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Effects of different anaesthetics on cytokine levels in children with community-acquired pneumonia undergoing flexible fibreoptic bronchoscopy

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Abstract

Objective: To determine the effects of propofol and sevoflurane on cytokine levels in children with community-acquired pneumonia undergoing flexible fibreoptic bronchoscopy (FFB).

Method: Children with community-acquired pneumonia were randomly assigned to receive 3–5 mg/kg propofol i.v. or 8% inhaled sevoflurane. Haemodynamic variables, stress hormone responses and serum cytokines were compared between the two groups.

Results: Out of 50 children aged 2–12 years (propofol, $n = 25$; sevoflurane, $n = 25$), there were no significant between-group differences in haemodynamic variables and stress hormones. Interleukin (IL)-6 and IL-10 decreased significantly following FFB in both groups. IL-6 levels were significantly lower in the sevoflurane group than propofol group at 4 h and 1 d following FFB (61.3 ± 11.9 versus 82.6 ± 19.7 pg/ml; 52.8 ± 9.7 versus 75.4 ± 13.6 pg/ml, respectively). IL-10 levels in the sevoflurane group were significantly lower than in the propofol group at 1 d following FFB.

Conclusions: In children with community-acquired pneumonia, use of sevoflurane was associated with lower circulating IL-6 and IL-10 levels compared with propofol, following FFB. Pneumonia severity is reflected by higher blood cytokine levels, thus, sevoflurane may be more beneficial to recovery from community-acquired pneumonia than propofol, however further studies are required to test this hypothesis.

Keywords

Bronchoscopy, cytokines, physiological, propofol, sevoflurane, stress

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Introduction

Community-acquired pneumonia continues to be a common and serious illness in children.[1] The host's inflammatory response to microorganisms involved in community-acquired pneumonia is associated with the release of proinflammatory and anti-inflammatory cytokines,[2] however excessive cytokine production can cause deleterious effects.[3] The severity of pneumonia is both reflected and predicted by higher levels of cytokines in the blood.[4]

Flexible fibreoptic bronchoscopy (FFB) is a technique that allows direct visualization of the tracheobronchial tree for diagnostic and therapeutic purposes in community-acquired pneumonia. During FFB, there are two factors that can influence serum cytokine levels. First, as an invasive procedure, FFB can irritate and damage the airway mucosa, activate the hypothalamic pituitary adrenal axis, and then induce the stress response and changes in immune function.[5] Secondly, anaesthetics used during FFB may have immunomodulatory properties, and can inhibit the release of cytokines.[6,7] Although these effects may be inconsequential in children with a normal functioning immune system, suppression of the immune response may have relevance in children with a pre-existing immune imbalance, for example in cases of community-acquired pneumonia.

Sevoflurane and propofol are widely used in the induction and maintenance of anaesthesia during FFB in children.[8] To the best of the authors' knowledge, there has been little work focusing on the relationship between these two anaesthetics and cytokine release in children with community-acquired pneumonia undergoing FFB.

In the present study, serum cytokines and stress hormones were compared in children with community-acquired pneumonia undergoing FFB, to investigate the immunomodulatory effects of sevoflurane and propofol.

Patients and methods

Study population

This randomized parallel-group trial was conducted at Hubei Maternal and Child Health Hospital, Wuhan, China between March 2015 and May 2015. Inclusion criteria comprised male and female children aged 2–12 years with a clinical diagnosis of community-acquired pneumonia undergoing FFB; and children classified with American Society of Anaesthesiologists physical status (ASA) II or III (http://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system). A diagnosis of community-acquired pneumonia was defined as radiographic evidence of pulmonary infiltrate consistent with acute infection requiring antibiotic therapy, and the presence of two or more indications of pneumonia: fever, shortness of breath, cough, chest pain, abnormal white blood cell count or physical signs of pneumonia on examination (e.g., rales on auscultation, dullness to percussion, or egophony).[9] Children with a history of immunosuppression, neutropenia, cardiovascular, endocrinological, hepatic or renal disorders, allergy to opioids, or recent use (within 3 months prior to study entry) of analgesics or psychoactive drugs were excluded from the study. Children who had experienced FFB within 3 months prior to study entry were also excluded.

The study protocol was approved by Hubei Maternal and Child Health Hospital Ethics Committee (Protocol number: 2015008, Date: March 2nd, 2015) and registered at www.chictr.org (ChiCTR-TRC-15006031). This study was conducted according to the Declaration of Helsinki. Written informed consent was obtained

from the legal proxies of all participants before the trial commenced.

