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CLINICAL RESEARCH

Effect of pre-administered flurbiprofen axetil on the EC50 of propofol during anesthesia in unstimulated patients: a randomized clinical trial

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KEYWORDS
Flurbiprofen axetil;
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Abstract
Background and objectives: Preoperative use of flurbiprofen axetil (FA) is extensively adopted to modulate the effects of analgesia. However, the relationship between FA and sedation agents remains unclear. In this study, we aimed to investigate the effects of different doses of FA on the median Effective Concentration (EC50) of propofol.
Methods: Ninety-six patients (ASA I or II, aged 18–65 years) were randomly assigned into one of four groups in a 1:1:1:1 ratio. Group A (control group) received 10 mL of Intralipid, and groups B, C and D received 0.5 $mg.kg^{-1}$, 0.75 $mg.kg^{-1}$ and 1 $mg.kg^{-1}$ of FA, respectively, 10 minutes before induction. The depth of anesthesia was measured by the Bispectral Index (BIS). The ''up-and-down'' method was used to calculate the EC50 of propofol. During the equilibration period, if BIS $\leq$ 50 (or BIS > 50), the next patient would receive a 0.5 $\mu g.mL^{-1}$-lower (or -higher) propofol Target-Controlled Infusion (TCI) concentration. The hemodynamic data were recorded at baseline, 10 minutes after FA administration, after induction, after intubation and 15 minutes after intubation.
Results: The EC50 of propofol was lower in Group C (2.32 $\mu g.mL^{-1}$, 95% Confidence Interval [95% CI] 1.85–2.75) and D (2.39 $\mu g.mL^{-1}$, 95% CI 1.91–2.67) than in Group A (2.96 $\mu g.mL^{-1}$, 95% CI 2.55–3.33) ($p = 0.023$, $p = 0.048$, respectively). There were no significant differences in the EC50 between Group B (2.53 $\mu g.mL^{-1}$, 95% CI 2.33–2.71) and Group A ($p > 0.05$). There were no significant differences in Heart Rate (HR) among groups A, B and C. The HR was significantly lower in Group D than in Group A after intubation (66 $\pm$ 6 vs. 80 $\pm$ 10 bpm, $p < 0.01$) and 15 minutes after intubation (61 $\pm$ 4 vs. 70 $\pm$ 8 bpm, $p < 0.01$). There were no significant differences among the four groups in Mean Arterial Pressure (MAP) at any time point. The MAP of the four groups was significantly lower after induction, after intubation, and 15 minutes after intubation than at baseline ($p < 0.05$).

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Conclusion: High-dose FA (0.75 mg.kg^{-1} or 1 mg.kg^{-1}) reduces the EC50 of propofol, and 1 mg.kg^{-1} FA reduces the HR for adequate anesthesia in unstimulated patients. Although this result should be investigated in cases of surgical stimulation, we suggest that FA pre-administration may reduce the propofol requirement when the depth of anesthesia is measured by BIS.

PALAVRAS-CHAVE
Flurbiprofeno axetil;
AINE;
Concentração efetiva mediana;
Propofol

Efeito da pré-administração de flurbiprofeno axetil na CE50 do propofol durante anestesia em pacientes não estimulados: estudo clínico randomizado

Resumo

Justificativa e objetivos: A administração pré-operatória de Flurbiprofeno Axetil (FA) é amplamente usada para a modulação da analgesia. No entanto, a relação entre FA e fármacos sedativos permanece obscura. Neste estudo, nosso objetivo foi investigar os efeitos de diferentes doses de FA na Concentração Efetiva mediana (CE50) do propofol.

Métodos: Noventa e seis pacientes (ASA I ou II, com idades de 18–65 anos) foram alocados aleatoriamente em quatro grupos na proporção de 1:1:1:1. Dez minutos antes da indução, o Grupo A (grupo controle) recebeu 10 mL de Intralipid, enquanto os grupos B, C e D receberam FA na dose de 0,5 mg.kg^{-1}; 0,75 mg.kg^{-1} e 1 mg.kg^{-1}, respectivamente. A profundidade da anestesia foi medida pelo Índice Bispectral (BIS). O método *up-and-down* foi usado para calcular a CE50 do propofol. Durante o período de equilíbrio, se o valor do BIS fosse $\leq$ 50 ou BIS > 50, o próximo paciente tinha a infusão de propofol ajustada para uma concentração alvo-controlada 0,5 μg.mL^{-1} inferior ou superior, respectivamente. Os dados hemodinâmicos foram registrados no início do estudo, 10 minutos após a administração de FA, após a indução, após a intubação e 15 minutos após a intubação.

