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Analgesic Effect of Pre-Emptive Gabapentin on Knee Surgery: A Systematic Review and Meta-Analysis

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We aimed to evaluate the effectiveness of preemptive oral gabapentin on postoperative analgesia after knee surgery. Gabapentin is widely known to reduce postoperative pain scores and opioid requirements following a variety of surgeries. We searched MEDLINE (January 1, 1976 to April 30, 2014), EMBASE (January 1, 1985 to April 30, 2014), the Cochrane Library (January 1, 1987 to April 30, 2014), and KoreaMed (June 1, 1958 to April 30, 2014). A total of 225 patients in 4 studies were included in the study. The overall pooled results from meta-analysis demonstrated that compared with placebo, pre-emptive analgesia could significantly reduce the postoperative pain score [mean difference (MD) −6.29; 95% confidence interval (CI) −10.17 to −2.42; $P = 0.001$; random-effect model]. The subgroup analyses found that gabapentin significantly reduced the postoperative pain score in patients who underwent general anesthesia (MD, −17.82; 95% CI, −21.82 to −13.81; $P = 0.47$; fixed-effect model). The subgroup analyses could not clarify the effectiveness of gabapentin on reducing postoperative pain in patients who underwent regional anesthesia (MD, 2.43; 95% CI, −1.14 to 6.00; $P = 0.78$; fixed-effect model). Pre-emptive gabapentin reduced early postoperative pain scores. However, it was unclear whether gabapentin reduces postoperative pain score in the setting of regional anesthesia or multimodal analgesic regimen.

Key words: Gabapentin – Knee – Analgesia

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Gabapentin is an anticonvulsant drug that is widely used for treatment of neuropathic pain, diabetic neuropathy, postherpetic neuralgia, and reflex sympathetic dystrophy.[1] Also, gabapentin has antihyperalgesic and anxiolytic properties.[2] The antinociceptive effects of gabapentin involve central sensitization.[1] Several studies have shown the role of preoperative gabapentin on decreases in postoperative pain scores and opioid requirements following a variety of surgeries: breast surgery, abdominal hysterectomy, spinal surgery, and ear-nose-throat surgery.[3–7]

Postoperative pain in knee surgery shows high pain scores that involve various mechanisms, involving peripheral mechanoreceptor stimulation, inflammatory, and neurogenic pain pathways.[8] In particular, central neuronal sensitization contributes to postoperative pain hypersensitivity.[9] Severe postoperative pain may lead to negative effects on the pulmonary, cardiovascular system, and movement limitation. Therefore, multimodal pain management includes opioid, nonopioid analgesics, as well as regional anesthetic techniques.[10]

Even though numerous studies have reported that preoperative administration of gabapentin decreases postoperative pain scores and opioid requirements, the findings are variable and the reported outcomes from several studies are conflicting.[3–7,11,12] Also, there is no systematic review of the effectiveness of gabapentin on knee surgery. Therefore, we aimed to determine the effectiveness of analgesic effect of pre-emptive gabapentin on knee surgery by performing a systematic review and meta-analysis.

Materials and Methods

The present systematic review was conducted in accordance with the PRISMA guidelines.[13]

Systematic search

We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) that investigated the analgesic effectiveness of pre-emptive gabapentin on knee surgery. We searched MEDLINE (January 1, 1976 to April 30, 2014), EMBASE (January 1, 1985 to April 30, 2014), the Cochrane Library (January 1, 1987 to April 30, 2014), and KoreaMed (June 1, 1958 to April 30, 2014). We put no restrictions on language or year of publication in our search. Search strategies were adapted for other databases based on the MEDLINE strategy. After the initial electronic search, we manually searched further relevant articles and the bibliographies from identified studies. The search strategy (Medical Subject Headings), which included a combination of free text, was described in the Appendix.

Study selection

The inclusion of all studies was independently decided by 2 authors BSR and AEJ based on the selection criteria. We scanned the titles and abstracts of the reports identified via the search strategies described previously. If a report was determined eligible from the title or abstract, the full paper was retrieved. Potentially relevant studies chosen by at least 1 author were retrieved, and full-text versions were evaluated. Articles that met the inclusion criteria were assessed separately by 2 authors (BSR and AEJ), and any discrepancies were resolved through discussion. If no agreement could be reached, a third investigator (KHJ) was involved to provide a resolution.

