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Prophylactic Methylprednisolone to Reduce Inflammation and Improve Outcomes from One Lung Ventilation in Children: A Randomized Clinical Trial

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Abstract

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Background—One lung ventilation (OLV) results in inflammatory and mechanical injury, leading to intraoperative and postoperative complications in children. No interventions have been studied in children to minimize such injury.

Objective—We hypothesized that a single 2-mg/kg dose of methylprednisolone given 45–60 minutes prior to lung collapse will minimize injury from OLV and improve physiological stability.

Methods—Twenty-eight children scheduled to undergo OLV were randomly assigned to receive 2 mg/kg methylprednisolone (MP) or normal saline (placebo group) prior to OLV. Anesthetic management was standardized, and data were collected for physiological stability (bronchospasm, respiratory resistance, and compliance). Plasma was assayed for inflammatory markers related to lung injury at timed intervals related to administration of methylprednisolone.

Results—Three children in the placebo group experienced clinically significant intraoperative and postoperative respiratory complications. Respiratory resistance was lower ($P = 0.04$) in the methylprednisolone group. Pro-inflammatory cytokine IL-6 was lower ($P = 0.01$) and anti-inflammatory cytokine IL-10 was higher ($P = 0.001$) in the methylprednisolone group. Tryptase, measured before and after OLV, was lower ($P = 0.03$) in the methylprednisolone group while increased levels of tryptase were seen in placebo group after OLV (did not achieve significance). There were no side effects observed that could be attributed to methylprednisolone in this study.

Conclusions—Methylprednisolone at 2 mg/kg given as a single dose prior to OLV provides physiological stability to children undergoing OLV. In addition, methylprednisolone results in lower pro-inflammatory markers and higher anti-inflammatory markers in the children's plasma.

Introduction

Video-assisted thoracoscopic surgery has made one lung ventilation (OLV) necessary in children.[1] Injury from OLV includes endothelial dysfunction, alveolar edema, disruption of type-1 pneumocytes, and infiltration of polymorphonuclear cells.[2-4] In this study, we took advantage of the fact that OLV is a pre-planned iatrogenic injury, allowing an opportunity to institute an intervention to minimize known associated injuries.

The intervention proposed here, a single dose (2 mg/kg) of methylprednisolone (MP) given prior to OLV, was studied in our piglet model of OLV.[5] It demonstrated reduced inflammatory markers both in plasma and the lung tissue and was shown to further decrease neutrophil infiltrates in the alveoli.[5] Our primary hypothesis for this clinical study was that MP given in a single dose of 2 mg/kg prior to OLV would result in improved physiological stability by decreasing the incidence of bronchospasm and failure of OLV in children. Our second hypothesis was that MP would decrease the pro-inflammatory markers tumor necrosis factor (TNF)-α and interleukin (IL)-6 while increasing the anti-inflammatory marker IL-10 during and after OLV in children.[6,7] We also examined the influence of MP on serum tryptase, which is a known marker of lung injury, resulting from ischemia-

reperfusion[8] as was evident from our own prior clinical experience with OLV-related complications.[*]

Methods

Study Design

The study was a randomized, double-blinded, placebo-controlled clinical trial of parallel design. After we obtained IRB approval, a study coordinator obtained parental consent and child's consent/assent to enroll children aged 3–18 years. The coordinator collected data and performed all assays of inflammatory markers and was blinded to the grouping of the subjects. Only the anesthesiologist responsible for the child was made aware of the grouping. Once enrolled, the children were randomized using a random number table and a simple random allocation to either the placebo group, who received 2 ml of normal saline intravenously, or to the MP group, who received a single dose of 2 mg/kg MP intravenously (maximum dose 80 mg) 45–60 minutes prior to OLV. The placebo and MP were prepared by a pharmacist (in a 2-ml syringe labeled *study drug*) who randomized patients and maintained the record for group assignment. This was the only individual with access to that database. Neither the investigator nor the child/parents knew the group assignment.

