magnesium and intrathecal opioids vs magnesium with both LA and opioids.

Results

Twenty-two RCTs were identified between 2002 and 2012, including unpublished data from Cannata and colleagues (Cannata F, personal communication, 2011) and Gardette and colleagues (Schoeffler P, personal communication, 2011). Seven of these studies were excluded (Fig. 1). Two thoracic studies were excluded due to administration of intrathecal morphine and fentanyl with magnesium, and the unavailability of the full text or relevant data. Two studies were excluded as intrathecal morphine was used, and two others because epidural magnesium was given. One study was excluded because the number of participants in each treatment arm could not be identified. Data for duration of spinal anaesthesia were excluded from one study because there were numerical differences in the mean and standard deviation between the text and the table. However, the postoperative analgesia outcome in this study was included in the final analysis. Data relating to postoperative analgesia were excluded from one study as it used diclofenac, which could not be standardized to morphine. One study was excluded as it examined intrathecal and epidural magnesium, against saline. Data were extracted using a control group of intrathecal and epidural saline, and an experimental group of intrathecal magnesium and epidural saline.

Of the 15 studies (Table 1), 13 were placebo-controlled (Cannata F, personal communication, 2011; Schoeffler P, personal communication, 2011). One study had three treatment arms: a placebo group, a magnesium group, and a dexmedetomidine group, only the placebo and magnesium group were considered for analysis. Another study had three treatment arms: a placebo group, a magnesium group, and an opioid group. One of the other 13 studies used a placebo group and three intervention groups, using three different doses of intrathecal magnesium. The 15 studies covered a range of specialities: eight studies covered lower limb orthopaedic procedures (Schoeffler P, personal communication, 2011), four covered obstetrics, two were in urology (Cannata F, personal communication, 2011), and one study investigated lower abdominal surgery and orthopaedic surgery. The number of participants in each study ranged from 38 to 100, with two trials having fewer than 20 participants in each trial arm.

Eight of the studies used LA with either intrathecal fentanyl (five studies—10–25 μg) or sufentanil (three studies—5–8 μg) (Schoeffler P, personal communication, 2011). Three studies used LA with no intrathecal opioids and one study added saline, fentanyl 25 μg, or magnesium...
to local anaesthesia, dependent on participant randomization. One study added saline, dexmedetomidine, or magnesium to the LA. Two studies used intrathecal fentanyl with saline or magnesium, with no local anaesthesia.

On accessing www.clinicaltrials.gov, there are two ongoing trials, Intrathecal magnesium and postoperative analgesia in total hip replacement with identifier NCT01205997, the full text of which was unobtainable. On the Jadad scale, nine studies scored 5, two studies scored 4, and the remaining two studies scored 3. The concealment to allocation by sealed envelopes was present in eight studies, whereas it was not mentioned in the others.

A funnel plot (Fig. 2) was constructed to look for evidence of funnel plot asymmetry which may be associated with publication bias. This study did not find any evidence of funnel plot asymmetry. Moreover, Egger’s regression test for asymmetry gave a non-significant P-value of 0.142. The shape of the funnel plot did not alter on excluding the outliers.

**Primary outcome**

**Duration of spinal anaesthesia**

Adding magnesium to intrathecal lipophilic opioid ± LA or LA only was associated with a significant increase in the duration of spinal anaesthesia [SMD −1.05 (−1.70, −0.41), P=0.001] (Table 2). The study population showed significant heterogeneity (I²=94%, P<0.00001) (Fig. 3).

**Subgroup analysis**

Within the non-obstetric population only, a significant increase in the duration of spinal anaesthesia was detected when magnesium was added to intrathecal lipophilic opioid+LA or LA only [SMD −1.38 (−2.11, −0.66), P=0.0002]. Heterogeneity remained high (I²=92%, P<0.00001). However, within the obstetric population, the increased duration of spinal anaesthesia on adding intrathecal magnesium did not reach statistical significance [SMD −0.55 (−1.87, 0.77), P=0.41, with I²=96%, P<0.00001].

