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Efficacy and safety of flurbiprofen axetil in the prevention of pain on propofol injection: A systematic review and meta-analysis

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Data Interpretation D
Manuscript Preparation E
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Background: Pain on injection is an acknowledged adverse effect (AE) of propofol administration for the induction of general anesthesia. Flurbiprofen axetil has been reported to reduce the pain of injection. However, results of published papers on the efficacy of flurbiprofen axetil in managing pain on injection of propofol are inconsistent.





Material/Methods: We conducted a comprehensive meta-analysis of studies to appraise the efficacy and safety of flurbiprofen axetil for controlling pain induced by propofol injection. The pooled risk ratio (RR) with corresponding 95% confidence intervals (CI) was calculated employing fixed- or random-effects models, depending upon the heterogeneity of the included trials.

Results: Compared with the placebo group, flurbiprofen axetil allows more patients to have no pain (RR 3.51, 95% CI 2.22–5.55, $p=0.000$), and decreases the cumulative number of patients with mild, moderate, and severe pain on injecting propofol (RR 0.70, 95% CI 0.58–0.86, $p=0.000$; RR 0.59, 95% CI 0.46–0.75, $p=0.000$; RR 0.25, 95% CI 0.16–0.38, $p=0.000$, respectively). In the stratified analysis by the doses, flurbiprofen axetil at a dose of over 50 mg was found to be effective in reducing propofol-induced pain on injection; however, there were no significant differences in relieving pain between treatment and placebo groups with flurbiprofen axetil at a dose of 25 mg. In terms of drug safety, there were no adverse effects (AEs) reported between flurbiprofen axetil-based regimens and placebo regimens.

Conclusions: Flurbiprofen axetil, an injectable prodrug of flurbiprofen, can significantly prevent or relieve the pain induced by propofol injection. More studies are required to assess its adverse effects.

MeSH Keywords: **Prevention • Injection Pain • Flurbiprofen • Meta-Analysis • Propofol**

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Background

Pain during the injection of propofol is a common clinical problem. Among 33 low-morbidity clinical outcomes assessed by expert anesthesiologists considering clinical importance and frequency, propofol-induced pain ranked seventh [1]. This pain occurs in approximately 90% of patients if a vein on the dorsum of the hand is used [2]. The mechanism by which propofol arouses pain on injection is unclear, but it has been ascribed to the release of a kininogen from the vein wall, which strikes a regional kinin cascade [3]. The effect of the products of the kinin cascade upon the nociceptor may be strengthened by prostaglandins [3]. Considering these mechanisms, eliminating propofol injection pain may be achieved by decreasing propofol contact with nerve endings and inhibiting the kallikrein-kinin system or bradykinin release.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported to inhibit prostaglandin synthesis and reduce kinin cascades and could therefore be used to decrease propofol injection pain [3]. FA, which is merged into lipid micro-balloon spheres that play the part of the carrier, is a pro-drug of NSAIDs that gathers at the site of the operative incision and the site of inflammation [4]. It has been covered that FA depresses the biosynthesis of prostaglandins [5], alleviates pain in reaction to the endogenous inflammatory factors, restrains peripheral sensitization and the compound of prostaglandins in the spinal cord, reduces nociception in the peripheral afferent nerve fiber, and relieves central sensitization [6].

During recent decades, pretreatment with Flurbiprofen axetil (FA) has been reported to alleviate the severity and incidence of pain induced by propofol injection [7,8–13]. However, the outcomes of these randomized controlled trials (RCTs) vary. Fujii et al. reported that FA efficaciously relieved the pain induced by propofol injection, and that it has to be administered at a dose of over 50 mg, preceded by venous occlusion [7,10–13], while Karasawa et al. and Nishiyama found no significant differences between the treatment groups and placebo groups [8,9]. Their findings were based on individual trials and lack adequate proof to assess the efficacy and safety of FA for controlling the pain associated with propofol injection. Based on a MEDLINE search (terms: flurbiprofen axetil, propofol, injection pain), no published meta-analyses were available for evaluating the efficiency of FA on alleviating pain associated with the propofol injection. Consequently, we conducted a systematic meta-analysis of relevant studies to evaluate the effectiveness of FA in controlling the pain associated with propofol injection.

