Transdermal fentanyl patch provides better pain relief and faster functional recovery after total knee arthroplasty:a meta-analysis

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Abstract

Background : Pain after total knee arthroplasty (TKA) was severe and should be effectively managed. This meta-analysis aimed to compare transdermal fentanyl patch (TFP) versus placebo for pain control after TKA.

Methods : PubMed, Embase, Cochrane library and Chinese National Knowledge Infrastructure (CNKI) were electronically searched. Potential clinical studies that investigated the effect and safety of TFP versus control in TKA patients were searched. The primary outcomes were total morphine consumption. Stata 12.0 was used for meta-analysis.

Results : Four randomized controlled trials (RCTs) involving 110 TKA patients were included in this meta-analysis. Compared with control group, TFP was associated with a reduction of total morphine consumption (WMD: -16.14; 95% CI: -25.82 to -6.46; P=0.001). Moreover, TFP could significantly reduce VAS at 2 h, 4 h, 6 h, 12 h, 24 h, 48 h and 72 h (P<0.05). There was no statistically significance between the nausea, vomiting, hypertension, sweating, respiratory depression, pruritus and urine retention (P>0.05).

Conclusion : The present meta-analysis showed that use of TFP for the management of moderate or severe TKA postoperative pain had more advantages compared to placebo. Further large-scale, prospective RCTs are required to verify the effect of TFP and optimal dose of TFP in TKA patients.

Introduction

Total knee arthroplasty (TKA) was applied for treatment end-staged osteoarthritis (OA) to restoring knee function, and improving life quality(1). However, approximately 30%-50% TKA patients suffered from moderate to severe postoperative pain(2). Severe postoperative pain could affect the patients' satisfaction and rehabilitation(3).

Pain management has become an important factor for evaluating the quality of life and the clinical approach. Due to the emphasis on postoperative pain management in joint replacement surgery, many studies have been conducted in the past decade, which improved postoperative pain control, including patient-controlled analgesia (PCA), patient-controlled epidural analgesia, spinal morphine, peripheral nerve block, and local intra-articular or peri-articular analgesic injection. However, there was no literature providing clear answers which method was the best, and most patients still suffer from acute or subacute pain after TKA.

Fentanyl, a low molecular weight synthetic opioid, has high potency analgesic effect which is 50 to 100 times than that of morphine(4). Due to its small molecule structure and high lipid solubility, it could be a good choice for transdermal use(5). The transdermal fentanyl patch (TFP) is a skin patch opioid that could constantly release fentanyl into the bloodstream according to the dosage used(6). Although these patches release the drug via the skin at a steady rate, the subsequent plasma level and clearance resemble the intravenous fentanyl(7). The blood concentration of fentanyl through transdermal method was equal to that of intravenous method after 8–12 h, and at least remained steady over 72 h till the patch was worn(8). If TFP was applied 12–14 h before surgery, it would powerfully and durably relieve postoperative acute and subacute pain after TKA(9).

Several randomized controlled trials (RCTs) have been performed recently to compare TFPs and other analgesic strategies in TKA. Thus, a meta-analysis and systematic review was conducted to investigate whether the TFPs provides better pain relief, faster functional recovery and better clinical outcomes.

Materials And Methods

This systematic review and meta-analysis was conducted according to the guidelines outlined in Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.

Literature search

A systematic retrieving of literature was performed through platforms of PubMed, Embase, Cochrane library and Chinese National Knowledge Infrastructure (CNKI) from the inception dates to January 2020, using key words including: "total knee arthroplasty", "total knee replacement", "transdermal fentanyl patch", "TFP", etc. The study searches were conducted by two independent researchers. In addition, the reference lists from identified articles were screened to detect other potential eligible studies.

Eligibility criteria

Studies were selected based on the following inclusion criteria for eligibility: (1) patients prepared for TKA; (2) studies comparing the efficacy of TFP with control as pain management; (3) RCTs; (4) outcomes included one of the below: total morphine consumption, VAS at 2 h, 4 h, 6 h, 12 h, 24 h, 48 h and 72 h, active flexion at day 1 and 3 and adverse effects. Exclusion criteria were: (1) duplicated studies; (2) studies designed as literature or systematic review, case series or case reports, letter to editors and conference abstract. The publication language was not restricted and there were no limitations on the participants' nationalities.

