Review Article

Periprocedural Medications for Post-Embolization Pain Control in Women with Uterine Fibroids or Adenomyosis: A Systematic Review and Meta-analysis

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Purpose: To evaluate the effects of periprocedural medications on postprocedural pain outcomes of uterine artery embolization (UAE) in a systematic review and meta-analysis.

Materials and Methods: We searched multiple databases until September 30, 2018 for eligible randomized controlled trials (RCTs). Patient demographics, sample size, administration routes, medication types, sedation levels, the use of patient-controlled analgesia, pain outcomes, adverse events, and trial quality were recorded. The maximal pain scores (in 0 – 10 numeric rating scale) and cumulative opioid consumption (in mg intravenous morphine equivalents) of subjects in 24 hours after UAE were analyzed and pooled with assessing heterogeneity by a random effects model. Subgroup and meta-regression analyses were performed, and publication bias was examined by funnel plots using the Begg and Egger's methods.

Results: Eight RCTs with 412 subjects were included. The mean difference (95% confidence interval [CI]) of the pooled effects favored periprocedural medications over control for maximal pain score (−2.51, 95% CI: −3.10 to −1.93) and cumulative opioid consumption (−4.39, 95% CI: −10.97 to 2.20) in 24 hours after UAE. High heterogeneity was present and decreased in subgroup analysis by administration routes, showing more significant effects in the vascular subgroup (maximal pain score: −2.87, 95% CI: −3.37 to −2.38; cumulative opioid consumption: −8.17, 95% CI: −13.19 to −3.14). Publication bias was not present.

Conclusion: Periprocedural medications could relieve postprocedural pain in women undergoing UAE to treat uterine myoma or adenomyosis. Vascular administration may have better analgesic and opioid-sparing effects than oral administration.

Key words: patient-controlled analgesia, randomized controlled trial, uterine artery embolization

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Introduction

Uterine artery embolization (UAE) has been considered an effective and safe uterine-preserving treatment option for symptomatic uterine fibroids or adenomyosis, with similar efficacy to alleviate symptoms comparable to that of surgery.[1-3] The most common adverse effect of UAE is postprocedural pain. Up to 90 − 100% of UAE patients need opioid analgesics during the first 24 hours after UAE,[4-7] which may cause opioid-related side effects, such as nausea, vomiting, and pruritus. Such pain is possibly due to tissue ischemia and could not be predictable by patient/lesion characteristics, operator experience, or embolic agents.[6-8] Therefore, pain management is usually required in UAE patients.

The strategies for pain management in UAE patients include periprocedural medications, conscious sedation, superior hypogastric nerve block, and postprocedural patient-controlled analgesia (PCA).[9] In clinical practice, periprocedural medications is relatively feasible and safe for interventional radiologists to use independently, whereas the other approaches mentioned above usually require the assistance of anesthesiologists. However, in despite of all randomized controlled trials (RCTs) over the last decades, the effect of periprocedural medications on postprocedural pain of UAE remains unclear, which could be due to different study protocols, diverse interventions, small sample sizes, and various populations in the trials. Thus, we performed a systematic review and meta-analysis of RCTs based on current evidence to determine the effect of periprocedural medications on postprocedural pain of UAE. Besides, we also evaluated the safety profiles of these periprocedural medications. Our findings could help clinicians develop bet-