Exclusion criteria were presence of malignant lesions, acute infections such as sepsis or pneumonia, hepatic or renal failure, autoimmune diseases, and use of oral steroids within three months prior to surgery. The only change in eligibility criteria during the course of study was the enrollment of Spanish speaking patients after the approval of the consent form in Spanish.

Anesthetic Background

The anesthetic was standardized to consist of premedication using midazolam followed by induction of general anesthesia using sevoflurane in 100% inhaled oxygen prior to securing an intravenous line. Anesthesia was maintained using infusions of propofol at 50–100 mcg · kg^{-1} · min^{-1}, fentanyl at 3 mcg · kg^{-1} · hr^{-1}, and sevoflurane 1–2% in 50% oxygen and air. The baseline measurements were done following tracheal intubation and arterial line placement, after which either the placebo or the study drug was given intravenously.

OLV Procedure

Using a flexible pediatric bronchoscope, an Arndt endobronchial blocker (Cook Critical Care, Bloomington, IN, USA) was placed under direct vision to either the right or left mainstem bronchus via the three-way adaptor that allows uninterrupted ventilation. After the patients were positioned in a lateral position, the balloon was inflated under direct vision to block the operative-side lung. Tidal volume (TV), positive end expiratory pressure (PEEP), and inspired oxygen (FiO_2) settings used for the study were as follows:

- Bilateral ventilation (BLV): TV, 8–10 ml/kg + PEEP, 5; FiO_2, 50%

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[*]Dixit D, Theroux MC, Shah S, Costarino A. Cardiovascular collapse in a patient undergoing single lung ventilation. ASA case presentation. SPA/ASA joint meeting, Oct 12, 2007, San Francisco, CA.

- OLV: TV, 5 ml/kg + PEEP, 5; FiO_2, 100%

The respiratory rate was adjusted to keep end-tidal CO_2 ($EtCO_2$) levels between 35–45 torr during (BLV) but was permitted to be in the range of 45–55 torr during OLV.

Outcome Measures Examined

Incidence of obstructive airway pattern was defined as: 1) a rise in $EtCO_2$ up to 65 mmHg or greater with an up-sloping of the EtCO2 wave form, with or without an associated decrease in oxygen saturation; 2) a 50% or greater rise in peak airway pressure compared to baseline (with no obvious occlusion of the endotracheal tube). Auscultation of lungs was not used as a criterion because of difficulty in accessing the chest during the procedure. Inability to tolerate OLV for any reason was also recorded. Respiratory mechanical parameters (**dynamic** compliance and resistance) were measured at baseline (before OLV) and 20 min after expansion of collapsed lung (end-OLV) using a commercially available, stand-alone pediatric monitoring system (CO2SMO Plus; Novametrix, Wallingford, CT, USA). The reported measurements were based on the average of at least 10 consecutive breaths. Peak inflation pressure, mean airway pressure (MAP), and blood gas parameters and glucose were measured at the same time points.

Measurement of Pro-Inflammatory Cytokines and Tryptase in the Plasma

The plasma cytokines were collected in blue-top tubes at time points referenced to the time when the study drug was administered as follows:

○	Baseline	Prior to study drug administration
○	OLV20	20 min after collapse of lung
○	OLV 6hrs	6 hours after study drug administration
○	OLV 18hrs	18 hours after study drug administration

After centrifugation, the levels of TNF-α, IL-6, and IL-10 in plasma samples collected were measured in duplicate with quantitative ELISA using human-specific Quantikine ELISA kits (R&D Systems, Minneapolis, MN, USA). The test sensitivities for respective immunoassays were as follows: TNF-α, 1.6 pg/mL; IL-6, 0.70 pg/mL; and IL-10, 3.9 pg/mL. Inter- and intra-assay coefficients of variance were < 10%. Blood was drawn for tryptase levels before OLV and 20 minutes after onset of OLV and sent to the clinical lab (Quest Diagnostics, Exton, PA) for tryptase assay.

