Efficacy of Additional Corticosteroids to Multimodal Cocktail Periarticular Injection in Total Knee Arthroplasty: A Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: As the ultimate method for the treatment of osteoarthritis, total knee arthroplasty (TKA) has been widely used in clinic. Local injection of multimodal cocktails, including corticosteroids, is commonly used for pain management after TKA. This meta-analysis aims to systematically evaluate the effect of periarticular injection of corticosteroids on postoperative pain relief and knee functional recovery in patients undergoing TKA.

Methods: PubMed, Cochrane Library, EMBASE and Web of Science databases were comprehensively searched for all randomized controlled trials (RCTs) published before July 1st, 2020 that investigated the efficacy of corticosteroids for TKA.

Results: Ten RCTs involving a total of 829 patients were assessed in the meta-analysis. Compared with the control group, the Visual Analogue Scale (VAS) score at rest of the corticosteroids group decreased significantly at postoperative day 1(POD1), POD2 and POD3($P<0.05$). Besides, the range of flexion motion of the knee joint in corticosteroids group at POD1 and POD2 was significantly increased($P<0.05$), at the same time, the range of extension motion at POD2 and POD3 showed the opposite trend between the two groups($P<0.05$). The morphine equivalent of postoperative analgesia was significantly reduced($P<0.05$), and the time required for straight leg raising(SLR) was significantly shortened($P<0.05$). There was no significant difference between the two groups in terms of postoperative drainage, length of hospital stay, and complications such as infection, nausea and vomiting($P>0.05$).

Conclusion: The additional corticosteroids to multimodal cocktail periarticular injection can relieve the early pain intensity at rest after TKA, increase the early range of motion(ROM) of the knee joint, reduce the dosage of postoperative analgesics, and shorten the duration of time required for SLR.However, it has no effect on reducing postoperative complications and shortening the length of hospital stay.

Background

Total knee arthroplasty (TKA) is the ultimate treatment for severe knee arthritis, but it often leads to unbearable postoperative pain and pain-related knee joint dysfunction[1, 2]. Perfect postoperative analgesia is essential to improve patient comfort and promote their rapid recovery[3, 4].

Periarticular infltration analgesia is widely used in clinic to relieve pain after TKA[5, 6]. It can suppress the inflammation at the surgical site, provide satisfactory analgesic effects, and maintain muscle strength, reduce the consumption of opioids and related complications[6–8]. Corticosteroids have been widely used in various surgical procedures as an anti-inflammatory drug[9, 10]. Some studies have reported that the addition of corticosteroids to multimodal cocktail periarticular injection can inhibit inflammation and provide additional analgesia[11, 12], while others have found no benefit and may even increase the risk of complications[13, 14]. Prior to this, some related meta-analysis has been conducted. The study of Fan et al.[15], Zhou et al.[16], and Meng et al.[17] combined the intravenous and local application of corticosteroids for analysis. Chai et al.[18] failed to distinguish between periarticular injection and intra-articular injection in the study, and did not convert different kinds of drugs in thel analysis of postoperative analgesic consumption. In addition, most of the previous meta-analysis included a small number of studies and sample sizes, and the above factors ultimately led to poor credibility of the existing meta-analysis,so it is necessary to make further analysis.

In order to solve this problem,this meta-analysis by analyzing the current RCTs, aims to clarify whether periarticular injection including corticosteroids can relieve postoperative pain, improve knee joint function, and explore its safety.

Methods

We conduct this meta-analysis according to the rules of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[19].

Search Strategies

The PubMed, Cochrane Library, EMBASE and Web of Science databases were comprehensively searched for randomized controlled clinical trials (RCTs) published before July 2020 that investigated the efficacy of additional corticosteroids to multimodal cocktail periarticular injection in TKA. In addition, the reference lists of all included studies were checked for any potential additional publications. We used the key words of knee arthroplasty, knee replacement, Glucocorticoids, glucocorticosteroid, corticosteroid, and so on. The detailed search strategies for each database were presented in the Supplemental materials (Supplementary Table. 1 Details about the search strategies).

Inclusion and Exclusion Criteria

Inclusion criteria:

(1) randomized controlled trials (RCTs); (2) the target population consisted of patients undergoing unilateral primary TKA; (3) additional corticosteroids added in multimodal cocktail for corticosteroids group; (4) no other difference between the corticosteroids group and control group besides the administration of corticosteroids; (5) only periarticular injection approach was administered; (6)the outcomes were related with VAS, range of motion(ROM) of the knee, postoperative drainage, duration of time required for straight leg raising(SLR), length of hospital stay, consumption of opioid for postoperative analgesia, incidence of complications such as postoperative infection, wound oozing, nausea and vomiting; (7) the full-text was available.

Exclusion criteria:

(1) patients under-going bilateral TKA, unicondylar knee arthroplasty or revision; (2) patients with a long history of corticosteroids medication; (2) intra-articular injection; (3) animal studies.

Data Extraction

Two reviewers independently screened the papers from their titles and abstracts and selected relevant studies met the eligibility criteria. Data were extracted and collated independently by the same two reviewers independently with any disagreement settled by a third reviewer. We would send an e-mail to the original investigators when requisite data were lacking in the publications.

The following items were extracted: (1) basic information: name of the first author, publication date, sample size, demographic data of participants; (2) techniques: corticosteroids type, dosages, drug regimens; perioperative medication and anesthesia method; (3)primary outcome: VAS scores at rest and on motion, range of motion(ROM) of the knee; (4) secondary outcome: postoperative drainage, duration of time required for straight leg raising(SLR), length of hospital stay, consumption of opioid for postoperative analgesia, incidence of complications such as postoperative infection, wound oozing, nausea and vomiting. The raw data were presented in the supplementary materials (Supplementary Table. 2 Raw data).

Statistical analysis

The meta-analysis was conducted using Review Manager Software (Revman 5.4, Cochrane Collaboration,Oxford, United Kingdom) . Conticnuous data was expressed by weighted mean difference (WMD) and 95% confidence interval (CI) , and dichotomous data was expressed by relative risk (RR) and 95%CI. Cochran's Q test and Higgins' I^2 statistical test were used to assess the statistical heterogeneity. The results showed low level of heterogeneity when I^2≤50%, and a fixed-effects model would be used. The results showed significant heterogeneity when I^2≥50%, then sensitivity analysis and subgroup analyses would be conducted to find the source of the heterogeneity. If the heterogeneity could not be eliminated, a random-effects model that estimated the uncertainty of results with sampling error and studies variance would be used when the related studies had no clinical heterogeneity. Descriptive analysis was used for data that cannot be merged.