Study design

All FFB procedures were performed during morning hours. Children were randomized at study entry, using a computer-generated list, into a propofol group or sevoflurane group. Coded, sealed envelopes were used for allocation concealment. The propofol group received 3–5 mg/kg propofol i.v. infusion, while the sevoflurane group received oxygen at a flow of 6 l/min and 8% sevoflurane by inhalation using a Dräger Fabuis GS Anaesthesia Machine (Dräger Medical AG & Co. KG, Lubeck, Germany); both groups received 1 μg/kg remifentanil i.v. injected for 60 s followed by 0.4 μg/kg/min remifentanil by i.v. infusion. Doses of propofol and sevoflurane were adjusted to keep the bispectral index between 40 and 50. The bronchoscope (Olympus Corporation, Tokyo, Japan) was introduced through a bronchoscopy adapter (Covidien LLC, MA, USA) and a laryngeal mask airway (WEILI Corporation, Guangzhou, China). Upon direct visualization of the vocal cords, 1% lidocaine (maximum 7 mg/kg) was injected for topical anaesthesia. Bronchoalveolar lavage was performed using 0.9% NaCl (maximum 5 mg/kg). All drugs were discontinued upon completion of the FFB procedure, and the laryngeal mask airway was removed when the children were fully awake.

Phenylephrine (0.05 mg/kg, i.v.) was administered when mean arterial pressure was $\geq 30\%$ reduction from baseline, and could not be controlled within 5 min by increasing the level of fluid infusion. Atropine (0.01 mg/kg, i.v.) was administered when heart rate was <80 beats per min.

Data collection

Heart rate and mean arterial pressure were monitored and recorded at baseline (T_0), on completion of FFB (T_1) and 4 h following FFB (T_2). Duration of the FFB procedure was also recorded.

Venous blood samples (3 ml) were taken at six time points: at baseline (T_0); on completion of FFB (T_1); 4 h following FFB (T_2); at 1 day following FFB (T_3); at 4 days following FFB (T_4); and at 7 days following FFB (T_5). The samples were drawn into tubes without anticoagulants, and cooled overnight at 4°C before centrifugation at 1000 *g* for 15 min at 4°C. Serum samples were then collected and stored at −20°C prior to use. Serum levels of stress hormones (noradrenaline, adrenaline and cortisol, measured at T_0, T_1 and T_2) and the cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-6 and IL-10 were determined by enzyme-linked immunosorbent assay using commercial kits (Human Noradrenaline ELISA, Human Adrenaline ELISA, Human Cortisol ELISA, Human Cytokine TNF-α ELISA, Human Cytokine IL-6 ELISA and Human Cytokine IL-10 ELISA; Wuhan Xinqidi Biological Technology Co., Ltd, Wuhan, China) and microtiter plates (Wuhan Xinqidi Biological Technology Co., Ltd) according to the manufacturer's instructions. A WHYM201 Elisa Microplate Reader (Poweam Medical Systems Co., Ltd, Jiangsu, China) was used to analyse the ELISA reactions.

Statistical analyses

The number of patients required for each study group was estimated according to the between-group differences in serum IL-6 levels observed in the authors' previous pilot study (data not shown). It was estimated that to have 80% power of detecting a 30% difference with a type-I error of 5%

using Chinese High Intellectualized Statistical Software (CHISS 2010; Yuanyitang Science & Technology, Beijing, China), a minimum of 22 children were required in each group. A 10% drop-out rate was anticipated, thus, a minimal sample size of 25 was recruited for each group. Data are presented as mean ± SD or *n* prevalence. Student's *t*-test was used to compare between-group age, weight, and duration of FFB. χ^2-test was used to analyse categorical data. Two-way repeated measures analysis of variance followed by multiple comparisons (least significant difference testing) was used to evaluate the effects of time, group, and interaction. Statistical analyses were performed with SPSS® software, version 13.0 (SPSS Inc., Chicago, IL, USA) for Windows®. A P value < 0.05 was considered statistically significant.

Results

Out of 56 eligible children initially enrolled, 50 were finally included in the study (25 received propofol and 25 received sevoflurane); six children were excluded because they refused to participate (Figure 1). There were no statistically significant between-group differences in demographic details or duration of FFB (Table 1). There were also no statistically significant between-group differences in type of infection (bacterial or non-bacterial pneumonia) or numbers who received steroid therapy (Table 2).

