Effect of Methylprednisolone on Pain Management in Total Knee or Hip Arthroplasty: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Guoming Liu, M.D1, Min Gong, M.D1, Youcui Wang, Ph.D2, Zhou Xiang, M.D1*
1 Department of Orthopaedics, West China Hospital, Sichuan University, Chengdu, China
2 Institute of Brain Science and Disease, Qingdao University, Qingdao 266071, China
* Corresponding author: Dr. Zhou Xiang, Department of Orthopaedics, West China Hospital, Sichuan University, No. 37 Guoxue Road, Chengdu 610041, Sichuan, China. Tel: +86-18980601393; Fax: +86-02885423438; E-mail: xiangzhou15@hotmail.com

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Introduction

Total knee or hip arthroplasty (TKA/THA) is considered to be a successful strategy for the treatment of degenerative knee or hip arthritis\(^1\). However, patients suffer from moderate to severe pain in the early postoperative period, and postoperative pain management after TKA/THA still remains challenging issue\(^2\). Although several strategies have been proposed to relieve postoperative pain by nerve block, local infiltration anesthesia and opioid painkillers, the adverse effects including weakened muscle strength, urinary retention, nausea and vomiting, are quite worrisome\(^3-5\). Poor pain relief, as well as postoperative nausea and vomiting (PONV), can lead to patient's discomfort and dissatisfaction\(^6\), which are detrimental to early rehabilitation. Therefore, an effective pain relief and improving PONV will play a critical role in the fast track joint arthroplasty.

Methylprednisolone (MP), as a kind of glucocorticoids, has been widely used in various operations for its potential effect\(^7,8\). It is well known that glucocorticoids provide effective pain relief by decreasing pro-inflammatory mediators and reduce PONV by exerting an antiemetic effect after surgical operation\(^9\). Bjerregaard et al reported that preoperative MP significantly reduced pain and improved nausea and fatigue without obvious adverse effects\(^10\). Romundstad et al demonstrated that MP had a useful pain-relieving effect and reduced opioid consumption, and supported the use of MP for pain control after orthopaedic surgery\(^11\). Similarly, MP was also promising in reducing pain and hastening functional recovery in total joint arthroplasty\(^12\). However, some studies had confirmed that there were no significant
benefits of MP in relieving pain and reducing opioid consumption\textsuperscript{13}. In addition, glucocorticoids might cause some side effects including an increased risk of infection, delayed wound healing and transient hyperglycemia\textsuperscript{14}, which hampered their regular use. Consequently, comprehensive evaluation of the efficacy and safety of MP is indispensable.

Currently, whether MP is effective and safe in reducing pain and opioid consumption, as well as preventing nausea and vomiting following TKA or THA remains unclear due to a lack of evidence-based medicine evaluation. Therefore, we carried out this systemic review and meta-analysis to assess the efficacy and safety of MP for management of pain in TKA and THA.

**Materials and methods**

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed while preparing this systematic review\textsuperscript{15}.

**Search Strategy**

PubMed, EMBASE and Cochrane Library were searched to identify relevant articles from their inception to October 2017. The search term was as follows: (knee arthroplasty or hip arthroplasty or knee replacement or hip replacement or joint arthroplasty or TKA or THA) AND (Methylprednisolone or glucocorticoid or steroid or prednisolone). Only published articles were considered. In addition, reference lists of relevant articles were manually reviewed to identify additional trials.
Inclusion criteria and exclusion criteria

Inclusion criteria: (1) Randomized controlled trials (RCTs) in which patients undergoing unilateral primary TKA or THA. (2) Intravenous or local application of MP for pain management, and control group received placebo or saline. (3) Reported data included one of the following outcomes at least: visual analogue scale (VAS) at 6, 24 and 48 hours postoperatively; morphine consumption during the first 24 hours; the occurrence of postoperative nausea and vomiting (PONV), the level of C-reactive protein (CRP) at 24 hours postoperatively, range of motion (ROM), the length of hospital stay (LOS) and complications including surgical site infection and wound complication. (4) The searches were restricted to the English language.