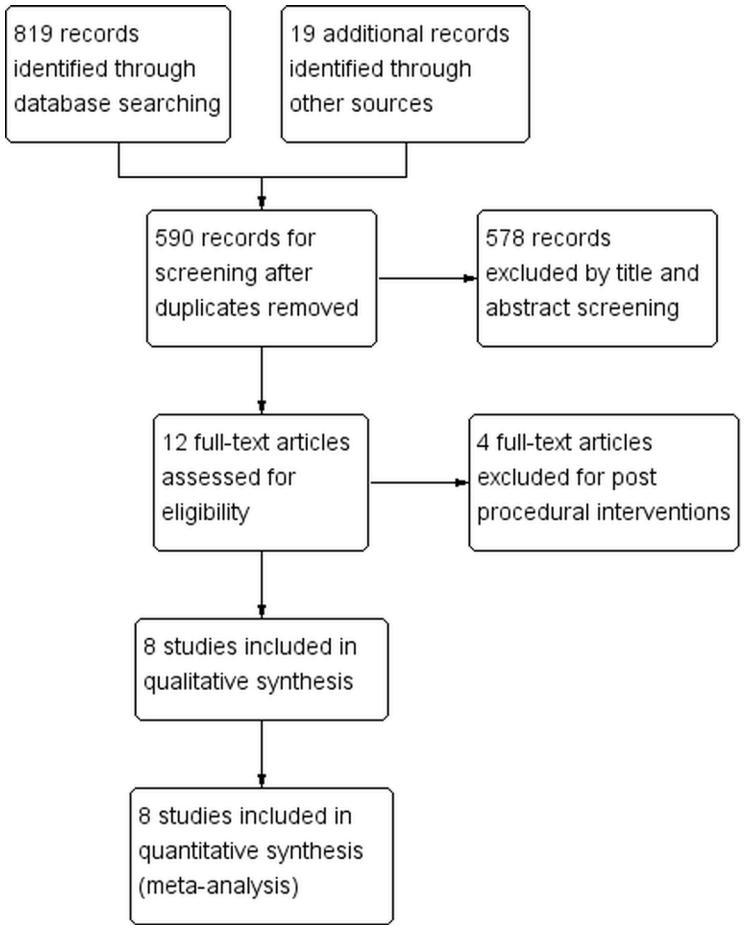

Fig. 1 Flowchart of study selection in the meta-analysis.

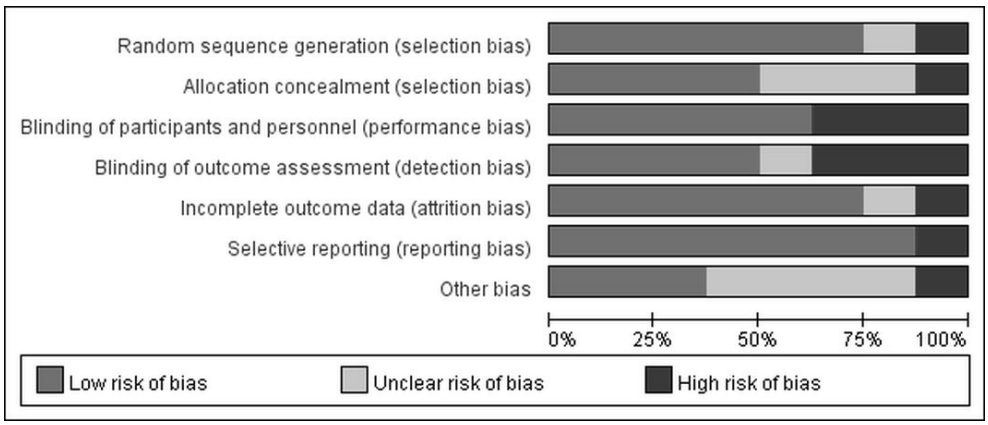

Fig. 2 Summary of risk of bias within included studies.

ter strategies for pain management in UAE patients.

Materials and Methods

We followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) when reporting this review,[10] and registered our protocol with PROSPERO (registration number: CRD42018087232). This study was exempted from institutional review board approval.

Data sources and searches

We performed a comprehensive literature search using Ovid EMBASE, the PubMed database, the Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews, for relevant studies from May 2001 until September 2018. Free text and medical subject headings terms including “uterus”, “embolization”, “leiomyoma”, "adenomyosis", “pain”, and “analgesia” were used for the search strategy developed by two of the authors collaborating with an experienced reference librarian. We also checked the bibliography of included studies to identify additional studies not found by the primary search methods. Details of the search strategy were provided in Appendix.

Study selection and quality assessment

Our eligibility criteria were RCTs evaluating postprocedural pain in women receiving UAE for uterine myoma or adenomyosis, with a periprocedural medication, compared to a control group (placebo or “no treatment”). The periprocedural medications in this study referred to preprocedural and intraprocedural medications. Trials evaluating the effects of anesthesia methods (such as general or spinal anesthesia), embolic agents (such as particle sizes or types), or postprocedural interventions (such as PCA regimens) were excluded to improve clinical homogeneity. Two of the authors independently screened titles/abstracts of the search records without restriction on language or minimum sample size. Duplicate and irrelevant articles were excluded at this phase. Further full text review on outcome measurements was performed for eligibility to meta-analysis. The primary outcomes were acute post-embolization pain in 24 hours after UAE, measured by pain scores or cumulative opioid consumption. If pain scores were reported at multiple time points, we assessed the maximal one within 24 hours. The secondary outcomes were adverse events, such as nausea, vomiting, and unstable vital signs. Disagreements were resolved by discussion among the evaluators. If an agreement could not be reached, a third reviewer was consulted. Figure 1 shows the flowchart of study selection.

