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Effect of Flurbiprofen Combined with Prednisolone on Interleukin-6 in Elderly Surgery Patients

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Abstract

Objective: To determine the effect of flurbiprofen combined with prednisolone on interleukin-6 in elderly surgery patients. **Methods:** In this double-blind randomized controlled study, patients aged 65 to 80 who were undergoing spinal fusion surgery for disc herniation were administered flurbiprofen 100 mg (P group, flurbiprofen group), prednisolone 0.6 mg/kg (D group, prednisolone group), prednisolone 0.6 mg/kg plus flurbiprofen 100 mg (P + D group, flurbiprofen + prednisolone group) or normal saline (S group, saline group) 15 minutes before the induction of anesthesia. Plasma samples were collected before surgery (T0) and on day 1 (T1), day 2 (T2) and day 3 (T3) following surgery. At the same time, systemic inflammatory response syndrome (SIRS) was assessed by SIRS criteria. The levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP) for collected samples were measured. **Results:** Other groups had significantly lower levels of IL-6, CRP and occurrence of SIRS than S group ($p < 0.05$). Compared to groups P and D, the levels of IL-6 and CRP in P + D group were significantly lower on T1 ($p < 0.05$). Peak levels of IL-6 in all groups were presented on T1 ($p < 0.05$). The levels of CRP within three days were significantly different but did not show peak levels ($p > 0.05$). **Conclusion:** Compared to prednisolone or flurbiprofen, combining flurbiprofen with prednisolone in elderly surgery patients led to an increased suppression of IL-6.

Keywords

SIRS, Systemic Inflammatory Response Syndrome, IL-6, Interleukin-6, CRP, C-Reactive Protein

1. Background

China is undergoing a remarkable demographic transition, due to a decrease in birth rates and an increase in longevity. By 2050, one out of every four Chinese, approximately 336 million people, will be aged 65 years or older [1]. Elderly patients are at greater risk of morbidity and mortality during surgery [2]. There is data that reveals that deregulated inflammation is responsible for perioperative morbidity and mortality in the elderly [3]. Furthermore, the perioperative administration of glucocorticoids improves the outcome in patients undergoing surgery, which shows that systemic inflammation is associated with adverse outcomes [4]. The anti-inflammatory mechanisms of glucocorticoids activate many anti-inflammatory genes and repress many pro-inflammatory genes that are active in inflammation [5]. Due to the dangerous side effects, including an increased risk of wound infection and anastomotic leak, prolonged administration of glucocorticoids such as dexamethasone is not recommended [6]. However, there is no increased risk with a single dose of glucocorticoids [7]. Nonsteroidal anti-inflammatory drugs are widely used to effectively relieve pain without respiratory depression in patients, and reduce inflammation by inhibiting cyclooxygenase (COX) [8]. There is a study that suggests that non-steroidal anti-inflammatory drugs can inhibit interleukin-6 by suppressing NF-κB activation and NF-κB-dependent gene expression [9]. Further studies are required in order to elucidate mechanisms of NSAID inhibiting interleukin-6. Whether nonsteroidal anti-inflammatory drugs combined with steroidal anti-inflammatory drugs prove to increase the suppression of IL-6 after surgery still remains to be determined.

The aim of this study was to determine the effect of flurbiprofen combined with prednisolone on interleukin-6 in elderly surgery patients.

2. Methods

2.1. Patients and Study Design

From April 2023 to October 2023, 160 patients aged 65 to 80 who were undergoing spinal fusion surgery of jointing two vertebrae for disc herniation were enrolled in the study. Exclusion criteria were as follows: patients with trauma, severe heart failure, renal insufficiency and liver dysfunction, autoimmune disease, malignancy, history of heart block or sinus bradycardia and a history of neurological and psychiatric disorders, patients who often use pain medications, age under 65 and refusal to participate, data-lacking patients. We randomly divided the 160 patients into four groups: P group, D group, P + D group and S group. One hundred milligrams of flurbiprofen were infused intravenously into patients 15 minutes before induction of anesthesia in P group, prednisolone (0.6 mg/kg) diluted with 15 ml of saline was administered to D group, prednisolone (0.6 mg/kg) plus 100 mg flurbiprofen diluted with 15 ml of saline to P + D group and equal amounts of normal saline to S group. Anesthesia administered by an independent anesthesiologist was in line with standardized procedure. Arterial

