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Effects of propofol vs methohexital on neutrophil function and immune status in critically ill patients

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Abstract
Purpose. Patients with severe brain injury often require long-term sedation and have a high incidence of nosocomial infections, causing an increased mortality rate. However, whether anesthetic drugs might contribute to immunosuppressive effects remains unclear.
Methods. In this prospective study, we investigated the effects of propofol (4–6 mg·kg^{-1}·h^{-1}) and methohexital (1–3 mg·kg^{-1}·h^{-1}) on neutrophil leukocyte function and immune status in 21 patients with brain injury who either received propofol ($n = 12$; 9 male, 3 female; mean age, 51 ± 15 years) or methohexital ($n = 9$; 8 male, 1 female; mean age, 48 ± 17 years) after admission to the intensive care unit (ICU). Both sedatives were administered over 7 days and individual dosage was adapted according to clinical requirements. Neutrophil leukocyte function was assessed as phagocytosis and respiratory oxidative burst activity. Furthermore, leukocyte subpopulations, and surface markers of lymphocytes and monocytes (CD3; CD4; CD45RO; CD4/CD45RO; CD25; CD4 and CD25; CD54; CD69; CD14/HLA-DR; CD8; CD3/HLA-DR; CD4 : CD8 ratio) were assessed. Blood samples were drawn on ICU admission, and on days 3, 7, and 14. Patients' demographics were compared by Wilcoxon test and laboratory results were compared by analysis of variance (ANOVA) for repeated measurements, with an all pairwise multiple comparison procedure.
Results. There were no significant differences in neutrophil oxidative burst and phagocytosis within or between the two groups at the different time points. With respect to cellular markers of lymphocytes and monocytes, all values throughout remained in the normal range.
Conclusion. Methohexital and propofol exhibited no significant effects on neutrophil function and immune status in patients with severe brain injury requiring long-term sedation.

Key words Neutrophil function · Immune status · Propofol · Methohexital · Severe brain injury

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Introduction

Patients with severe brain injury often require long-term sedation and have a high incidence of nosocomial infections, contributing to the high mortality rate of these patients. Experimental and clinical studies suggest that anesthetics may have a variety of immunosuppressive effects, especially on neutrophil leukocytes, lymphocytes, and monocytes, which all play a major role in the defense against invading microorganisms. It has been shown previously that anesthetics inhibit neutrophil leukocyte function and, thus, possibly enhance risk of infection. In-vitro studies have described an inhibition of the production of superoxide compounds which are physiologically induced in neutrophil leukocytes ("respiratory burst") for propofol, methohexital, and thiopental [1–6]. For instance, propofol has been shown to reduce neutrophil leukocyte respiratory burst, while phagocytosis (*Escherichia coli*) was found to be unaffected [7]. Also, these studies suggested a marked difference between propofol and methohexital in the degree of inhibition of this oxidative reaction by neutrophil leukocytes. Furthermore, anesthetics may also influence immune markers of leukocyte subpopulations, as has been shown in cultured human whole blood of healthy volunteers, i.e., the expression density of CD14 was reduced in the presence of thiopental and propofol, whereas HLA-DR was unaffected [8].

However, it still remains unclear how far these results are applicable to the clinical setting. There is evidence for possible clinical relevance, because an increased incidence of pneumonia and multiple organ failure has been found in a retrospective analysis of patients with multiple trauma [9]. For instance, Eberhardt et al. [10], who studied two thiopental groups (low and high dose) and a midazolam group, found that the pneumonia rates after 7 days of mechanical ventilation were 43.8% in the high-dose thiopental, 28.6% in the low-dose, and 23.1% in the control group. However, data on the effects of

anesthetics in patients with long-term sedation are scarce, and studies on the influence of long-term sedation on a variety of immune markers have not been published before. In this prospective clinical study, we compared the effects of methohexital and propofol on neutrophil leukocyte and immune markers in patients with brain injury requiring long-term sedation.