Heart rate and mean arterial pressure decreased in both groups at the end of FFB ($P = 0.003$, $P = 0.004$) compared with baseline, and there were no statistically significant between-group differences in these parameters at T_0, T_1 and T_2 (Table 3). Stress hormones (noradrenaline, adrenaline and cortisol) decreased at the end of FFB (T_1) and 4 h following FFB (T_2) versus baseline ($P < 0.01$), and there were no statistically significant between-group differences at T_0, T_1 and T_2 (Table 3).

Circulating serum IL-6 and IL-10 levels decreased significantly following the FFB procedure in both groups (Table 4). Circulating IL-6 levels were lower in the sevoflurane group than the propofol group at 4 h and 1 day following FFB (61.3 ± 11.9 versus 82.6 ± 19.7 pg/ml, $P = 0.008$; and 52.8 ± 9.7 versus 75.4 ± 13.6 pg/ml, $P = 0.017$, respectively). Circulating IL-10 levels were lower in the sevoflurane group than the propofol group at 1 day following FFB (7.2 ± 2.1 versus 9.5 ± 2.4 pg/ml, respectively, $P = 0.023$). Serum TNF-α was also decreased at 4 days and 7 days following the FFB procedure, and no statistically significant between-group differences were observed in terms of TNF-α at any time point (Table 4).

Discussion

The present study showed that in children with community-acquired pneumonia undergoing FFB, serum IL-6 and IL-10 levels were lower in children who received sevoflurane compared with those who received propofol, suggesting that different anaesthetics might influence the immunological response in these patients.

Community-acquired pneumonia is tightly regulated by cytokines produced by the immune system in response to causal microorganisms.[10] These cytokines serve to control infection by leukocyte recruitment and inflammation, however, persistent and toxic inflammation can induce an overly proinflammatory cytokine balance, and lead to poor patient outcomes.[11] Serum IL-6 concentration is a sensitive and specific measurement for assessing response to infection treatment, and might be predictive of death, and rapidity of shock onset.[12] Several studies have shown that IL-6 levels correlate with illness severity in patients with pneumonia.[13–15] As an anti-inflammatory cytokine, IL-10 is produced primarily by monocytes and Th-2 lymphocytes, and can