Exclusion criteria: (1) Studies were not RCT. (2) Studies did not analyze TKA or THA. (3) Other glucocorticoids including hydrocortisone, dexamethasone and triamcinolone acetonide. (4) Animal studies.

Eligible studies were selected by two reviewers based on above criteria. Titles and abstracts were first reviewed. Full texts were scrutinized if sufficient information could not be obtained from the abstracts. Disagreements regarding which studies to include were resolved by discussion, and a third reviewer was consulted when necessary.

Data Abstraction

Two authors independently extracted the following basic information: first author, year of publication, number of patients, patient characteristics, anesthesia types, and
intervening measures. The primary outcomes included pain score of activity at 6, 24 and 48 hours postoperatively, and incidence of PONV. The secondary outcomes were as follows: pain score of rest at 24 hours postoperatively, morphine consumption for 24 hours, CRP concentration, complications including surgical site infection and wound complication, range of knee motion at first day postoperatively, and the length of hospital stay. The postoperative pain intensity was measured by 10-point visual analogue scale (VAS). The 100-point VAS was converted to a 10-point VAS score. The amounts of postoperative opioid analgesics consumed in different dosage forms were converted to equianalgesic doses of morphine. Data in other forms (i.e. P value, median, interquartile range (IQR) and range) were converted to mean ± standard deviation (SD) according to Cochrane Handbook and the method of Wan et al. Data were extracted by the software “Engauge Digitizer 4.1” from histogram if they were not shown in articles directly. When a consensus could not be reached, discrepancies were resolved by re-examining the source data and asking the opinion of a third author.

Risk of bias assessment

Two authors assessed the risk of bias of included studies independently according to the Cochrane Handbook for Systematic Reviews of Interventions, which includes the following items: randomization, allocation concealment, blinding of participants; blinding of outcome assessors; incomplete outcome data, selective reporting and other sources of bias. Based on the information provided from included studies, each item was recorded by “Yes”, “No”, or “Unclear”. “Yes” indicates low risk of bias, “No”
indicates high risk of bias, “Unclear” indicates lack of information or unknown risk of bias. Disagreement was resolved by the third author.

Statistical analysis

The meta-analysis was conducted with Review Manager (RevMan). Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2010. For continuous outcomes, weighted mean difference (WMD) and 95 % confidence interval (CI) were used to test the overall effect, and relative risk (RR) and 95 % CI were calculated for dichotomous outcomes. Heterogeneity among studies was estimated using $I^2$ statistic, and $I^2 > 50\%$ was considered as substantial heterogeneity$^{21}$, then the random-effect model was used. Otherwise, we choose the fixed-effect model. Subgroup or sensitivity analyses were conducted to explore the source of the heterogeneity. Potential publication bias of VAS at 24h during activity was assessed by Egger’s test (Stata12.0, StataCorp, College Station, Texas). $P < 0.05$ was considered statistically significant.

Results

Study characteristics

Our literature search initially yielded 532 relevant articles from the three databases, 118 of which were excluded as duplicates. After reading the titles and abstracts, 371 studies were excluded according to the inclusion criteria. The remaining 43 full-text articles were retrieved for more detailed evaluation. Finally, 6 RCTs$^{22-27}$ were identified in our study (Fig. 1). The studies were published between 2009 and 2017.
The cumulative sample size of 350 in unilateral primary TKA or THA comprised of 179 with MP and 171 without MP. Five studies performed primary TKA and one performed primary THA. Patient adjunctive analgesia was applied in all participates for concomitant pain management. The main characteristics of the included studies were presented in Table 1.

**Risk of bias assessment**

The risk of bias summary and risk of bias graph are shown in Figures 2 and 3, respectively. All RCTs provided clear inclusion and exclusion criteria, and all studies reported appropriate methods of random sequence generation. Allocation concealment was implemented adequately in all included studies. Other assessment, including blinding of participants and personnel and blinding of outcome assessment were well performed. Risk-of-bias analysis revealed that all the trials have a low or medium risk of bias.