Risk of bias assessment was done by using Cochrane Collaboration tool (Cochrane, London, UK). Finally, a funnel plot was used to assess potential publication bias visually.

Results

Search results and study characteristics

A total of 675 articles were retrieved, and 271 of them remained after excluding duplicate articles. After reading the title and abstract, 199 articles were eliminated, leaving 72. 62 articles were discarded for various reasons(retrospective study, review article, unicondylar knee arthroplasty, case report, intravenous injection and expert consensus or guide) when the full text was browsed for further screening, and 10 studies[11, 12, 14, 20-26] finally met the inclusion criteria(Figure. 1 Flow chart of study selection). The characteristics of the 10 studies involved 829 participants were summarized in Table. 1 Characteristics of the included studies.

Primary Outcomes

VAS score at rest

The pooling results showed that the VAS score at rest of the corticosteroids group was significantly lower than that of the control group at postoperative day 1(POD1) (MD: -0.65; 95% CI: -1.29 to -0.01; p<0.05; I2=82%) , POD2 (MD: -0.33; 95% CI: -0.50 to -0.16; p<0.05; I2=0%) and POD3 (MD: -0.40; 95% CI: -0.69 to -0.12; p<0.05; I2=30%) day after operation. There was no significant difference in VAS score at the operation night, POD4, POD5, POD7 and 2 weeks after operation.The meta-analysis result at POD1 showed heterogeneity. Sensitivity analysis and subgroup analysis failed to find the source of heterogeneity. Considering that there was no clinical heterogeneity in these studies, a random effect model was used to analyze it. The rest of the data was analyzed using fixed effects. (Figure. 2 VAS score at rest).

VAS score on motion

The results showed that there was no significant difference in VAS score on motion between the corticosteroids group and control group at POD1, POD2 and POD3. The meta-analysis results showed obvious heterogeneity at POD1. Sensitivity analysis and subgroup analysis could not eliminate heterogeneity, so random effect model was used to analyze the relevant results. The rest datas were analyzed by fixed effect. VAS scores at other time points after operation were not analyzed because of the limited sample size. (Figure. 3 VAS score on motion).

Range of flexion motion

Compared with the control group, the range of flexion motion of knee joint was increased in the corticosteroids group at POD1 (MD: 5.38; 95% CI: 2.39 to 8.37; p<0.05; I2=0%) and POD2 (MD: 3.35; 95% CI: 0.53 to 6.17; p<0.05; I2=47%). However, there was no significant difference between the two groups at POD3, POD4, POD5, POD7 and 2, 4, 6, 12, 24 weeks after surgery.Heterogeneity was detected at 4 weeks after operation. Sensitivity analysis and subgroup analysis failed to eliminate the heterogeneity, so random effect model was used. (Figure. 4 Range of flexion motion).

Range of extension motion

The results showed that the range of extension motion in the corticosteroids group decreased at POD2 (MD: -2.09; 95% CI: -3.80 to -0.38; p<0.05; I2=23%) and POD3 (MD: -2.01; 95% CI: -3.54 to -0.49; p<0.05; I2=39%) compared with the control group. On the contrary, there was no significant difference between the two groups at POD1, POD4 and POD5. There was certain heterogeneity in the data at POD1, but it could not be eliminated after sensitivity analysis and subgroup

analysis. After confirming that there was no clinical heterogeneity in the related studies, the random effect model was applied.(Figure. 5 Range of extension motion).

Secondary Outcomes

Morphine equivalent for postoperative analgesia

A total of 5 studies, 389 cases involved opioid consumption for postoperative analgesi. All opioid doses were converted to corresponding morphine equivalent for statistical analysis in this meta-analysis. The results showed that the postoperative analgesic dosage of patients in the corticosteroids group was significantly less than that of the control group (MD: -4.68; 95% CI: -5.93 to -3.43; p<0.05; I2=0%). (Figure. 6 Morphine equivalent).

postoperative drainage

The postoperative knee joint drainage was recorded in 3 studies including 292 patients. The results showed that there was no significant difference in drainage volume between the two groups (MD: -9.41; 95% CI: -47.61 to 28.80; p0.05; I2=49%). (Figure. 7 Postoperative drainage).

Time required for straight leg raising(SLR) and length of hospital stay

The time required for SLR, was shown in 2 studies, involving 252 cases, and better outcome was shown in corticosteroids group (MD: -0.58; 95% CI: -0.81 to -0.35; p0.05; I2=0%). (Figure. 8 Time required for straight leg raising). The length of hospital stay was reported in 3 studies, with 278 cases, and the pooled outcomes showed no significant difference (MD: -0.78; 95% CI: -1.85 to 0.28; p0.05; I2=93%). (Figure. 9 Length of hospital stay). Random effect model was used to analyze datas about length of hospital stay, because related studies had clinical homogeneity, besides, sensitivity analysis and subgroup analysis could not eliminate the heterogeneity.

Incidence of complications

A total of 9 studies, 758 cases reported the occurrence of postoperative surgical site infection. Six of the studies showed that there was no postoperative infection occurred in the two groups. The meta-analysis results of the remaining three studies indicated that no significant difference existed in the incidence of infection between the two groups (RR: 1.98; 95% CI:0.37 to 10.66; p0.05; I2=0%). Two studies involving 202 cases reported no tendon rupture occurred in both groups. Five studies, involving 455 cases, recorded postoperative nausea and vomiting (RR: 1.08; 95% CI:0.69 to 1.69; p0.05; I2=0%), and 3 studies with 329 cases showed the wound oozing (RR: 1.30; 95% CI:0.55 to 3.07; p0.05; I2=0%). Pooled outcomes showed no significant difference. (Figure. 10 Incidence of complications).

