Magnesium sulphate attenuates acute postoperative pain and increased pain intensity after surgical injury in staged bilateral total knee arthroplasty: a randomized, double-blinded, placebo-controlled trial

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Abstract

Background: We evaluated the effect of magnesium sulphate on increased pain in 44 patients undergoing staged bilateral total knee arthroplasty (TKA).

Methods: The magnesium group (n=22) and the control group (n=22) received magnesium sulphate and isotonic saline, respectively, throughout the surgery. Postoperative pain (visual analogue scale, VAS) at rest and the amounts of patient-controlled analgesia (PCA, fentanyl) and rescue analgesia (ketoprofen) administered during the first 48 h were compared between the two groups and within each group between the first and second TKA.

Results: The VAS scores were significantly higher in the control group than in the magnesium group not only after the first TKA [29 (11) vs 19 (9) at 24 h and 33 (8) vs 24 (10) at 48 h; P<0.001] but also after the second TKA [44 (17) vs 20 (10) at 24 h and 43 (14) vs 25 (10) at 48 h; P<0.001]. In the control group, VAS scores were significantly higher for the second than for the first operated knee [44 (17) vs 29 (11) at 24 h and 43 (14) vs 33 (8) at 48 h; P<0.001 and P=0.006, respectively]. In the magnesium group, there were no significant differences in VAS scores between the first and second TKA. Magnesium significantly reduced the amounts of rescue analgesics and fentanyl administered over the first 48 h postoperatively.

Conclusions: Magnesium sulphate administration significantly reduced postoperative pain and minimized the difference in pain intensity between the first and second operations.

Clinical trial registration: KCT0001361.

Key words: magnesium; pain, postoperative; total knee arthroplasty

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Total knee arthroplasty (TKA) is a procedure that relieves pain in patients with severe symptomatic osteoarthritis, but it can be associated with postoperative pain, which hinders recovery. Recently, we reported evidence of increased pain in patients undergoing staged TKA, in whom the second operated knee had greater sensitivity (tertiary hyperalgesia) as a result of the surgical injury to the first operated knee.

The aim of perioperative pain control is to minimize delays in recovery, postoperative delirium, and pain-related stress responses that can lead to serious morbidity and poor outcomes. Numerous approaches to effectively control postoperative pain in TKA patients have been evaluated, as poorly controlled acute postoperative pain can be associated with persistent pain. Furthermore, increased pain intensity after surgery on the second knee seems to be closely associated with chronic post-TKA pain, with similar mechanisms underlying hyperalgesia or chronic pain. Magnesium sulphate is an effective analgesic adjuvant for postoperative pain. Its analgesic property seems to be associated with the regulation of calcium influx into the cells, or antagonism of N-methyl-D-aspartate (NMDA) receptors in the central nervous system. Additionally, magnesium is known to have an anti-inflammatory effect. Inflammatory state may accompany with pain via peripheral or central sensitization.

In this study, based on the hypothesis that magnesium can reduce postoperative pain and prevent increase of pain intensity, we examined the extent to which magnesium sulphate reduce postoperative pain for patients undergoing a second surgery of a staged bilateral TKA, one week after the first. The broader aim of this double-blinded randomized controlled study was to establish a therapeutic approach in reducing the increased pain intensity that often arises from this procedure.

Methods

The study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (Seongnam-si, South Korea, B-1411/275-008) and registered at the Clinical Research Information Service (CRIS, http://cris.nih.go.kr, KCT0001361). Written informed consent was obtained from all patients before participation. This study was conducted in Seoul National University Bundang Hospital between March and December 2015.

The 44 patients (age range: 50–80 yr) who participated in this study had ASA physical status I or II and were undergoing staged bilateral TKA under spinal anaesthesia. Preoperative exclusion criteria included the following factors: contraindication to spinal anaesthesia, including coagulopathy, pre-existing pain syndrome, history of stroke, chronic opioid use, allergy to study drugs, previous surgery on or trauma of the knee, BMI of >35 kg m$^{-2}$, cardiovascular disease, neuromuscular disease, calcium channel blocker medication, hypermagnesemia, bundle branch block, and the inability to comprehend VAS or to use patient-controlled analgesia (PCA) device. In our institution, the left knee is always operated on first in all patients undergoing a staged bilateral TKA.

