

Flurbiprofen Axetil For Prevention Of Propofol Injection Pain In Adult --- A Systematic Review

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Citation

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Abstract

Abstract: Purpose: This review evaluates the efficacy of flurbiprofen axetil for preventing pain on injection of propofol. Methods: The following databases were searched including Medline (1966-2009), EMBASE (1990-2009), CINAHL, The Cochrane Central Register of Controlled Trials, and Scopus for randomized controlled trials assessing flurbiprofen axetil intervention for propofol induced injection pain. Trials were included where adults were randomized to receive flurbiprofen axetil or control including placebo, no treatment, or other pharmacologic intervention. Data were abstracted on the incidence and severity of pain at the propofol injection site. Adverse effects related to flurbiprofen axetil were also extracted. Combined data were analyzed using a random effects model. Results: Ten clinical trials were included. The incidence of patients without pain was significantly higher in flurbiprofen axetil group compared with no treatment control or placebo control (Risk Ratio [RR]: 3.46, 95% CI: 2.18, 5.49) with number needed to treat (NNT) of 2.6. The NNT for the incidence of patients without pain was 2.5, 2.1 and 5.0 in flurbiprofen axetil 50 mg pretreatment without venous occlusion, flurbiprofen axetil 50 mg preceded by venous occlusion, and flurbiprofen axetil 25mg preceded by venous occlusion group, respectively. The incidence of moderate or severe pain was also significantly lower in patients receiving flurbiprofen axetil intervention compared with no treatment control (RR: 0.41, 95% CI: 0.31, 0.56). Conclusion: Flurbiprofen axetil reduces the incidence and severity of propofol induced injection pain.

INTRODUCTION

Propofol remains the most common induction drug for general anesthesia because of its unique properties.¹ However, propofol injection pain represents a clinical problem with incidence of 30-90% ranking seventh among 33 low morbidity clinical outcomes.²

A number of approaches have been proposed to attenuate the incidence and severity of this complication with varying degree of success. Pharmacological methods have been reported to be effective in preventing the pain induced by propofol injection.³⁻⁶ Flurbiprofen axetil, an injectable prodrug of flurbiprofen, has been used clinically for postoperative pain management as nonsteroidal anti-inflammatory drugs (NSAIDs).⁷ Several studies have been reported on the efficacy of intravenous administration of flurbiprofen axetil in reducing pain of propofol injection with contrasting results. The primary objective of this systematic review is to evaluate the efficacy of flurbiprofen axetil to prevent pain associated with propofol injection.

MATERIALS AND METHODS

Published reports of clinical trials evaluating flurbiprofen axetil to prevent pain on injection of propofol were sought according to QUORUM guidelines.⁸ Medline (1966-2010), EMBASE (1990-2009), CINAHL, The Cochrane Central Register of Controlled Trials, and Scopus were searched without language restriction. Free text and MeSH terms 'flurbiprofen', 'flurbiprofen axetil', 'propofol', 'injection', 'pain', and 'complication' were used in the search strategy. The bibliographies of these retrieved trials and database such as China hospital knowledge database (CHKD) were also searched for additional trials. The last manuscript search was in September 2010. Abstracts of matching studies were screened by two independent reviewers (Y.S and F.C). Relevant articles were obtained in full text for further review. We excluded data from letters, abstracts, case reports, experimental studies, or review articles.

SELECTION CRITERIA:

Randomized controlled trials (RCTs) of intravenous administration of flurbiprofen axetil for preventing pain of propofol injection in adults (age >18) were included. Trials

which reported relevant pain outcomes including pain score and incidence of pain were included. We excluded trials where only different strategies of flurbiprofen axetil administration were compared without a control group.

VALIDITY ASSESSMENT

All included trials were assessed by two independent reviewers (Y.S and F.C) using modified Oxford Scale.⁹ Discrepancies were resolved by consultation or by discussion with third reviewer (T.L). The minimum score of an included trial was 1, and maximum score was 6.

DATA ABSTRACTION

The following data points were extracted by two independent reviewers (Y.S and F.C) including flurbiprofen axetil intervention, group studied, number of patients, nature of the control group, site and size of vein cannulation, dosage of propofol, and flurbiprofen axetil related side effects. Dichotomous data such as incidence of patients with moderate or severe pain defined by pain score over 1 was abstracted. The incidence of patients without pain was also extracted. When the trial tested two or more intravenous techniques of flurbiprofen axetil administration, we combined the data to a single pair comparison. If the trial did not report appropriate data, we contacted authors on repeated occasions. The trial was not considered if the author did not respond adequately to our demand.