Two of the authors independently used the Cochrane Collaboration’s risk-of-bias tool to evaluate the methodological quality of the

included RCTs,[11] including bias domains of selection, performance, detection, attrition, reporting, and others (non-standard pain score and no sample size calculation). Disagreements were resolved by discussion among the evaluators. If an agreement could not be reached, a third reviewer was consulted. We summarized the risk of bias in all domains for included trials (Fig. 2). Details of the judgment were listed in Fig. S1 in supplement. Trials were not excluded or weighted in the analysis according to quality assessment.

Data extraction, synthesis and analysis

Two of the authors independently extracted data from RCTs using a standardized, web-based data extraction form, including patient demographics, sample size, administration routes, medication types, sedation levels, the use of PCA, maximal pain scores in 24 hours after UAE, cumulative opioid consumption in 24 hours after UAE, and maadverse events. Cumulative opioid consumption was converted to intravenous morphine equivalents (1 mg intravenous morphine = 3 mg oral morphine = 2 mg oral oxycodone = 10 mcg intravenous fentanyl).[12] Pain scores from visual analog scale or numeric rating scale were converted to a 0 – 10 numeric rating scale. Data were mainly extracted from tables or text. If data were not available in tables or texts, we derived data from figures. We requested missing or additional data for analysis by e-mailing with the corresponding authors. If the requested data could not be retrieved, data presented only as medians and ranges were converted to means and standard deviations.[13] Missing estimates of variance were imputed using previously described methodology.[14]

We applied a random effects model for the diversity in study designs and interventions. Trials with multiple eligible arms were included in the analysis if they had a comparable control and clinically meaningful to pool the effect of treatment, for example, concurrent or sequential administration of the drug during UAE versus controls. Continuous data of maximal pain scores and cumulative opioid consumption are reported with mean differences (MDs) and 95% confidence intervals (CIs), whereas dichotomous data of adverse events are reported with odds ratios (ORs) and 95% CIs. We assessed heterogeneity of the included studies using the I2 statistic, where I2 = 0 rep-

Table 1. Characteristics of the included trials.

Study, year[Ref.]	Number	Mean age	Sedation level	Medication & administration routes	PCA use
Freire, 2017[15]	30	36.43	conscious	oxycodone, oral	yes
	30	38.37		none	
Konstantatos, 2014[16]	20	42.8	conscious	oxycodone, oral	yes
	19	41.7		placebo	
Kim, 2013[17]	25	40	conscious	dexmedetomidine, intravenous	yes
	25	40		placebo	
Kim, 2016[18]	30	43	local	dexamethasone, intravenous	yes
	29	43		placebo	
Keyoung, 2001[19]	10	NM	conscious	lidocaine, intraarterial	yes
	8	NM		placebo	
Noel-Lamy, 2017[20]	20	47.1	conscious	lidocaine, intraarterial, concurrent	no
	20	44.8		lidocaine, intraarterial, sequential	
	20	48.4		none	
Zhan, 2005[21]	23	NM	conscious	lidocaine, intraarterial	no
	23	NM		placebo	
Pisco, 2008[22]	40	41.7	local	ketoprofen, intraarterial	no
	40	40.3		none	