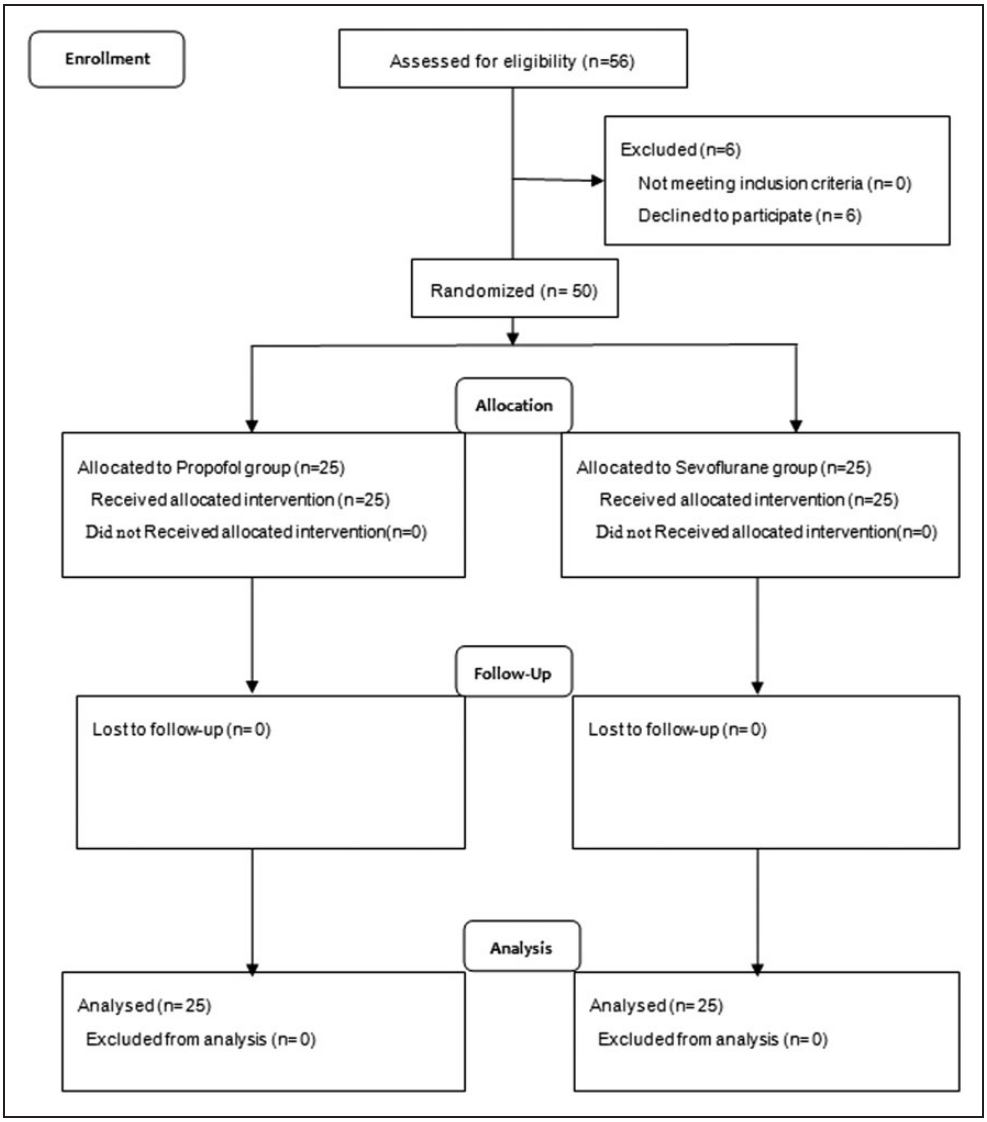

Figure 1. Flow diagram showing study enrollment, allocation, follow-up and analysis of 50 patients with community-acquired pneumonia, aged 2–12 years, who received 1 μg/kg remifentanil and either 3–5 mg/kg propofol (Propofol group) or 8% sevoflurane (Sevoflurane group) anaesthesia for flexible fibreoptic bronchoscopy.

inhibit the synthesis of proinflammatory cytokines and suppresses antigen presentation.[16] High or medium concentrations of IL-6 or IL-10 have been associated with higher mortality in patients with pneumonia, and the highest risk of death when both IL-6 and IL-10 levels were high.[17]

The present study evaluated changes in cytokine levels associated with two different anaesthetics, propofol and sevoflurane,

Table 1. Demographic characteristics and duration of flexible fibreoptic bronchoscopy (FFB) in 50 patients with community-acquired pneumonia, aged 2–12 years, who received 1 μg/kg remifentanil and either 3–5 mg/kg propofol or 8% sevoflurane anaesthesia.

	Characteristic			
Study group	Age, months	Weight, kg	Sex, Female/male	Duration of FFB, min
Propofol group ($n = 25$)	34.8 ± 9.6	13.5 ± 3.4	9/16	18.5 ± 6.6
Sevoflurane group ($n = 25$)	35.5 ± 8.1	14.1 ± 4.2	8/17	17.1 ± 5.2

Data presented as mean ± SD or *n* prevalence.
Student's *t*-test was used to compare between-group age, weight, and duration of FFB. χ^2-test was used to analyse categorical data.
There were no statistically significant between-group differences ($P \geq 0.05$)

Table 2. Type of infection and steroid use in 50 patients with community-acquired pneumonia, aged 2–12 years, who received 1 μg/kg remifentanil and either 3–5 mg/kg propofol or 8% sevoflurane anaesthesia for flexible fibreoptic bronchoscopy.

	Characteristic		
Study group	Bacterial pneumonia	Non-bacterial pneumonia	Steroid use
Propofol group ($n = 25$)	11 (44%)	14 (56%)	1 (4%)
Sevoflurane group ($n = 25$)	12 (48%)	13 (52%)	0 (0%)

Data presented as *n* (%) patient prevalence.
There were no statistically significant between-group differences ($P \geq 0.05$; χ^2-test)

in children with community-acquired pneumonia undergoing FFB. The results showed that serum TNF-α, IL-6 and IL-10 levels decreased over time in both groups. One of the main reasons may have been that FFB is beneficial to the identification of infection, and the therapeutic effects of bronchoalveolar lavage may influence treatment outcomes in cases of pneumonia. The present data were in contrast to another study,[18] in which serum proinflammatory cytokines increased following bronchoalveolar lavage in mechanically ventilated patients receiving midazolam sedation throughout bronchoscopy. The main difference between the two studies was selection of agents for sedation/anaesthesia and the experimental subject.