Resultados: A CE50 do propofol foi menor no Grupo C (2,32 μg.mL^{-1}, Intervalo de Confiança de 95% [95% IC] 1,85–2,75) e D (2,39 μg.mL^{-1}, 95% IC 1,91–2,67) do que no Grupo A (2,96 μg.mL^{-1}; 95% IC 2,55–3,33) ($p = 0,023$, $p = 0,048$, respectivamente). Não houve diferenças significantes na CE50 entre o Grupo B (2,53 μg.mL^{-1}, 95% IC 2,33–2,71) e o Grupo A ($p > 0,05$). Não houve diferenças significantes na Frequência Cardíaca (FC) entre os grupos A, B e C. A FC foi significantemente menor no grupo D do que no grupo A após a intubação (66 ± 6 *vs.* 80 ± 10 bpm, $p < 0,01$) e 15 minutos após a intubação (61 ± 4 *vs.* 70 ± 8 bpm, $p < 0,01$). Não houve diferenças significantes entre os quatro grupos na Pressão Arterial Média (PAM) em qualquer momento. A PAM dos quatro grupos foi significantemente menor após a indução, após a intubação e 15 minutos após a intubação do que na linha de base ($p < 0,05$).

Conclusão: FA em altas doses (0,75 mg.kg^{-1} ou 1 mg.kg^{-1}) reduz a CE50 do propofol, e 1 mg.kg^{-1} de FA reduz a FC durante níveis adequados de anestesia em pacientes não estimulados. Embora esse resultado deva ser investigado na presença de estimulação cirúrgica, sugerimos que a pré-administração de FA pode reduzir a necessidade de propofol durante anestesia cuja profundidade seja monitorada pelo BIS.

Introduction

Flurbiprofen Axetil (FA) is an injectable nonselective Cyclooxygenase (COX) inhibitor that is a Non-Steroidal Anti-Inflammatory Drug (NSAID).[1] Preoperative use of FA has been extensively adopted to achieve significantly lower postoperative pain scores[2–4] and earlier recovery of bowel motility.[5,6] Additionally, some anesthetists administer FA before induction due to the ability of FA to prevent pain induced by propofol injection.[7,8]

Several studies have indicated that NSAIDs can decrease the amplitudes of pain-related potentials and vigilance in humans[9–11] and regulate Electroencephalographic (EEG) activity in rats.[12] Recently, it was found that FA attenuates postoperative emergence agitation by reducing neuronal Prostaglandin (PG) synthesis.[13] In addition, FA has been reported to increase the hypnotic effects of remifentanil in patients undergoing extracorporeal shock wave lithotripsy of pancreatic stones.[14] Taken together, these results suggest that FA may alter the level of sedation by affecting the pharmacodynamics of general anesthetics during general anesthesia.

Propofol is a sedative-hypnotic agent that is widely used in general anesthesia. Few studies have explored the influ-

ence of FA on the median Effective Concentration (EC50) of propofol. In this study, we sought to determine the effects of preoperative administration of intravenous FA on propofol EC50 in unstimulated patients.

Methods

This study was approved by the research ethics committee of Zhongnan Hospital of Wuhan University. With written informed consent, we performed a prospective, double-blind study.

Patients

Ninety-six patients who were ASA (American Society of Anesthesiologists) I or II, aged 18–65 years, and scheduled to undergo elective operation were included. The exclusion criteria included (1) The use of NSAIDs or sedative hypnotics within the preceding 24 hours; (2) A history of allergy to any NSAID; (3) Peptic ulcer disease; (4) Clinically significant cardiac, respiratory, hepatic or renal disease; (5) Central nervous system or psychiatric disorders; (6) Coagulopathy; (7) Known difficulty in intubation; (8) Obesity (body mass index >30 $kg.m^{-2}$) or (9) Hypovolemia.