Power and Sample Size Calculation

Sample size was calculated based on the most known and frequently studied pro-inflammatory cytokine, IL-6,[9] and results of our pre-clinical study.[5] To observe a difference in levels of IL-6 between the groups by 80%, assuming a standard deviation of 60%, risk of type-1 error of 5%, to achieve a power of 80%, nine patients per group was estimated.

Statistical Analysis

Interval data (age, weight, duration of OLV, resistance, and weight-based compliance) were analyzed using Student *t* test; chi-squared test was used to analyze male-to-female ratio and laterality of the lung collapsed. Tryptase measured at baseline and repeated at 20 min after collapse of lung was analyzed using paired sample *t* test. Cytokine measurements were analyzed after Log_{10} transformation (to reduce the volatility and linearize the data)[9] using repeated measures ANOVA to identify group differences as well as group · time interactions. The duration of OLV was used as covariate to determine its influence on the cytokine levels. Where significant difference occurred, the effect size was reported using Cohen's *d* or partial eta-squared as appropriate.[10] All statistical analysis was done using SPSS 22 (IBM, Armonk, NY, USA). Probability values < 0.05 were considered significant.

Data and Safety Monitoring Plan

A Data and Safety Monitoring Board was established with the help of our IRB, and quarterly reports were submitted and approved by the board during the two-year study period.

Results

At the end of the two-year study period, 28 children had been enrolled in the study (placebo = 15; MP = 13). One child in each group had bilateral thoracoscopic procedures for recurrent blebs and was excluded from the results. The mean age and weight, ratio of male to female, and laterality of the lung (right/left) were not significantly different between the two groups (Table 1). Groups were similar for their core temperature, heart rate, mean arterial blood pressure, ventilatory rate, and tidal volume used (Table 2). There was no difference in the partial pressure of carbon dioxide or the ratio of partial pressure of oxygen (PaO_2) to fractional concentration of oxygen (FiO_2) (PF ratio) measured at any time points (Table 2). Glucose levels were also similar in both groups (Table 2). Surgical procedures are listed in Table 1.

Physiological Stability of the Subjects

No children in the MP group experienced bronchospasm, and all completed their course of OLV without complications. Two children in the placebo group had obstructive airway events during OLV with up-sloping of the EtCO2 waveform; these events were presumed to be due to bronchospasm. One of these two children had associated inadequate oxygenation, which did not improve with ketamine and epinephrine for bronchodilatation or with lung recruitment maneuvers, and surgery was completed via open thoracotomy. The other child in the placebo group who experienced bronchospasm received albuterol via endotracheal tube and ketamine intravenously for bronchodilatation and was able to complete the procedure but sustained respiratory failure and systemic inflammatory response syndrome (SIRS) postoperatively. A third child in the placebo group required bi-level positive airway pressure (BiPAP) ventilation postoperatively and also experienced SIRS. A fourth child in the placebo group had sub-segmental atelectasis in the right middle lobe of the collapsed lung and developed fever >101°F. Following cultures, he was placed on antibiotics empirically. He recovered without sequelae. One child in each group had minimal basilar

atelectasis on postoperative chest radiograph that resolved without specific treatment other than routine incentive spirometry.

Resistance increased from baseline to end-OLV[11] as expected; however, the increase was ameliorated in the MP ($P = 0.04$ t test) compared to placebo group (Fig 1A). Weight-adjusted compliance was decreased in both groups at end-OLV but was not significantly different between the groups (Fig 1B).

Mean duration of OLV was longer in the MP group, but this difference did not have a significant influence on any of the cytokine levels. Mean plasma level of IL-6 was greater ($P = 0.01$) in the placebo group (Fig 2A) with significant differences occurring at 6 hrs ($P = 0.03$) and 18 hours ($P = 0.02$) after study drug administration. Mean plasma value of TNF-α in the MP group showed an amelioration to treatment with MP but did not achieve a statistically significant difference ($P = 0.2$) for group · time (Fig 2B). The mean plasma level of the anti-inflammatory cytokine IL-10 was significantly higher ($P = 0.001$) in the MP group with a significant difference ($P = 0.001$) occurring at 6 hours following study drug administration (Fig 2C).

