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SPECIAL ARTICLE

Plasma levels of interleukin-10 and nitric oxide in response to two different desflurane anesthesia flow rates

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KEYWORDS
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Abstract
Objective: This study investigated interleukin-10 and nitric oxide plasma levels following surgery to determine whether there is a correlation between these two variables and if different desflurane anesthesia flow rates influence nitric oxide and interleukin-10 concentrations in circulation.
Materials and methods: Forty patients between 18 and 70 years and ASA I–II physical status who were scheduled to undergo thyroidectomy were enrolled in the study.
Interventions: Patients were allocated into two groups to receive two different desflurane anesthesia flow rates: high flow (Group HF) and low flow (Group LF).
Measurements: Blood samples were drawn at the beginning (t_0) and end (t_1) of the operation and after 24 h (t_2). Plasma interleukin-10 and nitric oxide levels were measured using an enzyme-linked-immunosorbent assay and a Griess reagents kit, respectively. Hemodynamic and respiratory parameters were assessed.
Results: There was no statistically significant difference between the two groups with regard to interleukin-10 levels at the times of measurement. Interleukin-10 levels were increased equally in both groups at times t_1 and t_2 compared with preoperative concentrations. For both groups, nitric oxide circulating concentrations were significantly reduced at times t_1 and t_2 compared with preoperative concentrations. However, the nitric oxide value was lower for Group HF compared to Group LF at t_2. No correlation was found between the IL-10 and nitric oxide levels.
Conclusion: Clinical usage of two different flow anesthesia forms with desflurane may increase interleukin-10 levels both in Group HF and Group LF; nitric oxide levels circulating concentrations were significantly reduced at times t_1 and t_2 compared with preoperative concentrations; however, at 24 h postoperatively they were higher in Group LF compared to Group HF. No correlation was detected between interleukin-10 and nitric oxide levels.

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PALAVRAS-CHAVE
Anestesia geral;
Interleucina;
Cirurgia;
Óxido nítrico;
Desflurano

Níveis plasmáticos de interleucina-10 e óxido nítrico em resposta a duas taxas de fluxo em anestesia com desflurano

Resumo
Objetivo: este estudo investigou os níveis plasmáticos de interleucina-10 e óxido nítrico após cirurgia para determinar se há correlação entre essas duas variáveis e se diferentes taxas de fluxo de anestesia com desflurano influenciam as concentrações de interleucina-10 e óxido nítrico na circulação.
Materiais e métodos: quarenta pacientes, entre 18 e 70 anos de idade, estado físico ASA I–II, programados para tireoidectomia foram incluídos no estudo.
Intervenções: os pacientes foram divididos em dois grupos para receber dois fluxos diferentes de anestesia com desflurano: fluxo alto (Grupo FA) e fluxo baixo (Grupo FB).
Mensurações: amostras de sangue foram colhidas no início (t_0) e final (t_1) da cirurgia e após 24 h (t_2). Os níveis plasmáticos de interleucina-10 e óxido nítrico foram medidos usando um ensaio imunossorvente ligado à enzima um estojo de reagentes de Griess, respectivamente. Os parâmetros hemodinâmicos e respiratórios foram avaliados.
Resultados: não houve diferença estatisticamente significante entre os dois grupos em relação aos níveis de interleucina-10 níveis nos tempos de medição. Os níveis de interleucina-10 aumentaram igualmente em ambos os grupos nos tempos t_1 e t_2 em comparação com as concentrações no pré-operatório. Em ambos os grupos, as concentrações circulantes de óxido nítrico estavam significativamente reduzidas nos tempos t_1 e t_2 em comparação com as concentrações no pré-operatório. No entanto, o valor de óxido nítrico foi menor no Grupo FA que no Grupo FB no t_2. Não houve correlação entre os níveis de IL-10 e óxido nítrico.
Conclusão: o uso clínico de dois fluxos diferentes em anestesia com desflurano pode aumentar os níveis de interleucina-10 tanto no Grupo FA quanto no Grupo FB; os níveis das concentrações circulantes de óxido nítrico estavam significativamente reduzidos nos tempos t_1 e t_2 em cmparação com as concentrações no pré-operatório; contudo, 24 h após a cirurgia, esses níveis estavam maiores no Grupo FB em relação ao Grupo FA. Não foi detectada correlação entre os níveis de interleucina-10 e óxido nítrico.