Material and Methods

Literature search and selection

We searched PubMed, Embase, and the Cochrane Register of Controlled Trials with various combinations of the terms “flurbiprofen axetil”, “propofol”, “injection”, “infusion” and “pain” published from 2000 to August 2013. The search was restricted to randomized controlled trials (RCTs) or clinical controlled trials (CCTs) and limited to English-language papers. In regard to duplicate papers, only the latest or most complete report of a clinical trial was enrolled. Additionally, we manually searched the reference lists of review papers and every publication retrieved to find any additional published articles. Studies included in our meta-analysis had to meet the following criteria: 1) research design (randomized or controlled trials), 2) trials contrasting the effectiveness of FA with a placebo or no intervention for prophylaxis of pain induced by propofol injection, 3) containing information about the morbidity and intensity of propofol-induced pain during propofol administration, and 4) has sufficiently effective data for extraction.

Data extraction

Two independent investigators reviewed the studies and extracted the data. Any discrepancy between the extracted data was resolved by consensus. For each publication, the following information was extracted: author's name, year of publication, country in which the study was conducted, study design, treatment arms, number of selected subjects, number of subjects and the total number of participants in treatment and placebo groups (where possible), participant age range, and drug dose. Safety in these publications was appraised by monitoring AEs, containing injection site (e.g., pain, edema, wheal, flare response), and symptoms and signs associated with gastrointestinal ulceration (e.g., burning pain, hemorrhage).

Quality assessment

The quality of the included studies was assessed by 2 reviewers according to the modified Jadad scale [14]. The Cochrane Reviewers' Handbook was used to evaluate the quality of included trials: A=all quality criteria met (low risk of bias); B=1 or more of the quality criteria only partly met (moderate risk of bias); C=1 or more criteria not met (high risk of bias) [15].

Statistical analysis

STATA version 10.0 (Stata Corporation, College Station, Texas, USA) was used for statistical analysis. Risk ratios (RRs) with their 95% confidence interval (CI) regarding incidence and intensity of pain associated with propofol injection for each study were calculated and pooled by using fixed-effects models

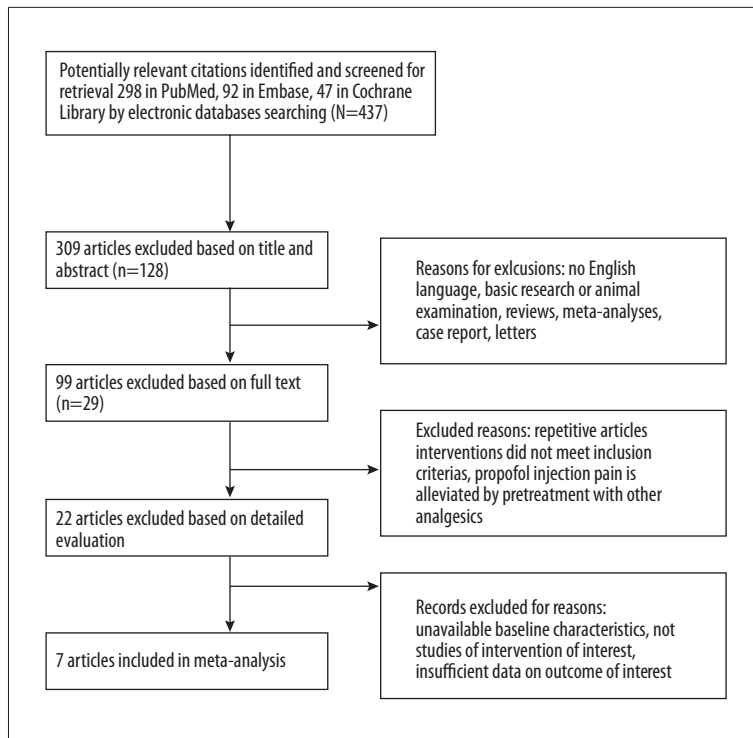


Figure 1. Flow chart showing study selection procedure.