The effect of adding magnesium in the presence of intrathecal opioids led to a significant increase in the duration of block [SMD −0.95 (−1.61, −0.29), P=0.005]. Heterogeneity remained high (I²=91%, P<0.000001). In contrast, the effect of magnesium added to LA without supplementary opioids did not significantly increase the duration of spinal anaesthesia (SMD −1.31 (−2.98, 0.35), P=0.12) and there was high heterogeneity (I²=97%, P<0.00001).

As the study by Paul and colleagues was an extreme outlier, the analysis was repeated as part of the sensitivity analysis, excluding this study, and it did not change the measure of effect size or change the direction of results. However, heterogeneity was reduced, I²=88%. A meta-regression performed by excluding Paul and colleagues from the analysis showed no statistically significant evidence (non-significant P-values) of an association between SMD and all the potential effect modifying factors such as sample size, dose of magnesium used, concentration of magnesium, Jadad score, type of LA used, amount of LA, type of study (obstetric or non-obstetric), type of control (opioid or saline), and volume of drugs injected. The results of the sensitivity analyses demonstrated that the duration of spinal anaesthesia remained significant even when the results of unpublished study data, use of larger doses of magnesium, and studies that estimated the mean and standard deviation were excluded. Further sensitivity analysis was undertaken by excluding the studies that did not use LA in the injectate for the primary outcome, and it did not change the measure of effect size or the change in direction of the results.

**Secondary outcomes**

**Sensory blockade**

The addition of intrathecal magnesium did not exert a significant delay on the onset of sensory blockade. Time taken for neuroaxial blockade to reach its highest level was slightly increased in participants receiving magnesium, although this did not reach statistical significance (Table 3). The difference in the duration of sensory blockade between intervention groups was also not significantly different.

**Motor blockade**

There was no statistical difference in time to achieve any observed motor block. Full motor recovery within these studies was defined as a score of zero on the modified Bromage scale. There was no delay in time to full motor recovery with the addition of magnesium.
Table 2 A summary of the primary variables and subgroup analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of studies/participants</th>
<th>Standardized mean difference (95% CI)</th>
<th>P-value</th>
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<td>−1.05 (−1.70, −0.41)</td>
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<td>Duration of anaesthesia—LA + saline</td>
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<td>−1.31 (−2.98, 0.35)</td>
<td>0.12</td>
<td>97</td>
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<tr>
<td>Duration of anaesthesia—LA + opioid</td>
<td>8/505</td>
<td>−0.95 (−1.61, −0.29)</td>
<td>0.005</td>
<td>91</td>
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</tbody>
</table>

Fig 3 Forest plot of duration of anaesthesia.

Postoperative analgesic consumption

Conversion of other opioids to morphine was undertaken before analysing total consumption. One study routinely gave participants i.v. paracetamol intraoperatively (Cannata F, personal communication, 2011). No other analgesics were given in the postoperative period. The period of monitoring postoperative analgesic consumption varied from 24 to 48 h. We were unable to analyse these data meaningfully due to widely differing doses of intrathecal magnesium being used in the included trials, marked variability in the methods used to analyse postoperative analgesic consumption, and the small number of studies involved.

Side-effects

There was no significant difference in the incidence of pruritus between groups, although frequency of reporting was slightly lower in the magnesium group. There was no observed difference in the incidence of hypotension.

Discussion

This meta-analysis demonstrates that the addition of intrathecal magnesium to intrathecal lipophilic opioid ± LA or LA only is associated with an increased duration of spinal anaesthesia (P=0.001). On subgroup analysis, the duration of spinal anaesthesia was found to be increased when magnesium was added to opioids and intrathecal LA compared with a combination of LA and opioid mixture (P=0.005).

When the studies which coadministered intrathecal opioids are removed from analysis, the addition of magnesium ± LA confers no additional benefit when compared with saline ± LA only (P=0.12). In a subgroup analysis of the non-obstetric population only, magnesium was still associated with an increased duration of spinal anaesthesia (P=0.0002), but within the obstetric population, the increase in the duration of spinal anaesthesia with magnesium was not statistically significant (P=0.41). This meta-analysis also demonstrated that adding magnesium exerted no significant effect on the onset of sensory or motor blockade. The incidence of adverse events (hypotension, pruritus) was not increased by adding intrathecal magnesium.