The present study also found that IL-6 was lower in the sevoflurane group at 4 h and 1 day following FFB compared with the propofol group. Two main factors that can induce serum cytokine changes during FFB are stress stimuli and anaesthesia, however, both groups employed the same bronchoscopist and displayed identical serum stress hormone changes, so it may be reasonable to infer that the different anaesthetics influenced the release of cytokines in the present study.

Anaesthetics and sedative agents are known to possess immunomodulatory activities.[19] Propofol pretreatment has been demonstrated to significantly suppressed the lipopolysaccharide-induced toll-like receptor 4, monocyte differentiation antigen CD14, and *TNF* gene expression in an *in vitro* study.[20] Similar immunomodulatory effects have been shown *in vitro* for sevoflurane, whereby sevoflurane reduced the release of inflammatory mediators in endotoxin injured alveolar epithelial cells.[21] A clinical study also suggested that inflammatory responses induced by one-lung

Table 3. Haemodynamic and hormone values in 50 patients with community-acquired pneumonia, aged 2–12 years, who received 1 μg/kg remifentanil and either 3–5 mg/kg propofol or 8% sevoflurane anaesthesia for flexible fibreoptic bronchoscopy.

	Time point		
Parameter	T_0	T_1	T_2
Heart rate, bpm			
Propofol group ($n = 25$)	105.2 ± 12.3	$89.5 \pm 8.6^{\Delta}$	$98.3 \pm 7.9^{\dagger}$
Sevoflurane group ($n = 25$)	103.6 ± 10.5	$91.1 \pm 9.2^{\Delta}$	$97.9 \pm 8.1^{\dagger}$
Mean arterial pressure, mmHg			
Propofol group ($n = 25$)	63.2 ± 5.1	$57.6 \pm 4.2^{\Delta}$	$60.3 \pm 5.1^{\dagger}$
Sevoflurane group ($n = 25$)	64.1 ± 4.9	$55.5 \pm 4.5^{\Delta}$	$61.4 \pm 6.3^{\dagger}$
Cortisol, μg/dl			
Propofol group ($n = 25$)	17.3 ± 2.5	$8.9 \pm 1.8^{\Delta}$	$8.5 \pm 2.2^{\Delta}$
Sevoflurane group ($n = 25$)	16.8 ± 1.9	$9.3 \pm 1.6^{\Delta}$	$9.1 \pm 2.1^{\Delta}$
Adrenaline, pg/ml			
Propofol group ($n = 25$)	92.5 ± 12.5	$63.5. \pm 10.7^{\Delta}$	$67.3 \pm 9.8^{\Delta}$
Sevoflurane group ($n = 25$)	88.2 ± 14.7	$64.7 \pm 11.8^{\Delta}$	$69.4 \pm 11.5^{\Delta}$
Noradrenaline, pg/ml			
Propofol group ($n = 25$)	387.5 ± 45.1	$257.5 \pm 34.3^{\Delta}$	$322.7 \pm 38.2^{\Delta\dagger}$
Sevoflurane group ($n = 25$)	391.2 ± 59.8	$267.8 \pm 41.6^{\Delta}$	$315.2 \pm 34.8^{\Delta\dagger}$

Data presented as mean ± SD.

$^{\Delta}P < 0.05$ versus baseline; $^{\dagger}P < 0.05$ versus T_1 (Two-way repeated measures analysis of variance followed by multiple comparisons [least significant difference testing]).

T_0, baseline; T_1, end of bronchoscopy; T_2, 4 h following bronchoscopy; bpm, beats per min.

ventilation during lung resection were significantly suppressed by sevoflurane compared with propofol.[22] The mechanism behind this immunomodulation may be reduction of inducible nitric oxide synthase protein levels and nitric oxide synthase activity by decrease in intracellular calcium concentration.[23]

Opioids have also been shown to have immunomodulatory effects. Stimulation of opioid receptors on monocytes leads to a reduction in intracellular cyclic adenosine monophosphate, followed by a reduction in cytokine production.[24] In the present study, both groups received identical opioid regimens, however, children who received sevoflurane showed reduced cytokine levels compared with those who received propofol. This may be because the effect of sevoflurane and propofol on cytokines is due to different mechanisms, and the alveolar epithelial cells may be influenced by direct contact with sevoflurane.[21] In addition, the bronchodilation effect of sevoflurane may make the bronchoalveolar lavage more thorough compared with use of propofol, which may be beneficial to recovery in patients with pneumonia, and thus impact the release of cytokines.