Similarly, mean serum tryptase was significantly lower ($P = 0.03$) after 20 minutes of OLV when compared to baseline values in the MP group, showing an attenuation by MP. In contrast, the placebo group had a higher mean value of tryptase after 20 minutes of OLV when compared to the baseline values even though the difference did not achieve statistical significance (Fig 3). Note that the mean tryptase level in the MP group is higher than the mean tryptase level in the placebo group for both baseline and OLV20 values. No significant differences were seen when the mean values were analyzed by t test (Baseline: 1.7 ± 0.9 vs 2.7 ± 1.5 [$P = 0.10$]; OLV20: 1.8 ± 1.3 vs 2.2 ± 1.3 [$P = 0.48$]), indicative of a random occurrence.

Discussion

In this study, we have systematically examined the benefits of a single dose of MP, a well-known anti-inflammatory agent, given prior to OLV to minimize resultant inflammatory injury and improve respiratory stability. We employed protective ventilation for all patients (as defined by the use of low-stretch ventilation of TV 5 ml/kg and PEEP of 5 cms during the OLV) for its known beneficial effects.[9,12,13] Physiological stability of the patients during OLV is threatened by bronchospasm due to multiple factors such as edema, secretions, and reflux bronchoconstriction. OLV simulates an endobronchial intubation, which is the most common cause of bronchospasm in the intraoperative arena, and the beneficial effect of MP was evident in the lower resistance seen in the MP group after OLV, which contributed to the absence of bronchospasm in this group. The anti-inflammatory effects of MP in our study are further supported by the lower levels of IL-6 and higher levels of IL-10 in the MP group. Levels of IL-6 have been correlated to mortality in adults in intensive care units[14] and in children when admitted with sepsis.[15]

Tryptase, a protease, is familiar to anesthesiologists as a marker of an immunoglobulin E (IgE)-mediated reaction and bronchospasm. Tryptase elevation also occurs due to injury

resulting from a flux of reactive oxygen species (ROS) and resultant mast cell degranulation.[16] Such a flux of ROS and mast cell degranulation may be anticipated during collapse and re-expansion of a lung, similar to that described during ischemia-reperfusion injuries[17,18] and in hyperoxic environments.[17,19] Episodes of hypoxemia that are not explained by the patient's preoperative conditions may occur during OLV,[20] as was observed in two patients in the placebo group. One mechanistic pathway for such episodes may be the flux of ROS and related cellular events, as we observed (see footnote), where a healthy child experienced cardiovascular collapse shortly after re-expansion of the collapsed lung. Suspecting an IgE-mediated allergic reaction, we had drawn a tryptase level, which was elevated, and further investigation showed it to be because of a **non-IgE**-mediated mast cell degranulation. This case, along with the literature describing reperfusion injury where mast cells are capable of recruiting leukocytes independent of IgE mediation,[16-19] helped us to understand the complex nature of lung injury during and after OLV. The significant decrease in tryptase level in the MP group after 20 minutes of OLV is a finding not described before in the anesthesia literature even though MP is commonly administered during anaphylactic episodes where mast cell degranulation is a major contributing event. Our choice of MP as an intervention was based on its well known ability to attenuate both neutrophil activation and recruitment[21] and its ability to treat IgE- and non-IgE-mediated conditions where both basophils and mast cells degranulate.[22] Methylprednisolone also has been shown at endothelial cell level to reduce inflammatory response[23] by suppressing cytokine (TNF-α) production when given preoperatively in asthmatic patients. Methylprednisolone may down-regulate cytokine release and reduce neutrophil sequestration and edema.[24]

Procedures that necessitate OLV in children are typically different than in adults.[13] Our understanding of OLV mostly relates to adult studies, where pneumonectomy or esophagectomies[9,25] are often the surgical procedure. Underlying parenchymal diseases such as emphysema or chronic obstructive pulmonary disease are much less prevalent in children. Thus, pathophysiological mechanism of OLV and its treatment in adults are not entirely applicable to children. One lung ventilation procedures are often performed in children with healthy lungs, and the physiological stability that MP imparts in these patients may be of significant clinical value to pediatric anesthesiologists.

