No Effect of Oral Mecobalamin on Skin Numbness at 3 Months After Total Knee Arthroplasty
A Randomized, Double-Blinded, Placebo-Controlled Superiority Trial

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Background: An area of skin numbness (AON) around an incision commonly occurs following total knee arthroplasty (TKA). Mecobalamin has been shown to facilitate peripheral nerve recovery in various conditions; accordingly, the present study aimed to investigate the ameliorative effect of mecobalamin on AON following TKA, as compared with a placebo.

Methods: This superiority study was a double-blinded, randomized controlled trial. All patients undergoing primary TKA were assessed for eligibility. Included patients were randomized to receive either mecobalamin (500 μg, twice daily) or placebo (corn starch powder; 500 μg, twice daily) for 3 months. The primary outcome was the change in the AON around the surgical site from 2 weeks to 3 months after TKA. Secondary outcomes included the rates of different adverse events, functional outcomes, and visual analogue scale patient satisfaction scores.

Results: A total of 154 patients were enrolled, with 77 patients each in the mecobalamin and placebo groups. The mean AON among patients in the mecobalamin group was 61.6 cm² at baseline (2 weeks) and 29.1 cm² at 3 months, compared with 55.9 cm² and 33.2 cm² among patients in the placebo group, respectively. Intention-to-treat analysis showed no significant difference in the change in AON around the surgical site between the 2 groups (mean difference, 7.5; 95% confidence interval, −4.2 to 25.3; p = 0.159). The rates of adverse events, functional outcomes, and visual analogue scale patient satisfaction score were also not significantly different between groups.

Conclusions: Mecobalamin did not demonstrate superiority over a placebo in reducing the AON around the surgical site at 3 months after primary TKA.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Although primary total knee arthroplasty (TKA) usually has a successful outcome, 11% to 19% of patients are still dissatisfied after surgery. There are many reasons for patient dissatisfaction following primary TKA, with persistent skin numbness being one of the most frequently reported. An area of skin numbness (AON) around the surgical site is common but unavoidable complication following primary TKA because, once the skin incision around the knee is made, an infrapatellar branch of the saphenous nerve (IPBSN) is completely dissected (i.e., neurotmesis). The reported incidence of numbness following TKA ranges from 37% to 100%. Tanavalee et al. reported the AON at 2 weeks after TKA to be as large as 51.7 cm², which gradually reduced to 2.1 cm² by 1 year postoperatively. Additional studies have reported the maximum AON to be approximately 191 cm² to 219 cm².

After IPBSN neurotmesis, the proximal stump usually regenerates, and the distal stump demonstrates Wallerian degeneration. Schwann cells, endoneurium, and new myelin sheath grow into the cut area and join the 2 ends after direct nerve suturing is performed. A newly generated axon sprouts and grows to reestablish the connection to the innervated cutaneous area. Previous experimental studies reported that various organic and inorganic compounds, including mecobalamin, could facilitate the natural host reparative process and promote targeted axonal outgrowth to maintain the efficacy of peripheral nerve reinnervation. Mecobalamin, a coenzyme form of vitamin B₁₂, is required during the reinnervation process to enhance the repair of the myelin sheath and is critical to the methylation of DNA and RNA. Previous studies
found that mecobalamin could facilitate sciatic nerve recovery in murine models\textsuperscript{18-21}, and that it can be utilized to treat diabetic peripheral neuropathy, peripheral neuropathy, or peripheral neuropathic pain in humans\textsuperscript{15,16,22}. Therefore, some surgeons prescribe postoperative mecobalamin as a routine supplement for patients who undergo primary TKA. However, evidence to support the use of mecobalamin to reduce the AON following primary TKA is lacking.

Accordingly, the aim of this study was to evaluate whether short-term mecobalamin supplementation could enhance nerve recovery by reducing the AON at 3 months after primary TKA, as compared with a placebo. The secondary objectives were to evaluate the short-term safety of mecobalamin and to assess patient-reported outcomes of paresthesia, cutaneous pain, satisfaction, and knee function.