Quality assessment

We assessed the study quality of each included trial according to the Cochrane risk of bias tool for RCTs. We assessed the following items: the generation for random sequence, concealment for allocation sequence, blinding of participants, incomplete outcome data, selective outcome reporting, and other sources of bias. For each included study, each type of bias was rated as high, low, or unclear and entered into the risk of bias table. The risk of bias was examined by two reviewers concurrently, and discrepancies were resolved by consensus.

Data extraction

Two investigators independently extract form data from included RCTs, which mainly including general characteristic (author, published year, country, anesthesia, number, age and BMI of the patients), intervention, control, study and follow-up. Moreover, outcomes were also extracted. The data were checked by a third reviewer, and any disagreements were resolved through discussion. When relevant data had not been reported, we contacted the authors by email or in other ways to attempt to obtain the missing information(10).

Statistical analysis

The statistical analysis was performed by Stata 12.0 (Stata Corp., College Station, TX) and a P-value of < 0.05 was considered statistically significant. We used weighted mean difference (WMD) and the risk ratio (RR) variables with 95% confidence intervals (CIs) to assess continuous and dichotomous variables respectively. We used the value of P and I^2 to assess the statistical heterogeneity among included studies. When I^2 < 50% and P > 0.05 we applied a fixed-effect model, otherwise a random-effect model was applied.

Results

General characteristic of the included studies

A total of 335 studies were identified from the electronic search, the manual search of the reference lists of relevant reviews did not yield new eligible studies. Of which 7 studies were excluded due to duplication. The full text was retrieved for the remaining 328 studies, 324 studies were excluded and 4 studies(5,11-13) were selected for the final analysis after detailed evaluations. The results of the study selection process are shown in Figure 1, and the general characteristics of the included studies are presented in **Table 1**.

Included studies published ranged from 2014 to 2015. Two studies perform general anesthesia and one study perform spinal anesthesia to conduct TKA surgery. Number of the included patients ranged from 16 to 26, and the mean number of the patients were 22. Age of the TKA patients ranged from 58.8 to 73.5. TFP administration dose were different in the included studies (12.5 μg to 50 μg). Follow-up duration from 2 days to 2 weeks.

Risk of bias

Figure. 2 and **Figure. 3** shown the risk of bias summary and risk of bias graph respectively. Only one study was at low risk bias of random sequence generation. Three studies were with low risk of bias for allocation concealment, blinding of participant and personnel and outcomes assessment. Incomplete outcome data and selective reporting were all with low risk of bias in all of the included studies.

Total morphine consumption

A total of two studies compared the effect of TFP and control on total morphine consumption postoperatively. Compared with control group, administration with TFP was associated with a reduction of the total morphine consumption (WMD: -16.14; 95% CI: -25.82 to -6.46; P=0.001; **Figure. 4**), and significant heterogeneity was observed (I^2 = 86.8%; P = 0.001).

VAS at 2 h, 4 h, 6 h, 12 h, 24 h, 48 h and 72 h

VAS at 2 h, 4 h, 6 h, 12 h, 24 h, 48 h and 72 h postoperatively can be seen in **Table 2**. Compared with control group, administration with TFP was associated with a significantly reduction of VAS at 2 h (WMD=-15.04; 95% CI: -22.48 to -7.60; P=0.000), 4 h (WMD=-16.15; 95% CI: -21.40 to -10.89; P=0.000), 6 h (WMD=-11.53; 95% CI: -17.27 to -5.79; P=0.000), 12 h (WMD=-18.03; 95% CI: -23.20 to -12.86; P=0.000), 24 h

(WMD=-15.86; 95% CI: -20.95 to -10.76; P=0.000), 48 h (WMD=-17.08; 95% CI: -20.90 to -13.25; P=0.000) and 72 h (WMD=-11.62; 95% CI: -14.79 to -8.45; P=0.000).

Active flexion at day 1 and 3

The summary results for the effect of TCP on active flexion at day 1 and day 3 are shown in **Table 2**. Overall, TCP has significant effect on increasing active flexion at day 1 (WMD=10.49; 95% CI: 5.81 to 15.17; P=0.000) and day 3 (WMD=5.33; 95% CI: 2.95 to 7.71; P=0.000) compared with placebo.

