Propofol and perioperative inflammation—the Intralipid® solvent may play a role

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Abstract

The inflammatory properties of propofol are still debated. Apolipoprotein A-I is involved in the inflammation. We sought to determine how propofol or its solvent Intralipid® modulate Apolipoprotein A-I and the inflammatory response after surgical stress. Patients undergoing laparoscopic inguinal hernia repair were allocated to anesthesia with propofol (n=25), isoflurane alone (n=27) or in combination with Intralipid® (n=27). Apolipoprotein A-I and inflammation were assessed before, during and after surgery. Following a decrease in all groups, Apolipoprotein A-I levels tended to recover significantly earlier when propofol or Intralipid® were given (p<0.05). Cortisol increased in the control group whereas it remained at baseline levels when lipids were given. In this study the administration of lipids, i.e. propofol during and after surgery, modulate Apolipoprotein A-I and the inflammatory response after surgical stress. Patients undergoing laparoscopic inguinal hernia repair were allocated to anesthesia with propofol (n=25), isoflurane alone (n=27) or in combination with Intralipid® (n=27). Apolipoprotein A-I and inflammation were assessed before, during and after surgery. Following a decrease in all groups, Apolipoprotein A-I levels tended to recover significantly earlier when propofol or Intralipid® were given (p<0.05). Cortisol increased in the control group whereas it remained at baseline levels when lipids were given. In this study the administration of lipids, i.e. propofol or its solvent Intralipid®, in the perioperative setting was associated with a more pronounced yet rapidly recovering acute phase reaction.

Introduction

Propofol produces a rapid onset of anesthesia and a fast recovery [1-3]. Its pharmacokinetic characteristics made it a widely used anesthetic agent for surgical procedures and for sedation in intensive care units [4,5]. Although some authors demonstrated that propofol could trigger a proinflammatory immune response [6-8], other clinical and laboratory studies showed that propofol would exert a suppressive effect on the immune system [9-14]. Propofol affects the lipid profile of patients due to its oil-in-water formulation for intravenous use. Long-term propofol sedation has been associated with hypertriglyceridemia [15-17], and propofol binds extensively to all lipoprotein fractions [18] including the high density lipoprotein (HDL) fraction. During inflammation, the metabolism of HDL is markedly affected [19], leading to decreasing levels of HDL. Low levels of HDL have been shown to be related to increased mortality in sepsis [20,21].

Apolipoprotein A-I (Apo A-I), the major protein component of HDL [22], is directly involved in the inflammatory process and is decreased during inflammatory situations as well [23,24]. In vitro, Apo A-I specifically inhibits the contact-mediated activation of monocytes by stimulated T cells, decreasing the production of inflammatory mediators [24]. In a previous study in critically ill patients, a low serum level of Apo A-I at ICU admission was associated with increasing signs of inflammation during their ICU stay [25]. In that study, it was noted that patients who had received propofol before ICU admission had shown a tendency toward an increased Apo A-I level [25,26]. This led to our hypothesis that propofol might modify the Apo A-I blood levels and the perioperative inflammatory course.

To test this hypothesis, we conducted a study to evaluate whether propofol modifies the levels of inflammatory markers, including Apo A-I and the concentration of lipids in response to minor surgical stress in healthy patients. The secondary objective was to determine whether this modulation was due to propofol itself or to the vehicle Intralipid®.

Materials and methods

Patients

Informed consent was obtained the day before surgery. The study protocol was approved by the local ethics committee of the University Hospital of Geneva and has been registered at www.clinicaltrials.gov (identifier NCT 01115179). The study was conducted in the operating room of a tertiary teaching hospital. Male patients between 30 and 70 years of age with an American Society of Anesthesiologists physical status classification (ASA) of I or II, and scheduled for uni- or bilateral elective laparoscopic totally extraperitoneal hernia repair were included after informed consent. For the sake of homogeneity of the population for this pathophysiological study, considering the different known basal level of Apo A-I and its potential variability between male and female subjects, only healthy male were chosen. Patients with the following criteria were excluded: a body mass index of less than 18.5 or

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Key words: propofol, isoflurane, intralipid, perioperative inflammation, Apolipoprotein A-I