Randomization and blinding

A randomization list was generated on a computer using permutated blocks of twelve before assignment, and 96 patients were assigned consecutively to one of four groups based on an assigned number: Group A (control group), Group B (0.5 $mg.kg^{-1}$ FA group), Group C (0.75 $mg.kg^{-1}$ FA group) and Group D (1.0 $mg.kg^{-1}$ FA group). Patients were allocated in a 1:1:1:1 ratio. The randomization list was locked by the third author (F.W.), who was not involved in patient treatment or statistical analysis.

Prior to administration, a 10 mL treatment syringe containing either the lipid emulsion or the appropriate dosage of FA was loaded by the fifth author (ZZ.Z.) who was blind to allocation and statistical analysis and then dispensed to the operating room. If the volume of FA to be administered was <10 mL, 0.9% isotonic saline was added to a total volume of 10 mL so that syringes were identical in appearance.

The randomization list and intervention assignment schedule were also blinded to the patients, the staff administering patient treatment (J.M. and M.P.), the statistical analyst (L. C), and the nurses in the operating room.

Monitor and anesthesia

No sedative hypnotics were used within the preceding 24 hours. Upon the arrival of the patient in the operating room, an 18-gauge venous cannula was inserted, and then 500 mL of acetated Ringer's solution was administered. Electrocardiogram, Heart Rate (HR), noninvasive blood pressure, and pulse oximetry were all monitored by a Philips Intellivue MP40 monitor, and the depth of anesthesia was measured by the Bispectral Index (BIS) (Model A-2000, Aspect Medical Systems, Natrick, MA, USA).[15,16]

Patients in Group A (control group) received 10 mL of lipid emulsion (Intralipid, Terumo, Tokyo, Japan) as a placebo 10 minutes before induction. Patients in groups B, C and D received FA (Tide Pharmaceutical Co Limited, Beijing, China) at 0.5 $mg.kg^{-1}$, 0.75 $mg.kg^{-1}$ and 1 $mg.kg^{-1}$, respectively. Intralipid and FA were injected intravenously over 1 minute.

A prefilled propofol Target-Controlled Infusion (TCI) syringe (Diprivan 1%, Astra Zeneca, UK) was administered via a Diprifusor TCI pump (Graseby 3500, Graseby Medical Limited, Herts, UK), and remifentanil was administered via a Graseby 3400 infusion pump. The initial concentration of propofol was set at 3.2 $\mu g.mL^{-1}$, and then 0.5 $\mu g.mL^{-1}$ was set as the incremental or decremental concentration step for the next patient.

After 10 minutes of administration of Intralipid or FA, anesthesia was induced by an intravenous infusion of propofol TCI to achieve a target BIS between 40 and 50 along with an intravenous injection of remifentanil (1 $\mu g.kg^{-1}$). Intubation was performed following muscle relaxation facilitated with vecuronium (0.1 $mg.kg^{-1}$). After intubation, the propofol infusion rates were immediately regulated according to the target concentration for the individual patient and then maintained for 15 minutes (equilibration period) to eliminate the effect of remifentanil and allow the effect-site concentration to decrease and stabilize at the target level.[18] Ventilation was adjusted to maintain the End-Tidal Carbon Dioxide Concentration (E_TCO_2) between 30 and 35 mmHg. During the equilibration period, the patients were unstimulated, and no surgical preparation was permitted.

The BIS was followed at all times. The ''up-and-down'' method[17] was used to calculate the EC50 of propofol for each group. During the equilibration period, if the BIS $\leq$ 50, the next patient would receive a 0.5 $\mu g.mL^{-1}$ lower concentration of propofol TCI. In contrast, if the BIS > 50, the next patient would receive a 0.5 $\mu g.mL^{-1}$ higher concentration of propofol TCI. However, if the BIS < 40 or >60, the concentration of propofol was immediately decreased or increased to prevent over-sedation or intra-anesthesia awareness. Patients with BIS < 40 or >60 were considered lost to follow-up, and the next patient would receive a 0.5 $\mu g.mL^{-1}$ lower (if BIS < 40) or higher (if BIS > 60) concentration, respectively, of propofol TCI.