Adverse effects

The summary results on occurrence of nausea, vomiting, hypertension, sweating, respiratory depression, pruritus and urine retention were shown in **Table 2**. Overall, no significant differences were noted in the incidence of nausea (RR: 1.09; 95% CI: 0.73 to 1.64, P = 0.675), vomiting (RR: 0.55; 95% CI: 0.23 to 1.27, P = 0.160), hypertension (RR: 0.50; 95% CI: 0.05 to 5.08, P = 0.558), sweating (RR: 0.50; 95% CI: 0.10 to 2.43, P = 0.390), respiratory depression (RR: 3.00; 95% CI: 0.13 to 69.52, P = 0.493), pruritus (RR: 1.67; 95% CI: 0.43 to 6.42, P = 0.458), urine retention (RR: 0.67; 95% CI: 0.12 to 3.57, P = 0.636) between TFP and control groups.

Discussion

The most significant finding of this present study was that TFP provided an alternative to the other analgesic strategies with significantly better pain relief, morphine-sparing effects, faster functional recovery, without increasing complications after TKA.

This is the first meta-analysis that assess TFP for pain control after TKA. We systematically searched relevant electronic databases and identified four RCTs. Previously, Wang et al.(6) conducted a meta-analysis and revealed that use of TFP could effectively relieving moderate or severe cancer pain.

Previous studies have found that TFP possess faster muscle strength recovery and ambulation scores, but not by range of motion or functional scores. Thus, more and more surgeons have focused on administration TFP for TKA patients.

Some authors argued that TFP could prevent acute opioid tolerance and hyperalgesia in the early postoperative period(14). Many studies have identified that TFP has a positive role in reducing pain intensity in patients undergoing abdominal hysterectomy(15), abdominal surgery(16) and osteoarthritis patients(17).

However, other scholar argued that there was no statistically significant difference in postoperative VAS pain scores between the TFP group and the control group(18). The reason may be that they administrated with TFP just within two hours before surgery, and thus the plasma concentration of TFP could not reach for effective dose. We identified total morphine consumption as the primary outcome. Compared with control group, administration TFP was associated with a reduction of morphine about 16.14 mg.

Minivlle et al(19) found that TFP application decreases pain scores and morphine consumption in the first 48 postoperative hours. Thus, TFP may be an alternative for patients-controlled analgesia. Moreover, we found that TFP has a beneficial role in reducing pain intensity until 72 h. This pain-relieving effect was enough to control pain after TKA. TKA causes severe postoperative pain during the first 24–72 h(20). This meta-analysis revealed that TFP was associated with reduced pain scores at 48 and 72 hours, this corresponded to a reduction of 17.08 and 11.62 point on an 110-point numeric rating scale.

Moreover, we compared the complications between TFP and control groups. Results found that there was no significant difference between the occurrence of nausea and vomiting. This can be explained as the TFP could significantly decreased the morphine consumption, and thus the morphine-related complications (nausea and vomiting) were decreased.

This meta-analysis had several limitations. The number of participants in most of the included studies was small, and need for more studies to further identify the pooled results. Further, many included trials also had methodological deficits, such as the description of the randomization process and/or the explanation of withdrawal and dropouts. The outcomes of several studies were criticized for their inaccuracy. Further, dose and frequency of TFP administration was different, further studies should be performed to identify the optimal dose of TFP for TKA. Finally, high heterogeneity was observed in places, limiting the ability to make strong inferences.

Conclusion

The present meta-analysis showed that TFP had favorable efficacy for pain control and morphine sparing in TKA without sacrificing safety profiles. Further large-scale prospective RCTs should be conducted to verify the comparison of TFP and control in TKA patients.

Abbreviations

TKA= total knee arthroplasty; TFP= transdermal fentanyl patch; CNKI= Chinese National Knowledge Infrastructure; RCTs= randomized controlled trials; OA= osteoarthritis; PCA= patient-controlled analgesia; PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-analysis; WMD= weighted mean difference; RR= risk ratio; CIs= confidence intervals.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

Authors' contributions

JQW, YML, and LFL conceived and designed the study. JW and LBM participated in the acquisition of data. JQW, YML, and LFL analyzed and interpreted the data. JW and LBM drafted the article. JW and LBM critically revised the article. JW and LBM contributed to important intellectual content. All authors gave final approval of the version to be submitted.

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Not applicable.