META-ANALYSIS

Dichotomous data were analyzed using risk ratio with 95% confidence interval (CI). If 95% CI around the RR did not include 1.0, it was interpreted that the difference between flurbiprofen axetil and the control group was statistically significant. For the incidence of patients without pain, relative risk ratio was calculated.^[3] The number needed to treat (NNT) was also calculated to estimate the clinical impact of beneficial intervention according to the incidence of patients without pain. Continuous data were analyzed as weighted mean difference (WMD) with 95% CI. If 95% CI included 0, we assumed that the difference between flurbiprofen axetil and control groups was not statistically significant. For combined data, a random model was used. Analyses were performed using ReviewManager software [version 4.2, Cochrane collaboration). Data were represented forest plot to evaluate treatment effect. The I² test was used to assess heterogeneity. A value greater than 50% is considered to have substantial heterogeneity. Three subgroup analyses were created to facilitate analysis based on the strategy of flurbiprofen axetil administration

(administration alone with or without venous occlusion before propofol injection, or administration as a mixture with propofol).

RESULTS

Twelve published trials using flurbiprofen axetil to prevent propofol induced injection pain were identified after screening all relevant trials. All trials were published between 2000 and 2009. Of these, one trial was excluded due to publication in a letter format.¹⁰ Same original data were found in two different full trials.^{11 12} We contacted authors for explanation but did not receive a response; we analyzed the data from one trial. A total of ten trials with 1320 patients meeting inclusion criteria were included in this analysis. (Figure 1) The characteristic of included trials were summarized in table 1. Three trials were published in Chinese^{11 13 14}, the rest in English.

Three methods of flurbiprofen axetil intervention were described in this review including pretreatment with flurbiprofen axetil without venous occlusion, flurbiprofen axetil preceded by venous occlusion and a mixture of flurbiprofen axetil and propofol. One trial had three comparisons to test all three methods.¹⁵ Flurbiprofen axetil at a dose of 50mg was used in majority of the trials. Two trials compared flurbiprofen axetil 25mg with placebo as control.^{16 17} Only one study used 75mg flurbiprofen axetil as one of treatment arms.¹⁷ Seven trials used other pharmacologic interventions as one of control arms, such as lidocaine and metoclopramide.^{11 13 14 18-21} Largest vein of hand was used as injection site in eight trials, the cephalic vein in one trial¹⁹ and superficial radial vein of the hand in one trial.²⁰ Flurbiprofen axetil was used in all included trials except in one trial where flurbiprofen was used.²⁰

Pain intensity was reported in all included trials using a 4-point verbal rating scale: 0=none (negative response to questioning); 1= mild (pain reported only in response to questioning without any behavioral signs); 2= moderate (pain reported only in response to questioning accompanied by behavioral signs or sign reported spontaneously without questioning); and 3 = severe (strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears).^{22 23} The incidence of patients without pain and incidence of moderate or severe pain was provided appropriately in all included 10 trials. A total of four trials reported pain score only as mean or median with ranges 15-17²¹. Standard deviation (SD) could not be reliably estimated from the range. Thus, these trials were excluded

from the analysis.

FLURBIPROFEN AXETIL VERSUS NO TREATMENT

Ten trials with thirteen comparison arms had adequate information for analysis.^{11 13-21}

Combined data showed that the incidence of patients without pain was significantly higher in flurbiprofen axetil group compared with control group (RR: 3.46, 95% CI: 2.18, 5.49) with heterogeneity (I²=71.9%) (Figure 2), NNT to prevent any injection pain of propofol was 2.6. Incidence of moderate or severe pain was also found significant lower in patients pretreated with flurbiprofen axetil (RR: 0.41, 95%CI: 0.31,0.56).

SUBGROUP ANALYSES

Three subgroup analyses were conducted as described at table 2. Flurbiprofen axetil 50 mg was administrated before propofol injection without venous occlusion in five trials.^{11 14 15 19 20} Combined data showed the significantly higher incidence of patients without pain in flurbiprofen axetil group compared with no treatment control (RR: 3.14, 95% CI: 1.41, 7.01) with heterogeneity (I²=85.7%) , NNT was 2.5. Incidence of moderate or severe pain was also found to be significant lower in patients received flurbiprofen axetil pretreatment (RR: 0.41, 95%CI: 0.31, 0.56)