Bias Assessment

We can learn from the risk of bias graph (Figure. 11 Risk of bias graph), two studies[14, 22] had high risk for attrition bias, while other studies have not found any high risk items. As for the publication bias, the funnel plot has no obvious asymmetry, so we concluded that there was no significant publication bias. (Figure. 12 Funnel plot).

Discussion

Severe postoperative pain of TKA significantly affects the patient's experience and postoperative rapid recovery. Exploring effective postoperative analgesia is of great significance.Patient controlled intravenous analgesia (PCIA) often requires large doses of opioid analgesics, which often lead to complications such as nausea and vomiting, skin itching and even respiratory depression[27]. Epidural block and femoral nerve block are effective methods for pain control after TKA, but they may weaken the strength of quadriceps femoris and affect the early rehabilitation of patients[6, 28, 29].Adductor canal block can provide the same postoperative analgesic effect as femoral nerve block without inhibiting the strength of quadriceps femoris, but it can not effectively cover the lateral and posterior part of the knee[30, 31]. From the above, it can be seen that conventional analgesic methods are difficult to provide perfect analgesic effect after TKA, and it is of great clinical value to explore new analgesic methods. Some studies have shown that periarticular injection can obtain good analgesic effect, and even improve the postoperative range of motion and promote rehabilitation[6, 32, 33]. Local injections often contain local anesthetics such as ropivacaine or bupivacaine, epinephrine, nonsteroidal antiinflammatory drugs and morphine[6, 21, 34]. In addition, some studies have added corticosteroids to multimodal cocktail periarticular injection, but the results are not consistent[12, 14, 21, 23, 24, 26, 35]. Although current studies have not found that corticosteroids increase the risk of serious complications such as postoperative infection, their clinical application is still concerned. The purpose of this meta-analysis was to evaluate whether the addition of corticosteroids to periarticular injection can relieve postoperative pain and promote knee function recovery after TKA, and to determine whether it is safe enough.

The results of this study showed that the addition of corticosteroids to the periarticular injection could relieve the pain score at rest from POD1 to POD3, improve flexion range of POD1 and POD2 and extension range of POD2 and POD3. In addition, it also reduces the postoperative consumption of opioids and promotes the recovery of straight leg raising function. Similar to previous studies, corticosteroids did not increase the incidence of adverse reactions such as infection, tendon rupture, wound oozing, nausea and vomiting. However, our research results show that corticosteroids are not significantly helpful in relieving pain scores on motion, reducing wound drainage, and shortening hospital stay.

There is a close relationship between postoperative pain and inflammatory response[36]. Some studies have shown that corticosteroids can alleviate pain by inhibiting inflammatory response[20, 37]. However, due to the lack of relevant studies, this meta-analysis did not make detailed statistics on inflammatory indicators such as C-reactive protein, erythrocyte sedimentation rate, IL-6. Better knee function recovery may be related to better pain relief. There was no significant difference in the range of knee joint motion between the two groups at POD4, which may reflect that corticosteroids cannot provide long-lasting

analgesia. In summary, our results show that although the addition of corticosteroids to multimodal cocktail periarticular injection does not significantly help the long-term rehabilitation after TKA, it can obviously alleviate the early postoperative pain and improve the early knee joint function, and it did not increase the incidence of related complications.

The limitations of our study mainly include the following aspects. (1) there were only 10 randomized controlled trials and 827 cases in our study. Therefore, a larger sample size is needed for further research, and it is even possible to compare and analyze the efficacy of different corticosteroids. (2) Meta-analysis of some ROM, VAS score and length of hospital stay showed heterogeneity, but sensitivity analysis and subgroup analysis failed to eliminate it. After excluding clinical heterogeneity, the random effects model is used for data processing, which may have a slight impact on the reliability of the result. (3) The included studies lack of inflammatory indicators such as IL-6, C-reactive protein and erythrocyte sedimentation rate, which can not explain the related mechanism in a deeper level.

Conclusion

Adding corticosteroids into periarticular injection can relieve pain score at rest and improve the ROM of the knee in early stage after TKA. In addition, it can reduce the consumption of opioids and promote the recovery of straight leg raising function. Moreover, the use of corticosteroids did not increase the incidence of adverse reactions such as infection, tendon rupture, wound ozzing, nausea and vomiting. However, it had no significant effect on relieving pain scores on motion, reducing wound drainage and shortening hospital stay.

List Of Abbreviations

abbreviations	Abbreviate from
TKA	total knee arthroplasty
RCTs	randomized controlled trials
VAS	Visual Analogue Scale
POD1	postoperative day 1
ROM	range of motion
SLR	straight leg raising
PRISMA	Systematic Reviews and Meta-Analyses
WMD	weighted mean difference
CI	confidence interval
RR	relative risk

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in published articles

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

QL and GM contributed to the articles screening, data synthesis and data collection. QL and MLC contributed to the study design and preparation of the primary manuscript. MLC contributed to the edited of this article.

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Tables

Table 1 Characteristics of the included studies

Study (author +year)	Sample size	Type of surgery	Type of anesthesia	basic information				Cocktail	Corticosteroids	Pos ana
				Age	Male/ Female	BMI	Corticosteroids /control group			
Kwon 2014	152	TKA	SA	69.3/69.3	0/76 0/76	25.9/25.9	76/76	morphine 10 mg, ropivacaine 300 mg, ketorolac 30 mg, 1:1000 epinephrine 300 ug	triamcinolone 40mg	NM
Yue 2013	72	TKA	GA	70.2±6.4 / 69.3±5.7	32/4 32/4	25.23±4.81 / 26.14±3.27	36/36	0.75% ropivacaine 30ml, 1:1000 adrenaline 0.5 ml	betamethasone 7 mg	pca (mo
Ikeuchi 2014	40	TKA	GA	77±6 / 76±3	2/18 4/16	NM	20/20	0.75% ropivacaine 20ml, Isepamicin 400 mg	dexamethasone 6.6 mg	pca (fer
Chia 2013	85	TKA	SA	66.8±7.5 / 65.1±8.4	NM	32.09±5.4 / 31.49±4.7	42/43	0.2% ropivacaine 100ml, 1:1000 adrenaline	triamcinolone 80mg	pca (mo spe
Seah 2011	100	TKA	GA21+SA29/ GA20+SA30	67.9/65.4	NM	26.7/27.3	50/50	1:200,000 epinephrine and 0.5 % bupivacaine 0.5 ml/kg	triamcinolone 40 mg	pca (mo
Christensen 2009	76	TKA	GA	65.8±1.1 / 65.2±11	16/23 7/30	32.9±6.5 / 35.1±8	39/37	bupivacaine 80 mg, morphine 4 mg, epinephrine 300 mg, clonidine 100 mg, cefuroxime 750 mg	methylprednisolone 40 mg	pca (mo
Kim 2015	86	TKA	SA	71.4±4.7 / 70.6±5.5	2/41 4/39	25.8±3.3 / 27.1±4.0	43/43	ropivacaine 180 mg, morphine sulphate 5mg, ketorolac 30 mg, cefazolin 1 g, 1:1,000 epinephrine 0.6 mL	methylprednisolone 40 mg	Pca (no dat
Takuya 2019	41	TKA	SA	72±7	2/19	26.4±4.1	21/20	ropivacaine(7.5 mg/mL) 40	methylprednisolone	dic soc