Patients and methods

The study was conducted in a 28-bed multidisciplinary surgical intensive care unit (ICU) of a university hospital. After approval by the local ethics committee and written consent by their relatives, 21 patients with severe brain injury requiring long-term sedation were enrolled in this observational study. Prior to ICU admission, the patients had undergone primary diagnostic and surgical procedures during which, according to our standard regimen, propofol and sufentanil were administered for analgesia and sedation. Morphine, which is known to considerably influence immune function, was not administered. Patients receiving corticosteroids were excluded, due to the interference of these agents with the potential immunomodulatory effects of anesthetics. No patient required extracorporeal organ assist systems, i.e., renal replacement therapy, extracorporeal membrane oxygenation (ECMO), or liver support therapy.

In the propofol group (n = 12; 9 male, 3 female), patients had a mean age of 51 ± 15 years (range, 28–74 years). In the methohexital group (n = 9; 8 male, 1 female), mean age was 48 ± 17 years (range, 18–64 years). Patients' demographics, APACHE II (Acute Physiology and Chronic Health Evaluation), SAPS II (Simplified Acute Physiology Score) and SOFA (Sepsis-related Organ Failure Assessment) scores and admission diagnosis are depicted in Table 1.

After admission to the ICU, patients either received propofol (Disoprivan 2%; Astra Zeneca, Wedel, Germany; 4–6 $mg \cdot kg^{-1} \cdot h^{-1}$) or methohexital (Brevimytal; Lilly, Bad Homburg, Germany; 1–3 $mg \cdot kg^{-1} \cdot h^{-1}$). Titration of dosage and final duration of drug administration were determined by clinical requirements. In both groups, opioids (sufentanil) and benzodiazepines (midazolam) were administered for analgo-sedation additionally.

Neutrophil function, subpopulations, and surface markers of lymphocytes and monocytes were assessed on ICU admission, and on day 3, day 7, and day 14 after ICU admission. At each time point, a blood sample (2.7 ml lithium heparin Monovette; Sarstedt Monovette, Sarstedt, Nuembrecht, Germany) was taken via an indwelling arterial line and analyzed immediately after withdrawal. Measurements of oxidative burst and phagocytosis were performed with commercially available kits (Phagoburst and Phegotest; Orpegen Pharma, Heidelberg, Germany), using flow cytometry [11]. In the Phegoburst test, 100 µl of heparinized full blood was used for the analysis and was incubated at 37°C with *Escherichia coli*, protein kinase C ligand (phorbol 12-myristate 13-acetate) as "high stimulus" and chemotactic peptide N-formyl-MetLeuPhe as "low stimulus". As fluorescent agent, 123-dihydrorhodamine (DHR) is part of this test kit. After 10 min, the reaction was stopped and leukocytes were isolated by lysis of erythrocytes. Formation of green fluorescent rhodamine (the oxidant product of 123-DHR) was assessed with a FACScan flow cytometer (Becton Dickinson, Copenhagen, Denmark), with a filter wavelength of 488 nm. In the Phagotest, phagocytosis of fluorescein isothiocyanate (FITC)-conjugated opsonized *Escheri-*

Table 1. Patients' demographics

	Propofol (n = 12)	Methohexital (n = 9)
Male/female (n)	9/3	8/1
SHT/ICH/SAH (n)	7/3/2	6/1/2
Age (years)	51 ± 15 (52; 28–74)	48 ± 17 (56; 18–64)
Height (cm)	175 ± 9 (175; 160–190)	177 ± 7 (180; 160–185)
Weight (kg)	81 ± 11 (80; 65–100)	88 ± 16 (90; 60–115)
APACHE II score	26 ± 4 (25; 21–32)	28 ± 6 (30; 21–39)
SAPS II score	39 ± 10 (36; 24–53)	42 ± 12 (47; 27–55)
SOFA score	9 ± 3 (9; 4–13)	10 ± 3 (11; 4–14)
Cumulative drug dose (g)	58.8 ± 32.2	35.2 ± 16.3
Infections (pneumonia; n)	7	6
ICU length of stay (days)	21 ± 7 (21; 11–31)	22 ± 8 (21; 14–37)
Nonsurvivors (n)	0	2