Seven trials used flurbiprofen axetil before propofol injection with venous occlusion. Venous occlusion involved manually compressing the forearm with rubber tourniquet for 2 minutes in six trials^{13 15-18 21} and 1 minute in one trial.¹¹ Of these, two trials used flurbiprofen axetil 25mg with venous occlusion to prevent injection pain.^{16 17} Combined data showed that flurbiprofen axetil 25mg pretreatment was associated with a higher incidence of patients without pain with a RR of 2.60 (95%CI:1.34, 5.23) without heterogeneity (I²=0). NNT was 5.0. Seven trials reported data when flurbiprofen axetil 50mg was given with venous occlusion before propofol injection.^{11 13 15-18 21} The incidence of patients without pain was significantly higher in patients who received flurbiprofen axetil 50mg with venous occlusion compared with no treatment control (RR: 4.41, 95%CI: 3.11, 6.26) without heterogeneity (I²=0). NNT was 2.1. When preceded by venous occlusion, the incidence of moderate or severe pain was also lower in flurbiprofen axetil group compared with no treatment control. However, the difference only reached statistically significant when flurbiprofen axetil was administrated at a dose of 50 mg (RR: 0.29, 95%CI: 0.21, 0.41) without

heterogeneity (I² =0)

One trial each reported flurbiprofen axetil administered as a single 75 mg dose¹⁷ and as a mixture with propofol¹⁵. Hence, meta-analysis was therefore no possible. In the later study, flurbiprofen axetil 50mg was given as a mixture with propofol and no significant difference was observed in the incidence of patients without pain and incidence of moderate or severe pain between flurbiprofen axetil group and the control group.

FLURBIPROFEN VERSUS LIDOCAINE:

Seven trials have suitable data for analysis.^{11 13-16 18 19 21} Pooled data showed no significant difference between flurbiprofen axetil and lidocaine group in the incidence of no pain, moderate or severe pain.(Table 2)

FLURBIPROFEN AXETIL RELATED SIDE EFFECTS

Seven trials reported on flurbiprofen axetil related side effects.^{14-19 21} Of those, six trials reported no side effects associated with flurbiprofen axetil administration. Only one trial reported adverse effects (phlebitis) on injection site which may not have been due to flurbiprofen axetil administration.¹⁴ The incidence of side-effect was not significantly different compared with control and resolved spontaneously.

Figure 1

Figure 1: flow chart for screened, excluded and analysis trials. RCT: Randomized controlled trial.

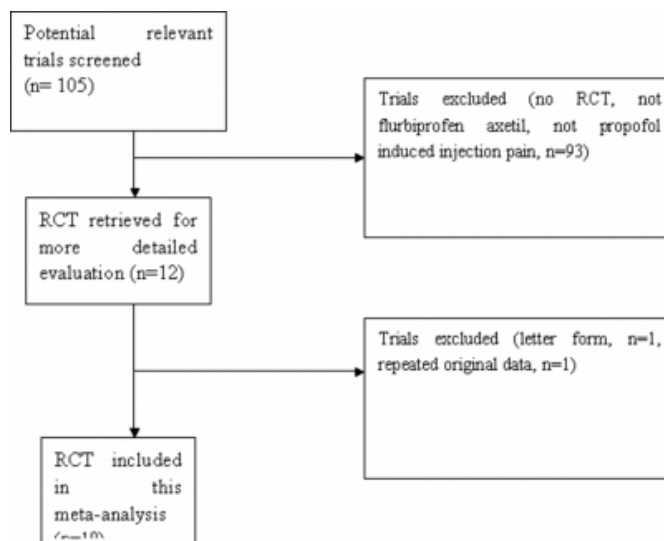
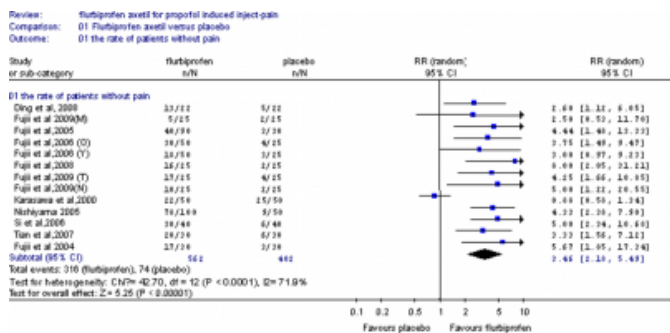


Figure 2

Figure 2: The incidence of patients without pain. RR: related risk, CI: confidential interval



DISCUSSION

This systematic review demonstrates that pretreatment with IV flurbiprofen axetil is effective for prevention of propofol injection pain. The result is consistent regardless of whether flurbiprofen axetil was administered with or without venous occlusion. The NNT for incidences of patients without pain was 5.0, 2.1 and 2.5 in flurbiprofen axetil 25mg or 50mg administration with venous occlusion and flurbiprofen axetil 50mg administration without venous occlusion before propofol injection, respectively. It appears that flurbiprofen axetil administered at dosage of 50 mg when preceded by venous occlusion before propofol injection provided better analgesic effect.