				/ 76±8	5/15	/ 26.3±3.7		mL, morphine hydrochloride hydrate(10 mg/mL) 0.8 mL, epinephrine(1.0 mg/mL) 0.3 mL, fketoprofen 50 mg	40 mg	pos
Tsukada 2016	75	TKA	SA	75/72	3/35 5/32	26.7/27.3	38/37	ropivacaine(7.5 mg/mL) 40 mL, morphine hydrochloride hydrate(10 mg/mL) 0.8 mL, epinephrine(1.0 mg/mL) 0.3 mL, ketoprofen 50 mg	methylprednisolone 40 mg	dicl soc pos spe
Wang 2020	102	TKA	GA	65.1±8.6 / 63.9±6.4	17/35 15/35	26±2.7 / 26.1±3.5	52/50	0.2% ropivacaine, epinephrine(2.0 ug/mL), 100ml	dexamethasone 10mg	pca (mo

SA Spinal Anesthesia, *GA* General Anesthesia, *TKA* Total knee Arthroplasty, *PCA* Patient Controlled Analgesia, *NM* Not mentioned

Figures

Figure 1

Flow chart of study selection

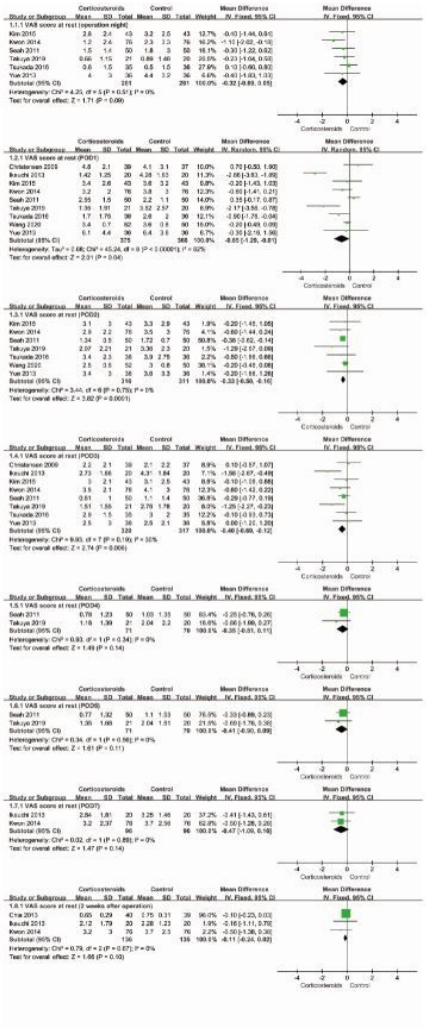

Figure 2

Forest plot showing VAS score at rest at POD1, POD2, POD3, POD4, POD5, POD7 and 2 weeks after operation

