

# BMJ Open Single-dose intra-articular bupivacaine plus morphine after knee arthroscopic surgery: a meta-analysis of randomised placebo-controlled studies

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## ABSTRACT

**Objectives:** To evaluate the efficacy and safety of single-dose intra-articular bupivacaine plus morphine after knee arthroscopic surgery.

**Design:** Meta-analysis.

### Data sources and study eligibility criteria:

A comprehensive literature search, using Medline (1966–2014), the Cochrane Central Register of Controlled Trials and Embase databases, was conducted to identify randomised placebo-controlled trials that used a combination of single-dose intra-articular bupivacaine and morphine for postoperative pain relief.

**Results:** 12 articles were included in this meta-analysis. The mean visual analogue scale (VAS) scores of the bupivacaine plus morphine group were significantly lower than those of the placebo group (weighted mean difference (WMD)  $-1.75$ ; 95% CI  $-2.16$  to  $-1.33$ ;  $p < 0.001$ ). The VAS scores at the last follow-up time point (last VAS scores) of the bupivacaine plus morphine group were also significantly lower than those of the placebo group (WMD  $-1.46$ ; 95% CI  $-1.63$  to  $-1.29$ ;  $p < 0.001$ ). The number of patients requiring supplementary analgesia was also significantly reduced (RR 0.60; 95% CI 0.39 to 0.93;  $p = 0.02$ ), while there was no significant difference in the time to first analgesic request (WMD 3.46; 95% CI  $-1.81$  to 8.72;  $p = 0.20$ ) or short-term side effects (RR 1.67; 95% CI 0.65 to 4.26;  $p = 0.29$ ).

**Conclusions:** The administration of single-dose intra-articular bupivacaine plus morphine after knee arthroscopic surgery is effective for pain relief, and its short-term side effects remain similar to saline placebo.

## INTRODUCTION

Knee arthroscopic surgery is a very common surgical procedure that usually does not require hospitalisation before or after surgery. In spite of its popularity, this type of surgery can sometimes cause severe pain.<sup>1</sup> Solheim *et al*<sup>2</sup> reported that around 60% of patients may experience moderate to severe

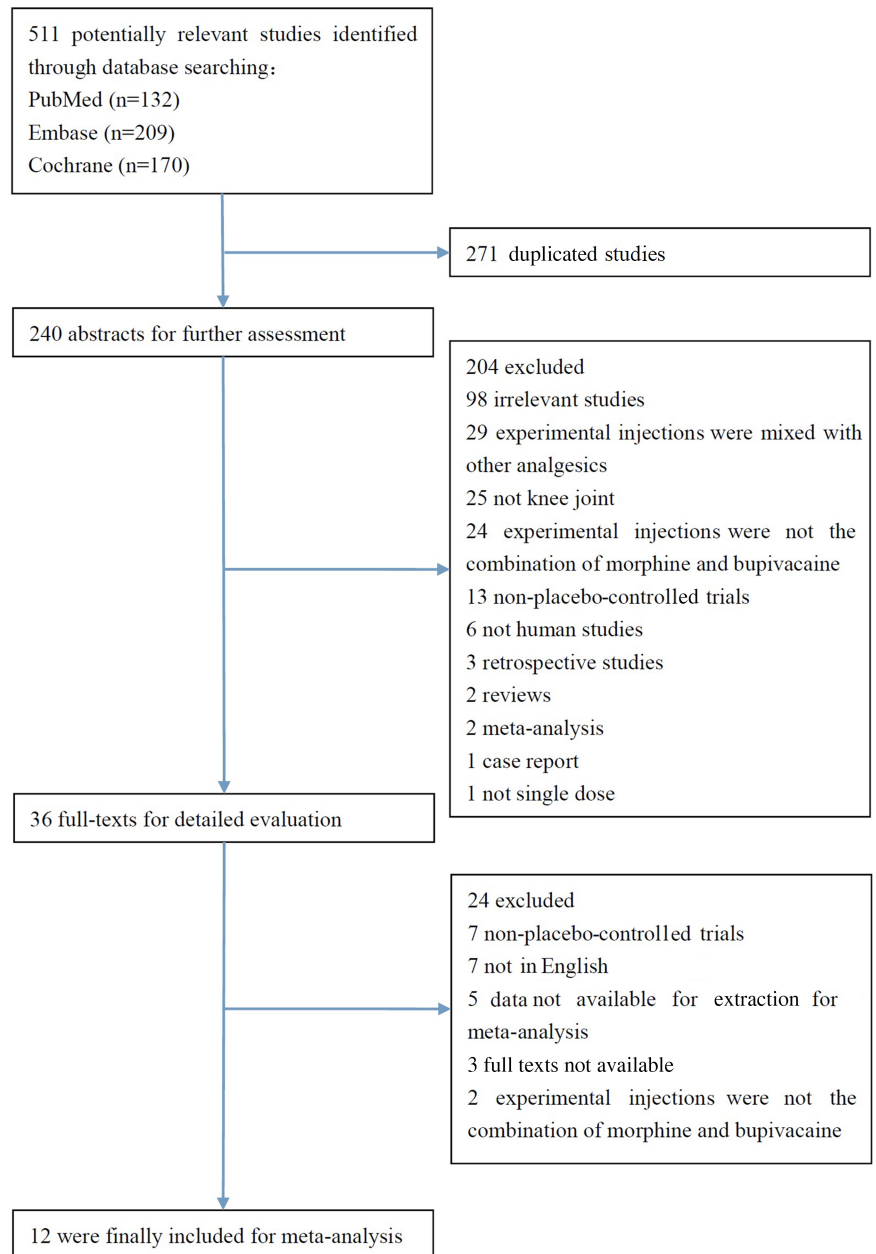
## Strengths and limitations of this study