Inclusion and exclusion criteria

Inclusion and exclusion criteria were determined before the systematic search. Study selection was made through 2 levels of screening: At the first level, we screened titles and abstracts of identified studies. At the second level, we screened the full text. Studies were included in our meta-analysis based on the following criteria: (1) randomized double blinded clinical trials; (2) the intervention was considered preoperative oral gabapentin treatment; and (3) the surgery was limited to knee surgery. Data from abstracts, posters, case reports, comments, or letters to the editor, reviews, and animal studies were excluded.

Study outcomes

The primary endpoints were postoperative pain VAS during postoperative 1 day. In all studies, pain was measured with visual analogue scale (VAS). Total morphine consumption during postoperative 1 day was also assessed. The adverse effects of gabapentin such as nausea and vomiting were secondary outcomes in the systematic review.

Subgroup analysis was performed by postoperative period 1 hour, 2 hours, 4 hours, 12 hours, 24 hours, 36 hours, 48 hours, and 72 hours in pain VAS. Also, subgroup analysis was performed in mor-

phine consumption by postoperative period 12 hours, 24 hours, 36 hours, 48 hours, and 72 hours. To rule out the effect of anesthesia, subgroup analysis was performed based on general or regional anesthesia.

Validity scoring

Two reviewers (KKW and CHR) independently assessed the methodologic qualities for each study using the "risk of bias" tool within the Review Manager software program (version 5.3, The Cochrane Collaboration, Oxford, UK). Quality was evaluated based on potential sources of bias including random sequence generation, allocation concealment, blinding of the participants, blinding of personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias, and the data were then cross-checked.

Data extraction

The 2 reviewers (BSR and AEJ) independently extracted data from each study using a predefined data extraction form. Any disagreement unresolved by discussion was put under the review of a third author (KHJ). The following variables were extracted from the tables or text of the published studies: (1) title, (2) authors, (3) name of journal, (4) publication year, (5) study design, (6) registration of clinical trial, (7) competing interest, (8) country, (9) risk of bias, (10) number of patients in study, (11) inclusion criteria, (12) gender, (13) age, (14) time and dose of gabapentin administration, (15) regional block, (16) anesthesia, (17) postoperative additional analgesics use, (18) premedication, and (19) adverse effects.

The data were initially extracted from tables or text. In cases involving missing or incomplete data, an attempt was made to contact the study authors to obtain the relevant information. If the author did not respond or did not have current information, the data were directly extracted from the graphs.

Statistical analysis

The review and meta-analysis were conducted using Review Manager software (version 5.3, The Cochrane Collaboration, Oxford, UK). For dichotomous data, a pooled odds ratio (OR) and 95% confidence intervals (CIs) were calculated. If the 95% CI included a value of 1, the difference was not considered statistically significant. We calculated the mean difference (MD) for continuous data, and reported the 95% CI. If the 95% CI included a value of 0, the difference was not considered statistically significant.

We used the Chi-squared test and the I-squared test for heterogeneity. If the P value was <0.10 or an I^2 value was $>50\%$, the heterogeneity was considered significant. A fixed-effects model was selected if P value for chi-square test >0.10 and the I^2 value was $<50\%$. In cases I^2 value $>50\%$, random-effects models were used.

Publication bias was not assessable in these trials. Tests for funnel plot asymmetry are generally only performed when at least 10 studies are included in the meta-analysis. As our analysis only included 4 studies, tests for asymmetry would be ineffective as they would be unable to differentiate chance from asymmetry.

Results

Literature search and study characteristics

A search of the MEDLINE, Embase, and CENTRAL databases returned 297 studies that were initially evaluated. After excluding duplicates, 237 studies remained. Another 174 studies were excluded following the review of titles and abstracts. Of the 63 studies that remained, 24 additional studies were excluded because they did not involve knee surgery. Sixteen studies were excluded because they were not randomized controlled trials. Fifteen studies were excluded because they involved chronic and not postoperative pain. The full texts of the remaining 8 studies were reviewed in detail, and 4 additional studies were excluded because 2 were review journal articles,[14,15] 1 did not involve knee surgery,[6] and 1 was a retrospective study.[16] Collectively, 4 studies met the inclusion criteria and were included in this systematic review and meta-analysis (Fig. 1).[2,17–19]

The characteristics of the 4 studies that met the inclusion criteria were summarized in Tables 1 and 2. In the Clarke study,[17] only group G1 and G2 were involved among the 5 groups, because patients in G3, G4, and G5 received postoperative gabapentin medication.