The 44 patients were preoperatively randomized into two groups as follows: the magnesium group received magnesium sulphate (50 mg kg$^{-1}$) in 100 ml of isotonic saline over 15 min during induction of anaesthesia, followed by a continuous magnesium sulphate infusion (15 mg kg$^{-1}$ h$^{-1}$) for the duration of each operation. The control group received the same volume of isotonic saline, administered according to the same method as in the magnesium group. All solutions were prepared by an anaesthesia nurse who was not involved in the study. The syringe used in the infusion was labeled ‘study drug’ and had no identifying markers indicating group allocation. The anaesthetists who cared for the patients were blinded to the group allocation. This study was a block randomized, double-blinded, placebo-controlled, parallel-group trial with 2 equally sized groups. The randomization chart was generated with a web-based randomized system (http://www.randomization.com) that uses the Wichmann and Hill number generator, as modified by McLeod. The allocation ratio was 1:1.

All patients were pre-medicated with 0.03 mg midazolam kg$^{-1}$, administered i.v. in the reception area of the operating suite. Upon patient arrival in the operating room, standard monitoring (pulse oximetry, ECG, and non-invasive arterial pressure) was established. All patients underwent femoral nerve catheterization and spinal anaesthesia, performed by one experienced anaesthetist who was blinded to the study protocol.

For the ultrasound-guided continuous femoral nerve block (FNB), a high frequency linear probe (6–13 MHz, HFL38x, SonoSite, USA) was used. A local anaesthetic agent (3–4 ml of 1% lidocaine) was used to obtain skin and subcutaneous tissue infiltration before needle insertion. After obtaining the target structure, including fascia iliaca, iliohypogastric, and ilioinguinal nerves, an 18-gauge Tuohy needle was inserted below the fascia iliaca and approached to the femoral nerve using the in-plane technique. The correct needle tip placement was confirmed by observing the spread of 0.9% saline 2–3 ml below the fascia iliaca and anterior to the femoral nerve. A catheter was advanced 1–2 cm past the needle tip. A test dose of 5 ml of 2% lidocaine, mixed with 5 µg of epinephrine, was administered via the femoral nerve catheter, and an adequate spread of the bolus injection around the femoral nerve was observed. After 10–20 min, the loss of cold sensation to an alcohol swab in the sensory region of the ipsilateral femoral nerve and at the anterior thigh was confirmed.

As for lumbar subarachnoid block, patients were in the lateral position for the insertion of a 25-gauge Quincke needle at L3–L4 using the midline or para-median approach. After confirming the cerebrospinal fluid flow, 2.0–2.5 ml of 0.5% hyperbaric bupivacaine (Marcaine Spinal 0.5% Heavy, AstraZeneca, Södertälje, Sweden) was administered with 10–20 µg of fentanyl. Ringer’s lactate solution, administered at a rate of 5 ml kg$^{-1}$ h$^{-1}$, was used to maintain fluid volume during the operation.

The operation was conducted by the same experienced orthopaedic surgeon (blinded to the study protocol) using the same surgical technique and prosthesis type in all patients. All patients were rehabilitated according to the standard protocol of our institution. Walking with crutches or a walker was started 48 h postoperatively. In addition, active and passive range-of-motion exercises were begun 72 h postoperatively.