blood samples were collected on the last day (T0) before surgery and on day 1 (T1), day 2 (T2) and day 3 (T3) in order to determine the levels of IL-6, CRP, TNF-α and white blood cell count. Meanwhile, we evaluated systemic inflammatory response syndrome (SIRS), assessed by SIRS criteria. SIRS is highlighted when at least two of the following four criteria are met: fever > 38.0˚C or hypothermia < 36.0˚C, tachycardia > 90 beats/minute, tachypnea > 20 breaths/minute, leukocytosis > 12 × 10 × 9/l or leucopoenia < 4×10^9/l [10]. An independent nurse measured the temperature, heart rate and respiratory rate of resting patients multiple times and then took the average. All data was recorded by independent people not involved in the survey. The protocol was approved by the Ethics Committee of the Eighth Affiliated Hospital, Sun Yat-sen University (Shenzhen, China). The study was conducted according to the guidelines of Good Clinical Practice and the principles expressed in the Declaration of Helsinki. Informed consent was obtained from all patients.

2.2. Anesthesia Management

No pre-medication was administered to any patients. After arriving at the operating room, all patients were monitored with pulse oximetry (SpO_2), 5-lead electrocardiography (ECG) and noninvasive blood pressure (NIBP). An arterial cannula was placed in the left or right radial artery under local anesthesia to monitor invasive arterial blood pressure. The bispectral index (BIS, Aspect, USA) was monitored by placing electrodes on patients' foreheads in order to measure the depth of sedation. Anesthesia was induced by intravenous administration of propofol (1.5 - 2 mg/kg), sufentanil (0.4 - 0.6 ug/kg), and cisatracurium (0.2 mg/kg). Following endotracheal intubation, mechanical ventilation was performed with a respiratory rate of 12 - 14 times/minute, a tidal volume of 8 - 10 ml/kg, an inspiratory to expiratory ratio of 1:2, and $PetCO_2$ was maintained at 35 - 45 mmHg (1 mmHg = 0.133 kPa). Anesthesia maintenance used medications which included remifentanil (0.1 - 0.5 ug/kg/min), propofol (4 - 12 mg/kg/h), and cisatracurium (0.06 - 0.12 mg/kg/h). BIS values of 40 - 55 were maintained. A heater was used for patients with a temperature lower than 36.5˚C. The placed position for arterial pressure transducers leveled the external auditory canal. Mean arterial pressure (MAP) of 60 - 65 mmHg was maintained, but with a baseline of 75% - 80% for patients with a history of hypertension. Methoxamine or ephedrine was injected intravenously following MAP lower than 55 mmHg or MAP decreased to <30% of the baseline values in patients with a history of hypertension. Heart rate was maintained between 60 - 90 bpm. Intravenous administering of anesthetics was stopped before closing the skin incision. A patient-controlled intravenous analgesia pump using 100 μg sufentanil was used for two days.

2.3. Measurement of Biomarkers

After collection, blood samples were then centrifuged (1610 g, 10 min) before being stored in frozen aliquots at −80˚C. The levels of IL-6, CRP and TNF-α

were determined batch-wise using commercial assays (Wuhan Baiqiandu Technology Co. Ltd, Wuhan, China), and measured using the quantitative sandwich enzyme immunoassay technique with an ELISA Kit (Cusabia, Houston, TX, USA). A microplate had been pre-coated with antibody. Standards and samples were pipetted into the wells and bound by the immobilized antibody. After removing any unbound substances, a biotin-conjugated antibody was added to the wells. After washing, avidin conjugated horseradish peroxidase (HRP) was added to the wells. Following a wash to remove any unbound avidin-enzyme reagent, a substrate solution was added to the wells and color developed in proportion to the amount bound in the initial step. The color development was stopped, and the intensity of the color was measured.

2.4. Statistical Analysis

Statistical analyses were performed using SPSS 22.0 (SPSS Inc, Chicago, IL, USA). Distributions of variables were reported as percentages and means ± standard deviation (SD). Data of the categorical variables was analyzed using the chi-square test. Student t-test was used to compare the differences from each other between two averages. A *p*-value lower than 0.05 was considered to be statistically significant.