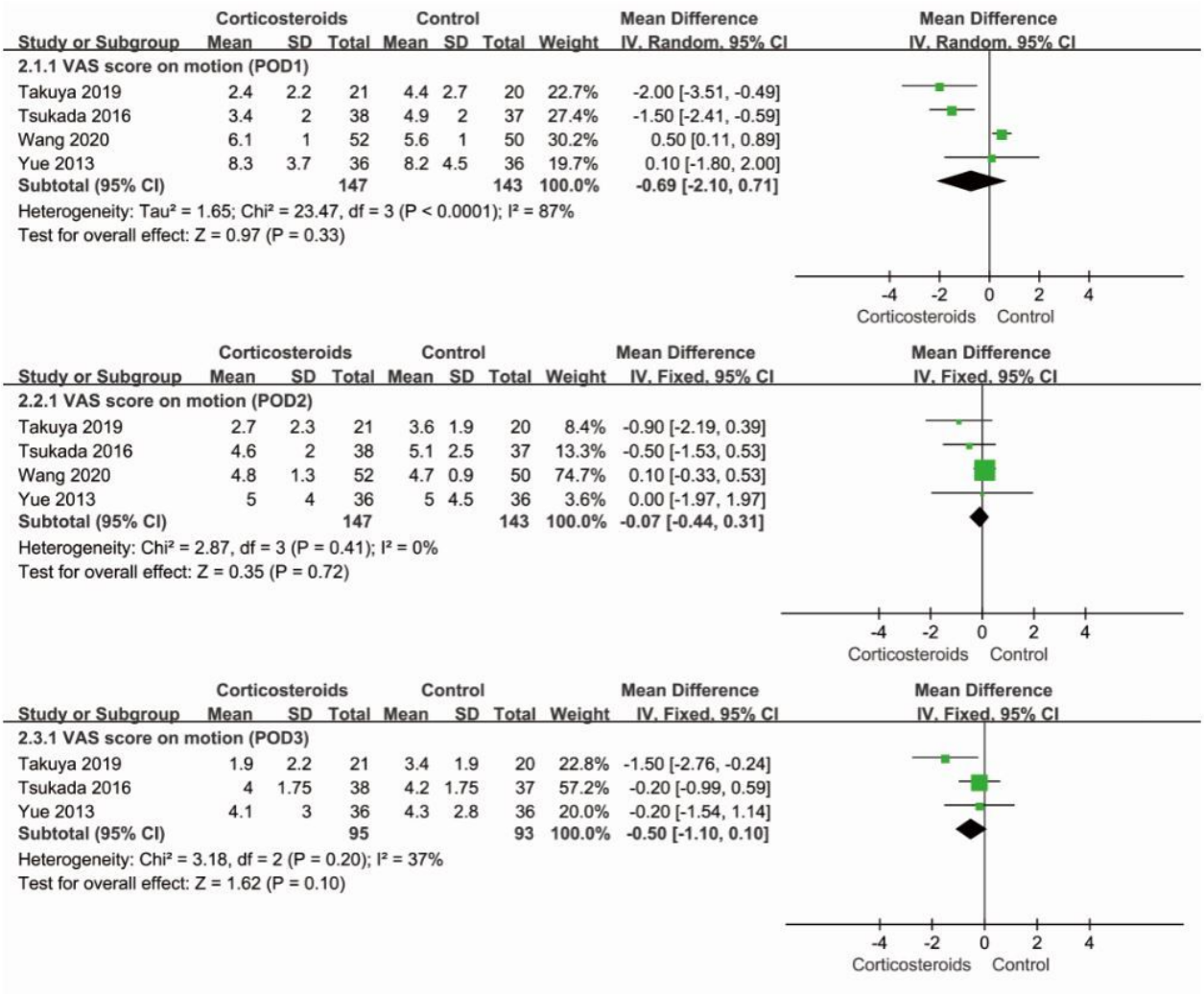

Figure 3

Forest plot showing VAS score on motion at POD1, POD2 and POD3

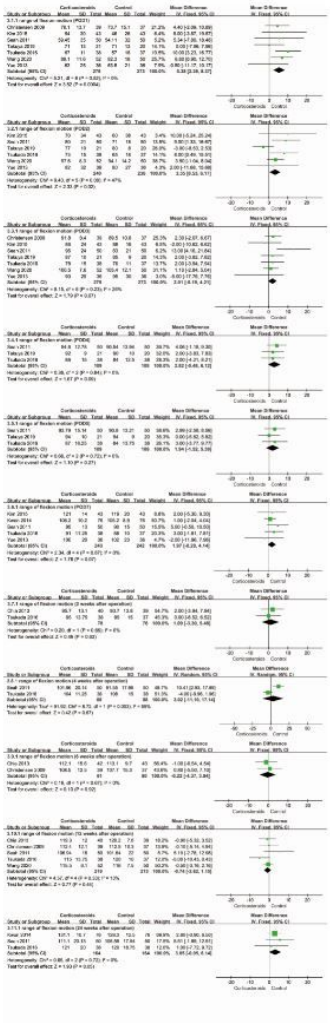

Figure 4

Forest plot showing ranges of flexion motion at POD1, POD2, POD3, POD4, POD5, POD7 and 2, 4, 6, 12, 24 weeks after operation