Received: July 13, 2015; Accepted: August 05, 2015; Published: August 10, 2015
more than 39.9 kg/m², treatment with steroids (>5 mg/d prednisone equivalent, for the last 30 days), with opioids/NSAIDs for chronic pain during the last 30 days, immunosuppression (AIDS, neutropenia <1000 cells/μL, transplant surgery, chemotherapy), a known lipid disorder (triglycerides >2.00 mmol/L, LDL-cholesterol >2.50 mmol/L or HDL-cholesterol <1.00 mmol/L), hypopilemic treatment before admission, thyroid metabolism disorder (thyroid-stimulating hormone >6.0 mUI/L or <0.4 mUI/L), renal insufficiency (creatinine >106 μmol/L), liver disorder (bilirubin >20 μmol/L, thromboplastin time >60%), insulin-depandent diabetes, parenteral nutrition or after any lipid-containing medication (propofol, Intralipid®, etomidate) during the last 30 days, antihypertensive medication with diiltiazem or other calcium channel blockers, known chronic alcoholism (men: >65-75 mL alcohol/day, multitudrug abuse (cocaïne, heroin, methadone, or other narcotics, sedatives or stimulants), mental illness and known allergy to propofol. The exclusion criteria after randomization were change of surgical strategy, protocol violation and major bleeding (>0.5 L).

Study design

Three different types of general anesthesia were compared in this prospective, randomized, controlled, double-blind trial:

a) Propofol group: induction with propofol (1.5 to 2 mg/kg) and maintenance of anesthesia with propofol 1% (target-controlled infusion with concentration levels of 3-5 μg/mL)

b) Intralipid group: induction of anesthesia with thiopental (3-5 mg/kg) and maintenance of anesthesia with isoflurane (end-expired concentration=0.5%-2.0%) as well as Intralipid 10%® (corresponding to a target-controlled infusion of propofol with concentration levels of 3-5 μg/mL)

c) Control group: induction of anesthesia with thiopental (3-5 mg/kg) and maintenance of anesthesia with isoflurane (end-expired concentration=0.5%-2.0%).

The investigators and the patients were blinded to the type of anesthesia performed. The anesthetist and the surgeon were aware of the study group, but were not involved in the evaluation of outcome.

On the day of admission, demographic and diagnostic data including age, sex, body weight, height, medication, ASA classification, and smoking status were assessed and the serum albumin, prealbumin, including age, sex, body weight, height, medication, ASA classification, and smoking status were assessed and the serum albumin, prealbumin, transferrin, total bilirubin, thyroid stimulating hormone (TSH), creatinine, gamma glutamyl transpeptidase (γGT), alcalin phosphatase (ALP) levels as well as the CD4/CD8 cell counts were measured.

Blood samples were collected from each patient before induction of anesthesia (Baseline=B), after the induction of anesthesia that is the first stressful event (T1), and 5 (T5) and 24 hours (T24) after skin incision. Apo A-I, total cholesterol, HDL-cholesterol, triglycerides, and albumin were measured by standard methods. CRP and Apo A-I were measured by nephelometry using a Beckman Image nephelometer and reagents (Beckman Instruments Inc., Fullerton, CA, USA). IL-6 was measured using a high sensitivity commercially available enzyme-immunoassay according to the supplier’s instructions (Human IL-6 Quantikine HS Elisa Kit, R&D systems, Minneapolis, MN, USA).

Statistical analysis and power calculation

Stata Statistical Software, Release 8.0® (Stata Corporation, College Station, TX, USA) was used for the statistical analysis. Lenth, R. V. (2006). Java Applets for Power and Sample Size [Computer software], retrieved from http://www.stat.uow.edu.au/~rlenth/Power were used for the sample size calculation. To detect a difference in the serum concentration of Apo A-I with and without propofol 5 hours after skin incision and according to our previous results [26], the β-test with a predetermined level of significance, alpha=0.05 and a power of 80%, required 20 patients in each group (mixed design ANOVA) [28].

