Journal of Orthopaedics 43 (2023) 11–16

Contents lists available at ScienceDirect

Journal of Orthopaedics

journal homepage: www.elsevier.com/locate/jor

# Is particulate or non-particulate steroid the determinant of periarticular injection efficacy for controlling postoperative TKR pain? Network meta-analysis

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ARTICLE INFO

*Keywords:*
Steroid
Periarticular injection
Total knee replacement
Pain

ABSTRACT

*Purpose:* Combining steroids for a periarticular injection (PAI) regiment has resulted in better pain control for postoperative TKR pain. Despite the available evidence, the most effective type of steroid for PAI still needs to be established. Network meta-analysis is conducted to analyze whether there is any difference in the effect of particulate compared to non-particulate periarticular steroid injection on post-TKR patients for pain control based on published literature.

*Method:* This study is conducted following the PRISMA guideline. In general, studies assessing the efficacy of periarticular injection analgesia added with either particulate (Triamcinolone, methylprednisolone, or prednisolone) or non-particulate (dexamethasone or betamethasone) steroid compared to the same regiment were analyzed.

*Results:* Ten studies were finally included from the 108 identified papers through database searching. VAS reduction on POD1 is found to be similar in particulate (0,91; CI95%: 0,45-1,37) compared to non-particulate (0,81; CI95%: 0,34-1,28) (Fig. 2). The difference becomes wider and favors non-particulate POD3. Subgroup analysis based on each steroid type was conducted. A stark difference can be observed for each pair of steroids (particulate and non-particulate), resulting in a similar cumulative effect of particulate and non-particulate steroids and inconsistent result on POD1 compared to POD3.

*Conclusion:* From the available evidence, we concluded that particulate or non-particulate steroid does not significantly affect post-TKR pain management. Instead, the specific type of steroid contributes more to postoperative VAS reduction.

*Levels of evidence:* Level III.

## 1. Background

Total knee replacement (TKR) is one of the most common and effective procedures in managing severe knee pathology. The aging population consequently increases the incidence of knee OA and the number of TKR procedures conducted yearly. TKR procedure is estimated to increase six-fold within 25 years and amount to 3.5 million procedures.[1,2] As with any surgery, postoperative pain is a common early problem. Approximately 75% of TKR patients had significant postoperative pain, and 60% did not receive adequate treatment.[3] Inadequate postoperative pain management hinders optimal recovery, complicates hip-knee spine syndrome, or progresses to chronic conditions.[4,5]

Intraoperative periarticular injection of analgesics is commonly done to prevent postoperative TKR pain. The idea was initially published by Kerr and Kohan in 2008 and has been researched in multiple studies ever since. The result of these studies was found to be promising.[6,7] By intervening in nociceptive pathways on different levels, a synergistic

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https://doi.org/10.1016/j.jor.2023.07.015
Received 12 July 2023; Accepted 16 July 2023
Available online 20 July 2023

combination effect will be achieved, and side effects may be reduced. This effect is believed to be much more effective as it is applied directly to the source location of the pain.[8]

One of the major mechanisms underlying the pathophysiology of postoperative pain is the inflammation of the tissue around the knee. Steroids have a potent anti-inflammatory effect and are thought to significantly improve the analgesic effect of periarticular injection.[9,10] Many studies have assessed and compared the addition of steroids to a PAI cocktail, resulting in better pain control than injections without steroids.[11,12] The addition of steroid also decreases edema, reduce intraoperative blood loss, and increase range of motion (ROM) recovery.[13,14]

Despite the available evidence, the most effective steroid type for PAI adjuvant still needs to be established. Injectable steroids can be broadly divided into particulate or non-particulate. The main difference is their particle size, with particulate steroids (Triamcinolone and Methylprednisolone) having larger particles.[15] This difference in particle size results in differences in efficacy, duration of action, and complication. In epidural injections, non-particulate steroids result in less spinal infarction occurrence[16]]. In the context of PAI for TKR postoperative pain, a previous systematic review has suggested that particulate steroid is better than non-particulate steroids.[17]

Given its promising result and the lack of evidence on the specific steroid which is best for PAI, a network meta-analysis is conducted to analyze whether there is any difference in the effect of particulate compared to non-particulate periarticular steroid injection on post-TKR patients for pain control based on published literature. Subgroup analysis will also be done to affirm whether the specific steroid has a more significant effect than the steroid's particle size.