Introduction

Immune response against surgery is known to be beneficial for defense mechanisms of the body, wound healing, and prevention of antibody formation against tissues.[1,2] Cytokines play a remarkable role in controlling and modulating the reactions of the organism against foreign antibodies and agents as well as in local and systemic inflammatory responses by regulating the intercellular interactions. Majority of the cytokines secreted from the immune system are interleukins and their main function is to stimulate the immune system cells.[3] There is a constant balance between the proinflammatory and anti-inflammatory cytokines. By *in vivo* and *in vitro* studies, anesthetic agents and techniques have been shown to have an influence over cytokine production.[4,5] However, there is no adequate number of studies focusing on the influence of desflurane over cytokine release.[6] Interleukin-10 (IL-10), known as the cytokine synthesis inhibitory factor, is one of the most potent immunosuppressive agents. During the surgical and anesthetic trauma, IL-10 and NO productions have been reported to change.[7] It is believed that IL-10 may also be an important factor in regulation of NO mechanism.[8]

NO is produced in the vascular endothelium from L-arginine as a response to physical and receptor stimulation, by nitric oxide synthase (NOS) which is known to be a calcium/calmodulin-dependent enzyme.[9] NO is a radical compound due to having a single unmatched electron in its outer shell. It is not toxic in low concentrations. While NO plays an important role in the management of cardiovascular function, neurotransmission, and blood pressure,[10] it also bears importance with regard to immune system.[11] Volatile agents have been reported to inhibit endothelial and neuronal NOS by way of inhibiting intracellular calcium mobilization.[11]

Low flow anesthesia is a technique that is gaining in popularity because it consumes less anesthetic gas, has a low cost, and reduces environmental pollution. To the best of our knowledge, there is no study focusing on the relationship between low flow anesthesia and cytokine release.

The objective of this study was to investigate plasma concentrations of NO and IL-10 in the perioperative period and evaluate whether different desflurane anesthesia flow rates could influence systemic NO and IL-10 responses. Furthermore, we explored the possibility of a correlation between circulating NO and IL-10 concentrations.

Materials and methods

Forty euthyroid patients of ASA I–II physical status, who were scheduled for thyroidectomy, were included in the study following approval by our Institutional ethics

Table 1 Patient characteristics, surgery duration, and anesthesia flow type.

	Group HF ($n=20$)	Group LF ($n=20$)	p
Age (years)	43.25 ± 14.54	44.65 ± 11.17	0.735
Height (cm)	167 ± 12	168 ± 15	0.200
Weight (kg)	63.95 ± 12.31	69.25 ± 10.91	0.158
Gender (F/M)	15/5	14/6	0.500
ASA I/II	15/5	13/7	0.366
Length of anesthesia (min)	128.15 + 21.23	114.25 + 28.34	0.087
Length of operation (min)	114.65 ± 21.43	99.25 ± 28.34	0.060

Data are expressed as mean ± SD or number of patients.

committee and acquisition of informed consent from patients. Criteria for exclusion were: age <25 or >75 years, pregnancy, renal and liver insufficiency, oncologic disease, infection, including HIV infection, immunological dysfunction and treatment with nitro-derivate compounds or immunosuppressive drugs. Patients were allocated randomly into two groups using the sealed envelope technique.

Patients who received no premedication were taken to the operating room and monitored for heart rate, noninvasive arterial blood pressure, and oxygen saturation (Julian Plus, Drager, Lübeck, Germany). An intravenous line was opened with an 18 F catheter in the back of the hand and anesthesia induction was performed.

Anesthesia induction was conducted with 1–2 μg/kg fentanyl (Fentanyl, Janssen-Cilag, Belgium) and 2–3 mg/kg propofol (Pofol, Dongkook, Pharm. Co. Ltd., Korea) until the eyelash reflex disappeared. Muscle relaxation was achieved with 0.1 mg/kg vecuronium bromide (Norcuron, Organon, Oss, Holland).

Group HF ($n=20$) received 6–8% desflurane (Suprane, Baxter, USA) in a mixture of 2 L/min O_2 + 2 L/min air intraoperatively, whereas Group LF ($n=20$) received a mixture of 1.4 L/min O_2 + 3.0 L/min air for 10 min followed by a reduction to 0.5 L/min O_2 + 0.5 L/min air in the fresh gas flow, while 6–8% desflurane was delivered throughout the entire operation independently of flow rate. Patients in both groups were properly extubated. The concentrations of propofol used for the induction, and fentanyl used for induction and maintenance, were noted.

Heart rate, blood pressure (mmHg), oxygen saturation (%), inhaled oxygen concentration (%) (FiO_2), inhaled desflurane concentration (%) (FiDes), end tidal desflurane rate (%), minimal alveolar concentration (MAC), and end-tidal CO_2 (%) (et CO_2) values were monitored and noted at 5, 10, 15, 20, 30, 45, 60, 75, and 90 min intraoperatively, and after extubation.