3. Results

3.1. Patients Characteristics and Outcome

The 160 elderly patients selected according to the inclusion criteria were randomly divided into four groups. However, five patients were subsequently excluded as surgery was cancelled. The remaining 155 patients were involved in the study. There were eight patients during research who refused further blood tests or were discharged. More details are shown in Figure 1. Baseline characteristics of patients in the four groups were compared (Table 1). There were no

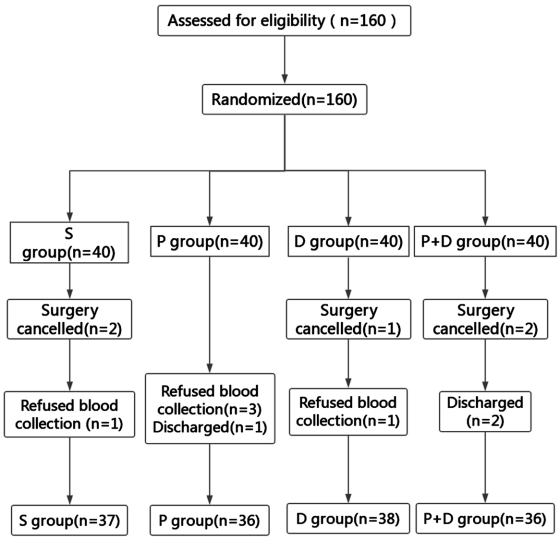

Figure 1. Patient flowchart.

Table 1. Baseline characteristics of patients and procedures.

Variable	S group (n = 37)	P group (n = 36)	D group (n = 38)	P + D group (n = 36)	*p*
Male, n (%)	21 (56.8)	20 (55.6)	21 (55.3)	19 (52.8)	0.989
Age, years	69.1 ± 4.1	68.5 ± 3.6	68.1 ± 2.8	70.3 ± 4.3	0.053
BMI, kg/m^2	23.2 ± 3.2	24.0 ± 3.1	23.0 ± 3.7	24.1 ± 3.9	0.417
Comorbidity					
Diabetes, n (%)	4 (10.8)	5 (13.9)	4 (10.5)	3 (8.3)	0.901
COPD, n (%)	10 (27.0)	9 (25.0)	10 (26.3)	7 (19.4)	0.926
Hypertension, n (%)	11 (29.7)	8 (22.2)	9 (23.7)	11 (30.6)	0.803
Coronary artery disease, n (%)	6 (16.2)	6 (16.7)	4 (10.5)	4 (11.1)	0.802
ASA physical status ≥ III, n (%)	9 (24.3)	8 (22.2)	6 (15.8)	5 (13.9)	0.618
Medication use					
Aspirin, n (%)	8 (21.6)	8 (22.2)	6 (15.8)	4 (11.1)	0.559
Statin, n (%)	9 (24.3)	9 (25)	7 (18.4)	6 (16.7)	0.765
RAAS inhibitors, n (%)	5 (13.5)	3 (8.3)	3 (7.9)	2 (5.5)	0.674
Other antihypertensive drugs, n (%)	6 (16.2)	5 (13.9)	5 (13.2)	6 (16.7)	0.968
Duration of surgery (min)	4.4 ± 0.5	4.3 ± 0.4	4.2 ± 0.4	4.2 ± 0.4	0.259
Blood loss (mL)	465.1 ± 59.9	470.0 ± 59.6	448.2 ± 57.2	443.1 ± 39.6	0.109

significant differences with regard to BMI ($p = 0.417$), gender ($p = 0.989$), age ($p = 0.053$), comorbidity ($p > 0.05$) and medication ($p > 0.05$).

The mean age was 69 years and 55% of all patients were male. There were 28 patients (19%) with an ASA physical status classification of 3 or greater. All patients included in the study were undergoing spinal fusion surgery for disc herniation. There was no significant difference between the four groups regarding blood loss ($p = 0.109$) and surgery duration ($p = 0.259$).

Further details of baseline characteristics are shown in Table 1.

3.2. Inflammatory Markers in Patients in Combined and Uncombined Groups

Preoperative levels of IL-6, TNF-α and CRP were similar in patients of all four groups (Figure 2). Postoperatively, the levels of IL-6 were increased with the peak level on day 1 ($p < 0.05$). The effects of combination on IL-6 were most pronounced on day 1 (192 pg/ml [P + D group] versus 278 pg/ml [P group] and 239 pg/ml [D group], $p < 0.05$). However, there were no significant differences between D group and P + D group on day 2 (138 pg/ml [P + D group] versus 188 pg/ml [P group] and 163 pg/ml [D group], $p > 0.05$), and P group, D group and P + D group had no differences on day 3 (105 pg/ml [P + D group] versus 120 pg/ml [P group] and 110 pg/ml [D group], $p > 0.05$). The levels of CRP were increased with the peak on day 3 ($p < 0.05$) and differed on day 1 (52 mg/ml [P + D group] versus 86 mg/ml [P group] and 77 mg/ml [D group], $p < 0.05$), day 2