(Mantel-Haenszel method) or random effects models in the meta-analysis [16]. The latter was calculated by using DerSimonian and Laird's method, which considers both within- and between-study alteration. The statistical heterogeneity amongst the studies contained in the meta-analysis was evaluated by using Cochrane's Q statistic, and the discrepancy was quantitated with the I^2 statistic; a value of 0% suggests no heterogeneity and values increase from 0% to 100% show gradual heterogeneity [17]. The hypothesis of homogeneity was invalid for P values <0.1 ; in this case, we reported a summary from the random effects models, or we reported the summary from fixed effect models. To survey the feasible causes for heterogeneity, we also contrasted the pooled scores of the above effect outcomes for subgroup stratified by the drug dose. Sensitivity analysis was conducted to evaluate the robustness of the consequences. Finally, publication bias was assessed by using a visual inspection of the funnel plot of the fixed or random effect RR of each study on the x-axis and the standard error of the variance of the log RR on the y-axis, and then by both Begg and Egger's tests [18,19]. All p-values were 2-tailed and less than 0.05 were regarded statistically significant.

Results

Search results and description of the studies

A total 437 reports were initially identified from database and manual search. By scanning titles and abstracts and removing

309 records of animal studies, case reports, letters, reviews, and meta-analyses, 128 reports were extracted. After careful reading of full texts and detailed evaluation, 7 articles (5 RCTs and 2 CCTs) with 13 trials including 770 patients were screened in this analysis (Figure 1). Characteristics of the included studies are presented in Table 1. Nishiyama (2005) contains 2 trails (NO. 2 and NO. 3), Fujii (2005) contains 3 trials (NO. 4, NO. 5 and NO. 6), Fujii (2006) contains 2 trails (NO. 7 and NO. 8), Fujii (2009) contains 3 trails (NO. 10, NO. 11 and NO. 12), and the search flow diagram is presented in Figure 1. There were no significant differences in baseline information between the treatments arms and placebo or control arms. In all of the studies, propofol was injected into the largest vein of a hand, and a 20-gauge catheter was used.

Methodological quality assessment

All article scores are shown in Table 2, indicating that most studies were categorized as high quality by the current rating system. Five studies scored ≥ 4 [7,10–13] and 2 studies scored <4 [8,9]. The main problems reflected in these studies were inappropriate randomization and no detailed information on allocation concealment, withdrawals and dropouts, and blinding method.

Efficacy

In trials with prevention of pain induced by propofol injection, FA was given before administering propofol to the treatment groups according to the protocol used by each trial. The

Table 1. Basic characteristics of the trials included in the meta-analysis.

Number	Study author	Year	Country	Regimen	Patient per arm (male/female)	Age, mean ±SD (years)	Weight (Kg)
1	Karasawa	2000	Japan	EG: flurbiprofen axetil 50 mg	EG 25/25	58±2	57.6±1.6
				PG: 0.9% saline 5 ml	PG 28/22	51±3	56.6±1.7
2	Nishiyama (1)	2005	Japan	EG1: flurbiprofen axetil 50 mg followed immediately by propofol	EG1 10/40	48±15	57±16
3	Nishiyama (2)	2005	Japan	EG2: flurbip rofen axetil 50 mg followed by propofol 1 min later	EG2 11/39	46±14	55±13
				PG: 0.9% saline 5ml	PG 8/42	53±14	58±13
4	Fujii (1)	2005	Japan	EG1: flurbiprofen axetil 25 mg	EG1 15/15	41±12	57±10
5	Fujii (2)	2005	Japan	EG2: flurbiprofen axetil 50 mg	EG2 16/14	41±12	58±10
6	Fujii (3)	2005	Japan	EG3: flurbiprofen axetil 75 mg	EG3 15/15	41±11	59±9
				PG: 0.9% saline 5ml	PG 16/14	42±12	59±10
7	Fujii (1)	2006	Japan	EG1: flurbiprofen axetil 25 mg	EG1 26/24	30±5	56±9
8	Fujii (2)	2006	Japan	EG2: flurbiprofen axetil 50 mg	EG2 25/25	31±5	59±9
				PG: 0.9% saline 5 ml	PG 25/25	31±4	58±9
9	Fujii	2008	Japan	EG: flurbiprofen axetil 50 mg	EG 12/13	42±12	58±9
				PG: 0.9% saline 5 ml	PG 11/14	41±11	60±9
10	Fujii (1)	2009	Japan	EG: flurbiprofen axetil 50 mg	EG1 12/13	42±8	59±9
11	Fujii (2)	2009	Japan	EG: tourniquet flurbiprofen axetil 50 mg	EG2 12/13	40±11	58±8
12	Fujii (3)	2009	Japan	EG: mixed flurbiprofen axetil 50 mg	EG3 12/13	40±12	59±10
				PG: mixed 0.9% saline 5 ml	PG 13/12	41±9	58±10
13	Fujii	2011	Japan	EG: flurbiprofen axetil 50 mg	EG 14/11	44±12	57±10
				PG: 0.9% saline 5 ml	PG 14/11	44±11	57±11