Our institutional multi-modal analgesia technique for the management of postoperative pain in TKA patients is as follows:
preemptive analgesic medication (pregabalin, celecoxib, acetaminophen, and dexamethasone) administered ~40 min before anaesthesia induction, preoperative continuous femoral nerve catheter placement, periaricular injection in the operative field, i.v. PCA, postoperative regular oral analgesics, and i.v. rescue analgesics. After prosthesis placement, a periaricular injection consisting of 300 mg of ropivacaine, 10 mg of morphine, 30 mg of ketorolac, 300 µg of 1:1000 epinephrine, and 750 mg of cefuroxime was infiltrated in divided doses into the sheath of the medial and lateral collateral ligaments and posterior capsule, synovium, quadriceps muscle, subcutaneous tissue, and joint capsule. At the end of the operation, all patients received continuous femoral nerve blockade consisting of 0.2% ropivacaine (5 ml h\(^{-1}\) for 50 h), i.v. PCA (regimen: 2000 µg of fentanyl for patients 60–70 yr of age and 1500 µg for patients >70 yr of age in 0.9% saline, total volume of 100 ml; no basal infusion, bolus 1 ml, lockout time of 10 min), and 0.3 mg of i.v. ramosetron to prevent postoperative nausea and vomiting. Continuous FNB and PCA were stopped at postoperative day three. Standard medications (650 mg of oral acetaminophen, 200 mg of celecoxib, and 75 mg of pregabalin) were supplied every 12 h after surgery; rescue analgesics (50 mg i.v. ketoprofen), and antiemetics (10 mg i.v. metoclopramide) were provided upon patient request.

After the sensory block level was confirmed, venous blood samples were obtained before and within 15 min after surgery to measure serum magnesium. The initial 5 ml of drawn blood was discarded; the remaining test blood sample was obtained immediately in serum separator tubes.

Baseline pain scores of both knees were assessed when the patient was at rest the day before first-stage surgery. Postoperative pain scores (VAS; 0=no pain, 100=the most severe pain imaginable, primary endpoint) at rest on the most recently operated knee at 24 and 48 h, the amounts of rescue analgesics at 24 and 48 h postoperatively (secondary endpoint), and cumulative amounts of i.v. PCA 48 h after surgery (secondary endpoint) were assessed by anaesthetists blinded to this study. Patients were instructed that the pain intensity must be reported separately for each knee at rest.

The pilot data (VAS score differences between the first and second operated knee at 24 h postoperatively) from 20 TKA patients were as follows: control group VAS score difference, 8.3 (4.4); magnesium group VAS score difference, 0.0 (8.9). Assuming this difference and aiming for a power of 80% and a risk of 0.05 for a type-1 error, 13 patients were required for each group. We selected 22 patients per group to anticipate a 40% dropout rate.

The data are expressed as mean (standard deviation), median (interquartile range) for non-normally distributed data, or number (percentage). All variables were tested for normality using the Shapiro-Wilk test. Statistical analyses were performed using Student’s t-test or a Mann-Whitney U-test, as appropriate, to compare the two groups. A paired t-test or Wilcoxon-signed rank sum test was used to compare within-group pre- and postoperative values.

Results

Of the 70 patients evaluated for eligibility, 44 were assigned to one of the two groups. The remaining 26 were excluded (24 met exclusion criteria and two refused to participate) (Fig. 1). The characteristics of the included patients are shown in Table 1. The baseline data from the first and second operations are provided in Table 2. The second TKA was performed one week after the first operation.

The VAS scores were significantly higher in the control group than in the magnesium group not only after the first TKA (P=0.001), but also after the second TKA (P<0.001) (Table 3). The amount of rescue analgesics (ketoprofen) used during the first 48 h after the second TKA was also significantly higher in the control group than in the magnesium group (P=0.001, Table 3). PCA consumption was significantly greater in the control group than in the magnesium group during the 48 h after the first (P=0.014) and second (P=0.001) surgeries (Table 3). However, the two groups did not significantly differ in the amount of rescue antiemetics (metoclopramide), either at 24 or at 48 h postoperatively (Table 3).