Postoperative pain score

This outcome was reported in 4 trials.[2,17–19] The overall pooled results from meta-analysis demonstrated that compared with placebo, pre-emptive

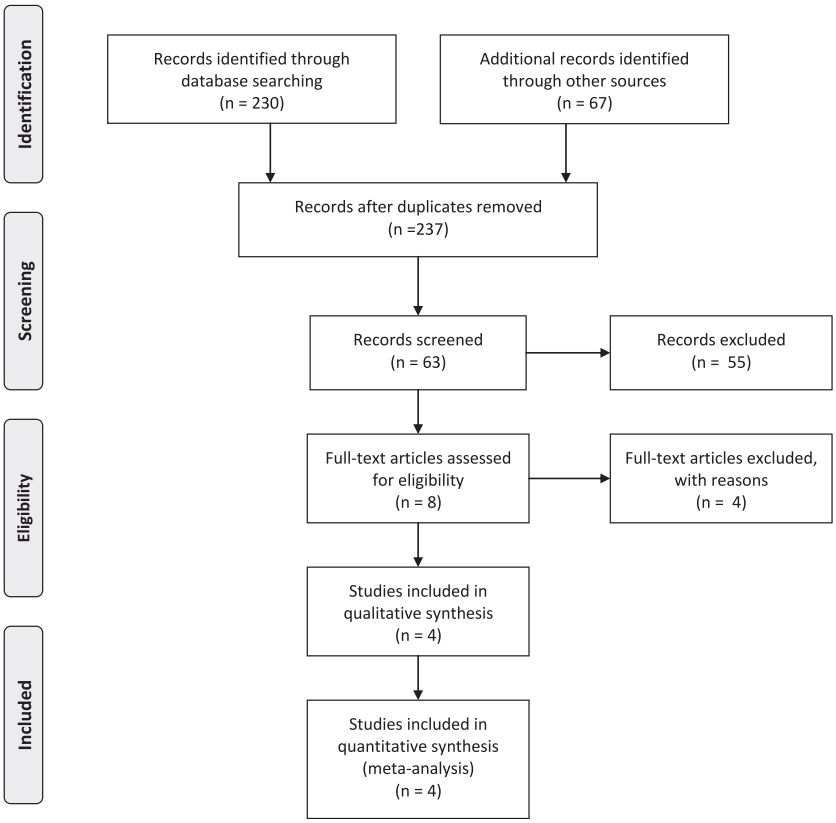

Fig. 1 PRISMA flow diagram of the search, inclusion, and exclusion of randomized controlled trials

analgesia could significantly reduce the postoperative pain score [mean difference (MD) –6.29; 95% confidence interval (CI) –10.17 to –2.42; $P = 0.001$; random-effect model; Fig. 2]. Stratified by postoperative period, subgroup analyses found that gabapentin significantly reduced the postoperative pain score at postoperative 1 to 4 hours (Fig. 2).

Effect of gabapentin in general anesthesia

Two studies analyzed the effectiveness of gabapentin in reducing postoperative pain score in patients who underwent general anesthesia.[2,18] The subgroup analyses found that gabapentin could significantly reduce the postoperative pain score (MD, –17.82; 95% CI, –21.82 to –13.81; $P = 0.47$; fixed-effect model).

Effect of gabapentin in regional anesthesia

Two studies analyzed the effectiveness of gabapentin in reducing postoperative pain score in patients who underwent regional anesthesia.[17,19] The subgroup analyses could not clarify the effectiveness of gabapentin in reducing postoperative pain (MD, 2.43; 95% CI, –1.14 to 6.00; $P = 0.78$; fixed-effect model).

Table 1 Data extracted from the included studies

Sources	Study design	Country	Inclusion criteria	Population (intervention/control)	Age	Gender (male/female)
Clarke H 2009	RCT	Canada	TKA	7/7	60.7 ± 6.6	8/6
Menigaux 2005	RCT	France	elective arthroscopic anterior cruciate ligament repair using hamstring autograft under general anesthesia	20/20	31 ± 8	27/13
Paul 2013	RCT	Canada	primary TKA	52/49	63.5 ± 6.7	37/64
Montazeri 2007	RCT	Iran	knee arthroplasty	35/35	34.6 ± 17.8	54/16

RCT, randomized controlled trials; TKA, total knee arthroplasty.

Values are expressed as mean ± SD.