EG – experimental group, PG – placebo group; Nishiyama (2005) – contains two trails (NO.2 and NO.3); Fujii (2005) – contains three trials (NO.4, NO.5 and NO.6); Fujii (2006) – contains two trails (NO.7 and NO.8); Fujii (2009) – contains three trails (NO.10, NO.11 and NO.12).

Table 2. Quality assessment of the trials included in the meta-analysis.

Study author	Year	Country	Random sequence production	Blinding method	Allocation concealment	Withdrawal	Quality level	Jadad score
Karasawa	2000	Japan	1	1	0	0	B	2
Nishiyama	2005	Japan	1	2	0	0	B	3
Fujii	2005	Japan	2	2	0	0	B	4
Fujii	2006	Japan	2	2	0	0	B	4
Fujii	2008	Japan	2	2	0	0	B	4
Fujii	2009	Japan	2	2	0	0	B	4
Fujii	2011	Japan	2	2	0	0	B	4

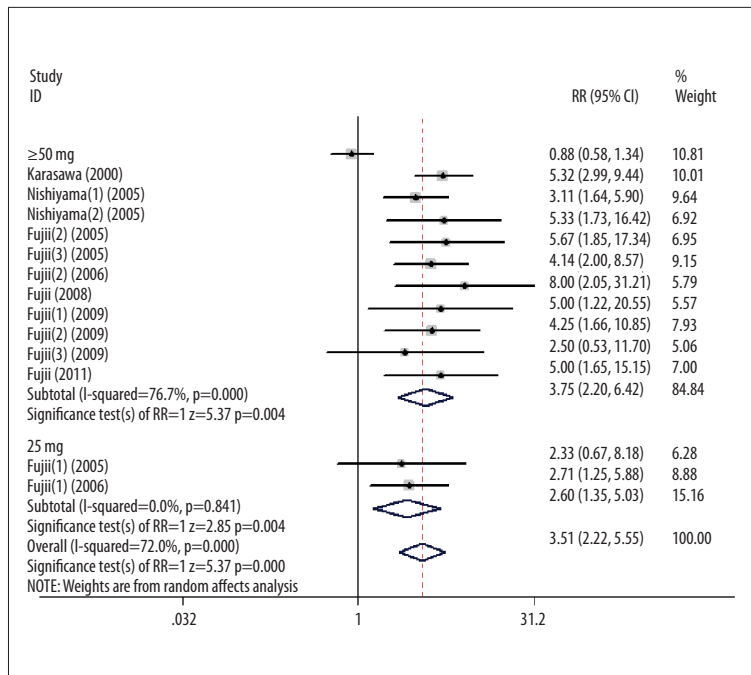


Figure 2. Forest plot of RR. FA regime and control regime on preventing propofol injection pain with 95% CI. Data for a random-effects model are shown because there was statistical heterogeneity.