**Pain scores**

Pain score was assessed by VAS at 6, 24, 48 hours during activity and 24 hours at rest. Two studies including 96 patients investigated pain score at 6 hours postoperatively, meta-analysis showed that the MP group had lower pain score than the control group (Fig 4A) (WMD= -3.06; 95%CI= -4.96 to -1.16; P=0.002; heterogeneity P=0.11, I²=61%). A random-effect model was used because of significant heterogeneity. Five articles including 287 patients reported the outcomes of VAS at 24 hours postoperatively during activity with substantial
heterogeneity ($I^2 = 71\%, P=0.008$). And a random-effect model was used to pool the data. Pooled results demonstrated that the MP group had lower pain score than the control group, but no significant difference was found between two groups (WMD=$-0.95$; 95%CI=$-2.17$ to $0.26$; $P=0.12$) (Fig 4B). Three studies involving 163 patients reported VAS scores at 48 hours. There was no significant difference between the MP group and the control groups (WMD=$-0.47$; 95%CI=$-1.13$ to $0.18$; $P=0.16$; heterogeneity $P=0.90$, $I^2=0\%$) (Fig 4C). Three studies involving 170 patients reported VAS scores at 24 hours at rest. There was no significant difference between the MP group and the control groups (WMD=$-1.07$; 95%CI=$-2.25$ to $0.12$; $P=0.08$; heterogeneity $P=0.02$, $I^2=74\%$) (Fig 4D).

Due to the great heterogeneity, sensitivity and subgroup analyses were conducted to determine potential sources of heterogeneity. We conducted a sensitivity analysis on VAS scores at 24 hours at rest by omitting one study because of different administration routes of MP. Meanwhile, a subgroup analysis was performed to determine the effects for intravenous approach and local administration of MP. The subgroup analysis indicated that intravenous MP was associated with a significant reduction in VAS scores at 24 hours during activity compared with the control group. Only three studies reported pain score at 48 hours during activity, thus it was not suitable to conduct subgroup analysis. These results were presented in Table 2. Meanwhile, the Egger's test ($P=0.510$) indicated no evidence of publication bias for VAS at 24 h during activity between MP group and control group (Table 3).

**The incidence of PONV**
Three studies involving 171 patients reported the occurrence of PONV. There was no statistical heterogeneity (heterogeneity $P=0.72$, $I^2=0\%$), and a fixed-effect model was applied. The pooled results indicated that patients using MP had significant reduction in the incidence of PONV ($RR=0.20$; $95\%CI=0.07$ to $0.55$; $P=0.002$). (Fig. 5)

**Opioid Consumption**

Four studies involving 212 patients assessed opioid consumption during the first 24 hours postoperatively with little heterogeneity ($I^2=10\%$). The combined data showed that there was no significant difference between the two groups ($WMD=-4.53$; $95\%CI=-9.77$ to $0.71$; $P=0.09$) (Fig. 6). Meanwhile, we performed a subgroup analysis to confirm the effect of MP on morphine consumption in TKA and THA respectively. The result was presented in Table 2.

**Inflammatory factor**

Four studies involving 199 patients reported data on inflammatory factors of CRP at 24 hours postoperatively with great heterogeneity ($I^2=79\%$). The pooled outcomes demonstrated that MP significantly decreased the inflammatory maker CRP compared with the control group ($WMD=-37.68$; $95\%CI=-57.07$ to $-18.28$; $P=0.0001$). (Fig. 7)

**Range of knee motion and length of hospital stay**

Two studies were included in this meta-analysis to assess the range of knee motion at the first day after surgery. The results did not find difference between both
groups (WMD=2.99; 95%CI=−11.11 to 17.10; P=0.68; heterogeneity P=0.0004, $I^2=92\%$) (Fig. 8)

The length of hospital stay was estimated in three trials\textsuperscript{22,25,26}. Meta-analysis revealed that no significant difference (WMD=−0.24; 95%CI=−0.74 to 0.25; P = 0.34) and evident heterogeneity ($I^2=67\%$) were found between both groups. (Fig. 9)