The hemodynamic data were recorded at baseline, 10 minutes after FA administration, after anesthesia induction, after intubation and 15 minutes after intubation.

Statistical analysis

Determination of the EC50 of propofol was performed according to the equation log $CE50 = (\sum Xi + dA)/N$, where Xi denotes the cumulated log dose levels for the N nominal sample size trials, d denotes the log dose interval (0.1), and A is a tabulated value, the numeric value of which depends on the difference between the numbers of successful and unsuccessful trials. The nominal sample size is the number of patients, beginning with the first pair of patients with unlike responses. A run of (>50, <50, >50) has a nominal sample size of two.[17] To determine the Standard Error (SE) of the estimated EC50 in each group, EC50 was determined in subgroups of consecutively studied patients, with each subgroup containing a nominal sample size of two. For

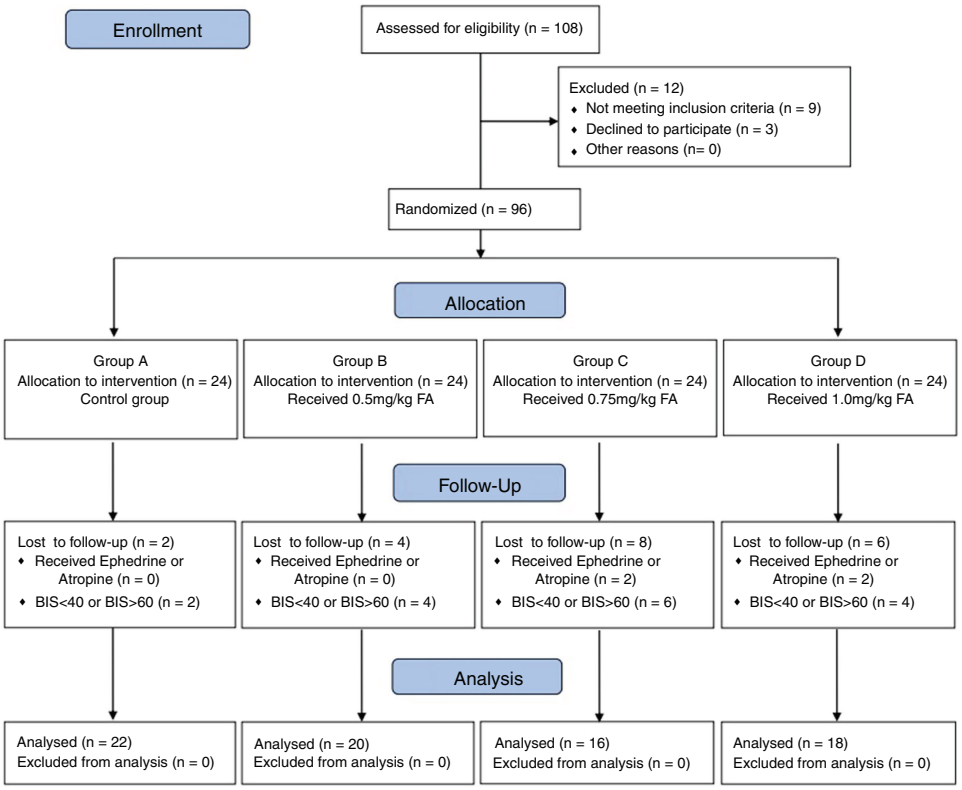

Figure 1 Consort flow diagram of the recruitment process.

each small series, EC50 was calculated from the equation $\log CE50 = Xf + dk$, where Xf is the final plasma concentration level, d is the log dose interval (0.1), and k is a tabulated value.[17]

The fourth author (C.L.), who was blinded to the grouping, performed the statistical analyses. Data were analysed with SPSS (Version 16.0, SPSS Inc., Chicago, IL). The EC50 results are expressed as the mean and 95% Confidence Interval (95% CI). The demographic and hemodynamic data are expressed as the mean ± Standard Deviation (SD). Intergroup differences in EC50 were compared by one-way analysis of variance (ANOVA). Demographic variables were compared among groups using ANOVA and the χ^2 test. The hemodynamic data were analysed by repeated measures ANOVA for differences among groups and unpaired *t*-tests for differences within each group.