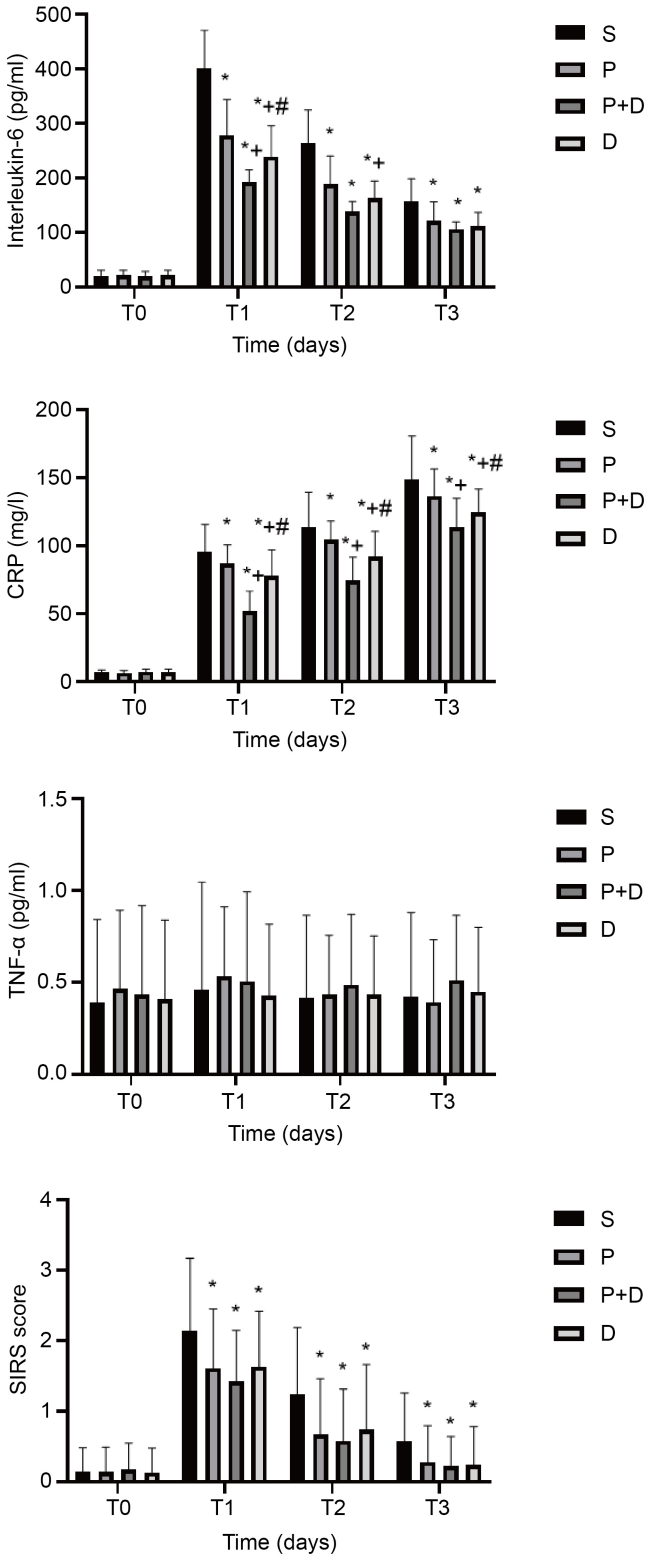

Figure 2. The levels of IL-6, CRP, TNF-α and SIRS scores before surgery (T0) and on days 1 (T1), 2 (T2), and 3 (T3) in the four groups. Data is expressed as mean ± standard error. *$p < 0.05$, compared with the S group; +$p < 0.05$, compared with the P group; #$p < 0.05$, compared with the P + D group.

(74 mg/ml [P + D group] versus 105 mg/ml [P group] and 91 mg/ml [D group], $p < 0.05$), day 3 (113 mg/ml [P + D group] versus 136 mg/ml [P group] and 124 mg/ml [D group], $p < 0.05$). TNF-α showed no peak and no difference between the combined group and uncombined group ($p > 0.05$). The SIRS score showed no difference between the combined group and uncombined group ($p > 0.05$). More information is shown in Table 2 and Figure 2.