Patients' temperature was kept approximately 36 °C and operation room temperature were approximately 25 °C. Patients in both groups received 75 mg diclofenac sodium intramuscularly for postoperative pain management and 4 mg ondansetron intravenously for nausea and vomiting prophylaxis 30 min prior to the end of the operation.

The blood specimens were centrifuged at 1500 × g for at least 10 min and the serum samples transferred to Eppendorf tubes for storage at −80 °C until measurement of IL-10 and NO. Serum IL-10 levels were measured using a solid phase sandwich ELISA (Human IL-10 Immunoassay Kit; Biosource International Inc., Camarillo, CA, USA). The calibration curve was prepared with IL-10 standards of 1, 7.8, 15.6, 31.25, 62.5, 125, 250, 500 pg/mL. The results are given as pg/mL. Nitrite/nitrate levels were measured as described by Tsuei et al.[8] Nitrate was reduced to nitrite with vanadium (III) and nitrite levels measured using Griess reagents, which reflect the total amount of nitrate and nitrite in the sample. Serial dilutions of 0.5–250 μM sodium nitrate (Merck, Germany) were used as standards and the results were expressed as μmol/L.

Statistical analyses were conducted with SPSS 13 for Windows. The results were expressed as mean ± SD and number of patients. The statistical difference between IL-10 and NO levels, continuous variables acquired by measurement, drug consumption, and length of anesthesia and operation were analyzed with independent t-test, whereas count data concerning categorical variables were evaluated by chi-square test. Correlation between plasma NO and IL-10 changes at the different time points was performed using Bravais–Pearson's correlation coefficient. Statistical differences between the mean values of hemodynamic parameters, saturation, FiO_2, FiDes, expiratory desflurane concentration, and MAC were evaluated by dependent t-test. $p < 0.05$ was recognized as statistically significant in all the analyses.

Results

The patient characteristics of the two groups, as well as anesthesia and surgery duration are summarized in Table 1. There were no significant differences between the two groups. Propofol and fentanyl concentrations delivered in the Group HF 163.00 ± 25.77 mg, 123.75 ± 42.51 μg and Group LF 165.00 ± 29.46 mg, 151.25 ± 44.77 μg ($p = 0.821$, $p = 0.054$, respectively). There was no statistically significant difference between groups.

There was no statistically significant difference between heart rate, mean arterial blood pressure, oxygen saturation, inhaled oxygen concentration, and et CO_2 values ($p > 0.05$).

The high flow group (Group HF) demonstrated significantly higher FiDess (%) at intraoperative times of 5, 10, 20 min and significantly higher expiratory desflurane concentrations (%) (Fig. 1). MAC values were higher at all measurement times except 30 min in the high flow group ($p > 0.05$).

Plasma IL-10 concentrations showed significant elevation at t_1 and t_2 compared with baseline values. No significant difference with respect to mean IL-10 values was

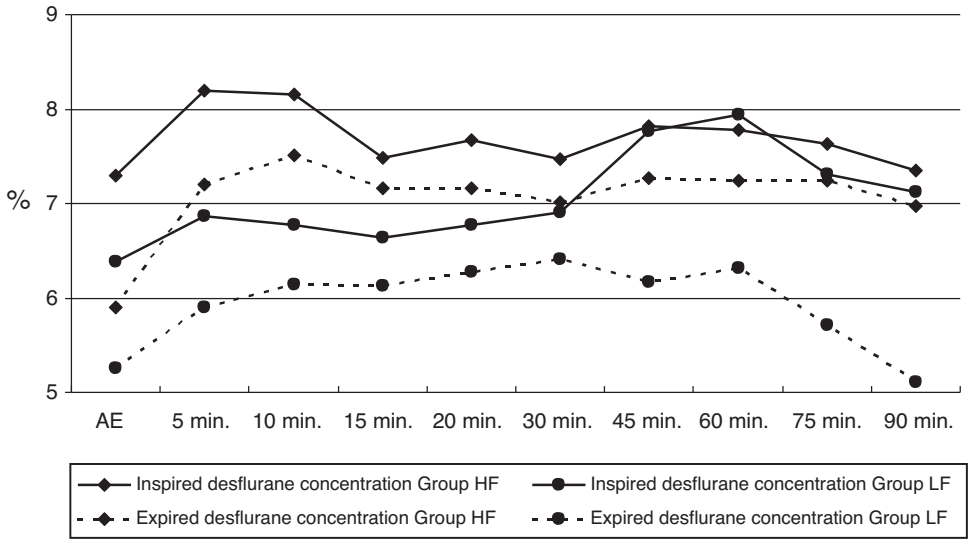


Figure 1 Inspired and expired desflurane concentration in the groups (AE, after intubation; Group HF, high flow desflurane anesthesia; Group LF, low flow anesthesia).

observed between the two groups throughout the study time (Fig. 2).