Magnesium exerts its analgesic action as a non-competitive NMDA receptor antagonist, blocking ion channels in a voltage-dependent manner. The addition of magnesium reduces the activation of C-fibres by inhibiting the slow excitatory postsynaptic currents produced by NMDA receptor activation. NMDA receptor antagonists abolish calcium and sodium influx into cells leading to central sensitization and wind-up.
attributed to peripheral nociceptive stimulation.\textsuperscript{10} \textsuperscript{46} \textsuperscript{47} They abolish hypersensitization by blocking NMDA receptor activation in the dorsal horn by excitatory amino acid transmitters, notably glutamate and aspartate.\textsuperscript{47} There are no selective NMDA receptor antagonists available for pain management; hence, drugs with other clinical uses, such as magnesium and ketamine, have shown promise as analgesics.\textsuperscript{48} Magnesium is also known as ‘nature’s physiological calcium channel blocker’. In animals, calcium channel blockers have demonstrated an antinociceptive effect,\textsuperscript{49} \textsuperscript{50} and in chronic pain patients, they potentiate the effects of morphine.\textsuperscript{51}

This study has not demonstrated an effect on duration of spinal anaesthesia with the addition of magnesium to LA alone. However, in the presence of intrathecal opioids, there is a beneficial effect, which may suggest that magnesium potentiates the effect of opioids. These findings correlate with those of Kroin and colleagues,\textsuperscript{16} who demonstrated that the addition of intrathecal magnesium increased the peak effect and area under the analgesic curve of intrathecal morphine in rats. These effects were more pronounced as lower doses of opioids were used. Potentiation of opioid antinociception occurs by blocking the spinally mediated facilitatory component evoked by repetitive C-fibre stimulation.\textsuperscript{16} This effect would be expected to continue into the postoperative period. However, we were unable to demonstrate the same effect in the postoperative opioid consumption analysis due to widely differing doses of intrathecal magnesium being used in the included trials, marked variability in the methods used to analyse postoperative analgesic consumption, and the small number of studies involved. In contrast, the binding and dissociation of non-competitive NMDA receptor antagonists is relatively slow, which may explain the continuation of anaesthesia into the postoperative period and the reduction in postoperative analgesic requirements.\textsuperscript{52} It is likely that intrathecal magnesium sulphate potentiates spinal anaesthesia by a localized action on spinal nociceptive pathways, explaining the absence of central side-effects after systemic administration of large doses of magnesium.\textsuperscript{26} The potential postoperative opioid-sparing effect of magnesium may have beneficial effects. The reduction in opioid side-effects may allow analgesia to be given orally rather than i.v. Demands on postoperative monitoring may be reduced as a consequence of reduced opioid consumption.

It is difficult to explain the inconsistency between the duration of spinal anaesthesia between obstetric and non-obstetric study populations. There were only four studies within the obstetric subgroup, which may have accounted for the difference or it is possible that a different population subset may have influenced the results. We suggest that the concentration of magnesium and the volume and dose of LA used in the obstetric studies may also have had an influence. There should be further high-quality RCT investigating this issue.

As intrathecal magnesium alone has been shown to induce sensory and motor block,\textsuperscript{17} \textsuperscript{18} it was expected that magnesium might potentiate the spinal block due to a synergistic interaction between NMDA antagonists and LA. However, we did not demonstrate such an effect. It is postulated that magnesium may have less effect than fentanyl because it may be removed from extracellular fluid more rapidly, or that it may be specific to the NMDA receptor channel and therefore has no influence on opioid receptor sites or opioid binding.\textsuperscript{26} Unlugenc and colleagues\textsuperscript{26} suggested that adding magnesium sulphate may alter the pH of the injectate and thus explain its effects. Further RCTs are required to clarify this.