The drawbacks of our study are the lack of homogeneity of surgical procedures our subjects experienced and the small sample size. We hope to have achieved comparable groups by randomization of subjects, thus eliminating the selection bias and balancing the two groups with respect to known and unknown confounding variables. In addition, the small sample size increases the likelihood of type II error, leading to the inability to detect a significant difference when the effect size was not large. We believe that our preclinical studies in the animal model helped mitigate the drawbacks in our clinical study and further strengthen our finding.[5,12,19]

Conclusion

Methylprednisolone, given at 2 mg/kg before OLV, decreases the pro-inflammatory marker IL-6 and increases the anti-inflammatory marker IL-10 in the plasma. Further, MP decreases

tryptase, a marker of mast cell degranulation known to occur due to ROS during OLV. Overall, our study results show that a single dose of MP (2 mg/kg) given prior to OLV will result in greater physiological stability by minimizing bronchospasm or **obstructive respiratory events** and enabling completion of OLV.

Acknowledgments

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What is Already Known about the Subject

- One lung ventilation in children results in inflammatory injury as evidenced by increase in pro-inflammatory markers, which may result in intraoperative complications.

- In earlier studies using a piglet model of OLV, the authors have demonstrated that a single intravenous dose of methylprednisolone (2 mg/kg) given prophylactically could minimize such inflammatory injury and improve physiological stability of the one lung ventilation procedure.

What this Article Adds

- This manuscript describes the translational study following the animal studies and examines the efficacy of methylprednisolone (2 mg/kg) given prophylactically in minimizing inflammatory parameters, and thus improving physiological stability, in children undergoing one lung ventilation.

- The results show that methylprednisolone decreases pro-inflammatory markers including tryptase and improves physiological stability of the patients undergoing one lung ventilation.

Implications for Translation

- One lung ventilation results in the iatrogenic injury of various severities. As the injury can be anticipated, it gives the anesthesiologist a unique opportunity to institute measures to minimize such injury.

- Methylprednisolone (2 mg/kg) given prior to one lung ventilation decreases inflammatory injury and should be considered as a preventative measure prior to one lung ventilation in children. Other anti-inflammatory agents may have similar results but need further studies demonstrating their efficacy.