## 2. Method

### 2.1. Search strategy

This study is done following the PRISMA guideline.[18] In general, studies assessing the efficacy of periarticular injection analgesia added with either particulate (Triamcinolone, methylprednisolone, or prednisolone) or non-particulate (dexamethasone or betamethasone) steroid compared to the same regiment but without the steroid for postoperative TKR pain management from PubMed, Web of Science, ProQuest and SAGE databases from January 2012 up until December 2022 were noted. The keyword for each search engine is listed in Table 1.

Filter filters to exclude reviews, exclude books and apply time limits will be used if available. Manual searches by hand-searching reference lists from the included studies and reviews were also done.

**Table 1**
Keyword on each search engine.

| No. | Search Engine | Keyword |
|---|---|---|
| 1. | PubMed | ("Peri-Articular" OR "Periarticular") AND ("Knee Arthroplasty" OR "Knee Replacement") AND ("Triamcinolone" OR "Methylprednisolone" OR "Betamethasone" OR "Prednisolone") |
| 2. | Web of Science | ALL = (("Peri-Articular" OR "Periarticular") AND ("Knee Arthroplasty" OR "Knee Replacement") AND ("Triamcinolone" OR "Methylprednisolone" OR "Betamethasone" OR "Prednisolone")) |
| 3. | ProQuest | ("Peri-Articular" OR "Periarticular") AND ("Knee Arthroplasty" OR "Knee Replacement") AND ("Triamcinolone" OR "Methylprednisolone" OR "Betamethasone" OR "Prednisolone") |
| 4. | SAGE Journal | ("Peri-Articular" OR "Periarticular") AND ("Knee Arthroplasty" OR "Knee Replacement") AND ("Triamcinolone" OR "Methylprednisolone" OR "Betamethasone" OR "Prednisolone") |

### 2.2. Inclusion and exclusion criteria

Reviews, case series, and case reports were excluded from this systematic review. Moreover, studies that compare unicondylar knee arthroplasty administered the injection, not intraoperatively, and that need to clearly state the preoperative and postoperative VAS outcome data will be excluded. The primary outcome is the pain scale on postoperative day 1 (POD1). If available, the pain scale on postoperative day 3 (POD3) will also be analyzed as a secondary outcome. Search and screening for inclusion are conducted by two authors (JAS and ZKP). Should there be any dispute, it will be resolved by other reviewers (MZC).

### 2.3. Quality assessment

The quality of Evidence for the included studies will be assessed using RoB2 tools[19] by Cochrane for RCTs or ROBINS-I for non-RCTs. Summarizing the result of these tools, all studies will be assessed using eight criteria, and each criteria would have a final assessment of "low risk," "unclear risk of bias," and "High risk of bias." The final score from each criteria will be classified as low risk of bias, unclear risk of bias, or high risk of bias. Studies with a high risk of bias will be excluded from this study. Studies with an overall score of high risk of bias will be excluded from this study.

### 2.4. Data extraction

Basic data from each study (sample size, sex, age, type of TKR, and the perioperative analgetic regiment) will be tabulated. Outcomes of VAS on POD1, VAS on POD3, and any complications report will be tabulated. Forest plots and Network plots are created using MetaXL 5.3 software. If the data is displayed in graphs only, the exact number will be approximated using an online digital approximator (https://apps.automeris.io/). If there is no SD value, but the mean and p-value are available, then the SD will be approximated by the tools provided by Cochrane.[20] Should there be incomplete data, the author will try to contact the corresponding author of each study.

## 3. Result

From the 108 identified papers through database searching, 36 were excluded due to duplicates. Fourteen full-text articles were assessed, and only ten were finally included in the qualitative synthesis. The flowchart is depicted in Fig. 1. Each study is then assessed for risk of bias. Six were RCTs and therefore were assessed using RoB tools; meanwhile, the other four were NRCTs and were assessed using ROBINS-I. All studies were assessed to have a low risk of bias. ROBINS-I and RoB tools result is displayed in Figs. S1 and S2.