NM: not mentioned; PCA: patient-controlled analgesia

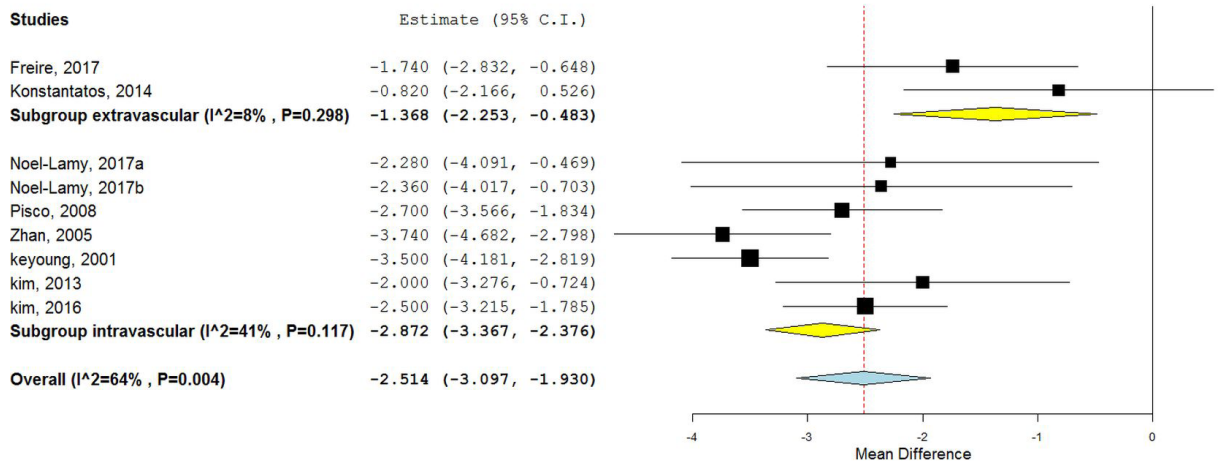

Fig. 3 Forest plot showing mean difference (with 95% CI) of maximal pain score in 24 hours after uterine artery embolization comparing periprocedural medications and controls in a random effect model, with subgroup analysis of administration routes.

resents perfect homogeneity and I2 = 100% represents the highest heterogeneity. We further evaluated potential sources of heterogeneity if the I2 was greater than 50%, using a priori planned subgroup and meta-regression analyses according to the following covariates: administration routes, medication types, conscious sedation, and the use of PCA. Publication bias was examined with funnel plots using the Begg and Egger's methods. A one-sided P value less than 0.05 indicated an asymmetric funnel plot. All analyses were conducted using OpenMeta Analyst software (http://www.cebm.brown.edu/openmeta/) and Stata software (Version 12; StataCorp LP, College Station, TX, USA).

Results

Study selection and study characteristics

We screened 838 records and finally enrolled eight RCTs[15-22] for meta-analysis (Fig. 1). Table 1 summarizes the characteristics of the enrolled RCTs. There were 412 women included, with mean age ranging from 35.9 to 48.4 years. All studies were two-arm trials comparing a group with periprocedural medication to a control group (placebo or "no treatment"), except one was three-arm trial which compared intraarterial lidocaine mixed with embolic agents, intraarterial lidocaine after embolization, and control group.[20] About the administration routes of medication, six trials used vascular administration (intraarterial and intravenous),[17-22] and two used oral administration.[15,16] About the medication types, six trials studied on non-opioids,[17-22] while two trials studied on opioids.[15,16] About the sedation level, six trials had conscious sedation,[15-17, 19-21] while two trials only had local anesthesia.[18, 22] About the combination of PCA, five trials combined PCA use,[15-19] while three trials did not.[20-22] Meta-regression identified the administration routes (i.e., vascular vs. oral) as the only significant study-level factor for the pooling outcomes ($p < 0.001$).

Risk of bias assessment

Risk of bias within the studies is presented in Figure 2. The most common risk was incomplete blinding of participants, personnel and outcome assessment with 37.5% of included studies due to no placebo.[15,20,22] A post-hoc meta-regression analysis did not identify an association between the placebo use and an effect on pain outcomes.

Max pain score in 24 hours

Eight studies reported maximal pain scores in 24 hours after UAE.[15-22] The overall effect of periprocedural medications showed

a significant decrease of maximal pain scores compared to controls (MD: −2.51, 95% CI: −3.10 to −1.93; Fig. 3). Heterogeneity was high (I2 = 64%). Subgroup analyses by administration routes decreased the heterogeneity with a more prominent effect in the subgroup of vascular administration (MD: –2.87, 95% CI: −3.37 to −2.38). The funnel plot did not show asymmetry (p = 0.17; Fig. 4).

Cumulative opioid consumption in 24 hours

Six studies reported cumulative opioid consumption in 24 hours after UAE.[15-20] The pooled analysis did not show a significant effect of periprocedural medications on cumulative opioid consumption compared to controls (MD: −4.39, 95% CI: −10.97 to 2.20; Fig. 5). Heterogeneity was high (I2 = 76%). Subgroup analyses by administration routes decreased the heterogeneity, showing a further distinguished opiod-sparing effect in the subgroup of vascular administration (MD: –8.17, 95% CI: −13.19 to −3.14). The funnel plot did not show asymmetry (p = 0.45; Fig. 6).