In the study by Unlugenc and colleagues,\textsuperscript{26} magnesium had no effect on the onset of motor or sensory blockade, while fentanyl induced both faster onset and higher level of sensory blockade than magnesium. Fentanyl binds to opioid receptors in the dorsal horn of the spinal cord, and may also exert a supraspinal action via intrathecal cephalad spread.\textsuperscript{53} \textsuperscript{54} Unlugenc and colleagues\textsuperscript{26} showed magnesium does not affect either onset or maximal level of sensory block, implying that intrathecal magnesium has an effect solely at the spinal level. Animal studies have suggested that magnesium does not reach supraspinal levels because it does not permeate across the blood–brain barrier.\textsuperscript{55} Animal studies have also found that magnesium sulphate may alter the effect of amide LA.\textsuperscript{56} It has been hypothesized that magnesium may activate bupivacaine hydroxylation by cytochrome P450 (CYP), reducing its duration of action. This may be because some cytochromes, including CYP3A, are sensitive to magnesium.\textsuperscript{57} \textsuperscript{58} Alternatively, the pharmacokinetic profile of bupivacaine may be altered by magnesium sulphate, reducing its duration of action.\textsuperscript{57} It has been

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of studies/participants</th>
<th>Standardized mean difference (95% CI)</th>
<th>P-value</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of sensory block</td>
<td>8/579</td>
<td>−0.39 (−1.34, 0.56)</td>
<td>0.42</td>
<td>96</td>
</tr>
<tr>
<td>Time to maximal sensory block</td>
<td>8/579</td>
<td>−0.38 (−0.89, 0.13)</td>
<td>0.15</td>
<td>88</td>
</tr>
<tr>
<td>Onset of motor block</td>
<td>4/270</td>
<td>−0.44 (−1.65, 0.76)</td>
<td>0.47</td>
<td>95</td>
</tr>
<tr>
<td>Duration of sensory block</td>
<td>9/617</td>
<td>−0.44 (−0.99, 0.10)</td>
<td>0.11</td>
<td>90</td>
</tr>
<tr>
<td>Time to complete motor recovery</td>
<td>10/677</td>
<td>−0.29 (−0.74, 0.16)</td>
<td>0.21</td>
<td>87</td>
</tr>
<tr>
<td>Incidence of pruritus (events—OR)</td>
<td>8/579</td>
<td>1.16 (0.73, 1.84)</td>
<td>0.54</td>
<td>0</td>
</tr>
<tr>
<td>Incidence of hypotension (events—OR)</td>
<td>10/697</td>
<td>1.09 (0.69, 1.71)</td>
<td>0.71</td>
<td>0</td>
</tr>
</tbody>
</table>
shown that the use of magnesium by the epidural route may improve postoperative pain by maintaining the magnesium concentration sufficiently high in the cerebrospinal fluid (CSF) to produce NMDA receptor blockade after operation. A similar mechanism could possibly explain our findings, deviations provided in the text and data tables. Buvanendran and colleagues were associated with destruction of laminae V–VII. However, another study reported a lack of neurotoxicity after serial injections of magnesium in rats.

The dose of intrathecal magnesium used within the studies to investigate the duration of spinal anaesthesia was consistent in all studies except two (Cannata F, personal communication, 2011) and there were two other studies that investigated the effect of varying doses of magnesium. However, both sets of results were excluded from the final analysis as one study did not identify the number of participants in each treatment arm, and the other study had discrepancies between the means and standard deviations provided in the text and data tables. Buvanendran and colleagues were the first study to investigate the effects of intrathecal magnesium in humans in a prospective, RCT. They conservatively extrapolated the dose in rats to humans, but the optimum dose of magnesium to administer in humans is as yet unknown. This study is unable to exclude the effect of baricity of magnesium-containing solutions. Buvanendran and colleagues measured the baricity of magnesium sulphate mixed with fentanyl using refractometry and found it (and fentanyl mixed in saline) to be slightly hypobaric with respect to CSF. However, they reported that magnesium 100 mg with fentanyl is hyperbaric in relation to CSF. Within this study, when hyperbaric bupivacaine was used, there was a significantly increased duration of spinal anaesthesia. However, there was no effect when magnesium was used to supplement isobaric bupivacaine. Verification of the baricity of magnesium containing solutions is required, including isobaric and hyperbaric bupivacaine, and further RCTs may then be able to distinguish whether baricity can account for the variability between studies.

The period of measured postoperative analgesic consumption between trials varied between 24 and 48 h. It has been assumed that the time intervals used for analysis are comparable between studies. There was marked variability in the methods used to analyse postoperative analgesic consumption. Two of the included studies measured from patient-controlled analgesia devices. One study gave tramadol 6 hourly orally, and one i.v. tramadol both on patient request. The other study used i.v. meperidine when pain scores were >4 on the visual analogue scale, which was given repeatedly until the pain was under control (Schoeffler P, personal communication, 2011). Of the studies looking into postoperative opioid consumption, (Schoeffler P, personal communication, 2011), only Dayioglu and colleagues found no difference in the total analgesic consumption in the first 24 h between the experimental and control groups.