In total, data from 935 operated knees from 10 papers were tabulated. The patients were aged, on average, 57,2 (47-88) years old. Six studies use Particulate steroids, three use Non-Particulate Steroids, and one compared both particulate and non-particulate steroids (Table 2).

Spinal anesthesia was mostly used for the TKA procedure. All PAI regiments used 150–300 mg ropivacaine and 0,3-0,6 mg epinephrine. Another commonly used analgesic is morphine added with one other analgesic, which varies from study to study: ketorolac, clonidine, isepamicin, or flurbiprofen. Celecoxib is commonly used as a preoperative analgesia regiment. Meanwhile, postoperatively patient-controlled analgesia (PCA) using fentanyl is the most commonly used (Table 3).

VAS reduction on POD1 is found to be similar in particulate (0,91; CI95%: 0,45-1,37) compared to non-particulate (0,81; CI95%: 0,34-1,28) (Fig. 2). The difference becomes wider and favors non-particulate on POD3 with VAS reduction of 1,01 (CI95%; 0,27-1,75) for non-particulate and 0,61 (CI95%; −0,12 - 1,34) for particulate steroid (Fig. 4). Network plots are also depicted next to each forest plot (Figs. 2–5).

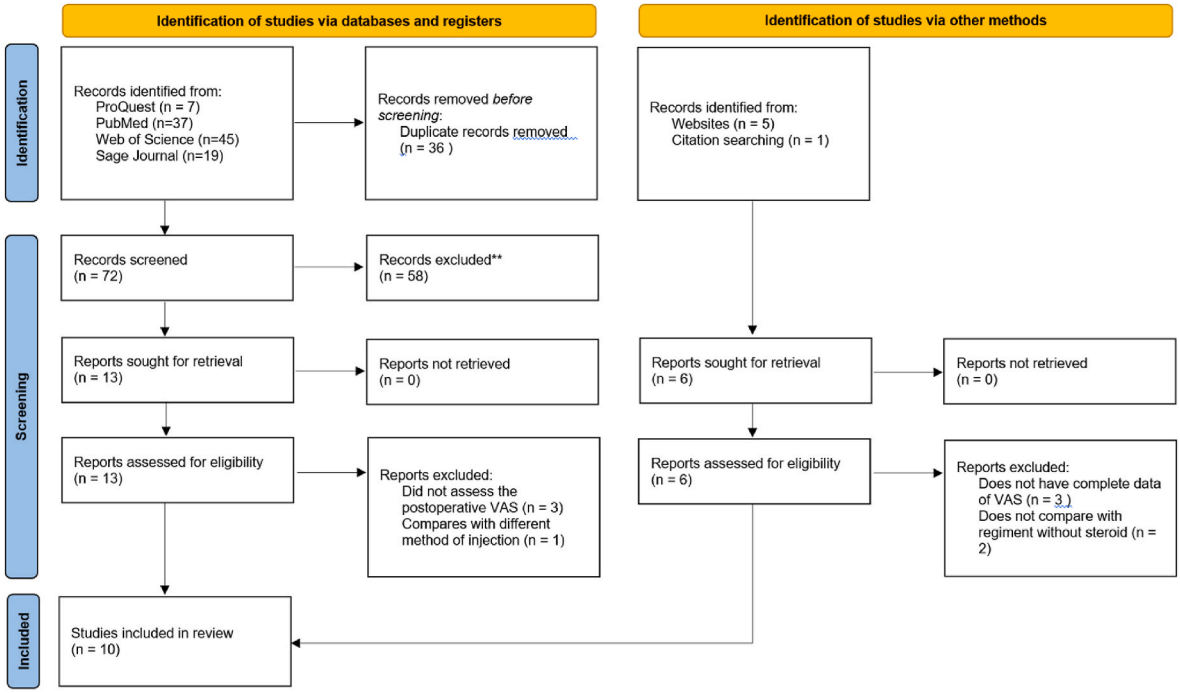


**Fig. 1.** Database searching flowchart.

**Table 2**
Basic Demographic Data from the Studies.

| Author,Year | Patients | Knee | Gender (Male) | Age | Type of TKR | Study Type | Type of Steroid for Treatment Group |
|---|---|---|---|---|---|---|---|
| **Chan VWK, 2020** | 46 | 92 | 30,40% | 65 ± 6 | One Stage Bilateral TKR (PS/CR not Mentioned) | RCT | 40 mg Triamcinolone |
| **Kim JI, 2019** | 100 | 100 | 10% | 73.1 ± 4.9 | Unilateral PS TKR | Retrospective Cohort Study | 40 mg Methylprednisolone |