The mechanism of flurbiprofen axetil associated relief of pain on injection is still not well elucidated. Some proposed mechanisms of propofol induced injection pain include relief of the endothelium irritation, osmolality changes, non pharmacologic pH 24 and attenuation of activation of pain cascade mediators like kinin.^{25 26} Of those, the most plausible mechanism of propofol induced injection pain was the activation of the plasma kallikrein-kinin system by the lipid solvent and produce bradykinin which modifies the local vein by its vasodilation and result in hyperpermeability. This modification in the local vein increases the contact between the aqueous phase propofol and free nervous ending, resulting in aggravation of pain on injection.^{25 26} This Phenomenon may be enhanced by prostaglandins ²⁷. NSAIDs have been found to decrease prostaglandins synthesis, therefore flurbiprofen axetil, as one of NSAIDs, might reduce the pain of propofol injection. Moreover, recent study suggested that the concentration of aqueous free propofol may play an important role in the pain on injection site. ²⁸ Ueki et al found that flurbiprofen axetil could decrease the concentration of free propofol, thereby reducing injection pain with propofol.²⁹

Lidocaine has been widely used to attenuate propofol-induced pain on injection.^{3 30} A previous systematic review suggested that IV lidocaine pretreatment with venous occlusion was the best method for prevention of pain on injection with propofol.³ In the subgroup analysis, we compared the efficacy between lidocaine and flurbiprofen axetil for preventing propofol injection pain. Our findings showed no statistical difference between flurbiprofen axetil and lidocaine, suggesting comparable efficacy between the two drugs. As such, flurbiprofen axetil could be an effective alternative for the prophylaxis of pain on injection with propofol especially when lidocaine is contraindicated. No flurbiprofen axetil related side effects have been observed even at the dose of 75mg.¹⁷ However, flurbiprofen axetil should be used with caution in patients with asthma, gastrointestinal ulceration and renal failure.³¹As flurbiprofen axetil is an NSAID, its administration may in addition benefit postoperative pain management.³² Unfortunately, no included trials reported any data related to postoperative pain outcomes.

Heterogeneity is often considered an important limitation of systematic review. In present review, heterogeneity of study results is variable due to the variability of propofol regimens and methods of flurbiprofen axetil pretreatment. Subgroup analyses might have lowered heterogeneity. Furthermore, all included studies have a relatively small group size ranging from 11 to 50. Small study bias is a potential limitation of this review which might cause an overestimation of effectiveness of intervention.³³ In addition, publication bias can not be ruled out.

Several areas have been identified in this review for further research. A newer formulation of propofol consisting of medium or long-term chain triglycerides has been reported with less pain on injection.^{34 35} Only one trial used this formulation as one of the control groups and showed significantly lower incidence of patients without pain using this formulation compared with flurbiprofen axetil pretreatment.²⁰ Further study is needed to investigate the preventive effect of study drug on injection pain with this formulation. Moreover, patient satisfaction, regarded as clinically meaningful measurement for pain, should be incorporated in future studies. Finally, adequately powered, well-designed trials are required to evaluate optimal method of flurbiprofen axetil to prevent propofol induced injection pain and meaningful postoperative outcomes.

In conclusion, flurbiprofen axetil pretreatment significantly reduces propofol induced injection pain. Flurbiprofen axetil

50mg preceded by venous occlusion provides the greatest benefit.

Figure 3

* MCT/LCT: medium chain triglyceride / long chain triglyceride; NA: not available; R: randomization; C: Concealment of allocation; DB: Double-Blinding; F: Flow of patients