**Materials and Methods**

This randomized, double-blinded, placebo-controlled superiority trial was conducted at the Faculty of Medicine Siriraj Hospital, Mahidol University. This study was prospectively registered at the clinicaltrials.in.th website (reg. no. TCTR20180722002). We prospectively assessed patients scheduled for primary TKA from December 2018 to December 2020. Patients with any of the following conditions were excluded: history of receiving mecobalamin or vitamin B complex prior to TKA, diagnosis of spinal stenosis with numbness of the lower extremities, diabetes with substantial sensory impairment or other polyneuropathy, peripheral vascular disorders, smoking within the past 12 months, systemic corticosteroid use within 30 days before surgery (excluding intranasal and topical corticosteroids)\textsuperscript{23-26}, prior open knee surgery or radiation around the knee, chemotherapy within the past 6 months, and/or having an occupation that required the handling of mercuric compounds.

**Randomization and Blinding**

Patients who met the inclusion criteria were registered and then were randomized (in a 1:1 fashion) into either the mecobalamin group or the placebo group. The allocation sequence was generated by a third party to achieve a sequence with block sizes of 4. A pharmacist prepared serially labeled sealed containers of the study drugs. The containers had an identical appearance with different numerical codes, and both the placebo and mecobalamin capsules appeared the same regarding their size, shape, weight, smell, and color. Because the mecobalamin dosage that was reported to effectively promote neuron regeneration varied from 10 to 1,500 µg per day\textsuperscript{27,28}, we utilized a dosage of 1,000 µg per day to facilitate better compliance while still falling within the therapeutic range\textsuperscript{27-29}. As such, patients in the mecobalamin group received Methycobal 500 µg (Bushu Pharmaceuticals Ltd., Eisai Marketing Co., Ltd./DKSH, Ltd.) in a regimen of 1 oral capsule twice daily for 3 months, whereas patients in the placebo group received 500 µg of corn starch powder in the same regimen. The patients, surgeons, and outcome assessors were all blinded to the trial medication.

**Operative Procedure and Postoperative Care**

All operations were performed by 2 experienced surgeons via a medial parapatellar approach, with the straight midline skin incision running from approximately 2 cm proximal to the upper pole of the patella toward the medial border of the tibial tubercle. The prostheses utilized in this study were either cemented cruciate-retaining or posterior-stabilized TKA designs, according to the discretion of the surgeon. The patella was selectively resurfaced on the basis of intraoperative findings\textsuperscript{30}. When the operation was completed, the knee capsule was closed with Stratafix (polydioxanone, violet monofilament synthetic absorbable; Ethicon, Johnson & Johnson Medical

Fig. 1

The area of skin numbness, which was the primary outcome, as determined by pinprick sensory evaluation through light translucent paper performed by a blinded assessor.
Devices). A number 2-0 polyglactin 910 suture with interrupted buried knots was utilized to take deep and superficial subcutaneous bites for subcutaneous approximation. The IPBSN was not directly repaired. The skin was then closed with subcuticular sutures. Following the operation, all patients underwent a standard 3 to 6-day in-hospital care protocol. All patients were mobilized out of bed and encouraged to start walking as tolerated on the first postoperative day. Deep vein thrombosis prophylaxis was performed with use of mechanical prophylaxis and, if indicated, medical prophylaxis. Postoperative pain was controlled with a combination of oral analgesics and intravenous morphine. The goal was to maintain a pain score of $\leq 3$ out of 10, as measured on the Numerical Pain Rating Scale. All patients were discharged to home without any prescription for drugs for neuropathic pain, such as amitriptyline, duloxetine, and pregabalin.

Assessment of Outcomes
Demographic and clinical characteristics were recorded at the time of enrollment. The primary outcome was the change in AON between 2 weeks and 3 months postoperatively. The secondary outcomes were adverse events related to the intervention during the trial period; symptoms of nerve injury, such as tingling or cutaneous pain, as assessed at the 3-month postoperative follow-up; postoperative length of stay; appearance of the skin incision site; and a modified knee score. Patient satisfaction, as measured with use of the visual analogue scale (VAS), was also assessed at 3 months postoperatively.

AON
The AON was evaluated according to the method proposed by Sundaram et al. and Borley et al. A sheet of translucent grid paper, with 1 cm$^2$ per square, was applied to the operative knee (Fig. 1). With their eyes closed, patients were asked to indicate the area that they felt to be numb on the translucent paper. This patient-reported AON was recorded as a value in cm$^2$. The change in the AON was calculated by subtracting the AON at 3 months postoperatively from the AON at 2 weeks postoperatively. A positive value indicated a reduction in the AON and vice versa.