I - A

I - B
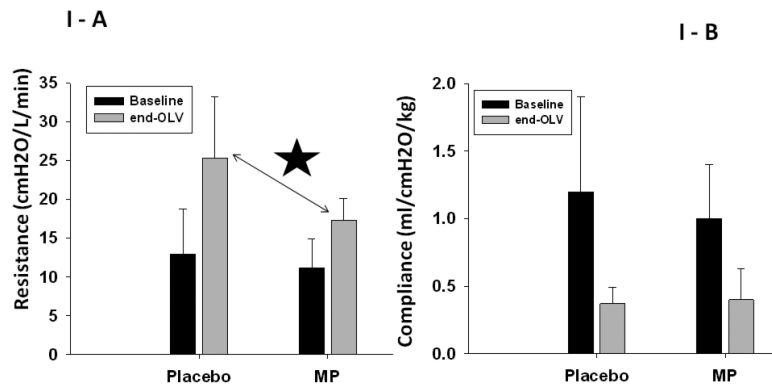
Fig 1.
Resistance **(1A)** and compliance **(1B)** measured at baseline and at termination of one lung ventilation (end-OLV is measured 20 minutes after re-expansion of collapsed lung). **Mean ± SD are given**. The arrow points to the placebo group measurements at end of OLV where the significant difference occurred ($P = 0.04$) as indicated by star. Note that mean resistance was slightly lower for the methylprednisolone group at baseline (11.2 ± 1.3 for methylprednisolone vs. 12.9 ± 1.5 for placebo), but it was not significantly different ($P = 0.44$).
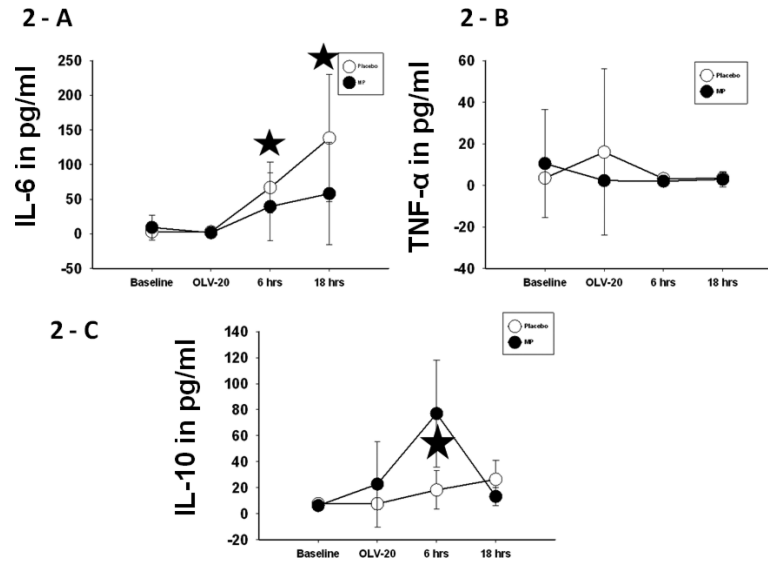
Fig 2.

2A: Interleukin (IL)-6 in plasma measured at baseline, 20 min after start of OLV (OLV20), and 6–8 hrs and 16–18 hours following administration of study drug. **Mean ± SD are given**. There was a group by time difference by repeated measures ANOVA ($P = 0.01$). Significant differences occurred between the groups at the 6-hr ($P = 0.03$) and 18-hrs ($P = 0.02$) time points as indicated by star (*t* test). Duration of OLV, which was longer in MP group, used as a co-variate, did not have a significant influence on the (IL)-6 values ($P = 0.65$). **2B**: Tumor necrosis factor (TNF)-α in plasma measured at baseline, OLV20, and 6–8 hrs and 16–18 hours following administration of study drug. The two groups were not significantly different by repeated measures ANOVA ($P = 0.2$). Duration of OLV, used as a co-variate, did not have a significant influence on the (TNF)-α values ($P = 0.82$). **2C**: Interleukin (IL)-10 in plasma measured at baseline, OLV20, and 6–8 hrs and 16–18 hours following administration of study drug. There was a significant group by time difference analyzed by repeated measures ANOVA ($P = 0.001$). Significant difference by *t* test occurred between the groups at the 6-hr time point ($P = 0.001$) as indicated by star. Similar to IL-6 and (TNF)-α analysis, duration of OLV, used as a co-variate, did not have a significant influence on the (IL)-10 values ($P = 0.16$).
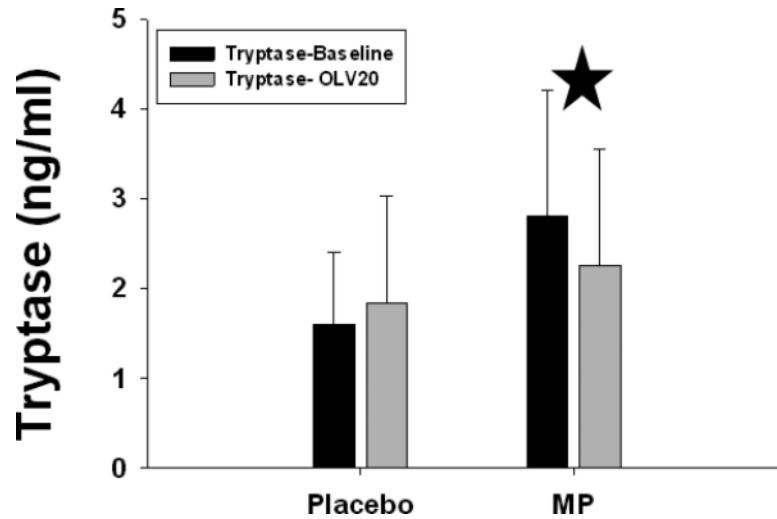
Fig 3.