Table 2 Further data extracted from the included studies

Sources	Gabapentin given time and dose	Regional anesthesia	Type of anesthesia	Postoperative additional analgesics use	Premedication
Clarke H 2009	600 mg, 2 hours preoperatively	femoral and sciatic NB	spinal anesthesia	celecoxib 200 mg every 12 h 4 day and IV PCA	celecoxib 400 mg 2 hours preoperatively
Menigaux 2005	1200 mg, 1–2 hours preoperatively	no	general anesthesia	ketoprofen 150 mg po bid, IV PCA	no
Paul 2013	600 mg, 2 hours preoperatively	no	spinal anesthesia	IV morphine PCA	acetaminophen 100 mg PO, ketorolac 15 mg IV 2 hours preoperatively
Montazeri 2007	300 mg, 2 hours preoperatively	no	general anesthesia	iv morphine	no

IV, intravenous; NB, nerve block; PCA, patient-controlled analgesia; PO, per oral.

Postoperative total morphine consumption

Morphine was used as postoperative analgesic medication in 4 trials.[2,17–19] However, we were unable to clarify the effect gabapentin on postoperative morphine consumption, as compared with placebo (Fig. 3).

Safety analysis

The incidence of nausea and vomiting among recipients was compared to controls in 3 studies.[2,18,19] The analysis of the combined findings showed neutral result in 2 studies involving nausea [odds ratio (OR), 1.15; 95% CI, 0.41 to 3.24; $P_{chi}^2 = 0.04$; $I^2 = 0\%$).[2,18] Vomiting appeared as a neutral result in Montazeri's study (OR, 1.38; 95% CI, 0.28 to 6.66).[2] However, nausea and vomiting had lower incidence in the study of Paul (OR, 0.39; 95% CI, 0.16 to 0.98).[19]

Risk of bias

All studies referenced the random sequence generation method, and only 2 studies described allocation concealment.[2,19] In 3 studies,[2,17,19] outcome assessors were blinded and no incomplete data was reported (Table 3).

Discussion

Our study showed that, in knee surgery, gabapentin decreases postoperative pain scores in the early postoperative period, as compared with the control group.

Although gabapentin is a structural analog of GABA, it does not act via GABA receptors and the mechanism of analgesic effect of gabapentin remains unknown.[1] The α2δ subunit of voltage-dependent calcium channels are up-regulated in inflammatory pain processing to the development and maintenance of hyperalgesia.[20] This unique binding to the α2δ calcium subunit explains the reduction of neurotransmitter release by gabapentin and thus its antinociceptive effect.[1] Also, activation of adenosine 5′-triphosphate-sensitive K+ channels or inhibition of nitric oxide synthase is proposed in the antiallodynic action of gabapentin.[1]

Pre-emptive analgesia is an antinociceptive treatment started before surgical stimulation, which is more effective in reducing postoperative pain than when started in the early postoperative period.[9] Moreover, because the mean maximum plasma concentrations are obtained in 2 to 3 hours,[7] the administration time of gabapentin is recommended 2 hours before surgical stimulation. However, the

Table 3 Risk of bias in the included randomized controlled trials

Biases/references	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome	Incomplete outcome data	Selective reporting	Other sources of bias
Clarke H 2009	yes	unclear	unclear	unclear	yes	yes	yes	yes
Menigaux 2005	yes	unclear	unclear	yes	unclear	yes	yes	yes
Paul 2013	yes	yes	yes	yes	yes	yes	yes	yes
Montazeri 2007	yes	yes	yes	yes	yes	yes	yes	yes