| **Kulkarni M. 2019** | 50 | 100 | 26% | 67 ± 7.5 | One Stage Bilateral PS TKR | NRCT | 40 mg Methylprednisolone |
| **Tsukada S, 2016** | 77 | 77 | 13% | 74 (47-88) | Unilateral TKA (PS/CR is not mentioned) | RCT | 40 mg Methylprednisolone |
| **Kwon SK. 2014** | 82 | 82 | 0% | 69.3 (62-77) | Two Stage Bilateral PS TKR | RCT | 40 mg Triamcinolone |
| **Reddy AVG, 2018** | 140 | 140 | NR | NR | Unilateral TKR (PS/CR is not mentioned) | NRCT | 100 mg Methylprednisolone |
| **Oshima A, 2022** | 102 | 102 | 20,60% | 73,1 ± 6,95 | Unilateral TKR (PS/CR is not mentioned) | Retrospective Cohort Study | 10 mg dexamethasone or 40 mg triamcinolone |
| **Ikeuchi M. 2014** | 20 | 20 | 10% | 77 ± 2 | Unilateral PS TKR | RCT | 6,6 mg Dexamethasone |
| **Peng H. 2021** | 60 | 120 | 6,67% | 65,1 ± 6,8 | One Stage Bilateral TKR (PS/CR is not reported) | RCT | 7 mg Betamethasone |
| **Wang Q, 2020** | 102 | 102 | 31,30% | 64,5 ± 7,6 | Unilateral PS TKR | RCT | 0,1 mg/mL dexamethasone (Specifice dose NR) |

Note: Studies highlighted in yellow used Non-Particulate Steroids, no highlight used both steroid, and highlighted in green used Particulate steroid
NR = Not Reported; TKR = Total Knee Replacement; PS = Posterior Stabilizing; CR = Cruciate Retaining; RCT = Randomized Controlled Trial; NRCT = Non-Randomized Controlled Trial

To assess this result further, subgroup analysis based on each steroid type is conducted (Figs. 3 and 5). Six studies reported their VAS result on POD3 and were analyzed. On POD1, the addition of methylprednisolone served as better addition to the PAI regiment as it resulted in the best VAS reduction (1,14; CI 95%; 0,4-1,88). Betamethasone has almost no effect on POD1. On POD3, the effect of methylprednisolone is less (0,39;