There are some limitations associated with the present study. First, this was a single centre trial and sample sizes are relatively small. Secondly, this study could not be blinded completely due to the odour of sevoflurane, which may have influenced the results relating to duration of bronchoscopy and anaesthesia. Thirdly, the effects of the two agents on long term outcomes, such as antibiotic use, inpatient costs, and patient outcomes, were not studied, and should be

Table 4. Cytokine levels in 50 patients with community-acquired pneumonia, aged 2–12 years, who received 1 μg/kg remifentanil and either 3–5 mg/kg propofol or 8% sevoflurane anaesthesia for flexible fibreoptic bronchoscopy.

	Time point					
Parameter	T_0	T_1	T_2	T_3	T_4	T_5
TNF-α, pg/ml						
Propofol group ($n=25$)	22.3 ± 5.1	20.5 ± 4.5	19.1 ± 3.9	21.8 ± 4.3	$15.3 \pm 3.3^{\Delta\dagger\ddagger}$	$13.3 \pm 2.9^{\Delta\dagger\ddagger\S}$
Sevoflurane group ($n=25$)	20.8 ± 4.8	19.9 ± 4.7	20.5 ± 4.1	20.1 ± 3.5	$16.1 \pm 2.8^{\Delta\dagger\ddagger}$	$12.5 \pm 2.7^{\Delta\dagger\ddagger\S}$
IL-6, pg/ml						
Propofol group ($n=25$)	98.5 ± 22.5	95.7 ± 22.1	$82.6 \pm 19.7^{\Delta}$	$75.4 \pm 13.6^{\Delta\dagger}$	$52.1 \pm 8.7^{\Delta\dagger\ddagger}$	$33.3 \pm 6.2^{\Delta\dagger\ddagger\S}$
Sevoflurane group ($n=25$)	96.1 ± 21.7	93.9 ± 23.6	$61.3 \pm 11.9^{*\Delta}$	$52.8 \pm 9.7^{*\Delta\dagger}$	$49.6 \pm 8.4^{\Delta\dagger\ddagger}$	$31.9 \pm 7.6^{\Delta\dagger\ddagger\S}$
IL-10, pg/ml						
Propofol group ($n=25$)	12.1 ± 2.9	12.8 ± 2.8	10.9 ± 2.5	$9.5 \pm 2.4^{\Delta\dagger}$	$7.1 \pm 1.9^{\Delta\dagger\ddagger}$	$6.6 \pm 1.7^{\Delta\dagger\ddagger\S}$
Sevoflurane group ($n=25$)	10.9 ± 2.7	11.5 ± 3.0	10.7 ± 2.2	$7.2 \pm 2.1^{*\Delta\dagger}$	$6.9 \pm 1.7^{\Delta\dagger\ddagger}$	$6.1 \pm 1.8^{\Delta\dagger\ddagger\S}$

Data presented as mean ± SD cytokine level.

$^{*}P < 0.05$, sevoflurane group versus propofol group; $^{\Delta}P < 0.05$ versus baseline; $^{\dagger}P < 0.05$ versus T_2; $^{\ddagger}P < 0.05$ versus T_3; $^{\S}P < 0.05$ versus T_4 (Two-way repeated measures analysis of variance followed by multiple comparisons [least significant difference testing]).

T_0, baseline; T_1, end of bronchoscopy; T_2, 4 h following bronchoscopy; T_3, 1 day following bronchoscopy; T_4, 4 days following bronchoscopy; T_5, 7 days following bronchoscopy; TNF, tumour necrosis factor; IL, interleukin.

investigated in a further randomized controlled study. Finally, the aim of the present study was to identify whether there was a difference in patient cytokine levels between use of propofol versus sevoflurane in FFB. The Chinese clinical trial registry [http://www.chictr.org.cn/showprojen.aspx?proj=10501] states that a healthy control group would be recruited to investigate cytokine levels in healthy children versus children with community-acquired pneumonia (propofol and sevoflurane groups). Patients with pneumonia have been shown to display higher levels of cytokines compared with healthy controls,[25] therefore, the healthy control group was not recruited.

In conclusion, the present results demonstrated that sevoflurane was associated with decreased circulating IL-6 and IL-10 levels compared with propofol, following FFB in children with community-acquired pneumonia. As the severity of pneumonia is reflected by higher cytokine levels in the blood, it could be inferred that sevoflurane may be more beneficial to the recovery of community-acquired pneumonia compared with propofol, however, further studies are required to test this hypothesis.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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