Modified Knee Score
The modified knee scoring system was adapted from the original Knee Society Clinical Rating System described by Insall et al. in 1989. The modified scoring system consists of 3 sections, including pain, range of motion, and stability. The overall score equals the sum of the scores in these 3 categories minus the scores for extension lag, flexion contracture, malalignment, and pain at rest. The modified knee score has a possible total of 100 points, with higher scores indicating greater knee function.

VAS Patient Satisfaction
VAS patient satisfaction was assessed by asking patients to indicate their satisfaction on a 100-mm horizontal line. The starting point of the line (i.e., 0 mm) represented the lowest level of satisfaction and the end of the line (i.e., 100 mm) represented the highest level of satisfaction. The length in millimeters was converted to an identical number of points; thus, VAS patient satisfaction scores ranged from 0 to 100.

Data Analysis and Sample Size Calculation
An a priori power analysis was performed to calculate the sample size for a superiority trial. According to the results of a previous study that reported a mean AON of 29.6 $\pm$ 33.8 cm$^2$ at 3 months postoperatively, we assumed that if mecobalamin could enhance nerve recovery and reduce AON by approximately 50% (to 14.8 $\pm$ 16.9 cm$^2$ at 3 months), then a sample of 70 patients per group would be required to provide 80% statistical power (alpha: 0.05; beta: 0.20) with use of a 2-tailed, unpaired t test. Assuming a loss to follow-up of 10%, 77 patients per group were needed for the present study.

Baseline clinical characteristics and the study results were compared between groups with use of the independent t test for continuous variables and the chi-square test or Fisher exact test for categorical variables, as appropriate. The Kolmogorov-Smirnov test was utilized to assess the distribution of data. Categorical were presented as the count and percentage, and continuous data were presented as the mean $\pm$ standard deviation (SD). An intention-to-treat analysis was performed as the primary analysis. We also performed a sensitivity analysis in...
which the primary end point, the change in the AON, was expressed as a percentage of the body surface area (BSA), calculated as follows: change in AON% = (change in AON/BSA) × 100. BSA was calculated with use of the following formula: BSA (cm²) = 94.9 × (weight [kg] × 0.441 × (height [cm] × 0.655)³⁵.

All analyses were performed with use of PASW Statistics for Windows (version 18.0; IBM). Significance was set at 0.05.

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This study was funded by the Siriraj Research Fund of the Faculty of Medicine, Siriraj Hospital, Mahidol University (grant number R016231002). The funding source had no influence on the interpretation of data, the final conclusions drawn, or the decision to publish.

Results
A total of 154 patients were included in the study, with 77 randomly allocated to the mecobalamin group and 77 to the placebo group. Of these, 6 patients were lost to follow-up and 4 had early discontinuation of the intervention; thus, a total of 144 (72 in each group) completed the trial protocol (Fig. 2). Patient demographics and baseline clinical characteristics were not significantly different between groups (Table I). Patient perioperative data were also not significantly different between groups (Table II).

| TABLE I Patient Demographics and Clinical Characteristics for the Placebo and Mecobalamin Groups* |
|---------------------------------|---------------------------------|----------------|
| Characteristics | Placebo Group (N = 77) | Mecobalamin Group (N = 77) | P Value |
| Age (yr) | 71.4 ± 7.0 | 69.7 ± 7.3 | 0.138 |
| Female | 65 (84.4%) | 64 (83.1%) | 0.827 |
| Operative side | | | 0.497 |
| Left side | 35 (45.5%) | 28 (36.4%) | |
| Right side | 36 (46.8%) | 43 (55.8%) | |
| Bilateral | 6 (7.8%) | 6 (7.8%) | |
| Body mass index (kg/m²) | 27.1 ± 3.7 | 27.8 ± 5.3 | 0.361 |
| Body surface area (m²) | 2.8 ± 0.5 | 2.9 ± 0.6 | 0.441 |
| Hip-knee axis (°) | 172.0 ± 6.5 | 174.0 ± 5.2 | 0.216 |
| Charlson Comorbidity Index | | | 0.221 |
| 0-1 | 2 (2.6%) | 4 (5.2%) | |
| 2-3 | 49 (63.6%) | 56 (72.7%) | |
| >3 | 26 (33.8%) | 17 (22.1%) | |
| Comorbidity | | | |
| No comorbidity | 10 (13.0%) | 13 (16.9%) | 0.498 |
| Diabetes mellitus | 18 (23.4%) | 19 (24.7%) | 0.815 |
| Chronic kidney disease | 2 (2.6%) | 2 (2.6%) | 0.989 |
| Others | 47 (61.0%) | 43 (55.8%) | 0.513 |
| Preoperative arc of motion (°) | 104.5 ± 15.8 | 105.0 ± 11.2 | 0.484 |
| Preoperative modified knee score | 68.0 ± 8.5 | 68.1 ± 8.6 | 0.694 |