**Complications**

All studies\textsuperscript{22-27} reported the incidence of complications including postoperative infection or wound problems. The pooling results manifested that MP did not increased the incidence of complications after TKA or THA (RR=1.50; 95%CI=0.67 to 3.36; P = 0.32). No heterogeneity was identified, so a fixed-effect model was selected ($I^2=0\%$). (Fig. 10)

**Discussion**

This meta-analysis evaluated the efficacy and safety of MP for reducing postoperative pain after TKA and THA. The pooled results indicated that intravenous MP significantly reduced pain scores at 6 and 24 hours during activity after TKA and THA, but local injection of MP had no clear benefit in reducing pain scores at 24 hours compared with the control group. There was no significant difference in VAS at 24 hours at rest and 48 hours during activity after TKA and THA. Meanwhile, intravenous MP was associated with a reduction of morphine consumption during the first 24 hours. Furthermore, patients receiving MP had an obvious inflammatory control and improving PONV compared with the control group. And the use of MP
was not associated with a significant increase in the risk of complications. In addition, there was no significant difference in the range of knee motion and length of hospital stay in both groups.

Pain is a major concern in patients undergoing total joint arthroplasty. In the beginning, the results of this meta-analysis indicated that MP might not improve the analgesic efficacy at postoperative 24 and 48 hours. But due to the high level of heterogeneity, subgroup and sensitivity analyses were performed. Pooled results revealed that intravenous MP significantly reduced postoperative pain at 6 and 24 hours during activity. It should be note that although Egger's test showed no significant publication bias for VAS at 24 h during activity between MP group and control group, the result should be interpreted with great caution because of the limited number of studies.

A previous meta-analysis found that steroids decreased postoperative VAS at 2, 3, and 7 days compared with the control group. However, studies with various glucocorticoids were included in that meta-analysis, and we were not sure that it was just MP can decrease pain intensity in this time period. Generally, different types and administration routes of glucocorticoids were regarded as the cause of heterogeneity, so we independently analyze the analgesic effect of MP rather than other glucocorticoids, and the result indicated that intravenous MP significantly relieved pain intensity in the early postoperative period.
Surgery-induced inflammation can cause pain, muscle weakness and fatigue\textsuperscript{29,30}. Corticosteroids improved early postoperative pain by reducing inflammatory response\textsuperscript{31}. In this meta-analysis, we demonstrated that intravenous MP provided effective pain relief within postoperative 24 hours, meanwhile, the level of CRP was also significantly suppressed in MP group during this period. Therefore, it was concluded that pain control with MP might be associated with the inflammation inhibition. In addition, the results of pain and PONV are consistent with the previous study\textsuperscript{32}.

PONV are frequently associated with morphine-related side effects, which pose a great challenge after TJA and directly lead to patient's discomfort. A large number of studies supported the efficacy of corticosteroids as prophylactic antiemetics for PONV after operation\textsuperscript{33,34}. Meanwhile, MP had been recommended for reducing baseline risks of PONV by the guideline of the Society for Ambulatory Anesthesia\textsuperscript{35}. According to this meta-analysis, we demonstrated that MP significantly reduced the occurrence of PONV. The reason might be that MP had potent anti-emetic effects and thus prevented PONV. In addition, when MP was used to relieve pain, it was associated with decreased opioid consumption, thus the risk of opioid-related complications (PONV) was reduced.