4. Discussion

NSAIDs are some of the most commonly used drugs in the United States and the rest of the world [11]. There are many applications in the medical field, including some little-known effects. In a previous study, a 35-year-old Japanese woman who was diagnosed with pheochromocytoma, which revealed positive staining using an antihuman IL-6 antibody by immunohistochemical study and showed increased IL-6 mRNA levels by northern blot analysis, showed marked inflammatory reactions and pyrexia as a result of excessive production of IL-6

Table 2. Comparison of IL-6, CRP, TNF-α and SIRS score on days 0, 1, 2, 3.

Groups/Days	T0	T1	T2	T3
S group				
IL-6	20 ± 10.3	400.2 ± 70.5[a]	262.9 ± 61.7[ab]	157.8 ± 40.7[abc]
CRP	6.8 ± 1.7	95.6 ± 20.2[a]	113.4 ± 25.8[ab]	148.4 ± 32.4[abc]
TNF-α	0.39 ± 0.45	0.46 ± 0.59	0.42 ± 0.45	0.42 ± 0.46
SIRS score	0.14 ± 0.35	2.1 ± 1.0[a]	1.2 ± 1.0[a]	0.57 ± 0.69[abc]
P group				
IL-6	22.0 ± 8.1	278.2 ± 64.8[a]	188.5 ± 51.6[ab]	121.0 ± 35.6[abc]
CRP	6.6 ± 1.6	86.8 ± 13.9[a]	105.1 ± 15.4[ab]	136.4 ± 19.8[abc]
TNF-α	0.47 ± 0.43	0.53 ± 0.38	0.43 ± 0.32	0.39 ± 0.34
SIRS score	0.14 ± 0.35	1.6 ± 0.84[a]	0.67 ± 0.79[a]	0.28 ± 0.51[b]
D group				
IL-6	21.6 ± 8.8	239.4 ± 56.2[a]	163.4 ± 31.1[ab]	110.8 ± 25.7[abc]
CRP	7.1 ± 2.2	77.9 ± 18.8[a]	91.9 ± 18.5[ab]	124.4 ± 17.1[abc]
TNF-α	0.41 ± 0.43	0.43 ± 0.39	0.43 ± 0.32	0.45 ± 0.35
SIRS score	0.13 ± 0.34	1.6 ± 0.78[a]	0.74 ± 0.92[a]	0.24 ± 0.54[bc]
P + D group				
IL-6	18.9 ± 9.2	192.1 ± 22.7[a]	138.2 ± 18.7[ab]	105.5 ± 13.7[abc]
CRP	7.3 ± 1.9	52.0 ± 14.5[a]	74.3 ± 17.1[ab]	113.4 ± 21.5[abc]
TNF-α	0.43 ± 0.48	0.50 ± 0.49	0.49 ± 0.38	0.51 ± 0.35
SIRS score	0.17 ± 0.38	1.4 ± 0.73[a]	0.58 ± 0.73	0.22 ± 0.42[b]

[a]$p < 0.05$, compared with the T0; [b]$p < 0.05$, compared with the T1; [c]$p < 0.05$, compared with the T2.