*Values are given as the mean ± SD or as the count with the percentage in parentheses.

| TABLE II Perioperative Data for the Placebo and Mecobalamin Groups* |
|-----------------|-----------------|----------------|
| Perioperative Data | Placebo Group (N = 77) | Mecobalamin Group (N = 77) | P Value |
| Straight midline incision | 77 (100%) | 77 (100%) | 1.000 |
| Incision length (cm) | 12.6 ± 1.3 | 12.4 ± 1.2 | 0.237 |
| Operative time (min) | 74.4 ± 23.1 | 77.5 ± 25.9 | 0.427 |
| Estimated total blood loss (mL) | 30.0 ± 54.4 | 39.7 ± 67.7 | 0.335 |
| Postoperative length of stay (days) | 5.0 ± 1.2 | 5.5 ± 3.3 | 0.163 |

*Values are given as the mean ± SD or as the count with the percentage in parentheses.
The mean AON decreased from 61.6 cm² at 2 weeks postoperatively to 29.1 cm² at 3 months postoperatively in the mecobalamin group (52.8% decrease; p < 0.001) and from 55.9 to 33.2 cm² in the placebo group (40.6% decrease; p < 0.001) (Fig. 3). The mean difference in the change in the AON at 3 months between groups was 7.5 cm² in favor of the mecobalamin group (Table III). There were no significant differences between groups in the postoperative AON and the change in the AON (p = 0.159 and p = 0.441, respectively). The mean difference in the change in the AON% between groups was 23.0% in favor of the mecobalamin group. Similar to the change in the AON, the change in the AON% was not significantly different between groups.

For the secondary end points, the mean modified knee score was 92.1 in the mecobalamin group and 91.9 in the control group at 3 months postoperatively (p = 0.854). The mean VAS patient satisfaction score was 89.3 in the mecobalamin group and 88.0 in the placebo group (p = 0.295). There were no significant differences in the incidences of numbness, tingling, cutaneous pain, or other adverse events between groups (Table IV).

**Discussion**

In primary TKA, complete dissection of the IPBSN (i.e., neurotmesis) is unavoidable once a skin incision is made. This procedure causes numbness around the surgical incision that can contribute to postoperative dissatisfaction in some patients. Mecobalamin has been hypothesized to effectuate a reduction in the AON around the surgical site by accelerating IPBSN regeneration. Some orthopaedic surgeons routinely prescribe mecobalamin as a supplement after primary TKA under this assumption. To our knowledge, no randomized controlled trial has evaluated the effect of mecobalamin on IPBSN neurotmesis in primary TKA patients.

In this randomized, double-blinded, placebo-controlled superiority trial, we found that mecobalamin was not significantly superior to a placebo in reducing the AON around the surgical site at 3 months after primary TKA. These results are discordant with previous murine in vitro and in vivo studies, which found that mecobalamin could enhance axon and neurite growth and improve functional sensory recovery following peripheral nerve injury. Most recently, Sayanagi et al. reported that a mecobalamin-impregnated sheet combined with an artificial nerve conduit applied to the nerve-injury site could increase peripheral sensory nerve function and myelinated axon area. The discordance between the results of previously published studies and those of the present study may be explained by differences in the study methods and drug regimens. The aforementioned murine models studied mecobalamin at ultra-high or high doses delivered by parenteral routes or localized release at the injury site, which could achieve high serum or localized concentrations that might not have been achieved in the present study. Furthermore, those murine models included patients with a crush injury both with and without repair of the cut nerve. In contrast, we did not perform nerve repair in the present study. It is highly improbable that the IPBSN finds its distal branch after TKA and subcutaneous suture.

Moreover, we found a comparable incidence of paresthesia and cutaneous pain between the mecobalamin and placebo groups. Although we did not calculate the necessary sample size for the secondary outcomes, mecobalamin seems to provide no enhancing effects in most of these parameters.