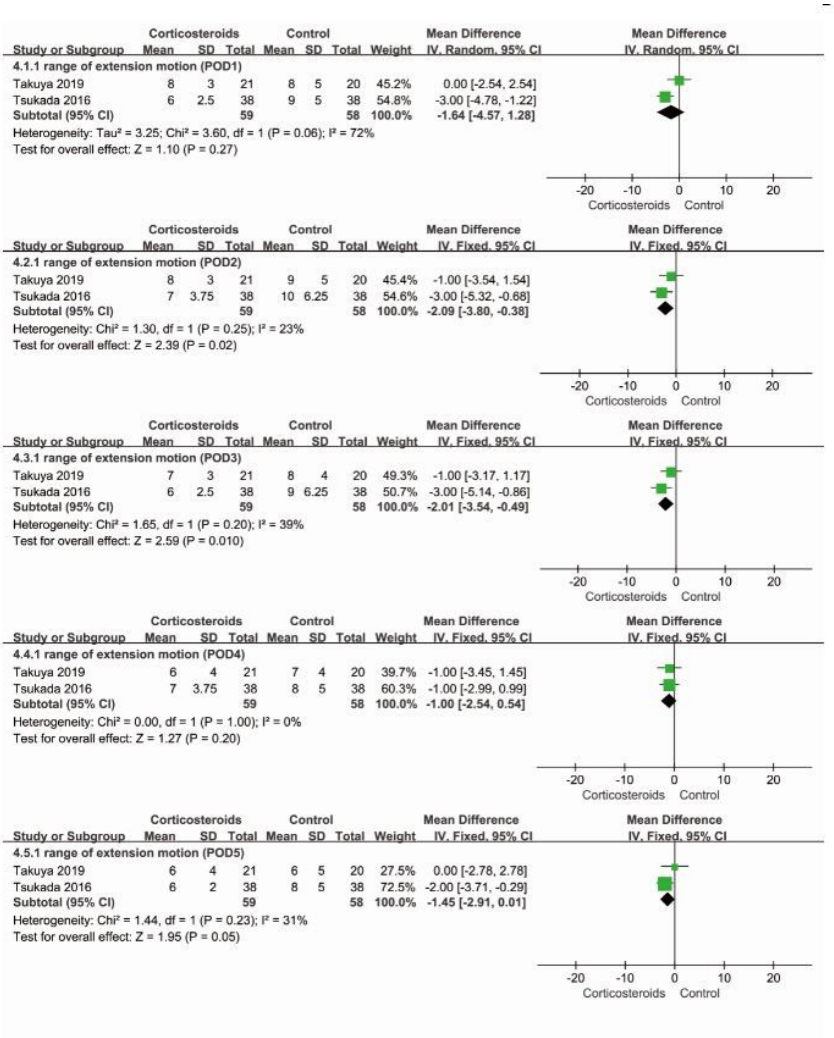

Figure 5

Forest plot showing range of extension motion at POD1, POD2, POD3, POD4 and POD5

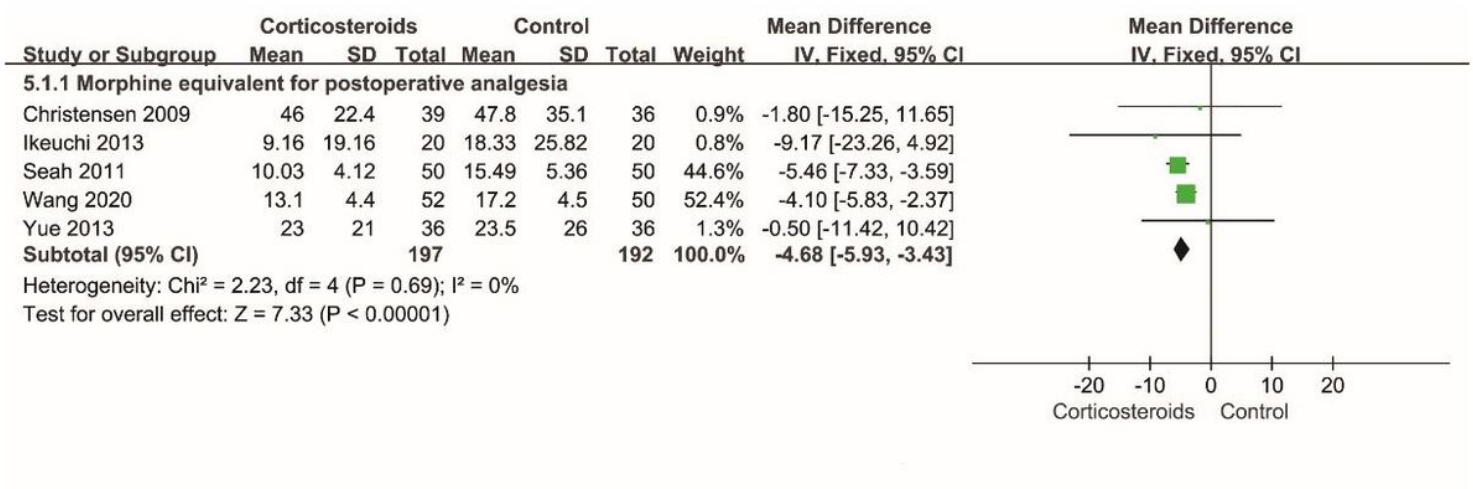

Figure 6

Forest plot showing morphine equivalent for postoperative analgesia

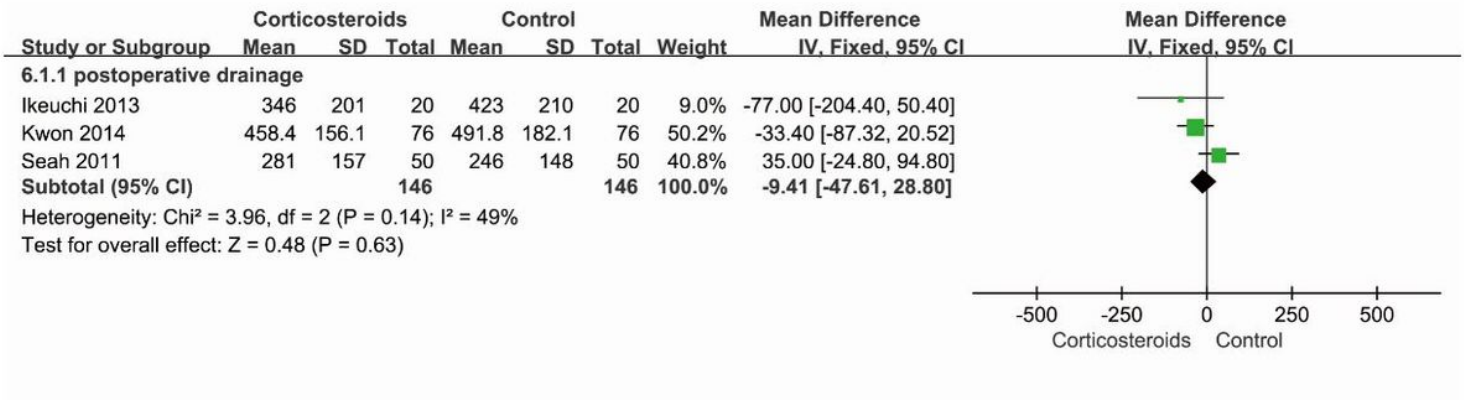

Figure 7

