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ORIGINAL ARTICLE

Flurbiprofen axetil provides a prophylactic benefit against mesenteric traction syndrome associated with remifentanil infusion during laparotomy

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Abstract
Purpose Mesenteric traction syndrome (MTS) is caused by PGI_2 release during abdominal procedures and is often observed during abdominal surgery. We have demonstrated that MTS occurs more frequently in cases using remifentanil than in those that are not. The aim of this study was to assess the prophylactic benefit of flurbiprofen axetil on MTS in patients undergoing abdominal surgery using remifentanil.
Methods Thirty ASA physical status I and II patients were enrolled. They were scheduled to undergo abdominal surgery under general anesthesia with remifentanil and were randomly assigned to receive flurbiprofen axetil (group F) or saline (group C) preoperatively ($n = 15$ each). MTS was defined according to our simplified diagnostic criteria. Arterial blood pressure and heart rate were recorded, and the plasma 6-keto-$PGF_{1\alpha}$ (a stable metabolite of PGI_2) concentration was measured just before skin incision and at 20 and 60 min after skin incision (T_0, T_{20}, T_{60}) to confirm the diagnosis of MTS.
Results Twelve of 15 (80%) patients developed MTS in group C, whereas only 1 of 15 (6.7%) patients in group F developed MTS. At T_{20}, the group C patients showed significantly lower arterial blood pressure ($P < 0.05$) and a faster heart rate ($P < 0.01$) than those in group F. The mean plasma 6-keto-$PGF_{1\alpha}$ concentration was significantly elevated in group C at T_{20} ($P < 0.01$), whereas the plasma 6-keto-$PGF_{1\alpha}$ level remained low throughout the observation period in group F.
Conclusions We found that preoperative administration of flurbiprofen axetil reduced the incidence of MTS during abdominal surgery with remifentanil analgesia.

Keywords Mesenteric traction syndrome · Prevention · Remifentanil · Prostacyclin · 6-Keto-$PGF_{1\alpha}$

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Introduction

We have demonstrated that mesenteric traction syndrome (MTS) occurs more frequently in cases of abdominal surgery in which remifentanil is used than in those in which it is not [1]. MTS is reported to be a major cause of perioperative myocardial ischemia [2] and sometimes causes refractory hypotension [3]. Thus, preventing MTS is important for safe anesthesia. Prostacyclin (PGI_2), which is released from endothelial cells, is a major causative agent of MTS [4–8]. PGI_2 production can be inhibited by nonsteroidal antiinflammatory drugs (NSAIDs), which have been reported to be prophylactic drugs for MTS [4, 5, 7–11]. However, remifentanil was not used in the aforementioned prophylactic reports, and it is not clear whether prophylactic treatments against MTS are affected by remifentanil. Prophylactic treatments against MTS when using remifentanil remain to be seen. We have conducted a prospective, randomized controlled trial of the MTS-prophylactic effects of NSAID in cases of major abdominal surgery performed under general anesthesia with the use of remifentanil.

Materials and methods

After receiving approval from the hospital ethics committee and obtaining written informed consent from the

participants, 30 consecutive adult patients who were scheduled to undergo abdominal non-laparoscopic surgery were studied using a prospective, randomized, double-blind, placebo-controlled protocol. The surgical procedures included intraabdominal surgery (gastrectomy, colectomy, pancreatic resection, and partial hepatectomy) and exploratory laparotomy. Patients who were taking steroids or nonsteroidal antiinflammatory drugs including aspirin were excluded from the study. Patients who were taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers did not receive these drugs on the day of surgery.

The patients were randomly assigned to receive flurbiprofen axetil or placebo saline using a sealed envelope procedure method. Fifteen patients received 50 mg flurbiprofen axetil (Ropion; Kaken Pharmaceutical, Tokyo, Japan) intravenously before surgery (group F), and the other 15 patients received saline as a control (group C). The drug injection was performed by an anesthesiologist who did not attend the case to ensure that the investigators remained blind to the treatment being administered. As flurbiprofen axetil is an emulsified agent, it would have been possible to recognize which agent was administered from the residual content of the intravenous line. To ensure the blindness of the attending anesthesiologist, the port from which the test agent or saline was administered was covered with drapes, and the subsequent drug administrations were performed using another site.