Considering potential drop-outs by secondary exclusions, 81 patients, 27 patients in each group, were planned for inclusion. The randomisation was performed according to a computer-generated table. Concealment of allocation was ensured with opaque envelopes opened immediately before anesthesia induction. Categorical variables were compared by Fisher’s exact test. Continuous variables were compared by the Kruskall-Wallis test according to their distribution. Repeated measurements were compared using Friedman’s test followed by Dunn’s test. All tests were two tailed, and a p value less than 0.05 was considered significant. All values are expressed as medians with 25th and 75th percentiles (interquartile range=IQR).
Results

Patients

One hundred fifty-one male patients scheduled for laparoscopic totally extraperitoneal hernia repair were consecutively examined for eligibility. Seventy patients were excluded and 81 patients were enrolled in the study. Two patients were secondarily excluded because of protocol violation (one patient received prednisone after anesthesia induction and another patient refused the fourth blood drawing). Of the 79 remaining patients, 25 were assigned to propofol group, 27 to Intralipid® group and 27 to control group (Figure 1). Patient characteristics such as age, body mass index, smoking status, and ASA class were similar among the three groups (Table 1). Before surgery, the laboratory values reflecting the liver, kidney, and endocrine functions as well as the nutritional and immune status of the patients were similar (Table 1).

Surgery data

Surgical procedures were similar in the three groups, data are summarized in Table 2.

Pre- and post-anesthesia medications

The anti-inflammatory and analgesic treatment throughout the study period did not differ among the three groups (Table 3). The amount of Intralipid 10% administered in the Intralipid® group was similar as the amount of propofol administered in the propofol group (P=NS).

Levels of cortisol, IL-6 and CRP

The profile of cortisol levels differed among the three groups (P=0.025). In the control group, the cortisol level (median (IQR): 272 nmol/L (189); P=0.004) and propofol (median (IQR): 284 nmol/L (200); P=0.0008) groups reached significantly higher levels in the propofol group (median (IQR): 287 nmol/L (209); P=0.0001). IL-6 remained at low levels until 5 hours after insult, and reached significantly higher levels in the propofol group (median (IQR): 11.8 pg/mL (8.2); P=0.02) compared to the control group (median (IQR): 8.1 pg/mL (6.3)) and the Intralipid® group (median (IQR): 10.4 pg/mL (4.1)). At 24 hours, IL-6 levels decreased in both the propofol and Intralipid® groups, whereas levels remained increased in the control group (Figure 2).

The level of cortisol was lower and the level of IL-6 higher in the Intralipid® groups compared to the control group (median (IQR): 13 mg/mL (8); P=0.02) compared to the control group (median (IQR): 19 mg/mL (16); P=0.002) and Intralipid® group (median (IQR): 15 mg/mL (17); P=0.02) groups compared to the control group (median (IQR): 13 mg/mL (8)) (Figure 2).

Evolution of lipid variables

The levels of triglycerides were similar in the three groups before induction of anesthesia. As expected, their levels increased significantly after induction in the propofol and Intralipid® groups (propofol group: Tₜ₅₀ median (IQR): 1.3 mmol/l (1.1); Tₜ1₀0 median (IQR): 1.9 mmol/l (1.2) P<0.0001) (Intralipid® group: Tₜ₅₀ median (IQR): 1.2 mmol/l (0.5); Tₜ1₀0 median (IQR): 1.6 (0.7-4.0) P=0.02) compared to the control group (median (IQR): 1.2 mmol/l (1.1); P=0.02). Of the 79 remaining patients, 25 were assigned to propofol group, 27 to Intralipid® group and 27 to control group (Figure 1). Patient characteristics such as age, body mass index, smoking status, and ASA class were similar among the three groups (Table 1). Before surgery, the laboratory values reflecting the liver, kidney, and endocrine functions as well as the nutritional and immune status of the patients were similar (Table 1).

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Levels of cortisol, IL-6 and CRP

The profile of cortisol levels differed among the three groups (P=0.025). In the control group, the cortisol level (median (IQR): 428 nmol/L (249)) increased after induction compared to the Intralipid® (median (IQR): 249) group (median (IQR): 272 nmol/L (189); P=0.004) and propofol (median (IQR): 284 nmol/L (200); P=0.0008) groups (Figure 2).