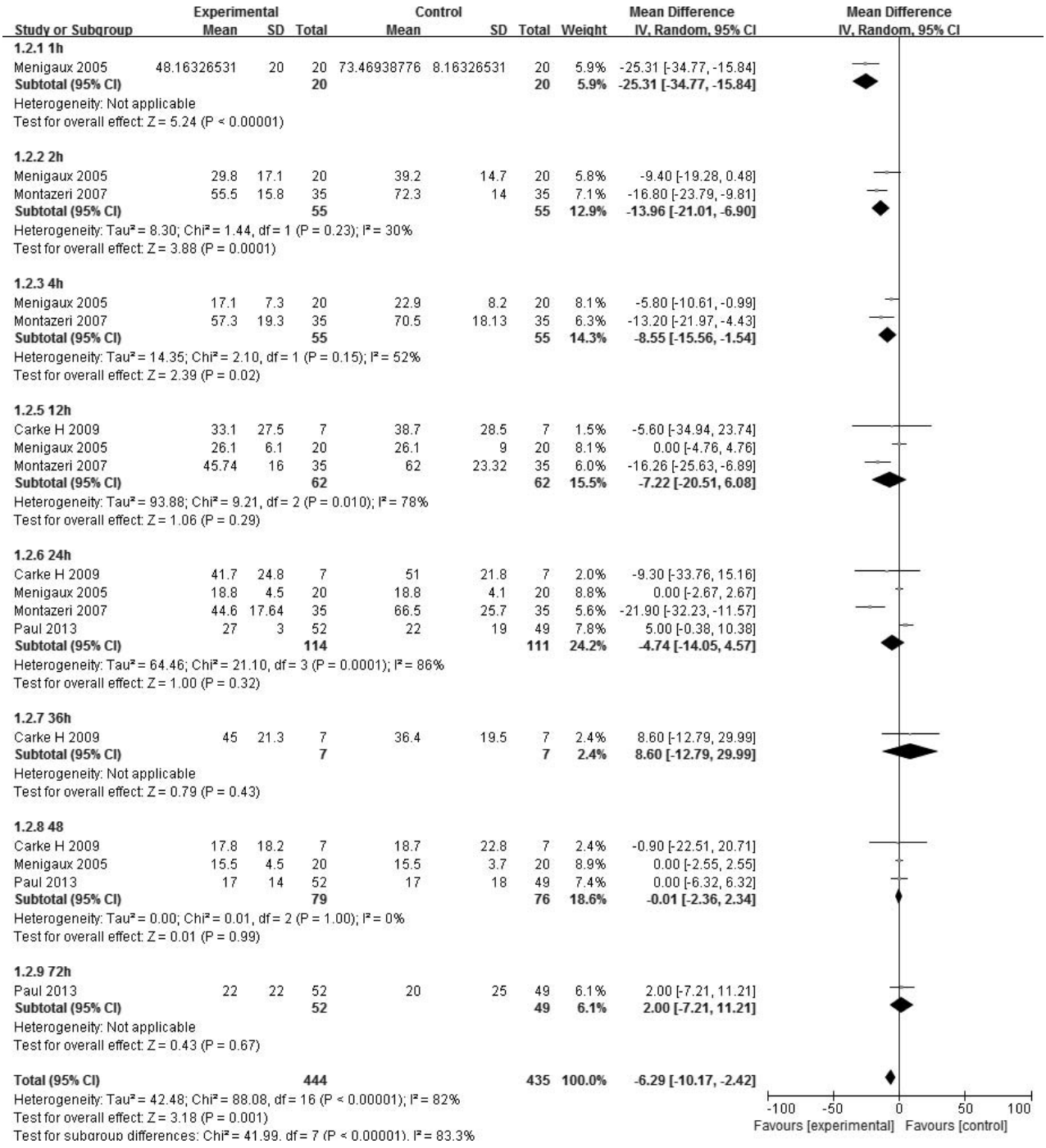

Fig. 2 Forest plot for postoperative pain score. The figure depicted individual trials as filled squares with relative size of sample size and solid line as the 95% confidence interval of the difference. The diamond shape indicates the pooled estimate and uncertainty for the combined effect.

overall outcome of postoperative pain score appeared to be reduced until postoperative 4 hours. These outcomes are drawn from the persistent effects of gabapentin for 2 days, which far exceeds the pharmacologic duration suggested by the drug's 5- to 9-hour half-life.[1]

The analgesic effect of preemptive gabapentin showed significant reduction in postoperative pain score in patients who underwent general anesthesia, while the combined analyses of studies in patients who underwent regional anesthesia could not clarify the analgesic effect of gabapentin. In the