Safety analysis

Nausea or vomiting: Four studies reported on the incidence of nausea or vomiting.[15-18] The aggregated effect of periprocedural medications did not show a significant difference in the incidence of nausea or vomiting compared to controls (52 of 105 treated subjects vs. 61 of 103 control subjects, OR: 0.65, 95% CI: 0.21 to 1.97, Fig. S2 in supplement).

Pruritus: Four studies reported on the incidence of pruritus.[15-18] The combined effects of periprocedural medications did not show a significant difference in the incidence of pruritus compared to controls (12 of 105 treated subjects vs. 18 of 103 control subjects, OR: 0.67, 95% CI: 0.25 to 1.83, Fig. S2 in supplement).

Unstable vital signs: Five studies reported on the incidence of unstable vital signs.[15-18,20] The pooled effect of periprocedural medications did not show a significant difference in the incidence of unstable vital signs compared to controls (7 of 125 treated subjects vs. 3 of 123 control subjects, OR: 1.93, 95% CI: 0.56 – 6.62, Fig. S2 in supplement).

Discussion

This meta-analysis shows the effect of periprocedural medications on pain relief in

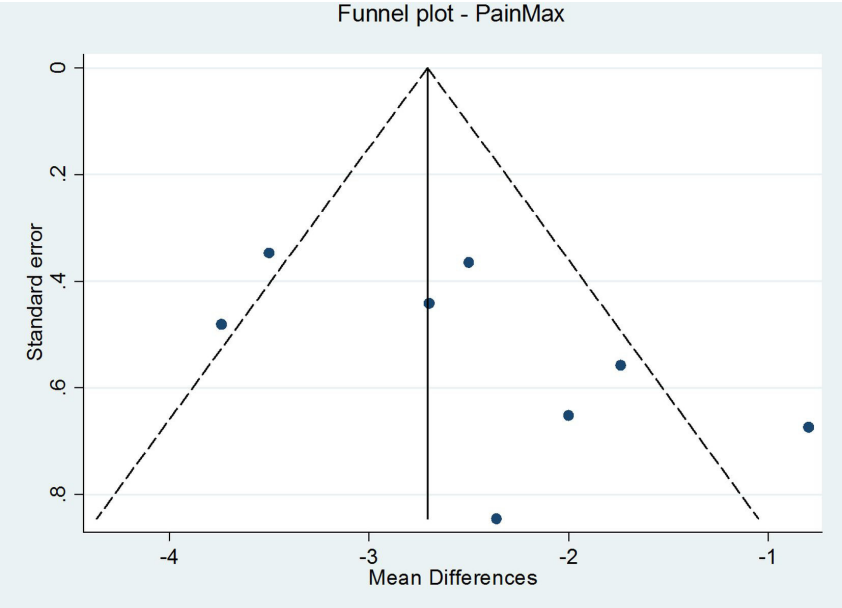

Fig. 4 Funnel plot of maximal pain score in 24 hours after uterine artery embolization assessing publication bias.

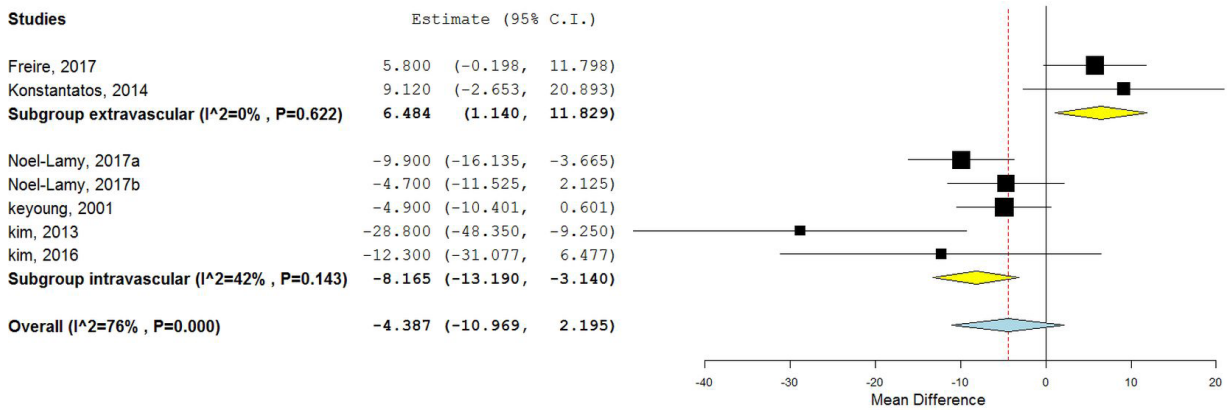

Fig. 5 Forest plot showing mean difference (with 95% CI) of cumulative opioid consumption in 24 hours after uterine artery embolization comparing periprocedural medications and controls in a random effect model, with subgroup analysis of administration routes.