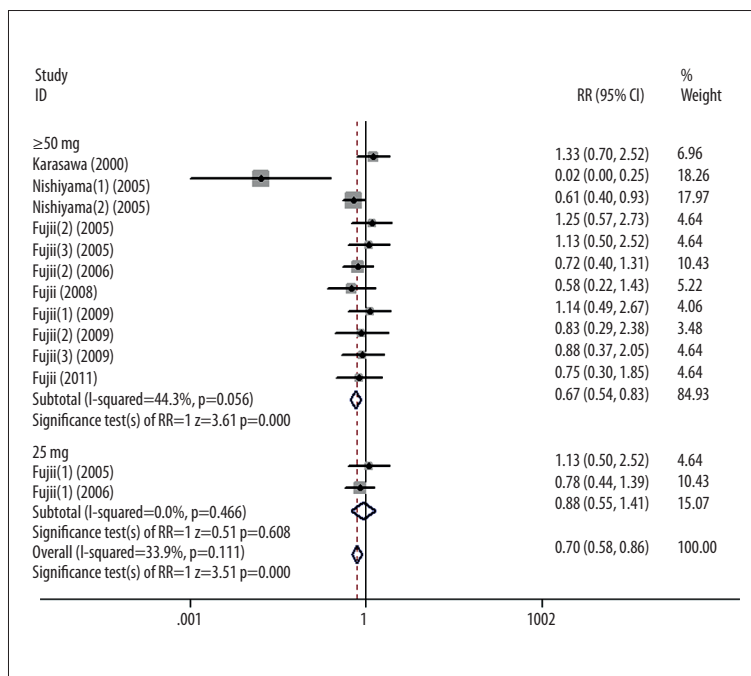


Figure 3. Forest plot of RR. FA regime and control regime in relieving the mild pain in injecting propofol with 95% CI. Data for a fixed-effects model are shown because there was no statistical heterogeneity.

cumulative number of patients was significantly reduced in each treatment group on various levels of pain (Verbal Rating Scale) compared to the placebo or control arms [20]. Compared with the placebo group, flurbiprofen axetil allowed more patients to have no pain (risk ratio [RR] 3.51, 95% confidence interval [CI] 2.22–5.55, $p=0.000$, Figure 2), with significant heterogeneity between trials detected (test for heterogeneity $p=0.000$), so a random-effects model was used for analysis. FA could decrease the cumulative number of patients with

mild, moderate, and severe pain on injecting propofol (RR 0.70, 95%CI 0.58-0.86, $p=0.000$; RR 0.59, 95%CI 0.46–0.75, $p=0.000$; RR 0.25, 95%CI 0.16–0.38, $p=0.000$, respectively, Figures 3–5), all with no major heterogeneity detected (test for heterogeneity $p=0.111$, $p=0.461$, $p=0.253$, respectively), and the fixed-effects model was used for analysis.

In the pooled analysis, treatment patients were randomized to receive FA I.V. at 1 of 3 doses (25, 50, or 75 mg). The

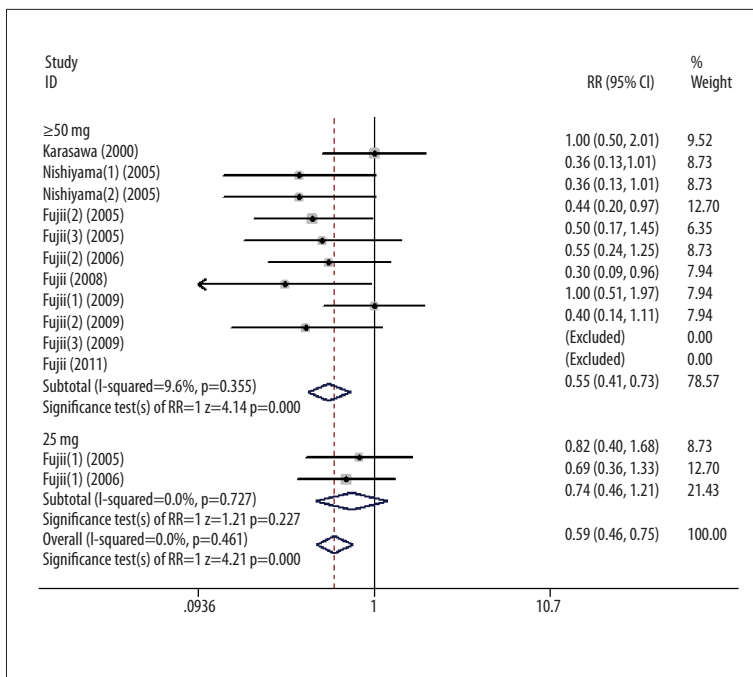


Figure 4. Forest plot of RR. FA regime and control regime on relieving the moderate pain in injecting propofol with 95% CI. Data for a fixed-effects model are shown because there was no statistical heterogeneity.