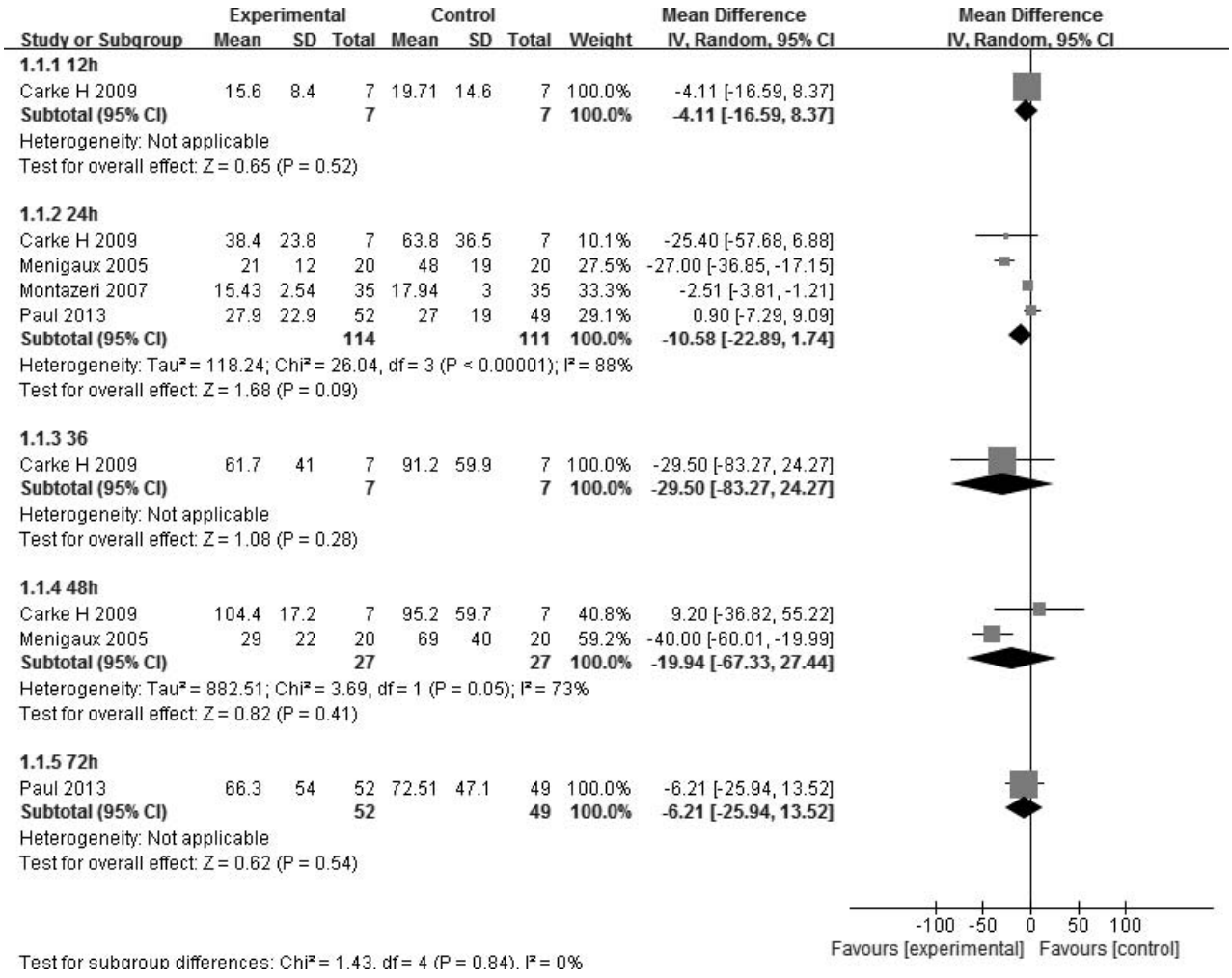

Fig. 3 Forest plot for total morphine consumption. The figure depicted individual trials as filled squares with relative size of sample size and solid line as the 95% confidence interval of the difference. The diamond shape indicates the pooled estimate and uncertainty for the combined effect.

study of Menigaux and Montazeri, all patients underwent general anesthesia without receiving any analgesia as a premedication.[2,18] However, in the study of Clarke and Paul,[17,19] not only regional anesthesia but also multimodal analgesia were applied. It is possible that the incremental benefit of gabapentin is negated by the effects of multimodal analgesia or regional anesthesia. Also, the same results were shown in the study of Dietrich, with no significant analgesic effect of gabapentin utilizing the multimodal analgesic regimen.[16]

There were discrepant outcomes between this meta-analyses and other meta-analyses of various surgeries. Several meta-analyses show that gabapentin is effective in reducing opioid consumption and pain overall nausea and vomiting.[21–23] However, in this meta-analysis, the effectiveness of gabapentin on postoperative total opioid consumption could not be clarified. Furthermore, the effectiveness of gabapentin on nausea and vomiting that are affected by opioid consumption could not be clarified.

There were some limitations to our study. First, the number of included studies is relatively small, which causes some underestimation or overestimation. Second, the dose of gabapentin varies from 300 mg to 1200 mg. Last, only published studies were included in our meta-analysis. Despite these limitations, the present meta-analysis provided the first systematic review regarding gabapentin in the management of postoperative pain after knee surgery.

In summary, pre-emptive gabapentin reduces early postoperative pain score. However, it is unclear whether gabapentin reduces postoperative pain score in the setting of regional anesthesia or

multimodal analgesic regimen. Therefore, further studies are needed.

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