- This is the first quantitative analysis to compare single-dose intra-articular (IA) bupivacaine plus morphine with saline placebo after knee arthroscopic surgery.
- All included studies in this meta-analysis adopted a randomised placebo-controlled design.
- A comprehensive report on the effects of single-dose IA bupivacaine plus morphine after knee arthroscopic surgery is provided.
- Substantial heterogeneity was observed in the number of patients requiring supplementary analgesia and the time to first analgesic request.
- None of the observation periods of the included studies were long enough to detect cartilage toxicity.

pain after knee arthroscopic surgery, which can delay rehabilitation and increase the risk of postoperative complications. Therefore, adequate postoperative pain control is essential and can improve postoperative convalescence.

The use of intra-articular (IA) anaesthesia after arthroscopic knee surgery became popular after a seminal publication by Stein *et al*<sup>3</sup> in 1991. Currently, bupivacaine as a local anaesthetic and morphine to relieve pain are widely used in combination to provide effective postoperative analgesia.<sup>4–10</sup> However, the efficacy and safety of this combination for patients undergoing knee arthroscopic surgery remains controversial. Some studies found that IA bupivacaine plus morphine provided effective pain relief for patients,<sup>11–19</sup> while others did not.<sup>20–22</sup> Consequently, this quantitative meta-analysis involving 12 randomised placebo-controlled trials (RCTs) was designed to examine the efficacy and safety of IA bupivacaine in combination with morphine for patients undergoing knee arthroscopic surgery.

**Figure 1** Flow diagram of screened, excluded and analysed articles.



## MATERIALS AND METHODS

### Search strategy

This meta-analysis was performed in accordance with the PRISMA guidelines.<sup>23</sup> PubMed/Medline (1966–2014), the Cochrane Central Register of Controlled Trials (CENTRAL) and Embase databases were searched for relevant studies comparing bupivacaine plus morphine with placebo in patients receiving a single-dose IA injection after knee arthroscopic surgery. Search terms were ‘arthroscopy’, ‘arthroscopic’, ‘arthroscope’, ‘morphine’, ‘bupivacaine’ and ‘randomised controlled trials’. No restrictions were imposed. The references and reviews of the retrieved studies were also assessed.

### Study selection

The citations and abstracts generated by the literature search were reviewed by two researchers independently.

Inclusion criteria were as follows: (a) patients undergoing knee arthroscopic surgery; (b) administration of combination therapy of single-dose IA bupivacaine and morphine for postoperative pain relief; (c) RCTs; and (d) administration of saline in the control group. Exclusion criteria were as follows: (a) non-RCTs; (b) non-placebo-controlled trials; (c) the combination therapy of single-dose IA bupivacaine and morphine not administered in the experimental group; (d) data not available for extraction; and (e) unavailability of the full text.

### Data extraction

The two independent researchers used Review Manager V.5.2 software (RevMan V.5.2; The Cochrane Collaboration, Oxford, UK) to record and manage information. The SD of outcome, if not reported, was estimated based on sample size, the SE or the 95% CI. Data were also extracted from figures by using GetData V.2.20