Tryptase in plasma measured at baseline and 20 min past start of OLV (OLV20). **Mean ± SD are given.** Tryptase levels were drawn at similar time points (OLV20) for all subjects and therefore duration of OLV is not a confounding factor for analysis of tryptase levels. Compared to baseline, mean tryptase at OLV20 was significantly lower ($P = 0.03$) by paired-sample t test in the MP group as indicated by star. Mean tryptase level in the MP group was higher than the mean tryptase level in the placebo group for both baseline and OLV20, which, when analyzed by t test, did not show a significant difference (1.7 ± 0.9 vs 2.7 ± 1.5 [$P = 0 .10$]; OLV20: 1.8 ± 1.3 vs 2.2 ± 1.3 [$P = 0.48$]). We believe this is a random occurrence.

Table 1

Demographic data for placebo and methylprednisolone groups.

	Placebo	Methylprednisolone	*P* value
Age (years)	11.8 ± 3.8	13.6 ± 3.5	0.2
Weight (kg)	45.2 ± 25	41.8 ± 14	0.6
OLV duration (min)	95 ± 65.6	118 ± 70.4	0.4
Right/left[*]	9/5	5/7	0.2
Male/female	8/6	7/5	0.6
Anterior spine surgery	5	6	0.89[**]
Biopsy mass	7	5	
Pulmonary bleb	2	1	

Means and standard deviations are reported. Analytical methods used are *t* test and chi-square.

[*] Indicates which lung was collapsed.

[**] Type of surgery was analyzed by chi-square for the three types, and therefore the *P* value of 0.89 applies to all three surgical procedures listed.

Table 2

Physiological variables during the course of one lung ventilation (OLV).

	Placebo			Methylprednisolone			P value
	Baseline	OLV 20min	BLV 20 min	Baseline	OLV 20min	BLV 20min	
Temp 0°C	35.5 ± 0.7	34.8 ± 0.7	35.2 ± 0.8	35.6 ± 0.3	34.9 ± 0.5	35.4 ± 0.8	0.78
Heart rate/min	101 ± 12.9	85.7 ± 17.6	85.9 ± 19	102.5 ± 24.8	89 ± 10.2	88.8 ± 17.7	0.39
MAP (mmHg)	72.6 ± 18.2	77.7 ± 13.4	68.7 ± 15.9	73.2 ± 12.3	77.3 ± 15.7	72.3 ± 9.8	0.41
Vent rate/min	12.6 ± 3.4	18.2 ± 5.7	13.3 ± 3.2	11.6 ± 3.1	16.3 ± 4.1	11.3 ± 4.5	0.74
TV (ml/kg)	9.9 ± 3.4	5.2 ± 0.6	8.2 ± 1.8	8.6 ± 3.3	5.0 ± 1.0	8.7 ± 2.0	0.62
PF ratio	468 ± 108	208 ± 107	389 ± 153	508 ± 70	258 ± 81	396 ± 148	0.4
PCO_2 (mmHg)	40.6 ± 5.4	50 ± 11.8	43.2 ± 11.2	40.8 ± 7.3	54.3 ± 5.9	44.0 ± 10.0	0.71
Glucose (mg/dl)	120 ± 54.7	115.2 ± 29.8	108.6 ± 23.4	111.9 ± 42	115.6 ± 32.6	125.7 ± 21.6	0.23

Means and standard deviations are reported. Analytical method used is repeated measures ANOVA. BLV, bilateral lung ventilation; MAP, mean airway pressure; Vent, ventilation; TV, tidal volume; PF ratio, ratio of partial pressure of oxygen to fractional concentration of oxygen; PCO_2, partial pressure of carbon dioxide.