In the control group, the VAS scores were significantly higher for the second TKA than for the first one at 24 h (P=0.001) and 48 h (P=0.006) (Table 3). The amount of rescue analgesics (ketoprofen) used during the first 24 and 48 h post-surgery was also significantly higher during the second than the first TKA (P=0.011 and P=0.004, respectively, Table 3). Cumulative PCA consumption during the first 48 h postoperatively was significantly greater after the second than after the first TKA (P<0.001, Table 3). The amounts of rescue analgesics were also significantly higher for the second than the first operated knee at 24 and 48 h postoperatively (P=0.017 and P=0.001, respectively, Table 3). The amounts of rescue antiemetics (metoclopramide) were significantly greater in the first TKA at 48 h postoperatively than in the second TKA at any time (P=0.042, Table 3).

In the magnesium group, however, the VAS scores did not significantly differ between the first and the second operation at 24 h (P=0.480) and 48 h (P=0.378) (Table 3). The amount of rescue analgesics at 48 h postoperatively also did not differ between the first and second TKAs (P=0.715, Table 3). However, the cumulative amounts of PCA during the first 48 h postoperatively and of rescue analgesics (ketoprofen) during the first 24 h were significantly higher in the second than in the first operation (P<0.004 and P=0.021, respectively; Table 3). The amount of rescue antiemetics (metoclopramide) was significantly greater in the first TKA at 24 h postoperatively than in the second TKA at any time (P=0.005, Table 3).

Serum magnesium concentrations in the two groups are shown in Table 4. In the control group, magnesium concentrations decreased significantly after the first TKA (P=0.014), whereas in the magnesium group they increased significantly after the first and the second TKAs (P<0.001 and P<0.001, respectively). Postoperative serum magnesium concentrations were significantly different between the two groups after the first and second surgeries (P<0.001 and P=0.001, respectively).

Secondary block failures of femoral nerve catheterization were not observed. Also, there were no complications, such as cardiac arrhythmia or excessive sedation (observer’s assessment of alertness/sedation score >4), during any of the procedures.

Discussion

The results of this study confirmed our previous findings: postoperative pain scores and analgesic consumption of the second TKA are higher than that of the first TKA. However, the present study also demonstrated that magnesium effectively attenuates not only postoperative pain, but also increased pain intensity without serious adverse effects.

The mechanism of anti-nociceptive effect of magnesium is still unclear. One of the most suggestive theories is that the anti-nociceptive effect of magnesium stems from its inhibition...
of the NMDA receptor.\textsuperscript{9,18} The analgesic adjuvant effect of magnesium after surgery has been described in several reports.\textsuperscript{9,17,19} In our study, patients who received magnesium sulphate during the operation showed to have less postoperative pain during both the first and second surgeries compared with patients who did not. These findings are in line with previous reports on the analgesia-potentiating effect of magnesium.\textsuperscript{9,20}

The mechanism behind magnesium’s reduction effect of the increased pain intensity is also unclear. There has been a previous report regarding the effect of magnesium on opioid-related hyperalgesia\textsuperscript{21}, however, to the best of our knowledge, its attenuating capacity with respect to increased pain intensity, induced by a remote surgical site, has never been clinically studied. In patients undergoing staged bilateral TKA, similar nociceptive stimuli would be expected in both operated knees, given the identical operation protocol and pathology (degenerative arthritis), and similar preoperative pain levels in the two knees. Nevertheless, in the control group, postoperative pain was more severe in the second operated knee than in the first operated knee, whereas the magnesium group showed a reduced difference in pain intensity between the two operated knees. Although we did not assess hyperalgesia, this result suggests that magnesium may prevent tertiary hyperalgesia. Further study is needed to clarify the mechanism of the effect of magnesium on the attention of increased pain intensity.