Although MP may play a pivotal role in pain management and improvement of PONV, but its safety must be paid attention. A systemic review including 56 trials showed that glucocorticoids did not impact on any wound infection after elective noncardiac surgery\textsuperscript{36}. Moreover, Sauerland et al revealed that the administration of
MP was not associated with a significant increase in complication rates in surgical patients. However, postoperative infection and wound complication are identified as catastrophic complications for TKA or THA, the concern for these complications still prevent the application of MP at present. Cancienne et al found that preoperative intra-articular steroid injections were associated with a significant increase in infection after TKA. Furthermore, Mills et al suggested that intra-articular corticosteroid injection into a pre-existing TKA should be avoided because of the dire consequences of infection following TKA. The present meta-analysis results indicated that MP did not increase the incidence of postoperative infection and wound problems after TKA and THA. Therefore, existing evidence have not confirmed that postoperative infection was caused by the use of corticosteroids. In this study, sensitivity and subgroup analyses indicated that intravenous MP effectively relieved postoperative pain at 6 and 24 hours during activity, while local application of MP was not associated with a significant reduction in VAS scores compared with the control group. Based on safety of perioperative MP, we would recommend the application of intravenous MP as a promising strategy in pain management after joint arthroplasty. Further investigations are required due to small number of the included studies.

This study has several limitations. This study included both total hip and knee arthroplasty, as well as different administration routes and anesthesia management, which may have caused the observed heterogeneity. Then, some data reported as medians and ranges were transformed into mean and standard deviation by
calculation, potentially leading to other bias. Finally, although we prevented heterogeneity by restricting retrieval strategies (such as restricting the search to the English language and manual search on relevant articles), publication bias in this meta-analysis may influence the results. Due to the limited number of studies, we did not evaluate publication bias by funnel plot, and more large-sample and high-quality RCTs are needed to confirm the reliability of this study.

**Conclusions**

The present meta-analysis demonstrated that intravenous MP significantly alleviated early postoperative pain during activity and reduced morphine consumption as well as the incidence of PONV after TKA and THA. Meanwhile, MP significantly decreased the level of CRP, and was not associated with an increased risk of complications. However, local application of MP had no obvious benefit in the management of pain after TKA or THA. Therefore, intravenous MP provide good efficacy and safety on pain management in fast-track knee or hip arthroplasty.

**Conflicts of interest**

The authors declare that they have no conflicts of interest concerning this article.
References


**Figure Legends**

Fig. 1 Flow diagram of the selection of studies included in the review.

Fig. 2 Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.

Fig. 3 Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.

Fig. 4A, B, C, D Forest plot comparing VAS at 6, 24, 48 hours during activity and at 24 hours at rest between two groups.

Fig. 5 Forest plot comparing the occurrence of postoperative nausea and vomiting.

Fig. 6 Forest plot comparing morphine consumption during the first 24 hours.

Fig. 7 Forest plot comparing the level of CRP at 24 hours postoperatively.

Fig. 8 Forest plot showing postoperative range of knee motion at the first day after surgery.

Fig. 9 Forest plot showing the length of hospital stay.

Fig. 10 Forest plots comparing the risk of complications postoperatively.
<table>
<thead>
<tr>
<th>Study</th>
<th>Total (MP/C)</th>
<th>Anesthesia</th>
<th>Surgery (unilateral)</th>
<th>MP intervention</th>
<th>Control</th>
<th>administration time</th>
<th>Concomitant Pain Management</th>
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<tbody>
<tr>
<td>Christensen CP 2009</td>
<td>76(39/37)</td>
<td>General and FNB spinal</td>
<td>TKA</td>
<td>periarticular</td>
<td>normal saline</td>
<td>during operation</td>
<td>bupivacaine, morphine, paracetamol, naproxen, acetaminophen, ibuprofen, oxycodone, celecoxib, oxycodone, acetaminophen, gabapentin</td>
</tr>
<tr>
<td>Lindberg Larsen V 2017</td>
<td>63(33/30)</td>
<td>spinal TKA</td>
<td>periarticular</td>
<td>40mg normal saline</td>
<td>during pre-operation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luna IE 2017</td>
<td>40(21/19)</td>
<td>intravenous TKA</td>
<td>Intra-articular</td>
<td>125mg isotonic saline</td>
<td>during pre-operation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lunn TH 2011</td>
<td>48(24/24)</td>
<td>spinal TKA</td>
<td>periarticular</td>
<td>40mg isotonic saline</td>
<td>during pre-operation</td>
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<td>Lunn TH 2013</td>
<td>48(24/24)</td>
<td>spinal KHA</td>
<td>intravenous</td>
<td>125mg isotonic saline</td>
<td>pre-operation</td>
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<tr>
<td>Tsukada S 2016</td>
<td>75(38/37)</td>
<td>spinal TKA</td>
<td>periarticular</td>
<td>40mg normal saline</td>
<td>during operation</td>
<td></td>
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</table>