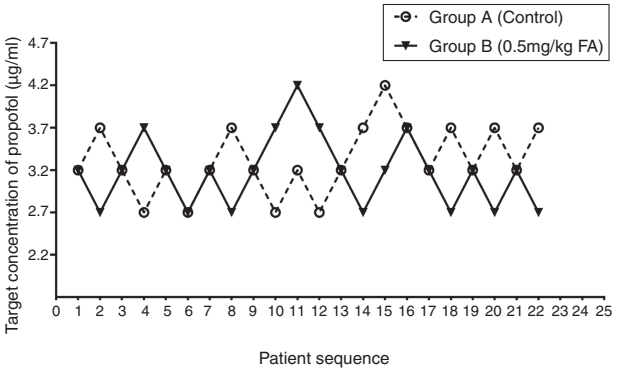

Figure 2 Individual target concentration of propofol based on the up-and-down sequence. The initial concentration was set at 3.2 $\mu g.mL^{-1}$, and 0.5 $\mu g.mL^{-1}$ was set as the concentration step for either increment or decrement in the next patient according to the Bispectral Index (BIS) of the previous patient.

Results

Ninety-six patients agreed to be included in the study and were randomized; of these patients, 16 (2 in Group A, 4 in Group B, 6 in Group C, and 4 in Group D) were lost to follow-up because of BIS < 40 or >60, and 4 patients (2 in Group C and 2 in Group D) suffered from sustained hypotension (systolic blood pressure < 90 mmHg) or bradycardia (heart rate <50 bpm) and received ephedrine or atropine, resulting in termination of the study in these patients (Fig. 1). There were no significant differences in the baseline demographics or clinical characteristics of the patients in different groups (Table 1).

The individual target concentrations of propofol sequences used in Group A and Group B are shown in Fig. 2, which demonstrates how the target concentration of each patient was selected based on the ''up-and-down'' method. The initial concentration of propofol was set at 3.2 $\mu g.mL^{-1}$, and a positive response (a prior patient with BIS $\leq$ 50) led to a 0.5 $\mu g.mL^{-1}$ decrease in the propofol target concentration in the next patient and vice versa. EC50 was calculated by isotonic regression estimators with adjustment for the Pooled Adjacent-Violator Algorithm (PAVA) in each group. The EC50 of propofol was lower in groups C (2.32 $\mu g.mL^{-1}$,

Table 1 Patients demographics and clinical characteristics baseline.

Characteristic	Group A (n = 22)	Group B (n = 20)	Group C (n = 16)	Group D (n = 18)	*p*-values
Age (years)	44.7 ± 10.7	41.1 ± 12.9	38.9 ± 11.7	40.7 ± 11.1	NS
Gender (M/F)	12/10	10/10	7/9	10/8	NS
Height (cm)	166.7 ± 5.5	164.5 ± 6.3	165.3 ± 5.5	166.0 ± 5.3	NS
Weight (kg)	61.5 ± 12.5	61.1 ± 9.8	61.5 ± 9.1	58.2 ± 11.6	NS
BMI ($kg.m^{-2}$)	22.3 ± 3.3	23.1 ± 3.7	22.8 ± 4.1	22.0 ± 3.9	NS
ASA (I/II)	19/3	17/3	12/4	16/2	NS
Intubation attempts	1 (100%)	1 (100%)	1 (95%)	1 (100%)	NS
	2 (0%)	2 (0%)	2 (5%)	2 (0%)	
	3 (0%)	3 (0%)	3 (0%)	3 (0%)	
BIS (baseline)	95.8 ± 2.0	97.2 ± 1.8	96.8 ± 1.4	97.2 ± 1.4	NS
HR (bpm)	74 ± 10	78 ± 10	78 ± 9	75 ± 11	NS
MAP (mmHg)	88 ± 9	94 ± 15	87 ± 13	89 ± 14	NS

Values are expressed as mean ± SD.
Group A, Control Group; Group B, 0.5 $mg.kg^{-1}$ FA group; Group C, 0.75 $mg.kg^{-1}$ FA group; Group D, 1.0 $mg.kg^{-1}$ FA group.
NS, Not Significant; BMI, Body Mass Index; BIS, Bispectral Index; HR, Heart Rate; MAP, Mean Arterial Pressure.
Variables were compared among groups using one-way analysis of variance and χ^2 test.