Data values for both groups are means ± SD (median; range) and were compared by Wilcoxon test
SHT, severe head trauma; ICH, intracranial hemorrhage; SAH, subarachnoid hemorrhage; APACHE II, Acute Physiology and Chronic health Evaluation; SAPS II, Simplified Acute Physiology Score; SOFA, Sepsis-related Organ Failure Assessment

chia coli is quantified and expressed as percentage of granulocytes. Furthermore, neutrophil leukocytes, lymphocytes, and monocytes were identified by their forward and side light-scatter characteristics. Surface CD markers of monocytes and lymphocytes were assessed with commercially available test kits (Simultest; Becton Dickinson, BD Biosciences, San Jose, CA, USA) and the FACScan technique. In detail, CD15, CD14, CD25, and CD4/CD45RO were assessed with a FITC-conjugated mouse anti-human monoclonal antibody. Furthermore, CD132, CD69, and CD54 were detected with an R-phycoerythrin (R-PE)-conjugated mouse anti-human monoclonal antibody. CD57 and CD8 were measured by two-color direct immunofluorescence (BD Biosciences, Franklin Lakes, NJ, USA). CD122 (anti-IL-2R p75) was assessed by single-color direct immunofluorescence (BD Biosciences) and CD116, with a monoclonal antibody with cytometry detection (Immunotech, Marseille, France).

In brief, we identified different subpopulations of lymphocytes and monocytes by specific markers: CD3 (T lymphocytes), CD19 (B lymphocytes), CD4 (T-helper lymphocytes), and CD8 (T-suppressor lymphocytes). Moreover, natural killer (NK) cells were identified by CD16&CD56 and CD57, which are expressed on NK lymphocytes and a subset of T lymphocytes. In addition, we determined:

- CD14, which is expressed at high levels on monocytes and has been identified as a high-affinity cell-surface receptor for complexes of lipopolysaccharide (LPS) and LPS-binding protein (LBP)
- CD15 as a cellular marker which is expressed on more than 95% of granulocytes, including neutrophils and eosinophils, and to a varying degree on monocytes, but not on lymphocytes or basophils
- CD116 as a granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor, which is not expressed on lymphocytes, but is expressed strongly on monocytes and granulocytes and their precursors
- CD45RO, which is a common leukocyte antigen, and CD4/CD45RO, which characterizes memory T-helper cells
- CD54, which is the intercellular adhesion molecule-1 (ICAM-1), and is expressed on inactivated and activated lymphocytes and monocytes
- CD69, which is known to react with a glycoprotein expressed early during the activation of lymphocytes and monocytes ("proliferation marker")
- CD25, which is expressed on activated (T and B) lymphocytes and monocytes
- CD122, as a marker on 5% to 15% of normal, resting peripheral blood lymphocytes, but not on granulocytes. CD122 may also be expressed on monocytes and within the resting lymphocyte population, but is preferentially expressed on NK lymphocytes
- HLA-DR, which is an MHC-II antigen and is expressed on monocytes, activated T lymphocytes, NK lymphocytes, and B lymphocytes, and
- CD132 (synonymous with interleukin [IL]-2Rγ), which is expressed on most peripheral T and B lymphocytes, NK cells, monocytes, and granulocytes.

Statistical analysis

Values for results are expressed as means ± SD (median; range). Patients' demographics were compared by a Wilcoxon test and laboratory results were compared by analysis of variance (ANOVA) for repeated measurements with an all pairwise multiple comparison procedure (Student-Newman-Keuls method). Statistical analysis and power calculation were done using SigmaStat for Windows, version 1.0 (Jandel Scientific, San Rafael, CA, USA). A P value of less than 0.05 was considered as statistically significant. Although not of primary interest in our study, given the mortality rates found in our study population (propofol 0/12 vs methohexital 2/9), a number of patients of 97 per group would have been necessary to detect a difference in mortality of at least 20% between the two groups (power 80%, $\alpha = 0.05$, using the χ^2 test).

Results

The two groups were well matched in terms of diagnosis, severity of illness, and ICU length of stay (Table 1). Unfortunately, two patients in the methohexital group died, due to intracranial hypertension refractory to therapy, while all patients in the propofol group survived the ICU stay. The rates of pneumonia were comparable in the two groups, i.e., 58% (propofol) vs 66% (methohexital).