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Tables

Study	Country	Anesthesia	No. of patients	Age of patients	Gender (male)	BMI	Intervention	Control	Study	Follow-up
Matsumoto 2015	Japan	General anesthesia	26/26	70.1/73.5	3/6	25.7/25.1	TFP (Durotep 12.5 μg/h, Janssen Cliag)	Placebo	RCT	2 weeks
Abrisham 2014	Iran	General anesthesia	20/20	61.2/58.8	3/6	28.8/28.8	Duragesic 25 μg/h, Fentanyl 4.2 mg per transdermal patch	Placebo	RCT	3 days
Hall 2015	New Zealand	NS	16/22	64/66	NS	NS	Fentanyl patch 12.5 μg or 25 μg	Placebo	RCT	1 week
Sathitkarnmanee 2014	Thailand	Spinal anesthesia	20/20	64.9/66.2	17/19	27.6/26.9	TFP (Duragesic® 50 μg/hour matrix fentanyl patch	Placebo	RCT	2 days

Table 1: General characteristic of the included studies; NS, not stated; RCT, randomized controlled trials; TFP, transdermal fentanyl patch; BMI: body mass index.

Variables	Study	Effect size (WMD/RR, 95%CI)	Heterogeneity (I^2, P value)	P value
VAS at 2 h	2	-15.04 (-22.48, -7.60)	33.5, 0.220	0.000
VAS at 4 h	2	-16.15 (-21.40, -10.89)	0.0, 0.967	0.000
VAS at 6 h	2	-11.53 (-17.27, -5.79)	0.0, 0.714	0.000
VAS at 12 h	2	-18.03 (-23.20, -12.86)	53.8, 0.141	0.000
VAS at 24 h	2	-15.86 (-20.95, -10.76)	0.0, 0.353	0.000
VAS at 48 h	2	-17.08 (-20.90, -13.25)	67.4, 0.047	0.000
VAS at 72 h	3	-11.62 (-14.79, -8.45)	0.0, 0.429	0.000
Occurrence of nausea	3	1.09 (0.73, 1.64)	39.8, 0.197	0.675
Occurrence of vomiting	4	0.55 (0.23,1.27)	0.0, 0.933	0.160
Hypertension	2	0.50 (0.05, 5.08)	0.0, 0.534	0.558
Sweating	2	0.50 (0.10, 2.43)	0.0, 0.928	0.390
Respiratory depression	3	3.00 (0.13, 69.52)	0.0, 0.105	0.493
Pruritus	4	1.67 (0.43, 6.42)	0.0,0.664	0.458
Urine retention	2	0.67 (0.12, 3.57)	0.0, 0.162	0.636
Active flexion at day 1	2	10.49 (5.81, 15.17)	58.7, 0.120	0.000
Active flexion at day 3	2	5.33 (2.95, 7.71)	0.0, 0.323	0.000

Table 2 Results summary for the clinical outcomes and adverse effects.