**Table 1** Characteristics of the included studies

| Study                                      | Year | Age (mean) | Sex (male/female) | n (B-M/C) | Doses (B, M) (mg) | Concentration | Time of follow-up (h)           | Type of anaesthesia | Epinephrine | Type of surgery   | Time of intra-articular injection             | MOS |
|--|------|------------|-------------------|-----------|-------------------|---------------|---------------------------------|---------------------|-------------|---|---|-----|
| Hosseini <i>et al</i> <sup>11</sup>        | 2012 | 25.2       | 40/0              | 20/20     | 100, 10           | 0.5%          | 0, 0.5, 1, 1.5, 2, 4, 6, 12, 24 | General             | No          | Arthroscopic ACL reconstruction                                     | 10 min before the release of the tourniquet   | 5   |
| Danieli <i>et al</i> <sup>12</sup>         | 2012 | 32.8       | 29/1              | 15/15     | 50, 1             | 0.25%         | 6, 24, 48                       | Spinal              | No          | Videoarthroscopy-assisted ACL reconstruction                        | At the end of arthroscopic surgery            | 6   |
| Goodwin <i>et al</i> <sup>13</sup>         | 2005 | 32.6       | 14/4              | 10/8      | 150, 1            | 0.25%         | 0, 1, 2                         | General             | Yes         | Arthroscopic surgery without concomitant ligamentous reconstruction | At the end of arthroscopic surgery            | 5   |
| Tetzlaff <i>et al</i> <sup>14</sup>        | 1999 | NA         | NA                | 10/10     | 150, 1            | 0.25          | 0.5, 1, 1.5, 2, 4, average      | General             | Yes         | Arthroscopic ACL reconstruction                                     | 20 min before incisions                       | 4   |
| De Andres <i>et al</i> <sup>16</sup>       | 1998 | 33.3       | 29/22             | 26/25     | 50, 1             | 0.25%         | 0.33, 4, 10, 16, 24             | General             | No          | Arthroscopic meniscectomy   | At the end of arthroscopic surgery            | 6   |
| Gatt <i>et al</i> <sup>15</sup>            | 1998 | NA         | NA                | 10/10     | 150, 1            | 0.25%         | 0, 0.5, 1, 1.5, 2               | General             | Yes         | Arthroscopic ACL reconstruction                                     | At the end of arthroscopic surgery            | 5   |
| Denti <i>et al</i> (group A) <sup>20</sup> | 1997 | NA         | NA                | 11/12     | 50, 2             | 0.25%         | 1, 3, 6, 12, 24                 | Spinal              | No          | Operative knee arthroscopy  | 10 min before the release of the tourniquet   | 5   |
| Denti <i>et al</i> (group B) <sup>20</sup> | 1997 | NA         | NA                | 10/10     | 50, 2             | 0.25%         | 1, 3, 6, 12, 24                 | General             | No          | Arthroscopic ACL reconstruction                                     | 10 min before the release of the tourniquet   | 5   |
| Aasbo <i>et al</i> <sup>21</sup>           | 1996 | 41         | 33/21             | 27/27     | 50, 3             | 0.25%         | 1, 2, 3, 4, 8, 12, 24, 72, 168  | General             | No          | Arthroscopic surgery  | 8 min before the release of the tourniquet    | 5   |
| Brandsson <i>et al</i> <sup>17</sup>       | 1996 | NA         | NA                | 20/20     | 75, 1             | 0.375%        | 1, 2, 4, 6, 24, 48              | General             | No          | Arthroscopic ACL reconstruction                                     | At the end of arthroscopic surgery            | 5   |
| Karlsson <i>et al</i> <sup>18</sup>        | 1995 | NA         | NA                | 10/10     | 75, 1             | 0.375%        | 2, 4, 6, 24, 48                 | General             | No          | Arthroscopic ACL reconstruction                                     | At the end of arthroscopic surgery            | 5   |
| Bjornsson <i>et al</i> <sup>22</sup>       | 1994 | 34         | 30/8              | 19/19     | 47.5, 1           | 0.25%         | 0, 0.5, 1, 1.5, 2, 8, 24, 48    | General             | No          | Arthroscopic surgery  | 5–10 min before the release of the tourniquet | 4   |
| Joshi <i>et al</i> <sup>19</sup>           | 1993 | 31.2       | 14/6              | 10/10     | 62.5, 5           | 0.25%         | 1, 2, 4, 8, 24                  | General             | No          | Diagnostic arthroscopies, arthroscopic meniscectomy                 | 10 min before the release of the tourniquet   | 4   |

ACL, anterior cruciate ligament; B, bupivacaine; C, control; h, hour; M, morphine; MOS, modified Oxford score; n, number of patients per group; NA, not available.