UAE patients. Our findings provide evidence that periprocedural medications have a role to reduce acute postprocedural pain in UAE patients. Compared to conscious sedation, nerve block, or PCA, which needs the expertise of anesthesiologists to perform, these periprocedural medications could be an accessible and useful approach for interventional radiologists to achieve pain control in UAE patients, especially in units without constantly available anesthesiologists.

Besides, we found that vascular administration of periprocedural medications had a better effect on pain management in UAE patients compared to oral administration. Vascular administration could take effect rapidly with accurate dose control and short duration of action, which is preferable for acute postprocedural pain management.[23] Several studies have demonstrated the benefit of intraarterial lidocaine to decrease postprocedural pain scores and opioid consumption in patients receiving hepatic chemoembolization.[24-28] Intravenous ketoprofen, dexamethasone, and dexmedetomidine have also been proved with similar effects in gynecologic and abdominal surgeries.[29-32] However, two included studies in this meta-analysis showed that oral oxycodone had only an effect on decreasing pain score but no opioid-sparing effect,[15,16] which corresponded to

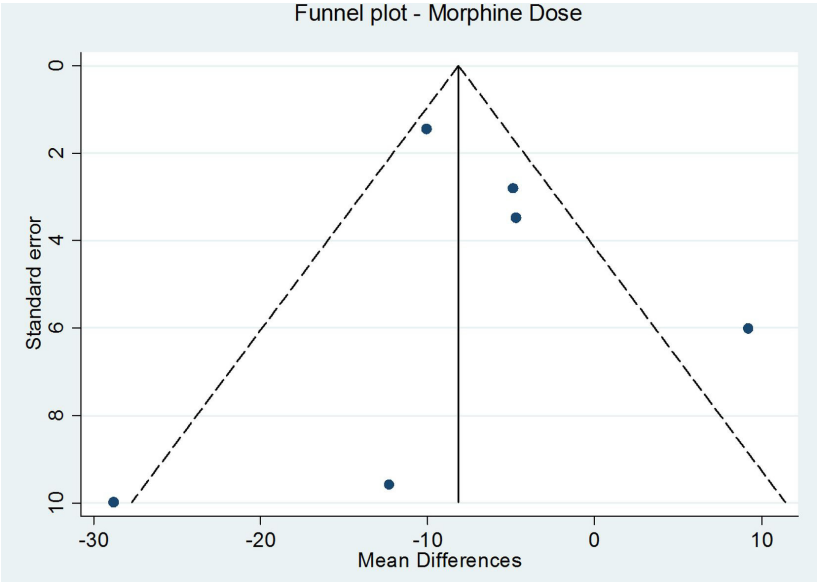

Fig. 6 Funnel plot of cumulative opioid consumption in 24 hours after uterine artery embolization assessing publication bias.

the recent review of oral oxycodone for acute postoperative pain.[33] About the safety analysis, the treatment group had a higher incidence of unstable vital signs compared to controls, though without a statistical significance. This may result from one study using dexmedetomidine plus fentanyl PCA,[17] which contributed six cases of unstable vital signs to the treatment group. The authors suggested that dexmedetomidine may potentiate fentanyl-induced bradycardia and hypotension.[17] A meta-analysis showed statistically higher incidence of bradycardia and hypotension using dexmedetomidine in gynecologic surgery compared with placebo.[30] Interventional radiologists should be aware of such cardiovascular complications when using dexmedetomidine.