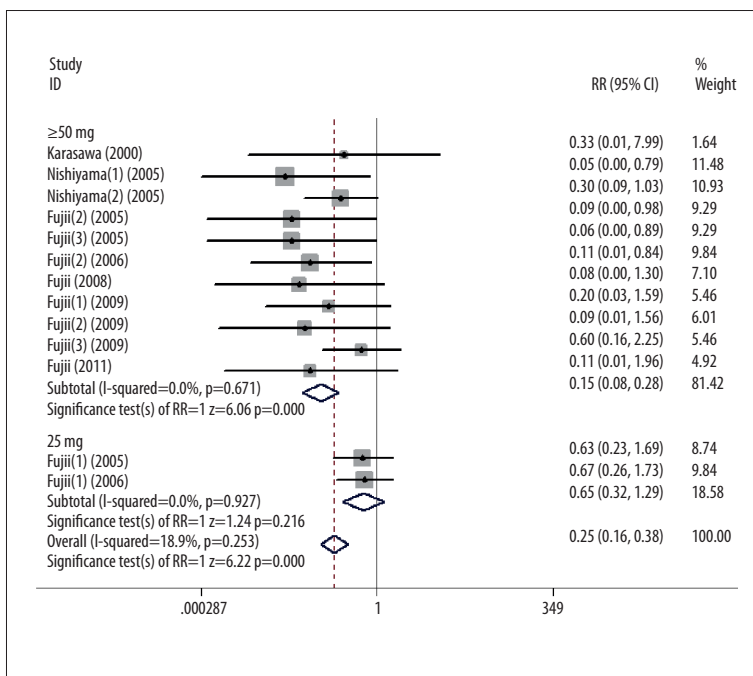


Figure 5. Forest plot of RR. FA regime and control regime on relieving the severe pain in injecting propofol with 95% CI. Data for a fixed-effects model are shown because there was no statistical heterogeneity.

difference among the doses of FA may affect the efficacy for preventing pain during the injection of propofol. Therefore, we conducted a subgroup analysis by dose of FA and showed that FA at doses of over 50 mg and at the dose of 25 mg were found to be effective in allowing more patients have no pain on propofol injection (RR 3.75, 95%CI 2.20–6.42, $p=0.000$; RR 2.60, 95%CI 1.35–5.03, $p=0.004$, respectively, Figure 2). FA at doses of over 50 mg was found to be effective in decreasing the cumulative number of patients in the

mild, moderate, and severe pain on injecting propofol (RR 0.67, 95%CI 0.54–0.83, $p=0.000$; RR 0.55, 95%CI 0.41–0.73, $p=0.000$; RR 0.15, 95%CI 0.08–0.28, $p=0.000$, respectively, Figures 3–5). However, FA at the dose of 25 mg did not show any superiority in relieving the mild, moderate, and severe pain on injecting propofol (RR 0.88, 95% CI 0.55–1.41, $p=0.608$; RR 0.74, 95%CI 0.46–1.21, $p=0.227$; RR 0.65, 95%CI 0.32–1.29, $p=0.216$, respectively, Figures 3–5) when compared with placebo groups.

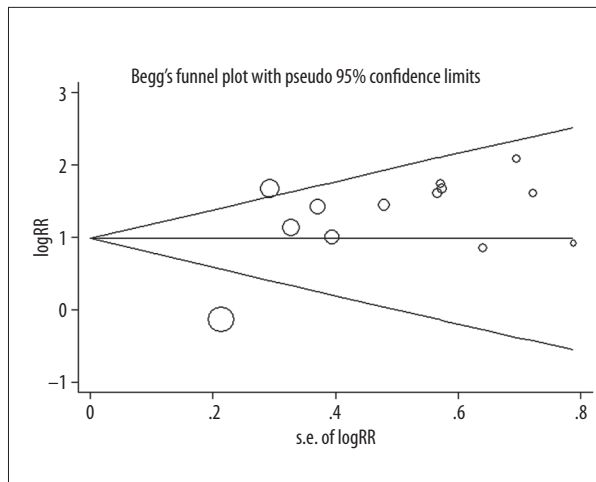


Figure 6. Begg's funnel plot of publication bias test. FA vs. control. Each point represents a separate study for the indicated association. Log (RR), natural logarithm of RR. Horizontal line, mean effect size.

Evidence of safety

Pain, edema, wheal, inflammation, and symptoms or signs associated with gastric or intestinal ulceration are the common AEs of FA, which were mentioned in 4 articles with 10 trials. We intended to perform a meta-analysis of safety with AEs; however, it might be impossible to perform a meta-analysis because there is no detailed data concerning AEs observed from flurbiprofen axetil-based regimens and placebo regimens.