**TABLE III Analysis of the Primary Outcome, the Change in AON and AON%**

|                      | Mecobalamin Group | Placebo Group | Mean Difference (95% CI)† | P Value |
|----------------------|-------------------|---------------|---------------------------|---------|
| Primary analysis: change in AON (cm²) | 33.0 ± 49.1       | 22.4 ± 43.6   | 7.5 (−4.2, 25.3)          | 0.159   |
| Sensitivity analysis: change in AON% x 10⁶ (%) | 117.0 ± 177.0     | 94.0 ± 194.2  | 23.0 (−36.0, 82.9)        | 0.441   |

*Values are given as the mean ± SD unless otherwise indicated. CI = confidence interval. †According to intention-to-treat analysis for all 77 patients in each group; multiple imputation was used to handle missing data. The mean difference column represents the difference in change from baseline (2 weeks) to 3 months postoperatively between groups, with a positive value indicating greater change in the mecobalamin group.
Nevertheless, the lower prevalence of numbness in the mecobalamin group at 3 months had a trend toward significance, although it was unclear whether this represented a random error or a true effect that might have been significant had the follow-up period been longer.

Interestingly, VAS patient satisfaction and modified knee scores were not significantly different between cohorts. This finding raised the question of whether numbness following primary TKA actually affects patient satisfaction and quality of life. A U.S. study found that numbness was not associated with patient satisfaction, whereas a British study found an association between numbness and difficulty kneeling and between difficulty kneeling and reduced patient satisfaction. In Asia, certain characteristics may lead to different satisfaction results because lifestyles in some Asian countries involve frequent use of high-flexion positions, such as kneeling or sitting on the floor. A study of South Korean women undergoing TKA found that patients rated such high-flexion activities to be important, and difficulty in kneeling was associated with substantial dissatisfaction. In addition, the lower prevalence of numbness in the mecobalamin group at 3 months had a trend toward significance, although it was unclear whether this represented a random error or a true effect that might have been significant had the follow-up period been longer.

In conclusion, mecobalamin supplementation did not result in a significantly different improvement in the AON around the surgical site at 3 months after primary TKA, as compared with a placebo. In addition, we found no significant superiority for mecobalamin with regard to functional outcomes and patient satisfaction. The results of the present study suggest no notable benefit to the use of mecobalamin for the reduction of skin numbness following primary TKA.

### Notes
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### TABLE IV Comparison of Adverse Events Between Groups at Baseline (2 Weeks) and 3 Months Postoperatively*

| Events                          | Placebo Group (N = 77) | Mecobalamin Group (N = 77) | P Value | Placebo Group (N = 72) | Mecobalamin Group (N = 72) | P Value |
|--------------------------------|------------------------|----------------------------|---------|------------------------|----------------------------|---------|
| Paresthesia and cutaneous pain |                        |                            |         |                        |                            |         |
| Numbness                       | 71 (92.2%)             | 71 (92.2%)                 | 1.000   | 54 (75.0%)             | 44 (61.1%)                 | 0.074   |
| Tingling                       | 54 (70.1%)             | 56 (72.7%)                 | 0.721   | 21 (29.2%)             | 19 (26.4%)                 | 0.710   |
| Cutaneous pain                 | 33 (42.9%)             | 36 (46.8%)                 | 0.627   | 11 (15.3%)             | 9 (12.5%)                  | 0.630   |
| Other adverse events           | 2 (2.6%)               | 1 (1.3%)                   | 1.000   | 0                      | 5 (6.9%)                   | 0.058   |
| Nausea                         | 2 (2.6%)               | 0 (0.0%)                   |         | 0 (0.0%)               | 1 (1.4%)                   |         |
| Anorexia                       | 0 (0.0%)               | 1 (1.3%)                   |         | 0 (0.0%)               | 1 (1.4%)                   |         |
| Skin rash                       | 0 (0.0%)               | 0 (0.0%)                   |         | 0 (0.0%)               | 1 (1.4%)                   |         |
| Vomiting                       | 0 (0.0%)               | 0 (0.0%)                   |         | 0 (0.0%)               | 1 (1.4%)                   |         |
| Diarrhea                       | 0 (0.0%)               | 0 (0.0%)                   |         | 0 (0.0%)               | 1 (1.4%)                   |         |

*Values are given as the count with the percentage in parentheses.
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