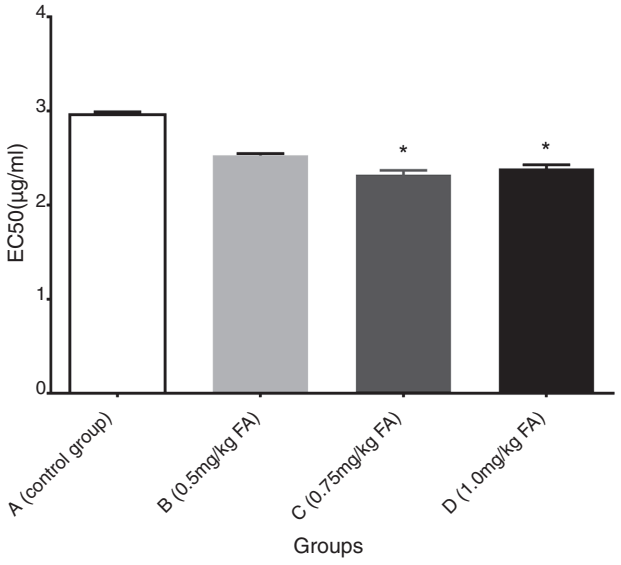

Figure 3 Median Effect Concentration (EC50) of propofol required to obtain a Bispectral Index (BIS = 50). *$p < 0.05$, compared to Group A.

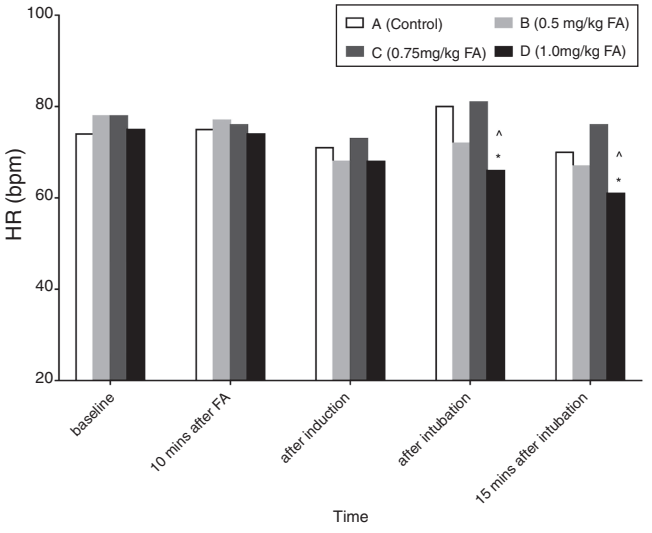

Fig. 4 Heart Rate (HR) at baseline, 10 minutes after administration of FA, after induction of anaesthesia, after intubation, and 15 minutes after intubation in 4 groups. *$p < 0.01$, compared to Group A; ^$p < 0.01$, compared to baseline.

95% CI 1.85–2.75) and D (2.39 $\mu g.mL^{-1}$, 95% CI 1.91–2.67) than in Group A (2.96 $\mu g.mL^{-1}$, 95% CI 2.55–3.33) ($p = 0.023$, $p = 0.048$, respectively). There were no significant differences between Group B (2.53 $\mu g.mL^{-1}$, 95% CI 2.33–2.71) and Group A (Fig. 3).

The Heart Rates (HRs) of groups A, B and C were similar at all time points. The HR was significantly lower in Group D after intubation and 15 minutes after intubation than at baseline ($p < 0.01$). There were no significant differences in HR among the four groups at baseline, 10 minutes after FA and after induction. The HR was significantly lower in Group D than in Group A after intubation (66 ± 6 bpm vs. 80 ± 10 bpm, $p < 0.01$) and 15 minutes after intubation (61 ± 4 bpm vs. 70 ± 8 bpm, $p < 0.001$) (Table 2, Fig. 4).