Our results have a couple of important clinical implications. First, magnesium could play an important role in the management of postoperative pain, not only after a single operation but also after multiple surgeries at short intervals, in which the risk of enhanced pain sensitivity may be increased. For example, patients who suffer from multiple traumas need effective postoperative pain control throughout their sequential surgeries. In this setting, the use of magnesium sulphate may contribute substantially to controlling the increased pain caused by multiple surgical injuries. Second, our results can be applied to the prevention

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**Table 1 Characteristics of Patients.** Data are expressed as mean (SD or range), number of the patients (n)

<table>
<thead>
<tr>
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<th>Control group (n=22)</th>
<th>Magnesium group (n=22)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>72.3 (60.0–87.0)</td>
<td>74.3 (65.0–84.0)</td>
<td>0.278</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>0/22</td>
<td>1/21</td>
<td>1.000</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60.9 (11.5)</td>
<td>63.2 (10.0)</td>
<td>0.491</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>149.4 (6.1)</td>
<td>152.3 (7.3)</td>
<td>0.157</td>
</tr>
<tr>
<td>BMI (kg cm(^{-2}))</td>
<td>27.2 (3.7)</td>
<td>27.2 (3.7)</td>
<td>0.971</td>
</tr>
<tr>
<td>ASA physical status score (I/II)</td>
<td>3/19</td>
<td>0/22</td>
<td>0.233</td>
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</table>
of chronic pain. Because chronic post-TKA pain has a reported prevalence of up to 47% and these patients have increased requirements for analgesic drugs, there is an urgent need to control acute postoperative pain, to avoid the development of chronic pain.\textsuperscript{7,22}–\textsuperscript{23} The administration of magnesium to effectively control post-TKA pain may address this need.

Our study also had a few limitations. First, the study population consisted mostly of elderly females. Guo and colleagues\textsuperscript{29} reported that age played no significant role in postoperative analgesia in adults achieved with magnesium. On the other hand, recent research demonstrates sex differences with respect to pain perception.\textsuperscript{24,25} Although the exact mechanism is still unclear and remains controversial, females have shown lower pain thresholds and tolerance to noxious stimuli in experimental studies than males\textsuperscript{26,27} with different response and efficacy to analgesic treatment.\textsuperscript{25} To extend our findings to the general

### Table 2 Baseline data of the first and the second operations. Data are expressed as mean (sn), median (interquartile range). TKA, total knee arthroplasty; VAS, visual analogue scale. P1, a comparison of the first and the second TKA values within the group using paired t-test; P2, a comparison of the first TKA values between the two groups using Student’s t-test; P3, a comparison of the second TKA values between the two groups using Student’s t-test. P1 < 0.05 was considered to indicate statistical significance; P2 and P3 < 0.025 were considered to indicate statistical significance

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Magnesium group</th>
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<tbody>
<tr>
<td></td>
<td>First TKA</td>
<td>Second TKA</td>
</tr>
<tr>
<td>Surgery time (min)</td>
<td>102 (12)</td>
<td>101 (12)</td>
</tr>
<tr>
<td>Anaesthesia time (min)</td>
<td>142 (14)</td>
<td>142 (17)</td>
</tr>
<tr>
<td>Dose of bupivacaine (mg)</td>
<td>11.5 (1.2)</td>
<td>11.5 (1.3)</td>
</tr>
<tr>
<td>Intrathecal fentanyl (µg)</td>
<td>17 (4)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Sensory block height 30 min after injection</td>
<td>T7 (T6–T9)</td>
<td>T7 (T6–T9)</td>
</tr>
<tr>
<td>Tourniquet time (min)</td>
<td>82 (19)</td>
<td>86 (13)</td>
</tr>
<tr>
<td>Tourniquet pressure (mm Hg)</td>
<td>282 (15)</td>
<td>275 (14)</td>
</tr>
<tr>
<td>Intraoperative blood loss (ml)</td>
<td>75 (37)</td>
<td>79 (34)</td>
</tr>
<tr>
<td>Postoperative blood drainage (ml)</td>
<td>45 (104)</td>
<td>25 (49)</td>
</tr>
<tr>
<td>Baseline VAS score</td>
<td>35 (11)</td>
<td>34 (11)</td>
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</table>