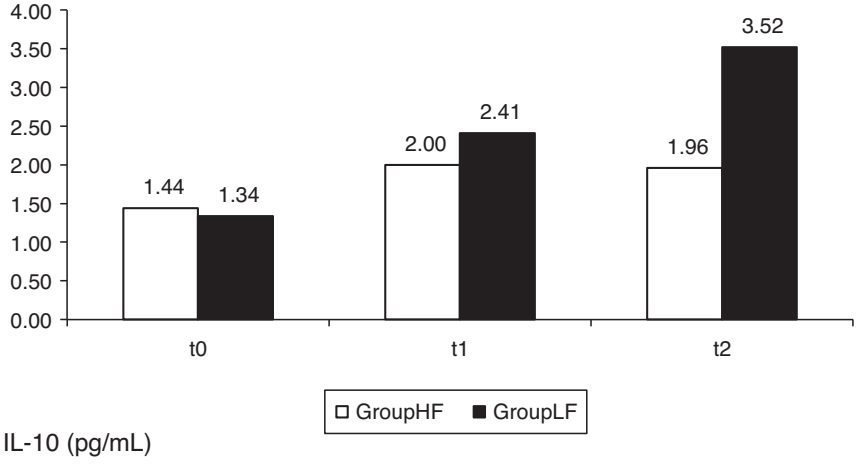
NO circulating concentrations were significantly reduced at times t_1 and t_2 compared with pre-operative time in both groups. Furthermore, there was a significant difference between Groups HF and LF with respect to mean NO values recorded at the t_2 time point (Fig. 3). The NO value was lower in Group HF compared to Group LF at t_2.

Finally, we found that there was no correlation between the decrease of circulating NO at t_1 and t_2 and the elevation in plasma IL-10 concentrations.

Discussion

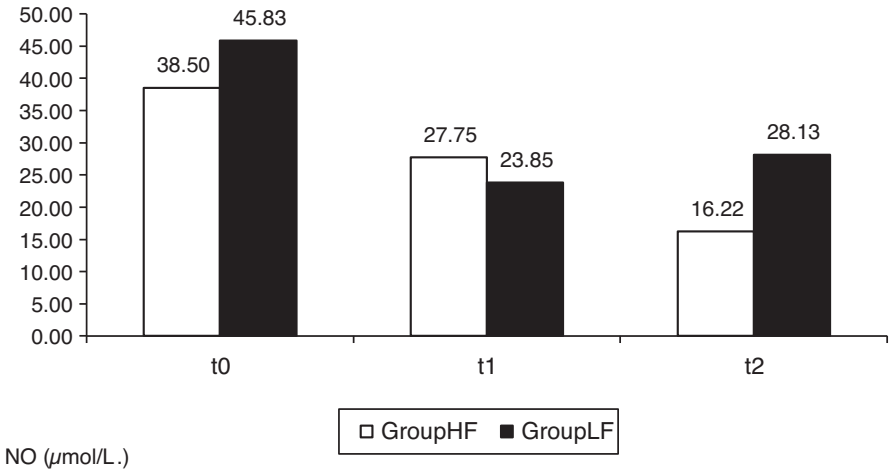
We demonstrate that in patients undergoing surgery with general anesthesia, clinical usage of two different flow anesthesia forms with desflurane may increase IL-10 levels both in Group HF and Group LF, NO levels circulating concentrations were significantly reduced at times t_1 and t_2 compared with preoperative concentrations; however, at 24 h postoperatively they were higher in Group LF compared to Group HF. No correlation was detected between IL-10 and NO levels. We also found that the high flow group demonstrated a significantly higher FiDes at intraoperative times of 5, 10, 20 min, as well as significantly higher expiratory desflurane concentrations and MAC values at all measurement times.

Surgical trauma and anesthesia are known to affect many functions of the immune system through various fashions.[12] Although majority of studies show that immune depression observed during the postoperative period may be primarily stemming from surgery-related stress, some *in vitro* studies demonstrate that anesthetic agents also have a role in this



Group HF; High flow desflurane anesthesia, Group LF; Low flow anesthesia.

Figure 2 Interleukin-10 levels relative to measurement time.