Figures

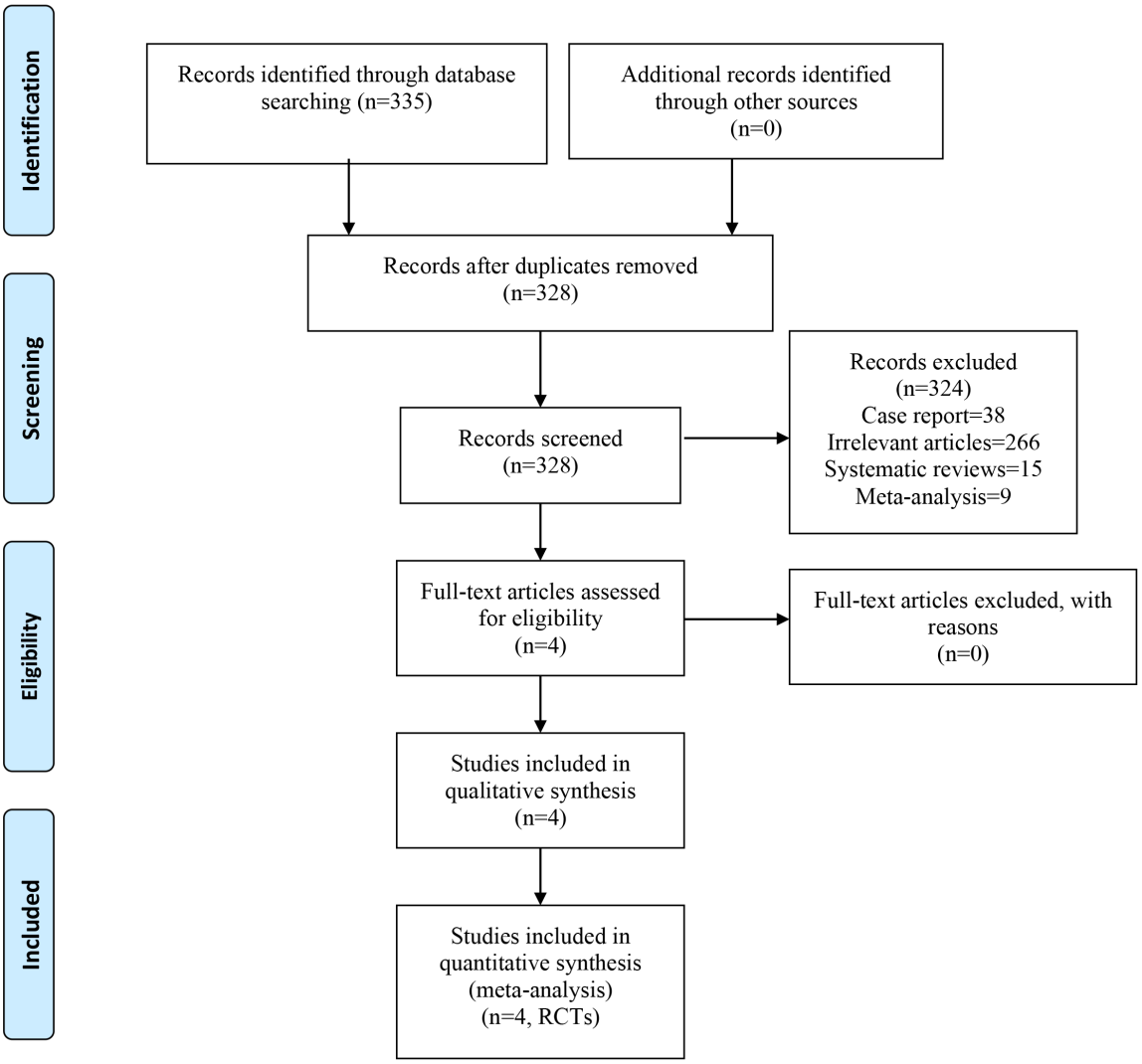

Figure 1

Study flow diagram for inclusion. RCTs, randomized clinical trials.