All patients received 1–3 mg intramuscular midazolam premedication 30 min before entering the operating room. An epidural catheter was inserted between the T10 and L2 vertebrae before the induction of general anesthesia. Two or three milliliters of 1% lidocaine with epinephrine was administered as a test dose. No other anesthetic drugs, such as morphine or local anesthetics, were administered epidurally during the observation period. General anesthesia was then induced with 1–2 mg/kg intravenous propofol, continuous infusion of 0.15–0.40 μg/kg/min remifentanil, and the inhalation of sevoflurane in oxygen. Tracheal intubation was facilitated after the intravenous injection of 0.6 mg/kg rocuronium. Anesthesia was maintained with sevoflurane, the concentration of which was controlled to achieve a BIS index between 40 and 60, and up to 0.5 μg/kg/min remifentanil was infused continuously according to each patient's needs. Muscle relaxation was maintained via the intravenous injection of 10 mg rocuronium and controlled by train-of-four stimulation. The lungs were ventilated using pressure-controlled ventilation with an oxygen–air mixture to maintain a percutaneous oxygen saturation (SpO_2) of greater than 97% and an end-tidal carbon dioxide pressure ($EtCO_2$) between 35 and 40 mmHg. A 22 G radial arterial line was inserted after the induction of anesthesia, and the patient's systolic and diastolic blood pressure were recorded. The operation proceeded routinely and the surgeon explored the abdominal cavity in all cases.

Blood samples were drawn from the radial arterial catheter to measure the plasma concentration of 6-keto-$PGF_{1\alpha}$, a stable metabolite of PGI_2. Collected blood samples were immediately centrifuged at 4°C and cryopreserved until the assay. Because the mean onset time of MTS was 16 ± 5 min after skin incision and the symptoms persisted over approximately 30 min in our pilot study [1], measurements of hemodynamic and anesthetic parameters and blood sampling were performed at three points: just before the flurbiprofen axetil or placebo was administered (time 0, T_0), 20 min after the skin incision had been made (time 20, T_{20}), and 60 min after the skin incision had been made (time 60, T_{60}). The blood samples were measured for 6-keto-$PGF_{1\alpha}$ with the ELISA (enzyme-linked immunosorbent assay) technique.

To simplify the diagnosis, MTS was defined as a flushing of the face during an intraabdominal surgical procedure within 1 h after making the skin incision in this study and was diagnosed by at least two anesthesiologists who had experience of the original study [1].

All results are given as means ± SD or as box plots displaying the median and 10th, 25th, 75th, and 90th percentiles. Demographic data and treatment effects were analyzed using the Mann–Whitney *U* test, Friedman's chi square *r* test, and Fisher's exact test. Variation in the data over time was analyzed using the Wilcoxon *t* test with Bonferroni's correction. All data were analyzed using the two-tailed test. *P* values <0.05 were considered significant.

Results

Demographic data for the flurbiprofen- and placebo-treated groups are summarized in Table 1. There were no significant differences in patient demographics or the type of surgery performed between the two groups, except for patient history of hypertension. Eleven patients in group R and 2 in group C suffered from hypertension. The hemodynamic parameters and plasma 6-keto-$PGF_{1\alpha}$ concentration at T_0 of the two groups were similar (Table 2). The anesthetic parameters of the two groups such as the effect-site concentrations of remifentanil and fentanyl, BIS index, end-tidal sevoflurane concentration, and volume of injected crystalloid at T_{20} were also comparable (Table 3). At T_{20}, the patients in group C displayed significantly lower arterial blood pressure ($P < 0.05$; sBP, $P = 0.015$; mBP, $P = 0.0018$; dBP, $P = 0.023$) and a faster heart rate ($P = 0.002$) than those in group F (Table 4). Moreover, the mean plasma concentration of 6-keto-$PGF_{1\alpha}$ was significantly elevated in group C at T_{20} ($P = 0.00003$). Vasoactive agents were not administered in any case before blood