**Table 3**
Analgetic Regiment from by Each Study.

| Author,Year | Preoperative analgesia regiment | Intraoperative Anesthesia | Intraoperative Analgesia Regiment (Control) | Postoperative analgesia regiment |
|---|---|---|---|---|
| **Chan VWK, 2020** | 1g paracetamol, 75 mg pregabalin, 200 mg celecoxib | Spinal Anesthesia + 16 mg IV dexamethasone | 150 mg ropivacaine, 15 mg ketorolac, and 1 mg adrenaline | NR |
| **Kim JI, 2019** | 200 mg of celecoxib and UltracetER semi® (325 mg of acetaminophen/37.5 mg of tramadol) | Spinal anaesthesia + tourniquet inflation 300 mmHg | 300mg ropivacaine, 5mg morphine sulphate, 60mg ketorolac, and 0.6mg epinephrine | 25-µg fentanyl patch and an IV PCA consisting of 2 mg fentanyl. 200 mg of celecoxib, Ultracet ER semi®, and 5 mg of oxycodone every 12 hours |
| **Kulkarni M. 2019** | 650mg paracetamol and 100 mg gabapentin | Spinal Anesthetic (0.5% bupivacaine) | 300mg ropivacaine, 30 mg Ketorolac, 90 mg Clonidine, and 0,3 mg Adrenaline | IV paracetamol 1g IV tramadol 50 mg Oral Diclofenac 75 mg |
| **Tsukada S, 2016** | NR | Spinal anesthesia | 300 mg ropivacaine, 50 mg of ketoprofen, 8 mg morphine hydrochloride hydrate, and 0,3 mg epinephrine | 50 mg flurbiprofen axetil on 4 hours postoperative and 60 mg of oral loxoprofen every 8 hours |
| **Kwon SK. 2014** | Oral analgesic pills (200 mg celecoxib, 362.5 mg ultracet, and 75 mg pregabalin) | Spinal Anesthetic (0.5% bupivacaine) | 300 mg ropivacaine, 50 mg of ketoprofen, 8 mg morphine hydrochloride hydrate, and 0,3 mg epinephrine | PCA of 500 mikrogram fentanyl and 30 ml 0.5% bupivacaine > 200 mg celecoxib dan 362.5 ultracet every 12 hours |
| **Reddy AVG, 2018** | NR | NR | 300 mg ropivacaine, 30 mg ketorolac, 10 mg morphine sulfate, and 0,3 mg epinephrine | 1 g paracetamol every 8 h, 75 mg pregabaline once daily, buprenorphine patch for 4 weeks IV morphine for rescue analgesia |
| **Oshima A, 2022** | 75 mg ropivacaine | General Anesthesia | 0,2% ropivacaine, 60 mg ketorolac, 8 mg morphine sulvate, and 300 ug epinephrine | 1g acetaminophen every 8 h, 15 mg intramuscular pentazocine, and 25 mg transrectal diclovenac |
| **Ikeuchi M. 2014** | NR | General Anesthesia | 150 mg ropivacaine | PCA of 200 mcg fentanyl + 180 mg loxoprofen until POD5 |
| **Peng H. 2021** | NR | NR | 150 mg ropivacaine and 400 mg isepamicin | PCA of 1 mg morphine continued with 2x40 mg parecoxib for 3 days. Followed by 60 mg loxoprofen |
| **Wang Q, 2020** | 2x200 mg of celecoxib | NR | Ropivacaine, adrenaline, flurbiprofen, tranexamic acid, and morphine (specific dose is not mentioned) | 200 mg of Celecoxib twice a day 10 mg of morphine as rescue analgesic |

Note: Studies highlighted in yellow used Non-Particulate Steroids, no highlight used both steroid, and highlighted in green used Particulate steroid