To our knowledge, this is the first meta-analysis to examine the effect of periprocedural medications on postprocedural pain of UAE. We conducted an extensive literature search to diminish the possibility of publication bias. However, several limitations existed in this study. We found significant heterogeneity among trials, which resulted from different study designs, drug types, administration routes, the sedation level, the combination use of PCA, and suboptimal study quality due to incomplete blinding of the participants in three out of eight trials. Although we did comprehensive subgroup analysis to decrease heterogeneity and improve the accuracy of outcomes, the results might have limited reliability due to relatively small sizes of the subgroups. Because of the paucity of included studies, we could not analyze the pure effect of periprocedural medications on postprocedural pain of UAE under the setting of no other pain-control modality. The data of fibroid volume in the included studies was incomplete, therefore we could not analyze the effect of fibroid volume in our study. Although the meta-regression showed no significant effects of other modalities on pain outcomes, such as sedation level or PCA use, the interaction between multimodality use might still exist. Furthermore, because of limited long-term measurements of pain outcomes and different protocols among these trials, we could only analyze effects of periprocedural medications on acute pain outcomes within 24 hours after UAE. Therefore, further large-scale trials are needed to confirm our findings and to explore the long-term effects of periprocedural medications on pain management in UAE patients.

In summary, periprocedural medications could relieve postprocedural pain in women receiving UAE for uterine myoma or adenomyosis. Vascular administration may have better analgesic and opioid-sparing effects than oral administration. However, the risk of cardiovascular complications should be carefully considered when using dexmedetomidine.

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Supplementary Material

Appendix

Search strategies

Database: PubMed < 1946 to September 30, 2018 >

Search Strategy: ("uterus"[MeSH Terms] OR "uterus"[All Fields] OR "uterine"[All Fields]) AND ("embolization, therapeutic"[MeSH Terms] OR ("embolization"[All Fields] AND "therapeutic"[All Fields]) OR "therapeutic embolization"[All Fields] OR "embolization"[All Fields]) AND ("leiomyoma"[MeSH Terms] OR "leiomyoma"[All Fields] OR "fibroid"[All Fields] OR "myoma"[All Fields] OR "adenomyosis"[MeSH Terms] OR "adenomyosis"[All Fields]) AND ("pain"[MeSH Terms] OR "pain"[All Fields] OR "analgesia"[MeSH Terms] OR "analgesia"[All Fields]) AND "randomized"[All Fields])

Search results: 49

Database: Embase < 1947 to September 30, 2018 >

Search Strategy: ('uterine'/exp OR uterine) AND ('embolization'/exp OR embolization) AND ('pain'/exp OR pain OR 'analgesia'/exp OR analgesia) AND (fibroid OR 'leiomyoma'/exp OR leiomyoma OR 'myoma'/exp OR myoma OR 'adenomyosis'/exp OR adenomyosis)

Search results: 708

Database: Cochrane Central Register of Controlled Trials: Issue 9, September 2018

Search Name: uterine embolization pain

Search results: 81

Risk of bias judgement

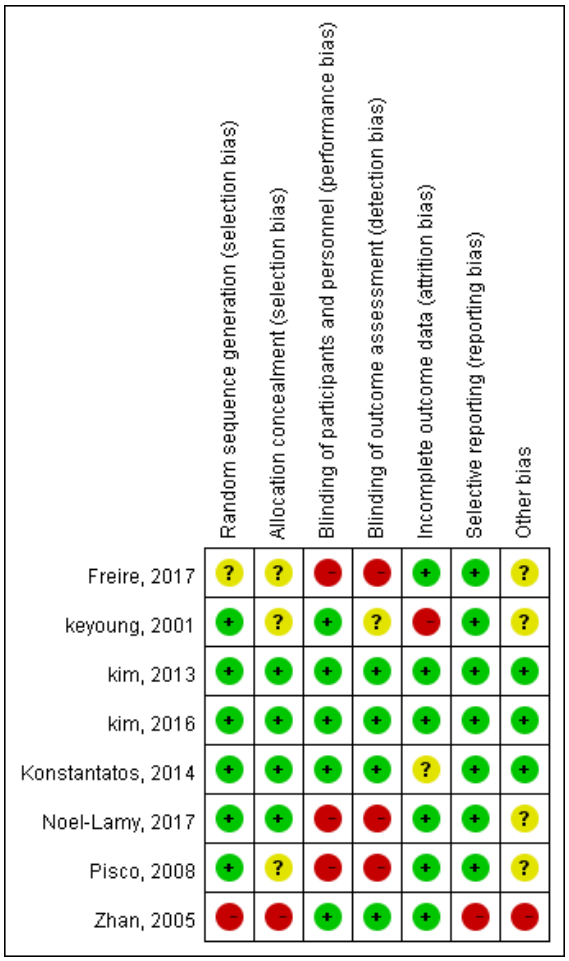

Fig. S1 Risk-of-bias judgment of included trials.