**Table 2** Modified Oxford scores of the included studies

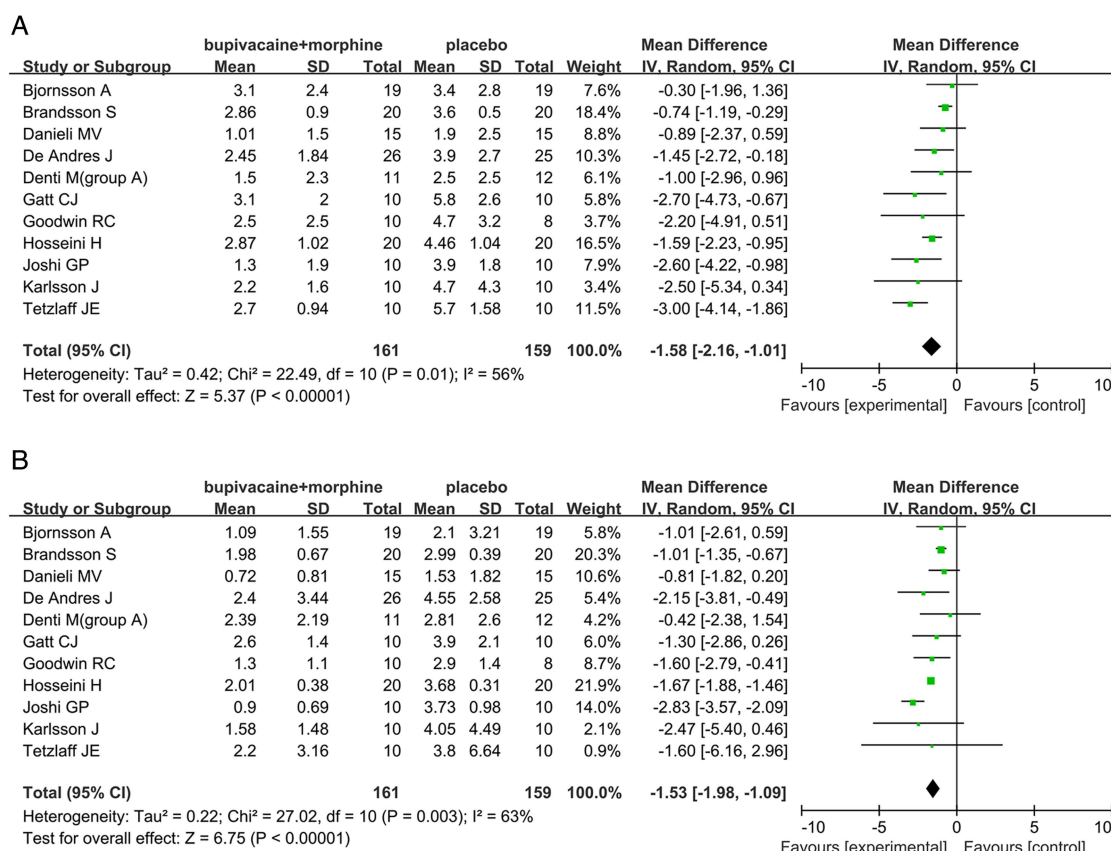
| Studies                              | Randomised method | Concealment allocation | Blinding | Follow-up | Total score |
|--------------------------------------|-------------------|------------------------|----------|-----------|-------------|
| Hosseini <i>et al</i> <sup>11</sup>  | 2                 | 1                      | 2        | 0         | 5           |
| Danieli <i>et al</i> <sup>12</sup>   | 1                 | 2                      | 2        | 1         | 6           |
| Goodwin <i>et al</i> <sup>13</sup>   | 1                 | 1                      | 2        | 1         | 5           |
| Tetzlaff <i>et al</i> <sup>14</sup>  | 1                 | 2                      | 1        | 0         | 4           |
| De Andres <i>et al</i> <sup>16</sup> | 2                 | 2                      | 2        | 0         | 6           |
| Gatt <i>et al</i> <sup>15</sup>      | 1                 | 1                      | 2        | 1         | 5           |
| Denti <i>et al</i> <sup>20</sup>     | 2                 | 1                      | 1        | 1         | 5           |
| Aasbo <i>et al</i> <sup>21</sup>     | 1                 | 1                      | 2        | 1         | 5           |
| Brandsson <i>et al</i> <sup>17</sup> | 1                 | 1                      | 2        | 1         | 5           |
| Karlsson <i>et al</i> <sup>18</sup>  | 1                 | 2                      | 1        | 1         | 5           |
| Bjornsson <i>et al</i> <sup>22</sup> | 1                 | 1                      | 1        | 1         | 4           |
| Joshi <i>et al</i> <sup>19</sup>     | 1                 | 1                      | 1        | 1         | 4           |

software. If there were more than two experimental groups in one study, data were extracted only for the bupivacaine plus morphine group and the placebo group.

The basic information extracted from the studies included: first author, year of publication, mean age, sex ratio, number of patients in the experimental and control groups, doses of bupivacaine and morphine, concentration of bupivacaine, follow-up time points, type of anaesthesia, epinephrine used, type of surgery, IA injection time, and modified Oxford scores (MOS).<sup>24 25</sup> MOS

was assessed by the two independent researchers and used to measure the quality of each study according to the method of randomisation, concealment allocation, blinding and follow-up. Any disagreements between the two researchers were resolved by discussion.

The primary outcomes of interest were pain intensity, which was assessed on a visual analogue scale (VAS), and side effects. The secondary outcomes were the number of patients requiring supplementary analgesia and the time to first request for analgesia.



**Figure 2** (A) Forest plot of mean VAS scores of postoperative pain intensity (0–10 points). (B) Forest plot of last VAS scores of postoperative pain intensity (0–10 points).

**Table 3** Results of sensitivity analyses

| Reason for exclusion of studies                             | Pooled results of the remaining studies |         | Heterogeneity of the remaining studies |         |
|---|---|---------|--|---------|
|   | WMD/RR                                  | p Value | I <sup>2</sup> (%)                     | p Value |
| <b>Mean VAS scores</b>                                      |   |         |  |         |
| Treated with a cooling system                               | -1.75 (-2.16 to -1.33)                  | <0.001  | 26                                     | 0.21    |
| Mixed with epinephrine                                      | -1.10 (-1.42 to -0.77)                  | <0.001  | 31                                     | 0.18    |
| Spinal anaesthesia  | -1.72 (-2.39 to -1.05)                  | <0.001  | 64                                     | 0.005   |
| Small sample size (less than 10 in control group)           | -1.56 (-2.16 to -0.96)                  | <0.001  | 59                                     | 0.009   |
| Mild pain score in control group (mean VAS value ≤3)        | -1.72 (-2.39 to -1.05)                  | <0.001  | 64                                     | 0.005   |
| <b>Last VAS scores</b>                                      |   |         |  |         |
| Treated with a cooling system                               | -1.70 (-1.89 to -1.50)                  | <0.001  | 41                                     | 0.09    |
| Mixed with epinephrine                                      | -1.54 (-2.06 to -1.01)                  | <0.001  | 74                                     | 0.0003  |
| Spinal anaesthesia  | -1.68 (-2.16 to -1.19)                  | <0.001  | 66                                     | 0.003   |
| Small sample size (less than 10 in control group)           | -1.52 (-2.01 to -1.04)                  | <0.001  | 67                                     | 0.001   |
| Mild pain score in control group (mean VAS value ≤3)        | -1.76 (-1.96 to -1.56)                  | <0.001  | 47                                     | 0.09    |
| <b>Number of patients requiring supplementary analgesia</b> |   |         |  |         |
| Mixed with epinephrine                                      | 0.66 (0.43 to 1.02)                     | 0.06    | 61                                     | 0.02    |
| Spinal anaesthesia  | 0.62 (0.41 to 0.95)                     | 0.03    | 66                                     | 0.007   |