PCA = Patient Controlled Analgesia

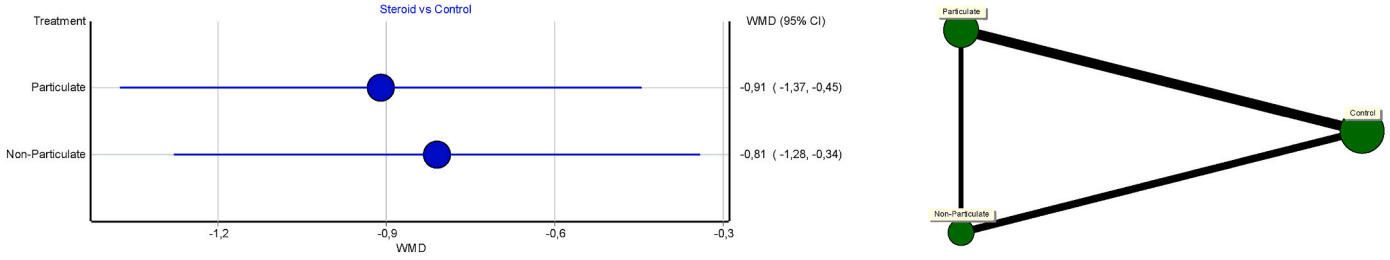


**Fig. 2.** Forest Plot and Network Plot for Particulate and Non-Particulate Steroids compared to Control on VAS POD1.

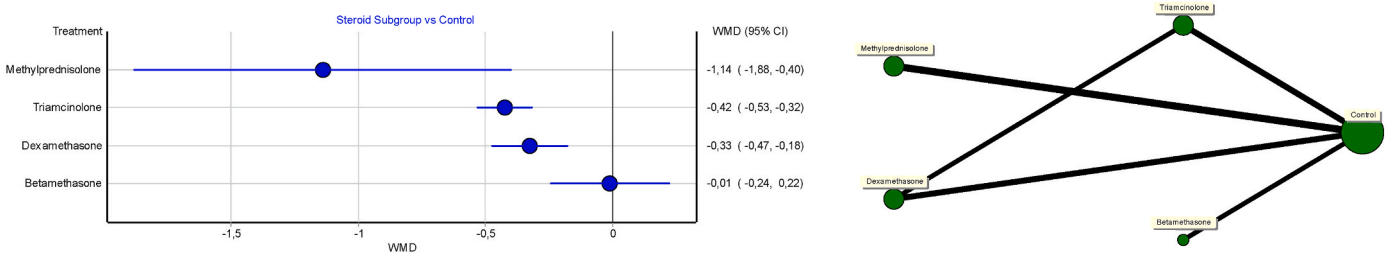


**Fig. 3.** Forest Plot and Network Plot Specific Steroids compared to Control on VAS POD1.

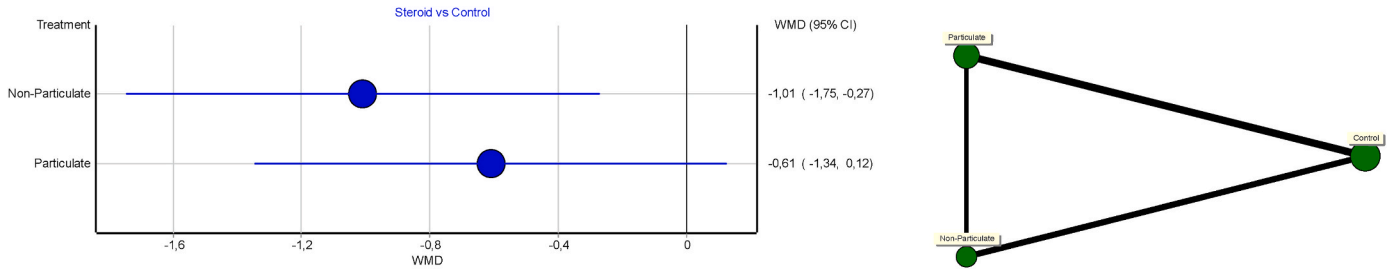


**Fig. 4.** Forest Plot and Network Plot for Particulate and Non-Particulate Steroids compared to Control on VAS POD3.

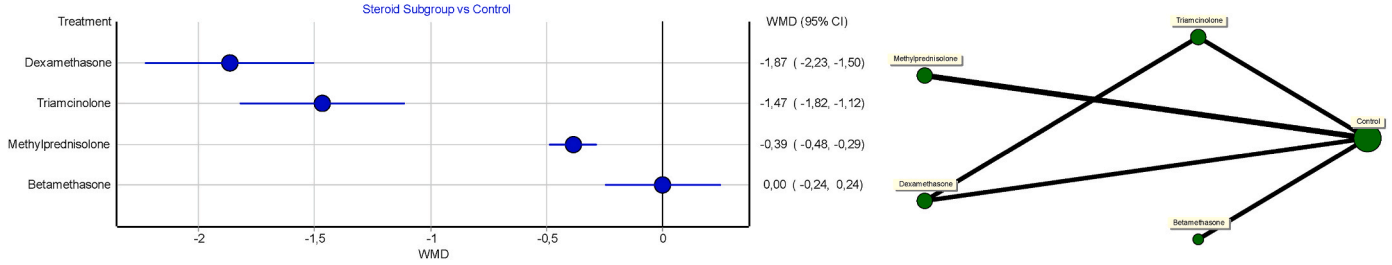


**Fig. 5.** Forest Plot and Network Plot for Specific Steroids compared to Control on VAS POD.

CI95%; 0,29-0,48), but the effect of dexamethasone (1,87; CI95%; 1,5-2,23) and triamcinolone (1,47; CI95%; 1,12-1,82) becomes greater. Betamethasone still becomes the worst performer compared to the other three steroids.

All the complications occurring in patients given steroids are tabulated in Table 4. From the available data, nausea and vomiting are the samples' most common complications. Wound oozing and nerve damage were common but theoretically unrelated to steroid use. None of the studies reported infection in the patients.