Table 1. The general characteristics of the included studies. MP: methylprednisolone, C: control, TKA: Total Knee Arthroplasty, THA: Total Hip Arthroplasty, NSAID: Non Steroid Anti-Inflammatory Drugs, FNB: Femoral Nerve Block.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Studies (n)</th>
<th>Patients (n)</th>
<th>P</th>
<th>WMD (95%CI)</th>
<th>Heterogeneity P (I²)</th>
<th>Model</th>
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</thead>
<tbody>
<tr>
<td>VAS at 24h (activity) Local injection</td>
<td>3</td>
<td>191</td>
<td>0.71</td>
<td>-0.28 [-1.70, 1.15]</td>
<td>0.03 (71%)</td>
<td>Random</td>
</tr>
<tr>
<td>Intravenous</td>
<td>2</td>
<td>96</td>
<td>0.03</td>
<td>-2.19 [-4.16, -0.22]</td>
<td>0.15 (51%)</td>
<td>Random</td>
</tr>
<tr>
<td>VAS at 24h (rest) Intravenous</td>
<td>2</td>
<td>96</td>
<td>0.29</td>
<td>-1.30 [-3.72, 1.11]</td>
<td>0.006 (87%)</td>
<td>Random</td>
</tr>
<tr>
<td>Morphine consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TKA</td>
<td>3</td>
<td>164</td>
<td>0.04</td>
<td>-8.73 [-17.16, -0.30]</td>
<td>0.41 (0%)</td>
<td>Fixed</td>
</tr>
<tr>
<td>THA</td>
<td>1</td>
<td>48</td>
<td>0.58</td>
<td>-1.88 [-8.57, 4.81]</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2. Subgroup and sensitivity analyses for VAS at 24 h during activity and at rest, and morphine consumption in TKA and THA, respectively. VAS: Visual Analogue Scale, TKA: Total Keen Arthroplasty, THA: Total Hip Arthroplasty. WMD: Weighted Mean Difference, CI: Confidence Interval.
| Std_Eff | Coef.   | Std. Err. | t  | P>|t| | 95% Conf. Interval |
|---------|---------|-----------|----|-----|-------------------|
| slope   | .9793292| 2.469352  | 0.40 | 0.718 | -6.87925 – 8.837909 |
| bias    | -2.602742| 3.490249 | -0.75 | 0.510 | -13.71027 – 8.504789 |

Table 3. Egger's test for VAS at 24 h during activity.
532 records identified in PubMed, EMBASE, and the Cochrane Library database