Table 1 Background information

	Group C ($n = 15$)	Group F ($n = 15$)	*P* value
Age (years)	63.3 ± 10.5	68 ± 8.6	0.23
Height (cm)	159.7 ± 9.0	162.7 ± 10.0	0.39
Weight (kg)	62.7 ± 13.8	66.5 ± 9.5	0.34
BMI (kg/m^2)	24.6 ± 5.0	25.1 ± 2.5	0.52
Male/female	8/7	12/3	0.25
Type of surgery (cases)			
Gastrectomy	7	4	0.46
Colectomy	1	5	
Proctectomy	5	2	
Other[a]	2	5	
Preoperative complications (cases)			
Hypertension	4	11	0.03*
Anemia	5	6	1
Diabetes mellitus	1	5	0.17

Data are shown as means ± SD

BMI body mass index, *group C* control group, *group F* flurbiprofen axetil group

* $P < 0.05$ was considered to be significant. Group C data were compared with group F data. No significant differences were detected between the groups with the exception of history of hypertension

[a] Other denotes hepatectomy, pancreatectomy, and exploratory laparotomy

Table 2 Parameters just before skin incision (T_0) (0 min)

	Group C ($n = 15$)	Group F ($n = 15$)	*P* value
sBP (mmHg)	99.5 ± 19.9	101.6 ± 12.9	0.25
dBP (mmHg)	53.5 ± 11.9	51.7 ± 6.27	0.49
mBP (mmHg)	68.8 ± 13.9	68.3 ± 6.6	0.52
HR (bpm)	71.9 ± 15.1	66.8 ± 11.6	0.38
Plasma 6-keto-PGF$_{1\alpha}$ (pg/ml)	19.7 ± 11.9	15.6 ± 6.7	0.2

$P < 0.05$ was considered to be significant. Group C data were compared with group F data

Data are shown as means ± SD

SBP systolic blood pressure, *dBP* diastolic blood pressure, *mBP* mean blood pressure, *HR* heart rate, *6-keto-PGF$_{1\alpha}$* 6-keto-prostaglandin F$_{1\alpha}$, *group C* control group, *group F* flurbiprofen axetil group

sampling at T_{20}. The incidence of MTS in this study is illustrated in Fig. 1. Twelve of 15 patients (80%) in group C were diagnosed with MTS whereas only 1 of 15 patients (6.7%) in group F was diagnosed with MTS ($P = 0.0001$). The plasma 6-keto-PGF$_{1\alpha}$ concentrations of each group are given in Figs. 2 and 3. In group C, patient plasma 6-keto-PGF$_{1\alpha}$ levels were significantly elevated after the skin incision (Fig. 2); in group F the plasma 6-keto-PGF$_{1\alpha}$ level

Table 3 Anesthetic parameters at 20 min after skin incision (T20)

	Group C	Group F	*P* value
Effect-site concentration of remifentanil	3.83 ± 1.4	3.57 ± 0.91	0.34
Effect-site concentration of fentanyl	0.34 ± 0.28	0.23 ± 0.21	0.17
BIS value	49.6 ± 7.0	51.8 ± 6.0	0.33
End-tidal concentration of sevoflurane (%)	0.99 ± 0.07	1 ± 0.15	0.44
20 min total dose of crystalloid (ml)	700 ± 105.2	750 ± 171.1	0.43

$P < 0.05$ was considered to be significant. Group C data were compared with group F data

Data are shown as means ± SD

BIS bispectral index, *group C* control group, *group F* flurbiprofen axetil group

Table 4 Parameters at 20 min after skin incision (T_{20})

	Group C	Group F	*P* value
sBP (mmHg)	101.2 ± 24.1	129.5 ± 24.1	0.007*
dBP (mmHg)	50.7 ± 14.2	65.5 ± 17.1	0.012*
mBP (mmHg)	67.5 ± 17.2	86.8 ± 16.3	0.0065*
HR (bpm)	84.7 ± 13.8	66.4 ± 10.9	0.0009*
Plasma 6-keto-PGF$_{1\alpha}$ (pg/ml)	1078.2 ± 784.1	20.5 ± 5.2	0.00003*

* $P < 0.05$ was considered to be significant. Group C data were compared with group F data

Data are shown as means ± SD

SBP systolic blood pressure, *dBP* diastolic blood pressure, *mBP* mean blood pressure, *HR* heart rate, *6-keto-PGF$_{1\alpha}$* 6-keto-prostaglandin F$_{1\alpha}$, *group C* control group, *group F* flurbiprofen axetil group