There were no significant differences in neutrophil oxidative burst and phagocytosis within or between the two groups at the different time points (Table 2). With respect to cellular markers of lymphocytes and monocytes, all values remained in the normal range at all time points. However, CD69 was significantly lower in the methohexital group on days 7 and 14, while CD4/CD45RO was significantly lower in the propofol group 2 weeks after ICU admission (Table 3). For the following parameters, no significant differences between or within the two groups were found: CD122, CD4&CD122, CD132, CD4&CD54, CD8/CD69, CD14/CD116, CD15/CD116, CD19, CD16&CD56, CD57, and CD8&CD57.

Table 2. Study results for leukocytes and their subpopulations (lymphocytes, monocytes, neutrophils)

Parameter	MET 1	PROP 1	MET 2	PROP 2	MET 3	PROP 3	MET 4	PROP 4
Lymphocytes ($1000 \cdot \mu l^{-1}$)	1.1 ± 0.7	1.0 ± 0.4	0.9 ± 0.4	0.9 ± 0.5	1.2 ± 0.4	1.2 ± 0.5	1.3 ± 0.3	1.3 ± 0.8
Monocytes ($1000 \cdot \mu l^{-1}$)	0.8 ± 0.7	0.5 ± 0.3	0.7 ± 0.3	0.6 ± 0.4	0.6 ± 0.3	0.6 ± 0.2	0.6 ± 0.3	0.6 ± 0.3
Neutrophils ($1000 \cdot \mu l^{-1}$)	8.4 ± 3.6	6.7 ± 2.8	7.6 ± 3.3	5.9 ± 3.5	9.2 ± 4.7	8.0 ± 3.0	8.3 ± 2.0	8.9 ± 4.1
Lymphocytes (%)	12 ± 7	13 ± 6	10 ± 7	13 ± 5	13 ± 7	13 ± 5	13 ± 4	13 ± 7
Monocytes (%)	7.0 ± 2.8	5.5 ± 2.3	7.0 ± 1.5	8.0 ± 3.5	6.0 ± 2.7	6.8 ± 4.1	5.2 ± 1.9	6.0 ± 1.8
Neutrophils (%)	81 ± 6	81 ± 7	82 ± 7	79 ± 7	81 ± 8	80 ± 6	82 ± 2	81 ± 7
Phagocytosis (%)	83 ± 15	90 ± 13	90 ± 8	82 ± 18	90 ± 6	90 ± 8	83 ± 11	91 ± 5
Oxidative burst (%)	83 ± 14	89 ± 8	77 ± 14	77 ± 16	77 ± 12	72 ± 18	86 ± 5	77 ± 16

Phagocytosis (% granulocytes with phagocytosis; normal, 90%–100%); oxidative burst (% oxidating granulocytes; normal, 70%–100%)
MET 1, MET 2, MET 3, and MET 4 (methohexital) and PROP 1, PROP 2, PROP 3, and PROP 4 (propofol) indicate the four time points within each study group, respectively

Table 3. Study results for phenotyping of leukocytes

Parameter	Normal range	MET 1	PROP 1	MET 2	PROP 2	MET 3	PROP 3	MET 4	PROP 4
CD3	59–85	64 ± 16	68 ± 10	59 ± 16	63 ± 11	64 ± 9	66 ± 12	71 ± 6	66 ± 9
CD4	29–61	38 ± 15	46 ± 8	37 ± 10	43 ± 10	45 ± 7	48 ± 10	48 ± 13	47 ± 9
CD45RO	31–51	25 ± 9	22 ± 8	28 ± 11	25 ± 12	28 ± 10	27 ± 12	40 ± 9	32 ± 9[1*]
CD4/CD45RO	18–38	18 ± 6	17 ± 7	21 ± 8	19 ± 9	23 ± 8	21 ± 9	30 ± 8	24 ± 8[2*]
CD25	3–16	12 ± 5	12 ± 4	16 ± 6	14 ± 6	20 ± 10[3*]	19 ± 6	18 ± 7	19 ± 8
CD4+CD25+	4–12	5.3 ± 1.9	5.0 ± 1.9	7.3 ± 3.6	6.8 ± 3.3	11.3 ± 5.7	10.2 ± 4.2	10.6 ± 2.9	10.1 ± 5.4
CD54	38–77	48 ± 16	50 ± 15	55 ± 14	57 ± 17	55 ± 14	57 ± 19	52 ± 18	59 ± 18
CD8	12–37	24 ± 8	23 ± 8	25 ± 8	21 ± 6	20 ± 7	19 ± 5	23 ± 6	20 ± 3
CD69	9–27	14 ± 5	14 ± 6	18 ± 6	20 ± 7	19 ± 8	24 ± 7[5*]	25 ± 5	28 ± 5[4*]
CD14/HLA-DR	90–100	69 ± 22	74 ± 17	77 ± 13	75 ± 16	71 ± 21	77 ± 20	80 ± 19	83 ± 11
CD4:CD8 ratio	0.9–3.6	1.7 ± 1.0	2.2 ± 0.7	1.5 ± 0.5	3.4 ± 4.3	2.8 ± 1.9	2.5 ± 0.7	2.5 ± 1.5	2.5 ± 0.8
CD3/HLA-DR	1–9	5.4 ± 7.8	5.1 ± 4.3	5.7 ± 4.9	7.0 ± 4.7	6.0 ± 4.0	8.4 ± 5.0	9.0 ± 5.6	7.2 ± 3.7