Publication bias

As shown in Figure 6, the shape of the funnel plot was asymmetrical, suggesting the presence of publication bias. Then, the Egger's test was used to provide statistical evidence of funnel plot asymmetry. As expected, the results showed obvious evidence of publication bias ($t=2.61$, $p=0.024$). A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual dataset on the pooled RRs, and the corresponding pooled RRs were not materially altered (data not shown), suggesting that our results are statistically robust.

Discussion

Propofol is the most widely using intravenous hypnotic for the induction and maintenance of general anesthesia due to its rapid onset time and short action duration [21]. However, pain during administration is one of the most distressing effects of propofol injection to the patient. The incidence of pain has been reported to vary from approximately 70% to 90% when it is injected into a vein on the dorsum of the hand [2], and is known as a severe challenge; it ranks seventh among the top

33 clinical morbidity outcomes [1]. Regarding the decrease of pain associated with intravenous injection of propofol, several studies used pharmacologic and non-pharmacologic methods. Particularly, research assessed variations in the injection speed and carrier fluids, dilutions, temperatures, and adjuvant therapies using anesthetics [22,23].

Karasawa F et al. evaluated the efficacy of FA without venous occlusion for reducing the incidence of propofol-induced pain, and they reported that it was not effective [8]. Fujii et al. showed that pretreatment with FA, after venous occlusion for 2 minutes, was effective for preventing pain during the injection of propofol [11]. The reason for this difference is unknown. However, there is a possibility that venous occlusion increases the time that FA remains within the vein to inhibit the local inflammatory response [24]. Fujii et al. performed a randomized, double-blind, vehicle-controlled, dose-finding trial, in which patients were randomized to receive FA I.V. at 1 of 3 doses (25, 50, or 75 mg), or vehicle, preceded by manual venous occlusion, for reducing propofol-induced pain on injection, and found that FA (50 or 75 mg) significantly reduced pain intensity compared with vehicle; however, the efficacy was not found with the 25 mg dose [10]. These findings show that FA 50 mg may be sufficient to minimize propofol-induced pain on injection. Fujii et al. found that no significant difference in the prevalence of pain during injection of propofol between patients in the mixed control group (92%) administered a mixture of placebo (saline) and propofol and those in the mixed FA group (80%) administered a mixture of FA 50 mg and propofol [7]. This suggests that mixing FA with propofol may be not effective in reducing such pain.

To resolve this conflict, a pooled analysis of 7 studies with 13 trials including 770 patients was conducted to provide the most comprehensive analysis of the efficacy and safety of FA in preventing the pain induced by propofol injection. In our pooled analysis, we found that compared with the placebo group, flurbiprofen axetil allowed more patients have no pain, and relieved the mild, moderate, and severe pain of injecting propofol. In our meta-analysis, we combined data in the subgroup analysis by FA dosage, and showed that FA at doses of over 50 mg were effective in relieving the mild, moderate, and severe pain of injecting propofol, but FA at a dose of 25 mg did not show any superiority in relieving the mild, moderate, and severe pain of injecting propofol when compared with placebo groups.

With regard to safety profile, FA was considered safe and tolerated in the pooled analysis. Most of these studies reported the well-known AEs of FA such as pain, edema, wheal, inflammation, or FA associated with gastric or intestinal ulceration [25]. But in these studies, these AEs did not occur in both FA-based and placebo groups.

Some limitations affecting the objectivity of the conclusions should be considered when interpreting these results. First, the small number of studies and sample size limited the ability to draw more solid conclusions. Second, because of lacking data, it was not possible to use a meta-analysis to address the important issue of AEs associated with FA. Third, the difference in gauge of catheter needle, flow rate of drug injection, vein diameter, and endothelial structure might account for the reduction in pain across trials was not considered properly or incorporated into the analysis. Finally, all of the studies included in this analysis were from Asia and the results need to be confirmed in other continents and ethnic groups regarding efficacy and safety.

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Conclusions

In conclusion, this is the first meta-analysis focused on assessing the efficacy and safety of FA for controlling pain induced by propofol injection. Our meta-analysis suggests that FA at doses of over 50 mg, preceded by venous occlusion, was effective in preventing or relieving the pain induced by propofol injection. Therefore, FA is a promising prophylactic agent to control propofol-induced pain, and it may be widely used in the future. Well-designed multi-center studies in various ethnic groups are warranted to validate our findings.

Conflict of interest disclosures

The authors have no conflicts of interests that are relevant to the content of this manuscript.