118 records after duplicates removed

43 records screened by full text

Excluded after reviewing title and abstract

Excluded based on full-text:
- Review articles
- Non-RCTs
- No MP treatment

15 studies included in the systematic review
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<tbody>
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<td>Christensen CP2009</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>LindbergLarsen V2017</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
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<td>Lunn TH2011</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
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<td>+</td>
<td>+</td>
<td>?</td>
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Adequate sequence generation? Yes
Allocation concealment? Yes
Blinding? Yes
Incomplete outcome data addressed? Yes
Free of selective reporting? Yes
Free of other bias? Yes
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<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio (95% CI)</th>
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<tr>
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<td>2</td>
<td>24</td>
<td>59.9%</td>
<td>0.17 [0.04, 0.67]</td>
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<td>1</td>
<td>24</td>
<td>30.0%</td>
<td>0.17 [0.02, 1.28]</td>
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<tr>
<td>Tsukada S2016</td>
<td>1</td>
<td>38</td>
<td>10.1%</td>
<td>0.49 [0.05, 5.14]</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>4</strong></td>
<td><strong>86</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.20 [0.07, 0.55]</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>20</strong></td>
<td></td>
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Heterogeneity: Chi² = 0.65, df = 2 (P = 0.72); I² = 0%
Test for overall effect: Z = 3.12 (P = 0.002)
<table>
<thead>
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<th>Total</th>
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<td>39</td>
<td>47.8</td>
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<td>21.87</td>
<td>24</td>
<td>30.26</td>
<td>21.87</td>
<td>24</td>
<td>17.9%</td>
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<td>6.86</td>
<td>24</td>
<td>15</td>
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<td>61.3%</td>
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<tr>
<td>Total</td>
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<td></td>
<td>108</td>
<td>104</td>
<td>100.0%</td>
<td></td>
<td>4.53 [-9.77, 0.71]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 3.34, df = 3 (P = 0.34); I² = 10%
Test for overall effect: Z = 1.83 (P = 0.09)
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>MP</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LindbergLarsen V2017</td>
<td>36.6</td>
<td>3.6</td>
<td>33</td>
<td>74.4</td>
<td>5</td>
<td>30</td>
<td>38.0%</td>
<td>-37.80</td>
<td>[-39.97, -35.63]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luna LE2017</td>
<td>190.55</td>
<td>103.89</td>
<td>21</td>
<td>139.64</td>
<td>103.89</td>
<td>19</td>
<td>7.3%</td>
<td>50.91</td>
<td>[-13.56, 115.38]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lunn TH2011</td>
<td>48.57</td>
<td>30.17</td>
<td>24</td>
<td>85.22</td>
<td>47.12</td>
<td>24</td>
<td>25.3%</td>
<td>-36.65</td>
<td>[-59.03, -14.27]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lunn TH2013</td>
<td>44.3</td>
<td>16.8</td>
<td>24</td>
<td>104.7</td>
<td>39.2</td>
<td>24</td>
<td>29.4%</td>
<td>-60.40</td>
<td>[-77.46, -43.34]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

102 | 97 | 100.0% | -37.68 | [-57.07, -18.28]

Heterogeneity: Tau² = 256.78; Chi² = 13.97, df = 3 (P = 0.003); I² = 79%
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>MP</th>
<th>Control</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christensen CP2009</td>
<td>2.6</td>
<td>3.5</td>
<td>26.9%</td>
</tr>
<tr>
<td>Lunn TH2011</td>
<td>2.35</td>
<td>2.35</td>
<td>0.0%</td>
</tr>
<tr>
<td>Lunn TH2013</td>
<td>1</td>
<td>1</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

- **Mean Difference**
  - MP: 2.6
  - Control: 3.5
  - **Weight**: 26.9%
  - **Mean Difference**: -0.90 [-1.55, -0.25]

**Heterogeneity**

- $\tau^2 = 0.13$
- $\chi^2 = 6.04$, df = 2 ($P = 0.05$)
- $I^2 = 67%$

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<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP</td>
<td>3</td>
<td>39</td>
<td>0</td>
<td>37</td>
<td>5.9%</td>
<td>6.65 [0.36, 124.51]</td>
</tr>
<tr>
<td>Control</td>
<td>0</td>
<td>33</td>
<td>0</td>
<td>30</td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Luna IE 2017</td>
<td>4</td>
<td>21</td>
<td>4</td>
<td>19</td>
<td>48.0%</td>
<td>0.90 [0.26, 3.12]</td>
</tr>
<tr>
<td>Lunn TH 2011</td>
<td>0</td>
<td>24</td>
<td>0</td>
<td>24</td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Lunn TH 2013</td>
<td>1</td>
<td>24</td>
<td>1</td>
<td>24</td>
<td>11.4%</td>
<td>1.00 [0.07, 15.08]</td>
</tr>
<tr>
<td>Tsukada S 2016</td>
<td>5</td>
<td>38</td>
<td>3</td>
<td>37</td>
<td>34.7%</td>
<td>1.62 [0.42, 6.31]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>179</td>
<td>171</td>
<td>100.0%</td>
<td>1.50 [0.67, 3.36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>13</td>
<td>8</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 1.73, df = 3 (P = 0.63); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.99 (P = 0.32)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>