This meta-analysis does have limitations. First, two abstracts were used within this meta-analysis, although both met the inclusion criteria. The multicentre trial in France by Schoeffler and colleagues was unable to be completed because of recruitment problems. Secondly, for all outcome variables, there is significant heterogeneity. A meta-regression was conducted to identify possible sources of heterogeneity, which showed no statistically significant evidence of an association between the individual mean differences and the sample size, concentration of magnesium used, Jadad score, type of LA used, amount of LA used, type of study, or type of control. When the study by Paul and colleagues was excluded from the analysis, it did not alter the level of significance of the primary outcome, although it decreased the heterogeneity $I^2=88\%$. We assume that due to the absence of concealment to allocation that particular study might have influenced the selection of patients explaining their findings. Meta-regression was not repeated for the subgroup analyses; hence, the effect of the type of opioid or dose of opioid was not investigated as a source of heterogeneity. Further limitations of this study are the different baricities of LA, doses, and types of lipophilic opioids used, although performing a sensitivity analysis based on baricity alone did not alter the level of significance of the primary outcome or the change in direction of the results.

There were insufficient studies to analyse whether the total volume given intrathecally had an association with the duration of spinal anaesthesia. Another criticism would be that there were only four studies, with 264 participants within the obstetric subgroup, and a high degree of heterogeneity, limiting the value of those results. Although we included both obstetric and non-obstetric studies, the test for subgroup difference was insignificant ($P=0.46$ and $I^2=21.5\%$). Furthermore, the majority of included trials looked at postoperative pain relief apart from one study which looked at labour pain relief from intrathecal magnesium. Future studies need to investigate whether there is a difference between the obstetric and non-obstetric subgroups, and whether any observed difference is due to an altered mechanism of action. Similarly, the limited number of studies in the subgroup comparison between LA vs magnesium alone precludes any meaningful conclusions regarding any independent effect of magnesium alone on duration of spinal anaesthesia. There were only four studies, with 264 participants, with marked variability between the results, reflected in the high heterogeneity. Further studies looking at the effect of magnesium alone would be able to clarify whether it is suitable for sole use as an adjunct to anaesthesia, or whether its effects are only elicited in the presence of opioids.

In conclusion, in this preliminary study, considering all the above limitations, it appears that the administration of intrathecal magnesium increases the time to first analgesic

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**References:**

3. Buvanendran and colleagues were the first study to investigate the duration of spinal anaesthesia. There were only four studies, with 264 participants within the obstetric subgroup, and a high degree of heterogeneity, limiting the value of those results. Although we included both obstetric and non-obstetric studies, the test for subgroup difference was insignificant ($P=0.46$ and $I^2=21.5\%$). Furthermore, the majority of included trials looked at postoperative pain relief apart from one study which looked at labour pain relief from intrathecal magnesium. Future studies need to investigate whether there is a difference between the obstetric and non-obstetric subgroups, and whether any observed difference is due to an altered mechanism of action. Similarly, the limited number of studies in the subgroup comparison between LA vs magnesium alone precludes any meaningful conclusions regarding any independent effect of magnesium alone on duration of spinal anaesthesia. There were only four studies, with 264 participants, with marked variability between the results, reflected in the high heterogeneity. Further studies looking at the effect of magnesium alone would be able to clarify whether it is suitable for sole use as an adjunct to anaesthesia, or whether its effects are only elicited in the presence of opioids.

**Conclusion:** In conclusion, in this preliminary study, considering all the above limitations, it appears that the administration of intrathecal magnesium increases the time to first analgesic...
request, but only when coadministered with opioids ± LA. However, there is no evidence to suggest that this effect is seen when magnesium is added to LA alone, or within the obstetric population. Therefore, superior quality RCTs are required comparing the efficacy of intrathecal magnesium vs LA alone, and the use of intrathecal magnesium in the obstetric population.

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Declaration of interest
None declared.

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