### Table 3 Postoperative VAS scores, rescue analgesics, antiemetics, and PCA consumption. Data are expressed as mean (sn). VAS, visual analogue scale; PCA, patient-controlled analgesia; TKA, total knee arthroplasty. P1, a comparison of the first and the second TKA values within the group using paired t-test; P2, a comparison of the first TKA values between the two groups using Student’s t-test; P3, a comparison of the second TKA values between the two groups using Student’s t-test. P1 < 0.05 was considered to indicate statistical significance; P2 and P3 < 0.025 were considered to indicate statistical significance

<table>
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<th>Control group</th>
<th>Magnesium group</th>
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<tbody>
<tr>
<td></td>
<td>First TKA</td>
<td>Second TKA</td>
</tr>
<tr>
<td>Postoperative 24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS at rest</td>
<td>29 (11)</td>
<td>44 (17)</td>
</tr>
<tr>
<td>Ketoprofen (mg)</td>
<td>7 (23)</td>
<td>25 (33)</td>
</tr>
<tr>
<td>Metoclopramide (mg)</td>
<td>3 (5)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Postoperative 48 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS at rest</td>
<td>33 (8)</td>
<td>43 (14)</td>
</tr>
<tr>
<td>Ketoprofen (mg)</td>
<td>25 (30)</td>
<td>80 (53)</td>
</tr>
<tr>
<td>Metoclopramide (mg)</td>
<td>2 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PCA consumption (fentanyl, µg)</td>
<td>525 (330)</td>
<td>870 (375)</td>
</tr>
</tbody>
</table>

### Table 4 The changes in serum magnesium concentration. Data are expressed as mean (sn). The reference range for magnesium is 0.62–1.03 mM. TKA, total knee arthroplasty. P1, a comparison of the first and the second TKA values within the group using paired t-test; P2, a comparison of the first TKA values between the two groups using Student’s t-test; P3, a comparison of the second TKA values between the two groups using Student’s t-test. P1 < 0.05 was considered to indicate statistical significance; P2 and P3 < 0.025 were considered to indicate statistical significance

<table>
<thead>
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<th>Control group</th>
<th>Magnesium group</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Preoperative</td>
<td>Postoperative</td>
</tr>
<tr>
<td>Magnesium (mM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First TKA</td>
<td>0.84 (0.08)</td>
<td>0.82 (0.07)</td>
</tr>
<tr>
<td>Second TKA</td>
<td>0.82 (0.07)</td>
<td>0.82 (0.06)</td>
</tr>
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population will require further studies aimed at clarifying the roles of age and sex on the effect of magnesium in pain control. Second, clinical pain in our patients was evaluated using the VAS pain score, instead of using quantitative sensory testing (QST). The latter is a well-validated experimental tool for evaluating and quantifying hyperalgesia with a stimulus-response gradient; however, it has been proved valuable in assessing primary and secondary hyperalgesia. As one of the aims of the present study was to identify the change in patients’ subjective perception of pain at a site remote from the initially damaged area, we used the clinical pain assessment (VAS score) method to evaluate increased pain intensity. Finally, we only assessed the postoperative pain at rest because of the limitation of mobilization. If we also evaluated the postoperative pain during movement, which could be regarded as a stimulus, this study could have explained with greater clarity the pain reducing effect of magnesium after the second TKA, and its preventive effect of “tertiary hyperalgesia.”

To the best of our knowledge, this is the first clinical report of the effect of magnesium sulphate on increased pain after sequential surgery. The benefits of magnesium demonstrated here include postoperative pain reduction and attenuation of increased pain intensity. Our results suggest that magnesium sulphate can greatly aid in managing the aggravation of surgical pain caused by multiple operations within a short time interval. Thus, magnesium sulphate should be considered as an adjuvant drug in multimodal analgesia protocol for patients undergoing sequential surgeries.

Authors’ contributions
Study design/planning: H.J.S.
Study conduct: E.Y.K., T.G.K.
Data analysis: H.S.N.
Writing paper: H.J.S.
Revising paper: all authors

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Declaration of interest
None declared.

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