## 4. Discussion

The underlying mechanism that underlies postoperative pain is complex. Broadly, the pain is caused by peripheral sensitization due to inflammation, secondary hyperalgesia due to central sensitization, and neuropathic pain. The concept of multimodal analgesia has improved the analgesic effect by attacking the three main mechanisms of postoperative pain without increasing the dose of certain drugs and reducing the adverse effect of certain drugs, especially opioids.[21] In the context of PAI, morphine is the most commonly used opioid.

Steroid, as an adjuvant for PAI, mainly reduces peripheral sensitization through its anti-inflammatory effect. Aside from its analgesic effect, administering steroids for postoperative pain management has also led to better postoperative ROM recovery, shorter hospital length of stay, and reduced opioid/morphine consumption.[22]

In theory, drugs with smaller size and higher solubility, as termed "Particulate" and "non-particulate" steroid, has an effect on their faster clearance time from the targeted tissue, shorter duration of action, and, consequently, their overall analgetic effect.[23] The difference in preservative content of the commercially available steroids might also contribute to the difference in efficacy of both steroid.[24]

Regarding particulate compared to non-particulate steroids, we found comparable results between both types of steroids on POD1 and POD3. The consistent result can be seen in POD1 result as the pair of specific steroids of particulate steroid (Triamcinolone and methylprednisolone) has a similarly high VAS reduction effect compared to the non-particulate steroids (dexamethasone and betamethasone). On the contrary, on POD3, stark differences can be observed for each pair resulting in the similar cumulative effect of particulate and non-particulate steroids.

Only one study used betamethasone for the treatment arm, which might affect the result of this study. In its study, adding betamethasone

**Table 4**
Complication reported.

| Author,Year | Complications | | | | | |
|---|---|---|---|---|---|---|
| | Infection | Wound Oozing | Nausea Vomiting | Pruritus | Nerve Damage | Fever |
| Chan VWK, 2020 | 0% | 0% | 0% | 0% | 0% | 0% |
| Kim JI, 2019 | 0% | 2% | 0% | 0% | 0% | 0% |
| Kulkarni M. 2019 | 0% | NR | NR | NR | NR | NR |
| Tsukada S 2016 | 0% | 0% | 3% | 3% | 8% | 0% |
| Kwon SK. 2014 | 0% | 8.3% | 16.6% | 0% | 0% | 0% |
| Reddy AVG, 2018 | 0% | NR | NR | NR | NR | NR |
| Oshima A, 2022 | NR | NR | 11,8% | NR | NR | 6% |
| Ikeuchi M. 2014 | 0% | 0% | 5% | 0% | 0% | 0% |
| Peng H. 2021 | 0% | 0% | 32% | 0% | 0% | 0% |
| Wang Q, 2020 | 0% | 8% | 36% | 0% | 2% | 0% |

Note: Studies highlighted in yellow used Non-Particulate Steroids, no highlight used both steroid, and highlighted in green used Particulate steroid

to the PAI regiment had an identical result to those injected without betamethasone.[25]

One of the most feared complications of steroid use on the knee is that steroids increase the possibility of infection and patellar tendon breakup.[26] None of this occurred in the studies included. Nausea and vomiting are related to the use of opioids. It is expected that the incidence of nausea and vomiting to be reduced with the addition of steroids because, with better pain control, there will be less postoperative total morphine consumption and, consequently, opioid-related adverse effects.[27]

## 5. Conclusion

From the available evidence, particulate or non-particulate steroid does not significantly affect post-TKR pain management. Instead, the specific type of steroid contributes more to postoperative VAS reduction. In particular, further research should focus more on dexamethasone and triamcinolone as both consistently provide postoperative pain control on both POD1 and POD3.

## Author contribution

MZC: Conceptualization, Methodology, Supervision, Validation; JAS: Investigation, Roles/Writing-original draft, Visualization; ZKP: Formal analysis, Investigation, Roles/writing-original draft; PSH: Validation, Data curation, Project administration, Writing-review editing; MU: Resources, Formal analysis, Validation.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgement

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jor.2023.07.015.

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