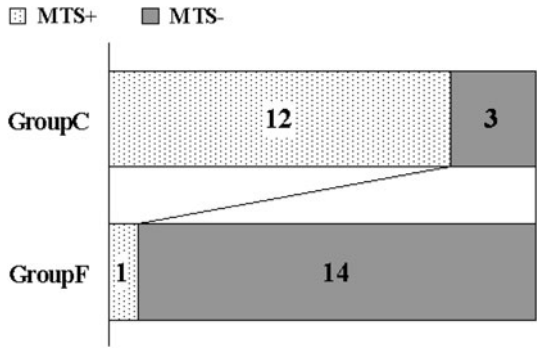

Fig. 1 Incidence of mesenteric traction syndrome (*MTS*) in *group C* (control group) and *group F* (flurbiprofen axetil group). Twelve of the 15 patients suffered from MTS in group C, while only 1 of 15 patients in group F suffered from MTS. The absolute reduction in risk achieved by flurbiprofen axetil was 73.3% (95% CI, 49.4–97.2%), and the number needed to treat was 1.36 (95% CI, 1.03–2.02)

did not increase significantly after the skin incision and remained low throughout the observation period (Fig. 3). To confirm the diagnosis of MTS, we plotted the fall in

systolic blood pressure from T_0 to T_{20} (ΔsBP) and the increase in the plasma 6-keto-$PGF_{1\alpha}$ concentration from T_0 to T_{20} (Δ6-keto-$PGF_{1\alpha}$) in the patients diagnosed with MTS. There was a significant correlation between ΔsBP and Δ6-keto-$PGF_{1\alpha}$ concentration (Fig. 4).

No side effect of flurbiprofen axetil was observed in any case in group F.

Discussion

In this prospective randomized study, we demonstrated that the preoperative administration of flurbiprofen axetil reduced the incidence of MTS, which is proved to be facilitated by remifentanil during abdominal surgery [1]. The absolute risk reduction achieved by flurbiprofen axetil was 73.3% (95% CI, 49.4–97.2%), and the number needed to treat (NNT) was 1.36 (95% CI, 1.03–2.02), which indicates the effectiveness of flurbiprofen axetil at preventing MTS.

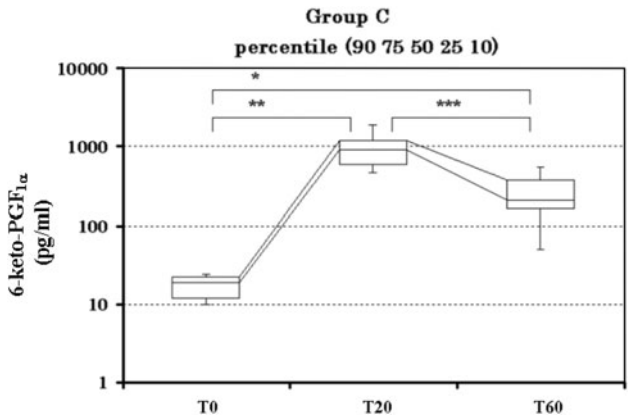

Fig. 2 Plasma 6-keto-$PGF_{1\alpha}$ concentration in group C. *Group C* control group, *6-keto-PGF*$_{1\alpha}$ 6-keto-prostaglandin $F_{1\alpha}$.*,***$P < 0.01$ in comparison to the values at T_0 (Friedman's chi-square r test and Wilcoxon t test with Bonferroni's correction); ***$P < 0.01$ in comparison to the values at T_{20} (Friedman's chi-square r test and Wilcoxon t test with Bonferroni's correction)