IL-6 levels changed significantly over time in the three groups. At 24 hours, IL-6 levels decreased in both the propofol and Intralipid® groups, whereas levels remained increased in the control group (Figure 2).

The level of cortisol was lower and the level of IL-6 higher in the Intralipid® groups compared to the control group (median (IQR): 13 mg/mL (8); P=0.02) compared to the control group (median (IQR): 19 mg/mL (16); P=0.002) and Intralipid® group (median (IQR): 15 mg/mL (17); P=0.02) groups compared to the control group (median (IQR): 13 mg/mL (8)) (Figure 2).

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median (IQR): 1.5 mmol/l (1.0) \( P < 0.001 \), and stayed significantly elevated at 5 hours in propofol group (T, median (IQR): 1.3 mmol/l (1.5) \( P < 0.001 \)) and in Intralipid® group (T, median (IQR): 1.2 mmol/l (1.0) \( P < 0.001 \)) compared to the control group (control group: T \( B \) median (IQR): 1.3 mmol/l (0.5); T \( 1 \) median (IQR): 1.1 mmol/l (0.4); T \( 5 \) median (IQR): 0.8 mmol/l (0.5)).

In propofol group, HDL-cholesterol levels began earlier to decrease after induction compared to the 2 other groups (\( P = 0.001 \)). In all 3 groups, HDL-cholesterol was lower than the baseline value 5 hours after the skin incision (median (IQR) mmol/L: \( B \) vs \( T 5 \): propofol group 1.18 (0.3) vs 1.01 (0.3); \( P = 0.001 \), Intralipid® group (1.07 (0.3) vs 1.00 (0.3); \( P = 0.001 \) and control group (1.18 (0.5) vs 1.01 (0.4); \( P = 0.001 \)). HDL-cholesterol levels increased again after 24 hours in the Intralipid® (median (IQR): 1.04 mmol/L (0.2); \( P = 0.01 \)) and propofol (median (IQR): 1.09 mmol/L (0.3); \( P = 0.01 \)) groups (Figure 3).

Apo A-I levels were similar in the three groups at baseline (median (IQR) mg/dl at \( T 0 \) : propofol group 142.0 (36.3); Intralipid® group 135 (23.8); control group 149 (37)). Apo A-I decreased in all three groups after the initial insult until 5 hours after incision (median (IQR) mg/dl at \( T 5 \) : propofol group 121.0 (29.3); Intralipid® group 124.0 (23.8); control group 127 (32.3)). At 24 hours, Apo A-I levels decreased further in the control group (median (IQR) mg/dl: 123.0 (26.3)), whereas they were increasing in the propofol (median (IQR) mg/dl: 131.0 (28.8)) and Intralipid® groups (median (IQR) mg/dl: 128.0 (24.0)).

Other outcome measures

The length of stay in the postanesthesia care unit was significantly shorter for the patients in the propofol group (mean ± SD: 80 ± 17 min; \( P < 0.001 \)) compared to patients in the Intralipid® (mean ± SD: 108 ± 35min) and control (mean ± SD: 111 ± 43 min; \( P < 0.002 \)) groups. The length of hospital stay did not differ between the three groups (Table 4).

Discussion

In this study we observed a distinct course and pattern of inflammatory mediators in association with perioperative

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**Figure 2. Levels of cortisol, interleukin-6 and C-reactive protein**

Changes of the levels of cortisol, interleukin-6 (IL-6) and C-reactive protein (CRP) at several time points during the study period in the propofol, solvent, and control groups.

Repeated measurements were compared by Friedman’s test followed by Dunn’s test.
administration of propofol or the Intralipid® solvent as compared to isoflurane anesthesia. The administration of both lipid solutions was associated with a shorter, earlier and more pronounced rise in the levels of proinflammatory mediators, and higher nicotine consumption present in the two lipid groups. More specifically, the inflammatory responses to stress involve coordinated and complex reactions of the immune, nervous, and endocrine systems. The release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) increase adrenocorticotrophic hormone (ACTH), and thereby cortisol production [38]. Corticosteroids dampen inflammation, and these adaptations work to restore homeostatic balance. One could hypothesize that the presence of high lipid levels induced by propofol or its solvent modifies the equilibrium of these regulatory mechanisms and induces a rapid, but transient proinflammatory state, explaining the lower level of cortisol, the increase of IL-6 and CRP, and the decrease of Apo A-I.