Forest plot showing postoperative drainage

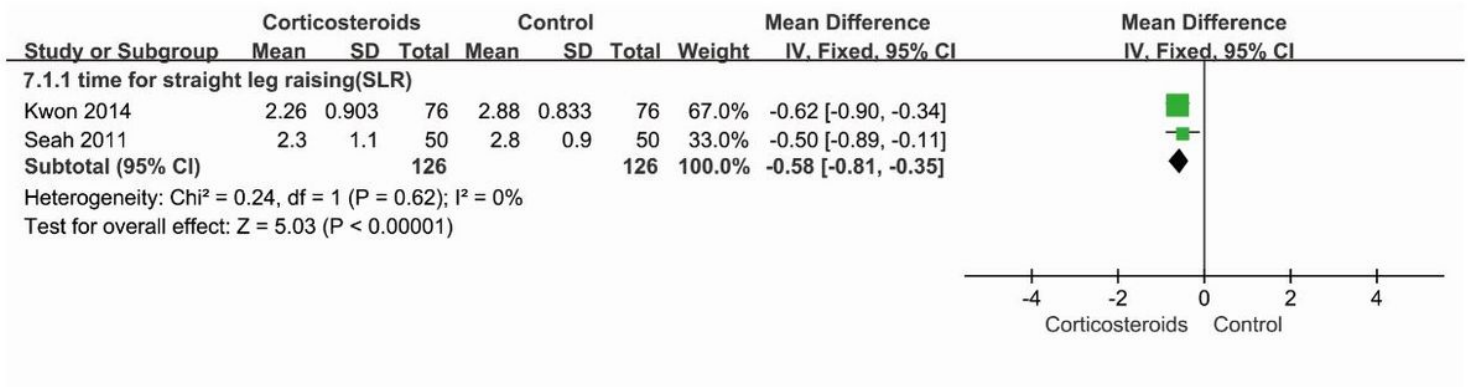

Figure 8

Forest plot showing time for straight leg raising

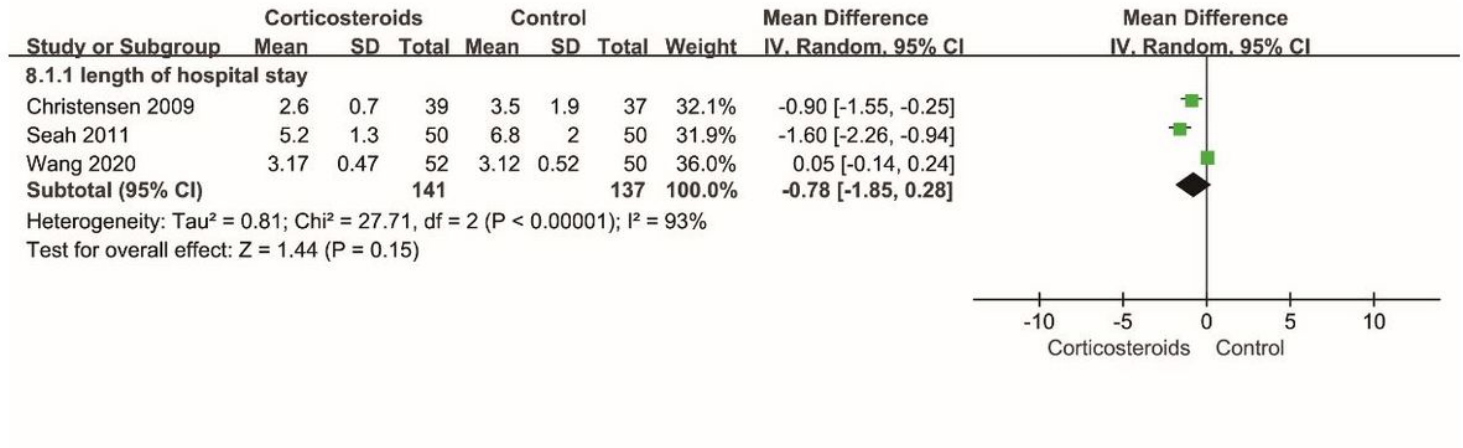

Figure 9

Forest plot showing length of hospital stay

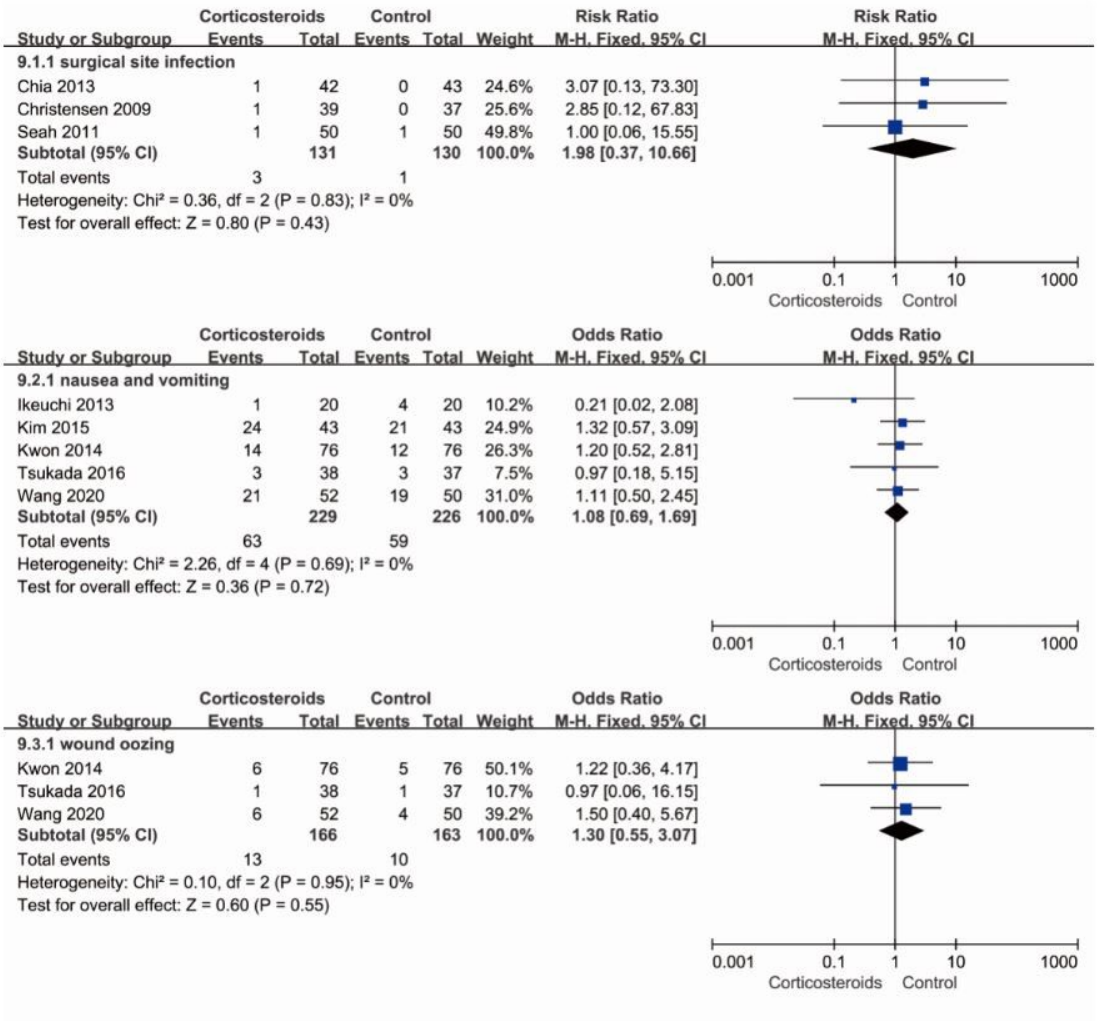

Figure 10