There were no significant differences in Mean Arterial Pressure (MAP) among the four groups at any time point. At 10 minutes after FA, the MAPs of the four groups were similar to measurements obtained at baseline. In each group, the MAP after induction was significantly lower compared with baseline ($p < 0.05$), and it was the same after intubation, or 15 minutes after intubation ($p < 0.05$) (Table 2, Fig. 5).

Discussion

This study found that while pre-administration of 0.75 $mg.kg^{-1}$ or 1 $mg.kg^{-1}$ FA changed the EC50 of propofol that was necessary to reduce BIS values to 50, 0.5 $mg.kg^{-1}$ FA had no effect. Few studies have explored the influence of FA on the EC50 or sedation level of propofol. FA may change the sedation level by reducing the synthesis of neuronal inflammatory factors, including Prostaglandin (PG). Indeed, the influence of COX inhibitors on the sedation

Table 2 The mean arterial pressure (MAP) and heart rate (HR)of four groups.

Item		Group A (n = 22)	Group B (n = 20)	Group C (n = 16)	Group D (n = 18)
Baseline	MAP (mmHg)	88 ± 9	94 ± 15	87 ± 13	89 ± 14
	HR (bpm)	74 ± 10	78 ± 10	78 ± 9	75 ± 11
10 min after FA	MAP (mmHg)	89 ± 10	90 ± 31	85 ± 13	88 ± 13
	HR (bpm)	75 ± 10	77 ± 13	76 ± 11	74 ± 10
After induction	MAP (mmHg)	70 ± 7[a]	70 ± 13[a]	69 ± 8[a]	72 ± 11[a]
	HR (bpm)	71 ± 9	68 ± 9	73 ± 8	68 ± 6
After intubation	MAP (mmHg)	74 ± 13[a]	72 ± 12[a]	77 ± 13[a]	72 ± 12[a]
	HR (bpm)	80 ± 10	72 ± 12	81 ± 9	66 ± 6[a]
15 min after intubation	MAP (mmHg)	76 ± 10[a]	73 ± 10[a]	71 ± 10[a]	68 ± 5[a]
	HR (bpm)	70 ± 8	67 ± 7	76 ± 8	61 ± 4[a]

Values are expressed as mean ± SD.
Group A, Control Group; Group B, 0.5 mg.kg^{-1} FA group; Group C, 0.75 mg.kg^{-1} FA group; Group D, 1.0 mg.kg^{-1} FA group.
[a] $p < 0.05$ compared to baseline in each group.
Variables were analyzed by repeated measures one-way analysis of variance for differences among groups and unpaired *t*-test for differences within each group.

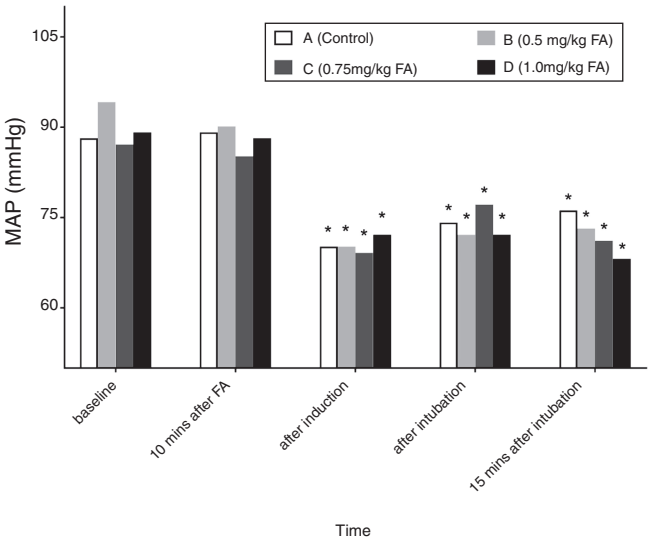

Figure 5 Mean Arterial Pressure (MAP) at baseline 10 minutes after administration of FA, after induction of anesthesia, after intubation, and 15 minutes after intubation in the 4 study groups. *$p < 0.01$ compared to baseline in each group.