In their recent animal studies Ma and coworkers found antiinflammatory effects of propofol [14]. They observed that propofol was able to up-regulate the apolipoprotein M (Apo M) expression in hepatocytes and macrophages [14]. Looking at the time scale of their experiments (maximal effect at 24 hours) one could argue that a similar direct effect of propofol (and Intralipid®) on apolipoprotein A-I expression was involved in our study. So, the initial higher proinflammatory profile in these groups [34-37]. More specifically, the inflammatory responses to stress involve coordinated and complex reactions of the immune, nervous, and endocrine systems. The release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) increase adrenocorticotrophic hormone (ACTH), and thereby cortisol production [38]. Corticosteroids dampen inflammation, and these adaptations work to restore homeostatic balance. One could hypothesize that the presence of high lipid levels induced by propofol or its solvent modifies the equilibrium of these regulatory mechanisms and induces a rapid, but transient proinflammatory state, explaining the lower level of cortisol, the increase of IL-6 and CRP, and the decrease of Apo A-I.

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Long-term administration of propofol was shown to be associated with hypertriglyceridermia [15-17]. According to our results such an elevation in the levels of triglycerides begins shortly after an induction dose of propofol or Intralipid® and remains significantly elevated (compared to the control group) in the hours following surgery. Similar levels of triglycerides in patients of the propofol and solvent

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**Table 3.** Medications administered perioperatively in patients receiving anesthesia with propofol, isoflurane alone or in combination with Intralipid® for laparoscopic inguinal hernia repair.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Propofol</th>
<th>Intralipid®</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopental, mean ± SD</td>
<td>During induction, mg</td>
<td>0</td>
<td>420 ± 85</td>
<td>452 ± 78</td>
</tr>
<tr>
<td>Fentanyl, mean ± SD</td>
<td>During induction, µg</td>
<td>148 ± 53</td>
<td>150 ± 50</td>
<td>154 ± 50</td>
</tr>
<tr>
<td>Rocuronium, mean ± SD</td>
<td>During induction, mg</td>
<td>36 ± 16</td>
<td>33 ± 25</td>
<td>26 ± 19</td>
</tr>
<tr>
<td>Propofol, mean ± SD</td>
<td>During induction, µg</td>
<td>1041 ± 537</td>
<td>0</td>
<td>4.04 ± 2.2</td>
</tr>
<tr>
<td>Intralipid®, mean ± SD</td>
<td>During induction, mL</td>
<td>16 ± 3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Morphine, mean ± SD</td>
<td>In first 5 hours, µg</td>
<td>2.5 ± 5.3</td>
<td>4.4 ± 5.8</td>
<td>3.1 ± 4.6</td>
</tr>
<tr>
<td>Tramadol, mean ± SD</td>
<td>In first 5 hours, mg</td>
<td>52 ± 75</td>
<td>85 ± 99</td>
<td>77 ± 85</td>
</tr>
<tr>
<td>Paracetamol, mean ± SD</td>
<td>In first 5 hours, g</td>
<td>2.2 ± 0.9</td>
<td>2.1 ± 0.8</td>
<td>2.3 ± 0.8</td>
</tr>
</tbody>
</table>

**Table 4.** Outcome measures of patients after anesthesia with propofol, isoflurane alone or in combination with Intralipid® for laparoscopic inguinal hernia repair.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Propofol</th>
<th>Intralipid®</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurrence of SIRS during study, n (%)</td>
<td>First VRS*, mean ± SD</td>
<td>1.4 ± 1.6</td>
<td>2.6 ± 2.5</td>
<td>2.0 ± 2.1</td>
</tr>
<tr>
<td>Length of stay</td>
<td>After induction, min</td>
<td>80 ± 17</td>
<td>108 ± 35</td>
<td>111 ± 43</td>
</tr>
<tr>
<td>Pain in postoperative recovery unit</td>
<td>In hospital (hour), mean ± SD</td>
<td>68 ± 15</td>
<td>68 ± 16</td>
<td>73 ± 15</td>
</tr>
</tbody>
</table>