RR, risk ratio; VAS, visual analogue scale; WMD, weighted mean difference.

### Statistical analyses

Quantitative analysis was performed for pain intensity reported using a VAS, and the time to first request for analgesia. We calculated weighted mean differences (WMDs) and their corresponding 95% CIs. Dichotomous data on side effects and number of patients requiring supplementary analgesia were summarised using risk ratios (RRs) and their corresponding 95% CIs. Bupivacaine and morphine were used in different doses, and pain intensity was reported at different follow-up time points in the various studies. In order to facilitate and standardise pooling of data, each group was regarded as a single study, and we computed the mean and SD of mean VAS scores across the different time points of each study. We also analysed the VAS scores at the last follow-up time point (last VAS scores). All VAS scores were converted to a scale ranging from 0 to 10.

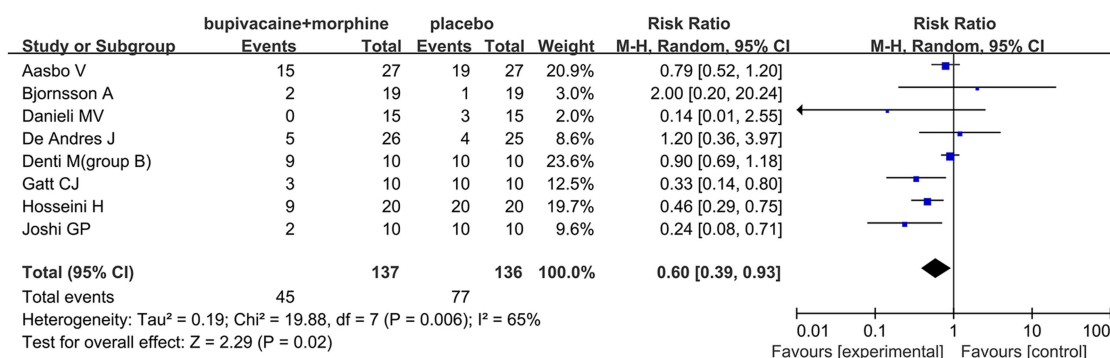
The homogeneity of effect size across trials was tested with the Q statistic ( $p \leq 0.05$  was considered heterogeneous). If there was significant heterogeneity among

studies, the random-effects model was used; otherwise, the fixed-effects model was employed. We also examined the I<sup>2</sup> statistic, which measures the percentage of the total variation across studies which results from heterogeneity rather than chance (I<sup>2</sup> ≥ 50% was considered moderately or very heterogeneous). A sensitivity analysis was conducted to examine the influence of various exclusion criteria on overall effect sizes.

Begg's tests<sup>26</sup> and funnel plots were used to assess publication bias. We used RevMan V.5.2 and STATA V.12.0 (StataCorp LP, College Station, Texas, USA) to perform statistical analyses.  $p < 0.05$  was considered to be statistically significant, unless otherwise stated.

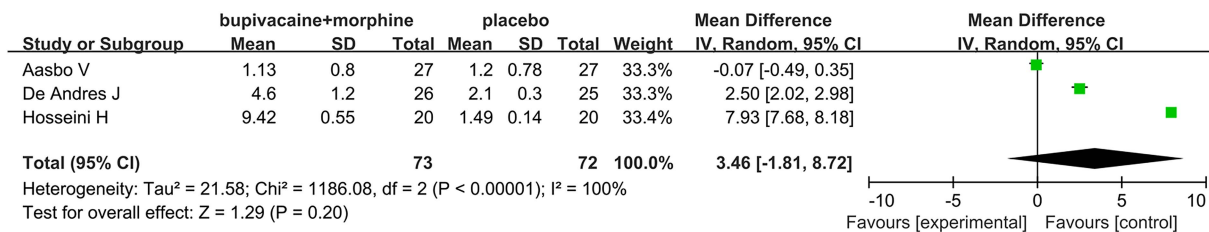
### RESULTS

The search strategy identified 511 articles, the full texts of 36 of which were assessed. Eventually, 12 articles<sup>11–22</sup> were included in the meta-analysis (figure 1). The characteristics of these 12 studies are given in table 1, and the MOS of each study are listed in table 2.