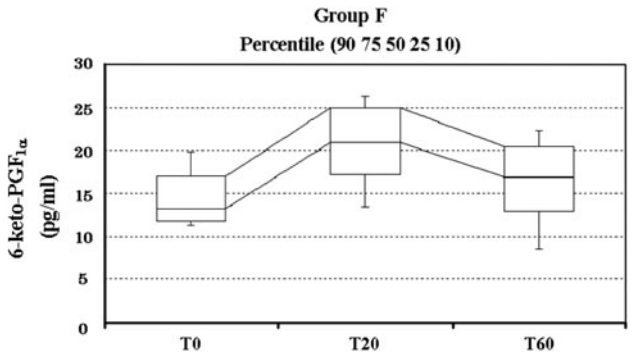

Fig. 3 Plasma 6-keto-$PGF_{1\alpha}$ concentration in group F

We have previously reported that the continuous use of remifentanil during general anesthesia increases the incidence of MTS compared with the bolus administration of fentanyl alone as an analgesic during major abdominal surgery [1]. Without any prophylaxis, MTS can cause severe hypotension that continues for about an hour. One case report stated that a patient suffered from MTS and needed to be administered up to 5 mg intravenous phenylephrine to obtain normotension [3]. Furthermore, Garnett et al. [2] demonstrated that MTS was the most common cause of perioperative myocardial ischemia in aortic surgery. Thus, it is important to prevent MTS when using remifentanil, which facilitates the onset of MTS [1], in general anesthesia.

Manipulation of the mesentery is required in the majority of abdominal surgical procedures. Without prophylaxis, most patients develop MTS [4–9, 11–14]. Of the patients in group C in our study, 80% were diagnosed with MTS. Mesenteric traction induces the release of PGI_2, a vasodilator, which causes systemic vasodilation; this results in hypotension and facial flushing, leading to compensatory tachycardia [5–9, 11, 13]. We measured the plasma concentration of 6-keto-$PGF_{1\alpha}$, a stable metabolite of PGI_2, in this study. There was a significant correlation between the change in hemodynamic parameters and the increase in the plasma 6-keto-$PGF_{1\alpha}$ concentration in the patients diagnosed with MTS. This finding supports the hypothesis that the strong vasodilator PGI_2 is a causative agent of MTS and indicates that our definition of MTS is appropriate.

There are no evidence-based diagnostic criteria for MTS, except for the presence of elevated plasma PGI_2 levels. We

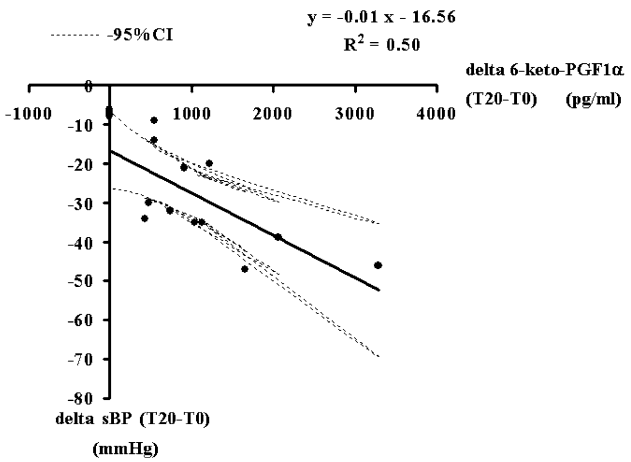

Fig. 4 Correlation between delta systolic blood pressure (ΔsBP) (T_{20}–T_0) and Δ6-keto-$PGF_{1\alpha}$ (T_{20}–T_0) in mesenteric traction syndrome (+) cases. *6-keto-PGF*$_{1\alpha}$ 6-keto-prostaglandin $F_{1\alpha}$. There was a significant correlation between ΔsBP (T_{20}–T_0) and Δ6-keto-$PGF_{1\alpha}$ concentration (T_{20}–T_0). $R^2 = 0.50$, $R_s = -0.71$ ($P = 0.0065$; Spearman's correlation)

defined MTS as facial flushing after mesenteric manipulation in this study. There are various reasons why we used such a simple definition. First, observation of the skin is simple and thus more practical than other diagnostic methods. In addition, the accuracy of our diagnostic process was assured because it was confirmed by two anesthesiologists. Also, the participants were randomly assigned to the treatment groups and there was no difference in the diagnostic process between the groups; therefore, there was no risk of overestimation or underestimation. With regard to the sensitivity and specificity of facial flushing to systemic vasodilation, the sensitivity of facial flushing ranged from 58% to 100% (mean, 73.3%) in previous investigations [6–9, 11, 12]. In this study, the incidence of MTS in the control group was 80% according to our criteria. We estimate that the specificity of facial flushing is high as the differential diagnoses for perioperative facial flushing are limited, for example, a type I allergy, facial congestion, and hyperthermia, which are easy to rule out clinically.