Table 3: Characteristics of included trials

Clinical trial	Study score (RUC/BBF)	Technique of flurbiprofen axetil (numbers of patients)	Control (numbers of patients)	Propofol (dose, injection site, IV cannula)	Propofol-induced injection pain	AEs associated with flurbiprofen axetil
Fuji et al, 2009 [17]	6 (20/22)	Flurbiprofen 50mg without occlusion (25) Flurbiprofen 50mg with occlusion (25) Flurbiprofen 50mg axetil with propofol (25)	Placebo (75)	0.5mg/kg, largest vein of hand, 20-gauge cannula	p=0.002 for without venous occlusion group p<0.001 for venous occlusion group NS for mixed group	No AEs reported
Fuji et al, 2005 [17]	6 (20/22)	Flurbiprofen 50mg with occlusion (30) Flurbiprofen 50mg with occlusion (30) Flurbiprofen 50mg with occlusion (30)	Placebo (30)	Propofol 2mg/kg, largest vein of the hand, 20-gauge IV cannula	P<0.01 50mg and 75mg group versus control group, NS 25mg group versus control group	No AEs reported
Kanama et al, 2008 [19]	3 (20/20)	Flurbiprofen 50mg without occlusion (50)	Lidocaine 40mg (50) Placebo (50)	Propofol dose: NA; cephalic vein; 20 gauge IV cannula	NS, compared with placebo P<0.001, pain score higher than lidocaine	No AEs reported
Fuji et al, 2006 [16]	6 (20/22)	Flurbiprofen 50mg with occlusion (young age (25), older age (25)) Flurbiprofen 50mg with occlusion (young age (25), older age (25))	Placebo (50)	0.5mg/kg, largest dorsal vein of hand, 20-gauge IV cannula	NS	No AEs reported
Fuji et al, 2003 [18]	6 (20/22)	Flurbiprofen 50mg with venous occlusion (25)	Lidocaine 40mg with venous occlusion (25) Metoclopramide 10mg with occlusion (25) Placebo (25)	0.5mg/kg, largest vein of hand, 20-gauge IV cannula	P=0.001 versus placebo, NS versus other two groups	No AEs reported
Fuji et al, 2004 [21]	6 (20/22)	Flurbiprofen axetil 50mg with occlusion (30) Both Flurbiprofen axetil 50mg with lidocaine 20mg (30)	Placebo Lidocaine 20mg	2mg/kg, largest vein of hand, 20-gauge cannula	Less pain in flurbiprofen axetil group compared with placebo. No difference between lidocaine and flurbiprofen axetil	No AEs reported
Si et al, 2006 [11]	3 (20/20)	Flurbiprofen axetil 50mg without occlusion (12) Flurbiprofen 50mg with occlusion (27)	Lidocaine 50mg (40) No treatment, standard propofol (40)	Dorsal VA, largest vein of hand, cannula NA	P<0.05 versus placebo	NA
Nishiyama et al, 2005 [20]	3 (20/20)	Flurbiprofen 50mg immediately followed by propofol without occlusion (flurbiprofen group) (50) Flurbiprofen 50mg 1 min later followed by propofol (flurbiprofen 1) (50)	Lidocaine 40mg (50) No treatment, standard propofol alone (50) MCT/LCT* group (50)	Dose: 2mg/kg; superficial radial vein of hand, 20-gauge IV cannula	Less pain (p<0.05) in flurbiprofen group compared with lidocaine, MCT/LCT, standard propofol alone group. P<0.05 flurbiprofen 1 vs. standard propofol	NA
Ding et al, 2008 [13]	3 (10/10)	Flurbiprofen axetil 50mg with occlusion (22)	Lidocaine 40mg (22) Placebo (22)	Dorsal VA Site and Cannula NA	P<0.05 versus placebo	itchiness
Tan et al, 2007 [14]	3 (10/10)	Flurbiprofen 50mg without occlusion (30)	Lidocaine 40mg without occlusion (30) Placebo (30)	100mg propofol, Largest dorsal vein of hand	P<0.05 versus placebo	NA

Figure 4

Table 2: Subgroup-analysis

	Incidence of patient with over moderate pain (n/N)			The incidence of patients without pain (n/N)			Trials (ref.)
	Intervention	Control	RR (95% CI)	Intervention	Control	RR (95% CI)	
Flurbiprofen axetil versus placebo							
Flurbiprofen axetil administration without venous occlusion before the injection of propofol							
50mg	33/245	68/195	0.44 (0.26, 0.74)	169/245	48/195	3.14 (1.41, 7.01)	2, 5 [11,14,15,19,20]
Flurbiprofen axetil mixed with propofol							
50mg	13/25	15/25	NA	5/25	2/25	NA	NA [11]
Flurbiprofen axetil administration with venous occlusion before the injection of propofol							
25mg	31/80	44/80	0.73 (0.51, 1.05)	26/80	10/80	2.60 (1.34, 5.03)	5, 0 [16,17]
50mg	31/195	123/222	0.29 (0.21, 0.41)	118/195	30/222	4.41 (3.11, 6.26)	2, 1 [11,13,15-18,21]
Flurbiprofen axetil versus lidocaine							
50mg	34/247	21/247	1.49 (0.82, 2.72)	169/247	183/247	0.91 (0.78, 1.13)	20 [11,13-15,18,19,21]

NNT = Number needed to treat; RR: Relative Risk; CI: Confidential interval; NA: not available

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