**Figure 3** Funnel plots with relative ratios or WMDs of all studies comparing single-dose intra-articular bupivacaine-morphine with placebo. The vertical axis represents effect value, and the abscissa represents the SE of the effect value. The horizontal line in the middle of the funnel plot represents a comprehensive effect value; the two diagonal lines represent the 95% CIs for a given SE. RR, relative risk; VAS, visual analogue scale; WMD, weighted mean difference.





**Figure 4** Forest plot of number of patients requiring supplementary analgesia.

### VAS values

All 12 included articles<sup>11–22</sup> reported pain intensity using VAS scores, but one<sup>21</sup> only reported the mean VAS score values. Therefore, 11 studies<sup>11–20, 22</sup> involving 320 patients were eligible for assessment of postoperative pain intensity. The bupivacaine plus morphine group demonstrated significantly lower mean VAS scores (WMD  $-1.58$ ; 95% CI  $-2.16$  to  $-1.01$ ;  $p < 0.001$ ) and last VAS scores (WMD  $-1.53$ ; 95% CI  $-1.98$  to  $-1.09$ ;  $p < 0.001$ ) compared to the placebo group. Substantial heterogeneity was observed in both mean VAS scores ( $I^2 = 56\%$ ;  $p = 0.01$ ) and last VAS scores ( $I^2 = 63\%$ ;  $p = 0.003$ ). The results are shown in figure 2A, B.

Sensitivity analysis explored the potential sources of heterogeneity between the bupivacaine plus morphine group and the placebo group and investigated the influence of various exclusion criteria on the overall risk estimate. The results are presented in table 3. The overall WMD of mean VAS scores did not vary substantially with the exclusion of any single study, and ranged from  $-1.15$  (95% CI  $-1.47$  to  $-0.83$ ) to  $-1.75$  (95% CI  $-2.16$  to  $-1.33$ ). The overall WMD of last VAS scores did not vary substantially with the exclusion of any single study either, and ranged from  $-1.46$  (95% CI  $-1.63$  to  $-1.29$ ;  $p < 0.001$ ) to  $-1.70$  (95% CI  $-1.89$  to  $-1.50$ ;  $p < 0.001$ ). In addition, the substantial heterogeneity in mean VAS scores was materially changed by excluding Brandsson's study ( $I^2 = 26\%$ ;  $p = 0.21$ )<sup>17</sup> and Tetzlaff's study ( $I^2 = 31\%$ ;  $p = 0.16$ ),<sup>14</sup> while the substantial heterogeneity in last VAS scores was also materially changed by excluding Joshi's study ( $I^2 = 38\%$ ;  $p = 0.10$ )<sup>19</sup> and Brandsson's study ( $I^2 = 41\%$ ;  $p = 0.09$ ).<sup>17</sup> In order to facilitate and standardise data pooling, the results (mean VAS scores: WMD  $-1.75$ ; 95% CI  $-2.16$  to  $-1.33$ ;  $p < 0.001$ ;  $I^2 = 26\%$ ,  $p = 0.21$ ; last VAS scores: WMD  $-1.46$ ; 95% CI  $-1.63$  to  $-1.29$ ;

$p < 0.001$ ;  $I^2 = 38\%$ ,  $p = 0.10$ ) obtained after excluding Brandsson's and Joshi's articles, respectively, were considered the final results. A Begg's funnel plot did not show any substantial asymmetry (figure 3), and Begg's rank correlation test did not indicate publication bias among the included studies (mean VAS scores:  $p = 0.755$ ; last VAS scores:  $p = 1.000$ ).

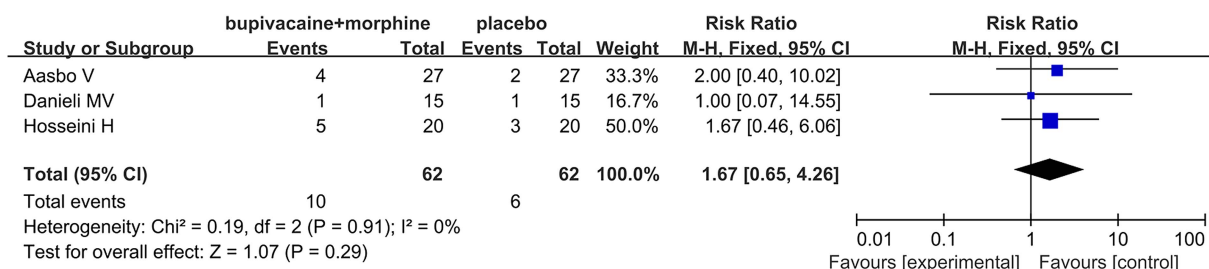
### Number of patients requiring supplementary analgesia

Eight articles<sup>11, 12, 15, 16, 19–22</sup> reported the number of patients who required supplementary analgesia. This number was significantly lower in the bupivacaine plus morphine group than in the placebo group (RR 0.60; 95% CI 0.39 to 0.93;  $p = 0.02$ ). Substantial heterogeneity was observed ( $I^2 = 65\%$ ;  $p = 0.02$ ). The results are shown in figure 4.