NSAIDs inhibit the production of PGI_2 by blocking cyclooxygenase and prevent the occurrence of MTS. In previous studies, pretreatment with oral or anal ibuprofen at 90 or 120 min before surgery and the intravenous injection of ibuprofen at 15 min or just before surgery prevented MTS [4, 5, 7, 8, 11], whereas the administration of an ibuprofen suppository just before surgery did not [14]. There are no reports about the relationship between flurbiprofen axetil and MTS. We succeeded at preventing MTS by intravenously administering flurbiprofen axetil just before making the initial skin incision. Flurbiprofen axetil is a prodrug of a strong NSAID that acts rapidly. Injected flurbiprofen axetil is promptly converted to its activated form, flurbiprofen, by esterase in plasma, and its plasma concentration peaks within 5 min. In addition, the $T_{1/2}$ of flurbiprofen axetil was found to be 5.8 ± 0.4 h (mean $\pm$ SE). Thus, administering a single dose before making the initial skin incision is sufficient to prevent MTS, and its prophylactic effect might continue for several hours during surgery.

There was only one case of MTS in group F. Although facial flushing was confirmed by two anesthesiologists in this case, the patient's plasma concentration of 6-keto-$PGF_{1\alpha}$ was low and comparable with those of the other patients in group F, and no hemodynamic changes (hypotension or tachycardia) were observed. Thus, vasodilatory substances other than PGI_2 might have been responsible for the facial flushing in this case. Histamine is a candidate for the causative agent of MTS. A recent study suggested the participation of histamine in the onset of MTS [15, 16]; however, the relevance of histamine to MTS remains controversial [9, 17, 18].

MTS might be promoted by the vasodilation mediated by the synergistic or additive effects of remifentanil. The use of opioids, such as fentanyl and remifentanil, results in systemic vasodilation. Remifentanil induces vasodilation by blocking the sympathetic nerves via the production of nitric oxide and by inhibiting calcium ion channels [19–21]. Ünlügenç et al. [21] reported that endothelium-derived nitric oxide and PGI_2 production is responsible for the vasodilatory effect of remifentanil. However, the results of our study showed no significant relationship between the concentration of 6-keto-$PGF_{1\alpha}$ and the effect-site concentration of remifentanil at T_{20} in the control group, despite the possibility of remifentanil directly affecting PGI_2 production. The hemodynamic response to remifentanil is not related to the plasma concentration of histamine [22].

The dose of flurbiprofen axetil required for MTS prophylaxis is not clear. We did not verify the dosage of flurbiprofen axetil precisely. We administered a dose of 50 mg flurbiprofen axetil to all medicated participants on the basis of the recommended dose for postoperative pain. No adverse effects were observed in this study although the number of medicated participants was limited to 15. Among all adverse effects, platelet dysfunction can be serious during the perioperative period. A lower dose might be sufficient to prevent MTS, particularly in small patients and would reduce the frequency of adverse effects. A dose-finding trial might be necessary.

There are some limitations to this study. First, we did not select the control agent as lipid emulsion, but chose saline instead. Because flurbiprofen axetil is emulsified with soybean oil, egg yolk lecithin, and glycerine, these components might have pharmacological action affecting cyclooxygenase activity and might disrupt our results. Second, the diagnosis of MTS (the observation of face flushing after mesenteric manipulation) was dependent on the assessment of each anesthesiologist. As we mentioned previously, this method is simple and practical and allows a relatively accurate diagnosis to be made. Third, hypertensive patients were distributed more in group F than in group C by chance. The influence of hypertension on MTS is not clear. Although patients with essential hypertension show lower plasma PGI_2 level than those without it [23], hypertensive patients, who tend to have less extensible blood vessels and circulatory complications, might be affected by vasodilative agents such as PGI_2. In this study, flurbiprofen axetil prevented MTS in those patients who had hypertension. Last, the number of patients enrolled in this study was relatively small, and the exploration of adverse events might be insufficient. A further study including a larger number of patients might therefore be needed.

In conclusion, we have demonstrated that the preoperative administration of flurbiprofen axetil provides prophylactic benefit against MTS facilitated by remifentanil infusion during laparotomy. When we attend the anesthesia

of an abdominal surgery and expect minimal intraoperative hemodynamic changes, we believe that flurbiprofen axetil is worth using.

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