Forest plot showing incidence of complications

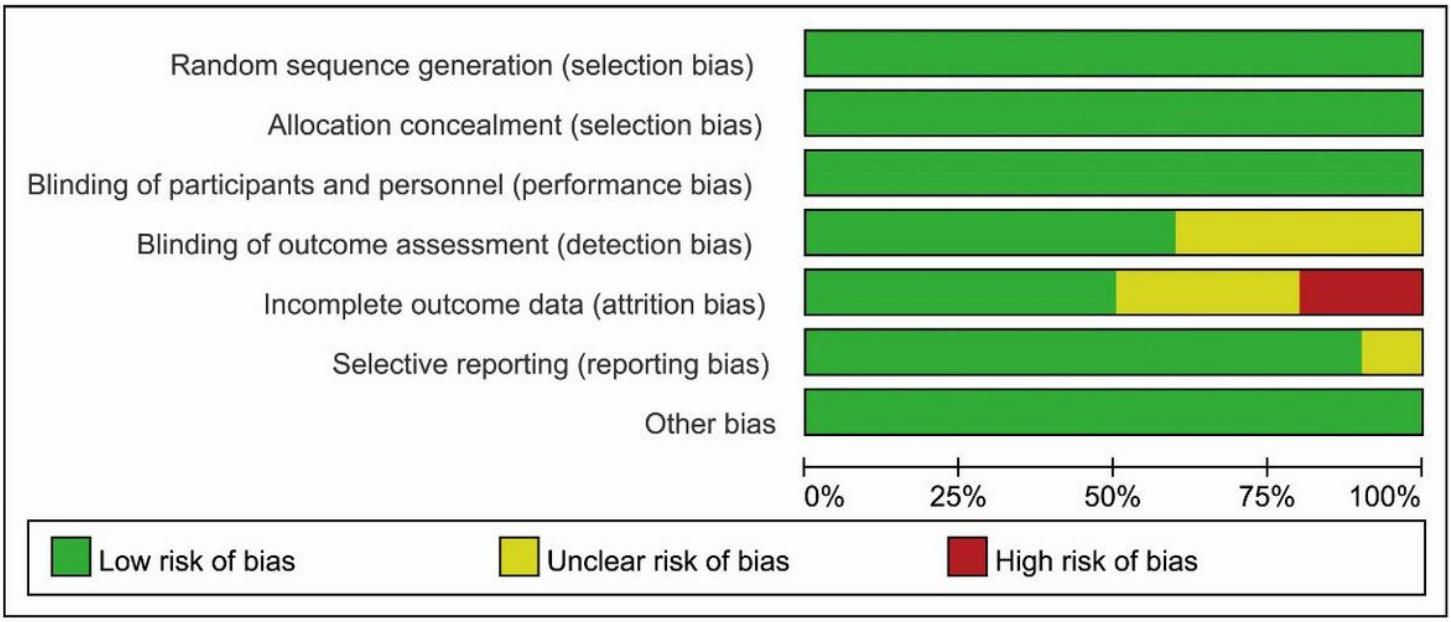

Figure 11

Risk of bias

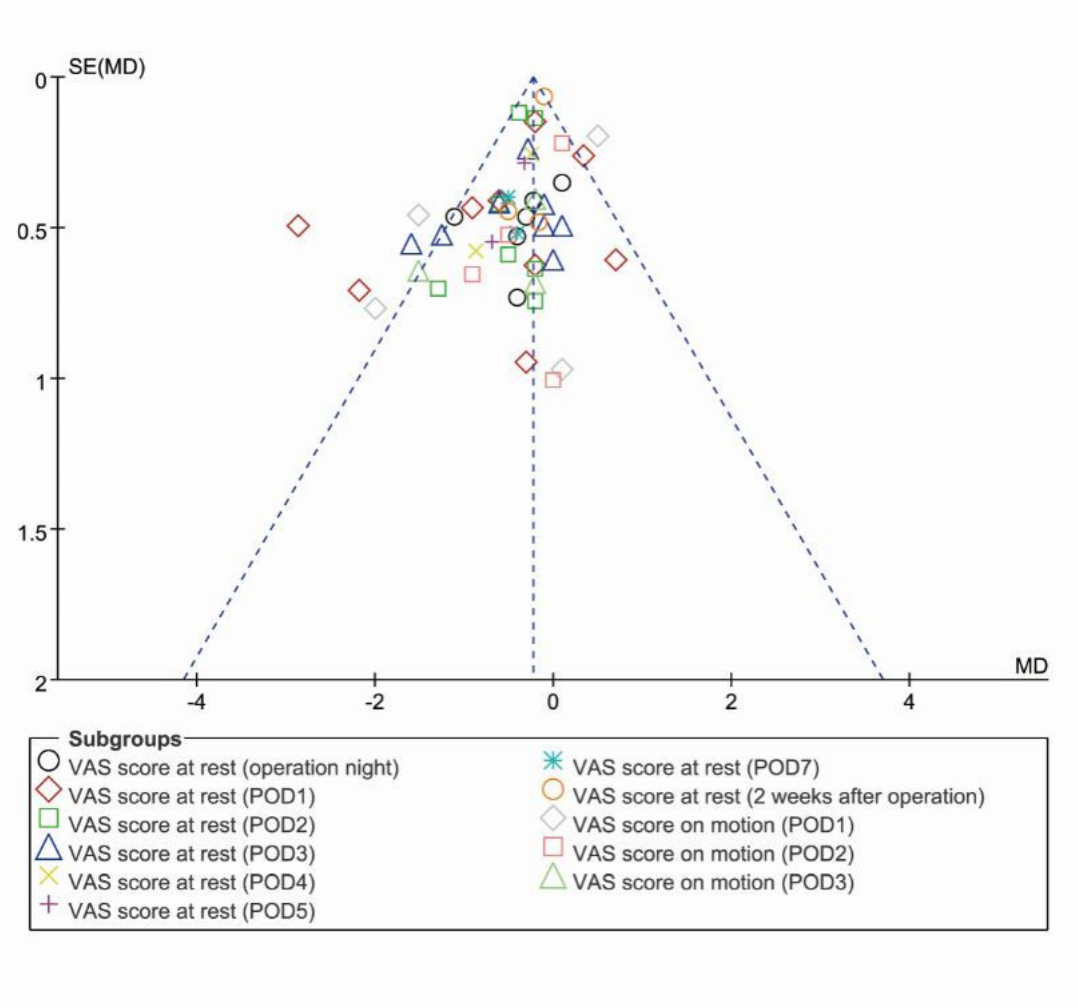

Figure 12

Funnel plot

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable2Rawdata.docx
- SupplementaryTable1Detailsaboutthesearchstrategies.docx