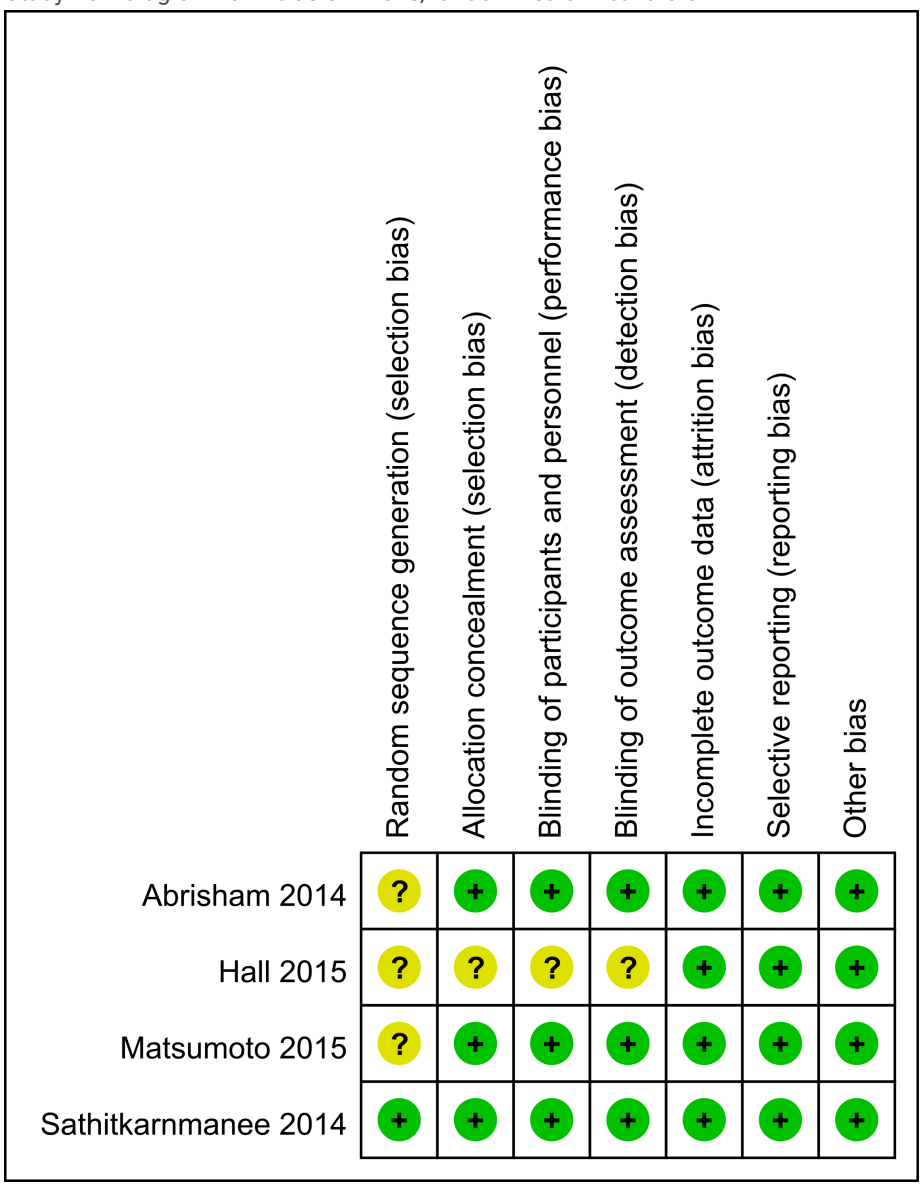

Figure 2

Risk of bias summary of the included RCTs

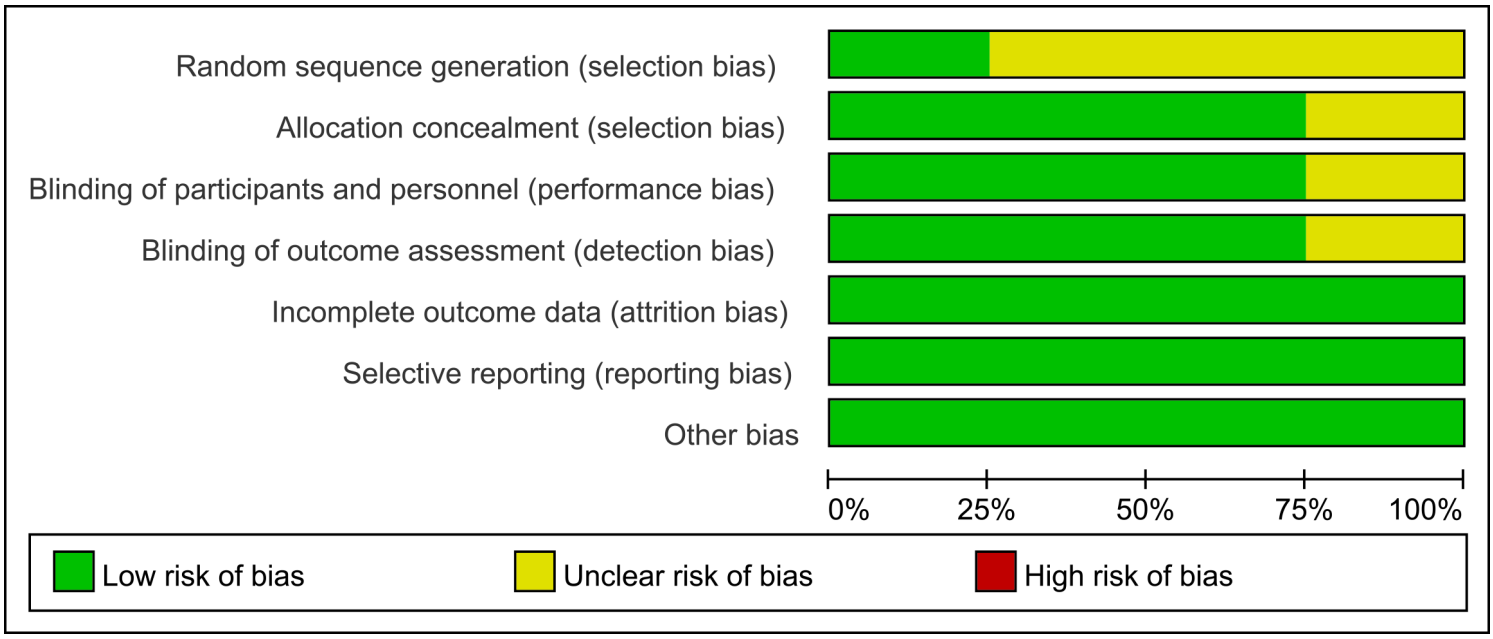

Figure 3

Risk of bias graph of the included RCTs.