Risk of Adverse Events

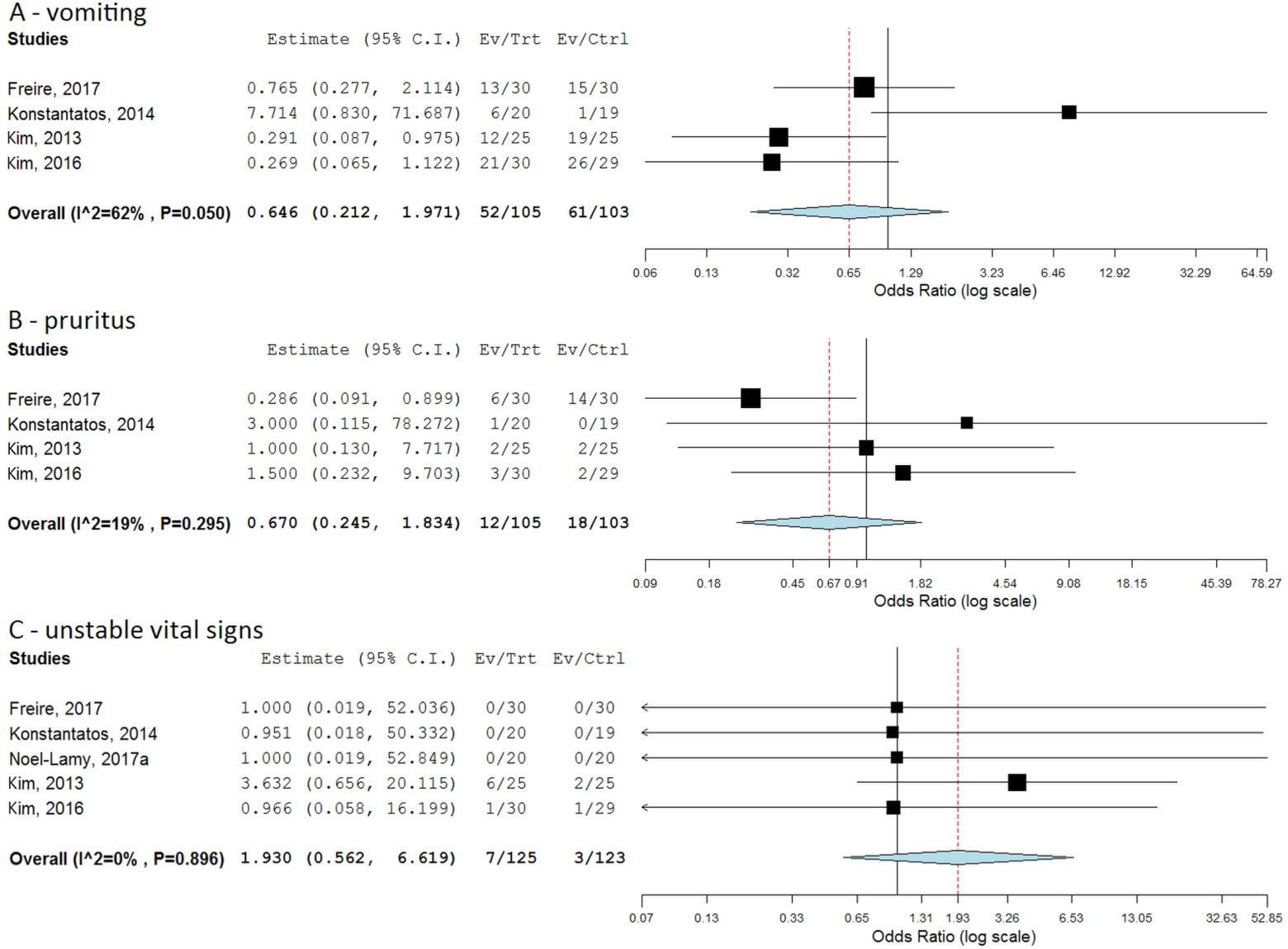

Fig. S2 Forest plots showing odds ratios (with 95% CI) of adverse events (A) vomiting, (B) pruritus, (C) unstable vital signs, comparing periprocedural medications and controls in a random effect model.