Statistically significant differences ($P < 0.05$) between different time points or groups are indicated as follows: [1*] $P < 0.05$ vs PROP 1, MET 1, PROP 2, MET 2, PROP 4; [2*] $P < 0.05$ vs PROP 1, MET 1, PROP 2, PROP 3, MET 3, PROP 4; [3*] $P < 0.05$ vs PROP 1; [4*] $P < 0.05$ vs PROP 1, MET 1, PROP 2, MET 2, MET 3; [5*] $P < 0.05$ vs PROP 1
All values are in percentages. CD markers are more or less specific for the following leukocyte subpopulations: CD3, T lymphocytes; CD4, T-helper lymphocytes; CD45RO, common leukocyte antigen; CD4/CD45RO, memory T-helper-lymphocytes; CD25, activated lymphocytes and monocytes; CD54, lymphocytes and monocytes; CD69, lymphocytes and monocytes "proliferation marker"; CD8, T-suppressor lymphocytes; CD14, monocytes

Discussion

In this observational study, methohexital and propofol exhibited similar effects on neutrophil function and immune status in patients with severe brain injury requiring long-term sedation.

In previous in-vitro and in-vivo studies, the immunomodulatory effects of anesthetics, especially on polymorphonuclear nentrophil (PMN) leukocyte function, have been extensively described [1–7]. In vitro, incubation of blood from healthy volunteers for 1 h with propofol, thiopental, midazolam, or ketamine agents at clinically relevant concentrations had only minimal effects on PMN leukocyte phagocytosis and oxygen free-radical production [5]. At higher concentrations, thiopental and ketamine may affect phagocytosis and thiopental may impair intracellular cytolysis. Skoutelis et al. [12] studied the effects of thiopental and propofol at low (thiopental $10 mg \cdot l^{-1}$, propofol $2 mg \cdot l^{-1}$) and high (thiopental $40 mg \cdot l^{-1}$, propofol $6 mg \cdot l^{-1}$) clinically relevant concentrations on PMN leukocyte adherence, chemotaxis, phagocytosis, and killing in vitro. They demonstrated that thiopental, at both concentrations, significantly decreased all PMN leukocyte functions tested and had a direct influence on the PMN leukocytes in terms of their chemotactic response. In contrast, propofol decreased significantly only PMN chemotaxis, but not adherence, phagocytosis, or killing. The effect of propofol was not attributable to the lipid carrier vehicle, as a lipid carrier with same formulation had no effect on PMN leukocyte function. In a more recent study, propofol was shown to significantly inhibit chemotaxis, phagocytosis, and reactive oxygen species (O_2^-, hydrogen peroxide [H_2O_2], OH·) production of neutrophils in a dose-dependent manner [13]. The interpretation of these different studies is rendered some-

what difficult, as concern has been raised in terms of the technique used for the assessment of respiratory burst activity. Zhao et al. [14] suggest that the influence of cell preparation methods should be considered when the in-vitro effects of anesthetics on PMN leukocyte functions are studied with flow cytometric methods.