*Continuous variables compared by Fisher’s exact test.
*Continuous variables compared by the Kruskall-Wallis test.
*VRS: verbal rating score (0=no pain, 10-maximum imaginable pain)
groups confirm that both groups received similar amounts of lipids in our study. Furthermore, the fact that the solvent tended to show similar results as propofol, suggests that the inflammatory effect of propofol is mainly due to its lipid vehicle rather than to the propofol molecule itself. Of note, the innocuity of the use of Intralipid® in pancreatitis or acute lung injury was debated over the years and more recently, the propofol infusion syndrome renewed concerns about the use of lipid solution and propofol in critically ill patients. The causes of these effects may be different than the outlined inflammatory approach discussed above. Especially in the case of the propofol infusion syndrome, where inhibition of normal mitochondrial function has been observed [44]. However, inflammatory modulation may also play a role [45].

The biological findings of our study were not accompanied by clinical signs of inflammation. This can be explained by the fact that the surgical insult was too weak to induce a clinically relevant effect, as sustained by the low peak levels of all inflammatory markers. The shorter length of stay in the recovery room after anesthesia with propofol is consistent with the recognized shorter anesthetic effect of propofol and our observation of lower pain ratings in the recovery room period in the propofol treated group confirms previous data [46-49].

Our study has some limitations. Indeed, as stated earlier, some confounding factors may have influenced the perioperative inflammation. The number of bilateral interventions was higher in the propofol and Intralipid® groups as compared to the isoflurane group. However, the difference was not significant. Second, as the proportion of smokers in the isoflurane group was smaller and cigarette smoking is known to impact on the immune system [50], we cannot exclude that smoking did affect our results. Third, the 24 hours observation period was too short. IL-6 levels at 24 hours were already decreasing in the propofol and solvent groups, whereas they were still increasing in the control group. CRP levels appeared to be higher in the propofol and solvent groups. Considering the protracted course of CRP, the evolution of its levels after 24 hours would have been interesting. Although we had performed a pilot study in order to identify the best timings to measure our different molecules, we missed the adequate time points for CRP and IL-6. Finally, our model generated a low level of tissue injury reflected by only modest postoperative levels of

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Figure 3. Levels of the lipid parameters.
Changes of the levels of triglycerides, HDL-cholesterol and apolipoprotein A-I (Apo A-I) at several time points during the study period in the propofol, solvent, and control groups. Repeated measurements were compared by Friedman’s test followed by Dunn’s test.
inflammatory mediators and a very low incidence of SIRS during the observation period. More aggressive surgery would have produced more pronounced effects on the inflammation, both clinically and on the different molecules measured [33]. This limitation is due to our intent to characterize the effects of propofol on inflammation in a very standardized setting. Additionally, as the level of Apo A-I is known to be more variable in women, we chose to include only men. Therefore, our findings may apply to men only. Finally, it is unclear how the findings of this study model are applicable to other settings such as the intensive care unit where propofol and continuous infusion of Intralipid® are used. The pathophysiological state and the various stressors and multiple hit insults that evolve in the critical ill are likely to be different.

In conclusion, administration of lipids, i.e. propofol or its solvent Intralipid®, in the perioperative setting may be associated with a more pronounced but rapidly recovering acute phase reaction. In our study, ApoA1 recovery was faster with intralipid administration (not propofol alone) but there were no differences between the three groups at the stated time intervals. Additionally, the inflammatory markers had a variable association with administration of intralipid and propofol. However, our results should be looked with criticism since they may not be generalisable to other clinical models, such as major surgery or intensive care. A study with more extensive insult is warranted in order to confirm our findings and to determine the pro-/anti-inflammatory role of propofol and its solvent Intralipid®.

Acknowledgements

The authors would like to thank Allison Dwileski, B.S. (Administrative Assistant, Department of Anesthesia, University Hospital, University of Basel, Switzerland) for the editorial assistance and help with manuscript submission.

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