level has been previously described. It has been found that COX inhibitors modulate electrocortical activity in rats.[12] Another study[10] reported that azapropazone (one type of NSAID) reduced the α, δ and θ frequency bands of spontaneous EEG. Another study found that FA attenuated postoperative emergence agitation by reducing neuronal PG synthesis.[13]

FA may influence sedative-hypnotic receptors, which are potential targets of propofol. It is well known that gamma-aminobutyric acid type A receptors ($GABA_A$Rs) have been extensively investigated as molecular targets for propofol.[19] It has been shown that $GABA_A$Rs-mediated pain behaviour after acute formalin treatment was abolished by the cyclooxygenase inhibitor indomethacin,[20] and we suggest that FA may change the sedation level of propofol by affecting $GABA_A$Rs. In addition, Transient Receptor Potential Vanilloid Subfamily 1 (TRPV1) is known to be modulated by propofol in a biphasic manner: it is activated at low clinically relevant concentrations and inhibited at higher concentrations,[21,22] indicating that the effects of pain of injection and anaesthetic potency depend on the Central Nervous System (CNS) distribution of the TRPA1 receptor and the concentration of propofol. NSAIDs are a novel class of potent and reversible direct agonists of TRPA1,[23] and it is therefore reasonable to propose that FA may influence the hypnotic effects of propofol by affecting TRPA1. However, both hypotheses require further study for validation.

FA may enhance the effects of propofol by changing its free concentration. The free fraction of propofol after intravenous administration is only 1.2%–1.7%,[24] and FA may increase the free propofol concentration to enhance the effect of sedation by competitively binding to albumin.[25] In addition, although up to 50% of propofol is bound to erythrocytes,[26] FA has no effect on the area under the concentration-time curve for acetazolamide (one type of diuretic) in erythrocytes,[27] and the influence of FA on lipid-soluble agents (such as propofol) bound to erythrocytes will require further investigation. A higher free propofol concentration leads to deeper sedation and more obvious side effects (such as decreased HR).

This study also found that MAP was significantly lower after induction, after intubation, and 15 minutes after intubation than at baseline in each group, and the HR was significantly lower in patients in Group D than in those in Group A both after intubation and 15 minutes after intubation. These decreases in MAP are caused by the cardiovascular side effects of propofol.[30] The HR significantly decreased during the equilibration period of propofol in Group D but not in groups A, B and C. We assume that (1) The overall incidence of bradycardia was lower than that of hypotension caused by propofol (4.8% vs. 15.7%) and that bradycardia and hypotension were not commonly associated.[31] HR variations require larger sample sizes for confirmation. (2) FA may change the free concentration of propofol to enhance its effects,[24,25] and 1 mg.kg^{-1} FA may result in a higher free concentration of propofol than 0.5 mg.kg^{-1} or 0.75 mg.kg^{-1}, leading to a decrease in HR.

Our study has some limitations. First, we only evaluated cases of no stimulation, and cases of surgical stimulation remain to be investigated. Second, the accuracy of the Marsh model remains controversial in Chinese people. It has been shown that the using the TCI system with propofol pharmacokinetic parameters of the Marsh model could lead to initial overshot and an underestimation of the measured plasma propofol concentration in Chinese people.[28] Conversely, another study reported that the control of depth of anesthesia was good in all patients who underwent an upper abdominal surgical operation, and the predictive performance of the 'Diprifusor' target-controlled infusion system was considered acceptable for clinical purposes in Chinese patients.[29] Last, FA has some potential adverse effects, such as drug-induced kidney or liver damage, gastrointestinal bleeding and thrombocytopenia. High dose FA induced adverse effects remain to be investigated in the future.

Conclusion

In summary, high-dose FA reduced HR and the EC50 of propofol for adequate anesthesia in unstimulated patients. Although cases of surgical stimulation remain to be investigated, we suggest that administering FA before induction may reduce the propofol requirement when the depth of anesthesia is measured by BIS.

Conflicts of interest

We declare that we have no financial or personal relationships with other people or organizations that could inappropriately influence our work.

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