Sensitivity analysis showed inconsistency in the results (table 3). There was no significant difference in the results (RR 0.66; 95% CI 0.43 to 1.02;  $p = 0.06$ ) after excluding one study<sup>15</sup> where treatment also included epinephrine. Further exclusion of single studies indicated that the overall RR only changed substantially when the study by Hosseini *et al*<sup>11</sup> was excluded (RR 0.64; 95% CI 0.39 to 1.05;  $p = 0.08$ ). Begg's funnel plot did not show any substantial asymmetry, and Begg's rank correlation test did not indicate publication bias among the included studies ( $p = 0.902$ ).

### Time to first analgesic request

Three articles<sup>11, 16, 21</sup> reported the time interval until the first request for additional analgesia. The combined data suggested no significant difference (WMD 3.46; 95% CI  $-1.81$  to 8.72;  $p = 0.20$ ) between the bupivacaine plus morphine group and the placebo group. Great heterogeneity ( $I^2 = 100\%$ ;  $p < 0.001$ ) was observed. The results are presented in figure 5. Begg's funnel plot did not



**Figure 5** Forest plot of time to first analgesia request.

show any substantial asymmetry, and Begg's rank correlation test did not indicate publication bias among the included studies ( $p=1.000$ ).

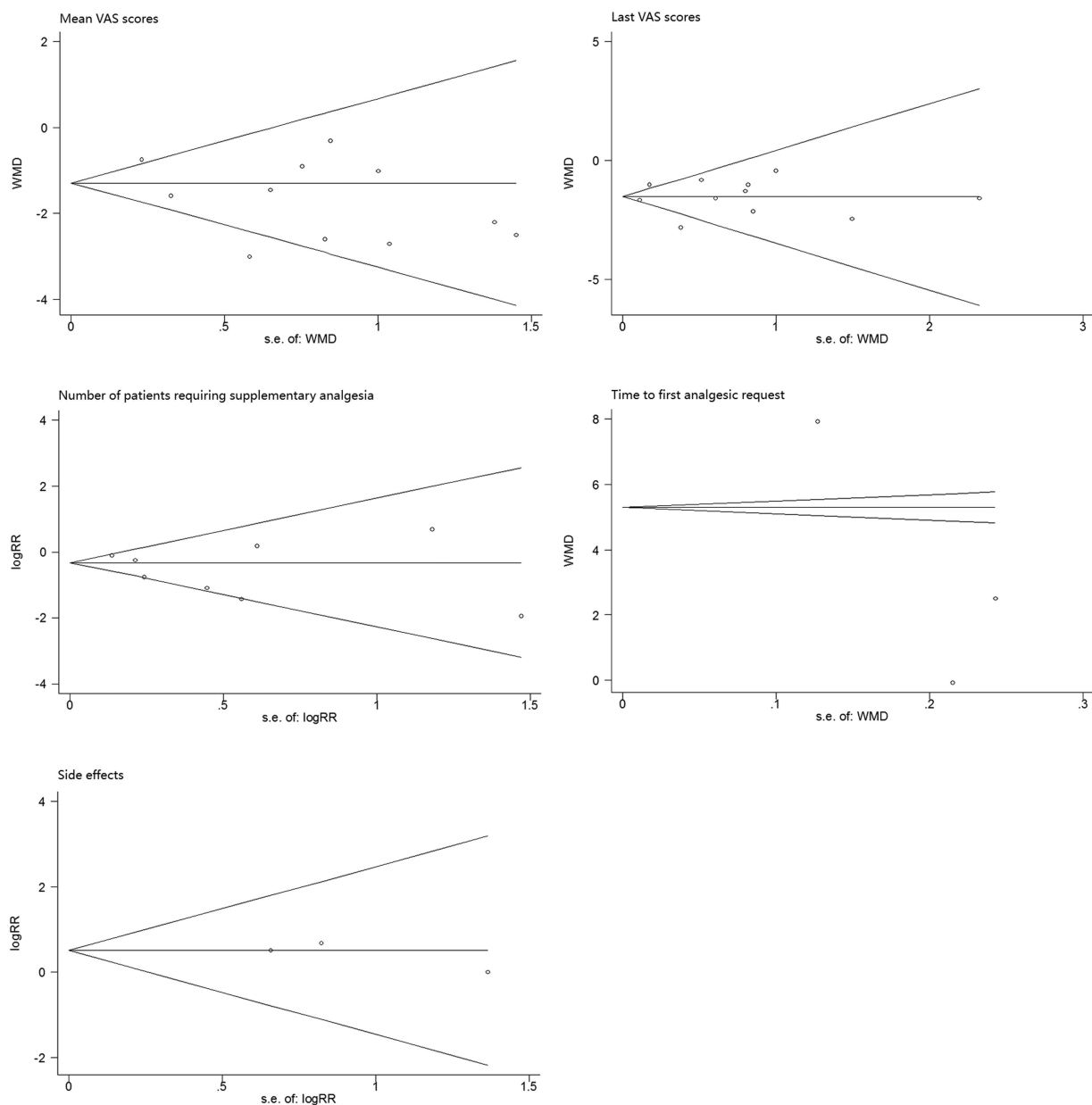
### Side effects

Three articles<sup>11 12 21</sup> evaluated side effects including nausea, vomiting, headache, pruritus and respiratory depression. Pooled data analysis revealed that there was no significant difference in side effects between the bupivacaine plus morphine group and the placebo group (RR 1.67; 95% CI 0.65 to 4.26;  $p=0.29$ ). No substantial heterogeneity was observed ( $I^2=0\%$ ;  $p=0.91$ ). The results are presented in figure 6. Begg's funnel plot did not show any substantial asymmetry, and Begg's rank correlation test did not indicate publication bias among the included studies ( $p=1.000$ ).