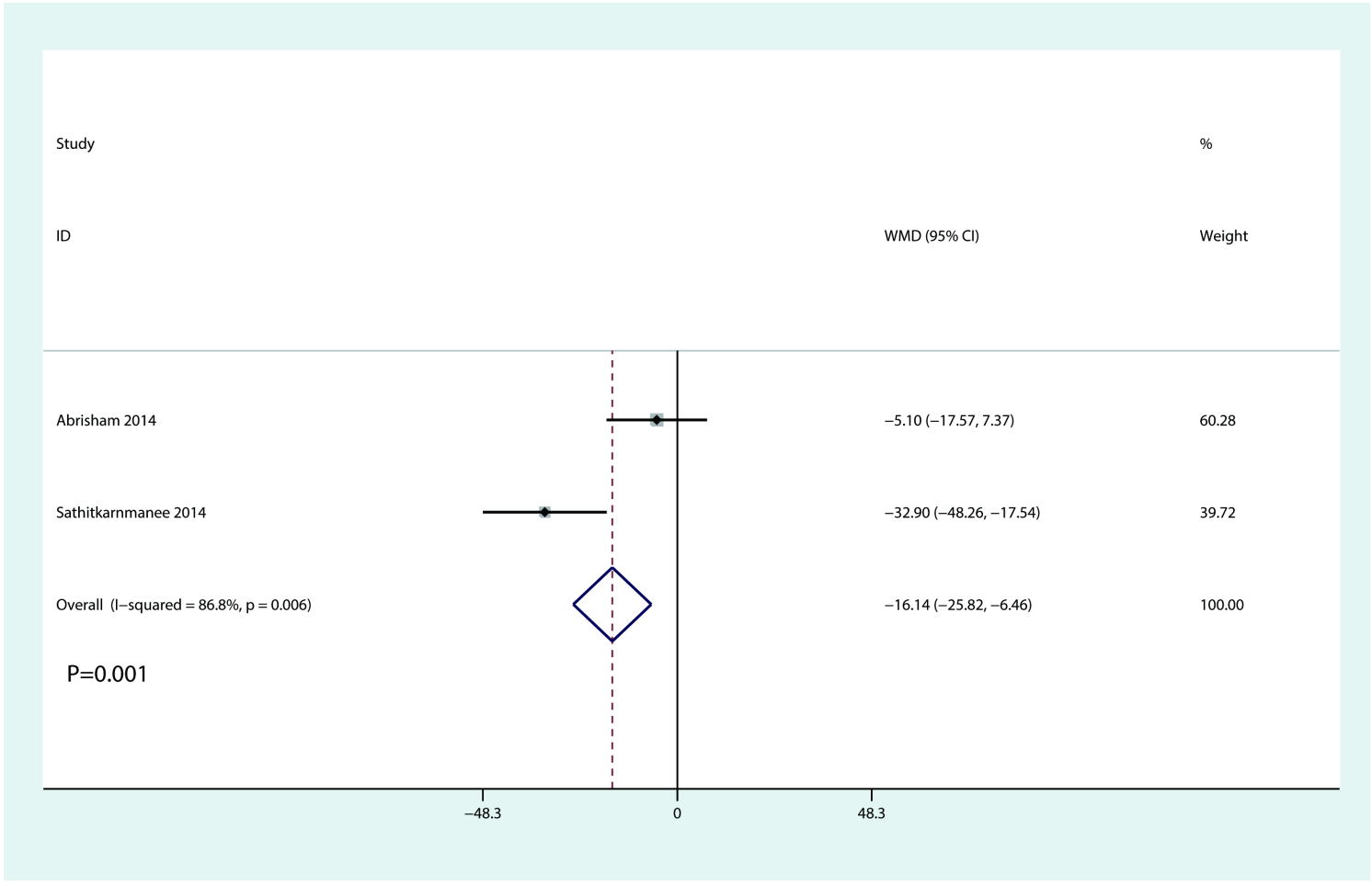

Figure 4

Forest plot that comparing total morphine consumption between TFP and control groups.