In vivo, in a rat model of abdominal sepsis, Inada et al. [15] showed that propofol depressed neutrophil H_2O_2 production more than midazolam, whereas adhesion molecule expression was minimally affected by both anesthetics. In patients undergoing elective interventional embolization of cerebral arteriovenous malformations, 4 h of propofol or isoflurane anesthesia had only a minimal effect on the bacterial phagocytosis of *Escherichia coli* (93.2% and 94.3%, respectively, compared to that before anesthesia) [7]. In contrast to isoflurane, the percentage of PMN leukocytes with respiratory burst activity following tumor necrosis factor (TNF)-alpha stimulation was significantly reduced after 2 h (80.9%) and 4 h (53.7%) of anesthesia with propofol compared with the values before induction. However, in contrast to in-vitro studies, 4 h of anesthesia with propofol did not reduce the phagocytotic capacity of human blood PMN leukocytes more than isoflurane anesthesia. Weiss et al. [16] found that propofol impaired the chemiluminescence of neutrophils in a drug-specific manner, even in the therapeutic concentration range.

The effects on neutrophil function of thiopental and methohexital have also been compared. In one study, complement factor 5a-induced hydrogen peroxide production was significantly impaired by thiopental, but not by methohexital [17]. In whole blood samples of 20 volunteers, Muhling et al. [18] determined superoxide anion (O_2^-) and H_2O_2 production, and the activity of released myeloperoxidase (MPO) photometrically. In terms of PMN leukocyte immune functions, methohexital significantly decreased O_2^- and H_2O_2 formation and MPO. Krumholz et al. [19] compared the effects of methohexital, etomidate, ketamine, fentanyl, and morphine on the activity of lysozyme and beta-glucuronidase released from PMN leukocytes in an in-vitro study. High methohexital concentrations inhibited lysozyme activity, while the other drugs did not influence this oxygen-independent bactericidal mechanism.

In our study, with respect to cellular markers of lymphocytes and monocytes, all values remained in the normal range at all time points. Two CD markers, CD69 and CD4/CDR45O, were significantly different between the two groups, at one and two time points, respectively. However, the clinical relevance remains unclear: CD69 is known to increase during early activation and cell proliferation or during apoptosis, and increased CD4/CDR45O indicates a higher transfer rate of T-helper cells to memory cells.

In the clinical setting, one study comparing intravenous propofol and combined isoflurane anesthesia in 20 patients undergoing ophthalmic surgery found a similar immune response in the two groups, as assessed by CD3, CD4, CD8, CD20, CD16, and monocytes (CD14) [20]. The percentage of T-helper cells (CD4) increased significantly in the propofol group but not in the isoflurane group. In a similar design [21], a study in 30 patients undergoing major surgery found no significant differences in lymphocyte subpopulations (CD3, CD4, CD8, CD19, CD16, and HLA-DR+CD3). Measurements were made preoperatively, at the end of the operation, and on the first and fifth postoperative days. One study [8], of the concentration-dependent effects of thiopental and propofol in whole blood samples of volunteers, found that both anesthetics elicited only minor effects on spontaneous cytokine release, even at pharmacological concentrations. However, the expression density of CD14 was reduced in the presence of thiopental and propofol, whereas HLA-DR was unaffected. More recently, Loop et al. [22] have demonstrated that thiopental inhibits the activation of NF-kappaB and may thus provide a molecular mechanism for some of the immunosuppressive effects associated with thiopental therapy. However, other barbiturates (methohexital) and propofol did not affect NF-kappaB activation, which is involved in the activation of CD3+ lymphocytes and CD69 expression.

In contrast to the study of Eberhardt et al. [10], which described a dose-dependent increase in the rate of pneumonia (up to 43.8%) after 7 days of mechanical ventilation when compared to midazolam (23.1%), the incidence of pneumonia in our study was similar in our two groups (propofol 58% vs methohexital 66%). The relatively high rate of pneumonia in our study is most likely due to the longer study period, of 14 days.

To our knowledge, this is the first in-vivo study comparing the effects of propofol and methohexital on neutrophil function and immune status during long-term sedation. However, our study is limited by the relatively small patient population and the fact that a variety of factors other than sedatives may have influenced cellular and immune function.

Conclusion

Methohexital and propofol exhibit no significant effects on neutrophil function and immune status in patients with severe brain injury requiring long-term sedation.

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