### DISCUSSION

This quantitative meta-analysis involving 12 RCTs<sup>11-22</sup> showed that the combination therapy of single-dose IA bupivacaine and morphine is effective for pain relief after knee arthroscopic surgery. There was no significant difference between the two groups in terms of side effects.

Separate IA administration of bupivacaine or morphine alone has been reported to provide good post-operative analgesia after arthroscopic knee surgery.<sup>27-29</sup> Eroglu *et al*<sup>30</sup> further demonstrated the efficacy and safety of low-dose IA bupivacaine and morphine for spinal anaesthesia in outpatients after knee arthroscopic surgery. However, the efficacy and safety of combination therapy with IA bupivacaine and morphine remain controversial. This meta-analysis suggests that the administration of single-dose IA bupivacaine plus morphine is



**Figure 6** Forest plot of side effects.

effective for pain relief after knee arthroscopic surgery, while its short-term side effects are similar to those of saline placebo.

The results described above are supported by some studies<sup>11–19</sup> but not by others.<sup>20–22</sup> The conflicting findings may be due to various factors. Ruwe *et al*<sup>21</sup> suggested that patients with preoperative pain were more likely to experience postoperative pain, so they regarded preoperative pain as a significant variable. Epinephrine may be another confounding factor. Haynes *et al*<sup>32</sup> reported that the addition of epinephrine could decrease the effectiveness of morphine in the combination group. However, Allen's study<sup>27</sup> indicated that the addition of epinephrine did not weaken the analgesic effect of IA bupivacaine plus morphine, but could rather prolong the duration of analgesia. Furthermore, Reuben and Sklar<sup>33</sup> suggested that inflammation at the site of surgical trauma would cause increased postoperative pain, but this was not considered in our study.

The findings of this meta-analysis suggest that there was no significant difference (WMD 3.46; 95% CI –1.81 to 8.72;  $p=0.20$ ) between the bupivacaine plus morphine group and the placebo group in terms of time to first analgesic request. However, McSwiney *et al*<sup>34</sup> reached an opposite conclusion. They considered that the combination therapy of single-dose IA bupivacaine plus morphine should provide longer duration of analgesia. However, the small number of studies included in their report may have influenced this finding.

In this meta-analysis, three studies<sup>11 12 21</sup> reported the rate of side effects in both the bupivacaine plus morphine group and the placebo group. Most of the included studies<sup>13 14–20 22</sup> suggested that side effects were infrequent, and there was no statistically significant difference between the two groups. However, it is worth noting that in none of the included studies was the observation period long enough to detect the important side effect of cartilage toxicity following IA bupivacaine or morphine. Some reports<sup>35–39</sup> indicated that IA bupivacaine might cause cartilage toxicity, while other claimed that IA bupivacaine is safe.<sup>40–42</sup> However, IA morphine appeared to be an effective and less toxic analgesic.<sup>43 44</sup> Therefore, we can only conclude that single-dose IA bupivacaine plus morphine after knee arthroscopic surgery is safe in the short term.

This meta-analysis has several strengths. First, all included studies adopted a randomised placebo-controlled design, which improves comparability between groups and reduces the risk of selection bias. Second, it provides a comprehensive report of the effects of single-dose IA bupivacaine plus morphine after knee arthroscopic surgery. Based on pooled evidence from 12 RCTs conducted in a wide range of geographical locations, with different patient characteristics, baseline illness status and ethnicity, the findings of this meta-analysis have sufficient external validity to be generalised to a broader population. Last, this is the first quantitative analysis to compare single-dose IA

bupivacaine plus morphine with saline placebo after knee arthroscopic surgery. The findings are therefore more reliable than those of previous reviews and RCTs.

The limitations of this meta-analysis should also be acknowledged. First, some potentially relevant RCTs were excluded for reasons such as publication in a language other than English, non-availability of extractable data, and non-availability of the full text. Therefore, the statistical power of the tests was limited due to the relatively small number of studies available for analysis of each variable. Second, substantial heterogeneity was observed in the number of patients requiring supplementary analgesia and the time to first analgesic request. Various potential confounding factors, such as variable dosage of administered medications and different follow-up times, may have contributed to this heterogeneity. In particular, although there was no significant difference in the time to first analgesic request between the two groups, the result was not absolutely reliable because of the great heterogeneity among the three studies<sup>11 16 21</sup> ( $I^2=100\%$ ;  $p<0.001$ ). Finally, observation periods were not long enough to determine if cartilage toxicity, an important side effect, was caused by IA bupivacaine or morphine.

## CONCLUSIONS

In conclusion, this meta-analysis of RCTs suggests that the administration of single-dose IA bupivacaine plus morphine after knee arthroscopic surgery is effective for pain relief, and that its short-term side effects are similar to those of saline placebo.

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