with serum IL-6 level 262 ng/l (normal; <4.0 ng/l). Following the administration of the nonsteroidal anti-inflammatory drug, naproxen, fever and inflammatory markers were largely overcome [12]. There was, however, no explanation why NSAIDs inhibited IL-6 secretion. In another previous study, after 14 days of treatment with celecoxib or nimesulide, a researcher observed a significant reduction in IL-6 levels in the synovial fluid of patients with knee OA [13], and Schumacher *et al.* [14] demonstrated that IL-6 levels decrease in the synovial fluid of osteoarthritic patients after two weeks of oral etodolac. Similarly, diclofenac, ibuprofen and celecoxib used for OA treatment decrease IL-6 and the explanation for the NSAID-induced reduction of the IL-6 concentration is the part inhibition of prostaglandin (PG) production [15]. Prostaglandins have previously been proven to stimulate the production of IL-6 by bone cells [16]. The results of a previous study indicated an inverse correlation, and a higher amount of NSAID application bringing a better outcome, between the amounts of NSAIDs applied and systemic IL-6 and CRP levels in patients with SAH [17]. Basically, NSAIDs have an ability to suppress IL-6 secretion, but more detailed mechanisms need to be elucidated. Our results showing that patients with the administration of flurbiprofen had lower levels of IL-6 after surgery also confirm this. Glucocorticoids are metabolic hormones which possess the ability to suppress immune responses and are used as a therapeutic approach to treat inflammatory diseases caused by an overactive immune system [18]. In an earlier article, the administration of methylprednisolone was proven to have a marked association with a lower incidence of organ failure and pulmonary disorder by reducing levels of the IL-6 and IL-8 inflammatory cytokines and higher PaO_2/FiO_2 ratios by POD 3 [19]. Our results demonstrate that patients with administration of prednisolone had lower levels of IL-6 after surgery, the same as in the above-mentioned researches. The suppression of inflammatory cytokine response was dependent on Toll-like receptor signaling in which the activation of the NF-κB pathway was targeted at several levels, including inhibition of IkB phosphorylation and NF-κB DNA-binding activity as well as upregulation of IkBa synthesis [20]. More notable is that our results demonstrate that patients who have received flurbiprofen and prednisolone had lower levels of IL-6 on day 1, meaning the combination proves an increased suppression of IL-6 after surgery. The increased suppression stems largely from two different mechanisms which inhibit inflammation after surgery. There were examples which have proved NSAIDs and glucocorticoids show different effects on cognitive function after surgery and the development of Alzheimer's disease for different mechanisms, in which NSAIDs could improve cognitive function after surgery and inhibit AD, but not glucocorticoids [21] [22]. According to our results, the levels of IL-6 after surgery were highest on day 1 (T1), which dropped rapidly on days 2 (T2) and 3 (T3), explaining why there were no significant differences between groups with combined and uncombined medication on T2 and T3, the same as in previous researches [23].

According to our results, the levels of CRP within three days never show a

peak and combination of flurbiprofen and prednisolone proved an increased suppression of CRP on each of the three days. Therefore, combined is better than uncombined medication. The levels of CRP are regarded as an early monitor of the condition of a patient over time after surgery [24]. However, CRP was only used as a supplementary predictor for increased complications. In a recent meta-analysis, including 1832 patients who were undergoing colorectal surgery, levels of CRP for the prediction of postoperative complications were assessed, suggesting that the ability of CRP to predict postoperative infectious complications was at its worst on day 1 (area under the curve 0.64) and at its highest on day 4 (area under the curve 0.81) [25]. A distinct possibility for the result is that CRP was increased slowly. TNF-α is major mediators of the acute-phase protein response to tissue damage caused by surgical intervention [26]. However, the levels of TNF-α in our study show no differences between the four groups and four periods (T0, T1, T2, T3). We believe that the smaller sample is the major reason and more patients need to be included in order to confirm this. Our results show that either flurbiprofen or prednisolone could lower the SIRS score. However, combined did not increase the potency. The SIRS score can be determined as fulfilling at least two of the following four criteria: fever > 38.0˚C or hypothermia < 36.0˚C, tachycardia > 90 beats/minute, tachypnea > 20 breaths/minute, leukocytosis > 12×10^9/l or leucopoenia < 4×10^9/l [10]. Perhaps one of two, either flurbiprofen or prednisolone, is surely enough to lower the body temperature, then lower the heart rate. Furthermore, in another study, SIRS was proved not to be a contributor to the prediction of postoperative complications [27].

Our study had several limitations. Firstly, it included relatively small groups of patients. We need larger groups in order to decrease the uncertainty. Secondly, the observation was limited to the measure of inflammation markers without a postoperative follow-up, especially the length of the hospital stay and being confined to bed. This has limited our judgment on the benefits of flurbiprofen combined with prednisolone. We will be careful to avoid this inconvenience in our future research. Thirdly, time between surgery and blood sample collection on days 1, 2, and 3 was somewhat variable between patients as was the time of initiation of surgery, which altered the dynamics of levels of IL-6, CRP and TNF-α. Finally, we only investigated inflammatory biomarkers before surgery and on days 1, 2 and 3. This was a little short for the length of a hospital stay.

5. Conclusion

In conclusion, flurbiprofen combined with prednisolone in elderly surgery patients proved to inhibit the levels of inflammatory biomarkers, including increased suppression of IL-6 and CRP.

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Authors' Contributions

Jiaxin Lin conceived and designed the study. Hui Yang, Shaofen Chen, and Jiao Xu gathered the data and participated in data analysis, with all authors revising it critically for intellectual content. All authors have read and approved the final version of this manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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