Group HF; High flow desflurane anesthesia, Group LF; Low flow anesthesia.

Figure 3 Nitric oxide levels relative to measurement time.

depression. Therefore, the number of studies focusing on the relationship between anesthesia and immune system has increased.

Volatile anesthetics have been reported to suppress cytokine release from mononuclear cells, reduce lymphocyte proliferation, lead to lymphocyte apoptosis, and inhibit neutrophil functions in a dose-dependent way.[12–15] Moreover, they have been shown to cause proinflammatory gene expression in the alveolar macrophages.[16] However, studies focusing on the influences of volatile anesthetics over cytokine production report differing results.[17–20]

Desflurane may increase proinflammatory cytokine expression in the alveolar macrophages.[21,22] Desflurane has been noted to produce more proinflammatory response compared with the sevoflurane.[23] Moreover, desflurane is known to have no effect over IL-6 release in endotoxemic rats and it is reported to cause considerable decreases in the levels of other proinflammatory cytokines such as TNF-α and IL-10.

While researching the effects of anesthesia over the immune system, responses against different anesthesia techniques have been studied as well.[24,25] Although the definitive mechanism concerning the influence of anesthetics over cytokine production is not understood, calcium is known to play an important role in cytokine regulation.[26]

To the best of our knowledge, there is no study focusing on the relationship between low flow anesthesia and cytokine release, particularly concerning low flow desflurane and cytokine release. In the current study, we investigated the effects of desflurane, delivered at two different flow rates, over IL-10 and NO levels.

High flow desflurane was found to increase IL-10 level at the end of the operation and this increase was shown to be continuing with a mild drop during the postoperative period. Low rate desflurane was observed to elevate the IL-10 level at the end of the operation as well and this elevation was shown to continue during the postoperative period. While there was no statistically significant difference between the two groups with regard to the increases, the elevation in the low flow desflurane group was higher. Increases in IL-10 level may be influenced by many factors such as surgical stress, anesthetic drugs, blood loss, and stress hormones.[27,28]

While there are studies indicating that desflurane causes a higher increase in proinflammatory cytokines, in the current study, desflurane elevated anti-inflammatory cytokine levels in both of the groups and contributed to the proinflammatory/anti-inflammatory balance in a positive way. This influence occurs to be more remarkable in the low rate anesthesia group which may be secondary to generation of more physiological conditions in the respiratory tract by low flow anesthesia. Nonetheless, further studies focusing on the influence of desflurane over anti-inflammatory cytokines, and particularly those concerning the effects of low flow anesthesia over cytokine release, are required.

Changes observed in the IL-10 and NO concentrations during anesthesia and surgical trauma raise the question whether IL-10 has any influence over NO metabolism or not. In the study of Ochoa et al., elevated IL-10 was found to have an important role in NO production following trauma, which was associated with the arginase activity.[26] While a relationship between IL-10 and NOS in septic animal models under surgical stress was shown by one study,[27] no correlation could be found between IL-10 and NO by another study.[7]

While basal NO is required for many normal functions of the body, NO released upon stimulation may lead to various damages. TNF-α, IL-4, IL-10, and macrophage differentiation inducing factor inhibit inducible NOS.[29] In face of trauma, NO synthesis is reduced because of increases in the extrahepatic arginase I activation. Reduced NO levels allow maintenance of blood flow in the organs following trauma.[27] During the postoperative period, reduced NO levels in the circulation may be secondary to various factors. Fujioka et al. proposed that hypoperfusion could lead to defects in NO production and they found lower postoperative serum nitrite and nitrate values in patients who received major surgery.[30]

Synthesis of NO from macrophages is the first response against bacteria. Lipopolysaccharide (LPS) administration

has been shown to promote NO production in the animal trials.[31] In a similar study, following induction of sepsis, urinary nitrate concentration was increased and plasma arginine level was decreased.[32] NO is synthesized from L-arginine by NOS. The most important function of NO produced by iNOS is to induce a cytotoxic effect over the tumor cells. In addition to its antimicrobial influence, NO also plays a role in the cytokine production, apoptosis, and signal transduction.[33]

NO is an important molecule that also takes part in the anesthetic process and contributes to mechanisms of action concerning certain anesthetic agents. While NO plays a part in excitatory synaptic transmission *via* glutamate, inhibition of excitatory transmission may suppress NO production or influence.[34]

Johns et al. showed that beforehand delivery of NO-synthase inhibitors reduced MAC value of halothane.[27] Halothane, isoflurane, and sevoflurane have been shown to inhibit endothelial NOS[35] along with NMDA-mediated neurotransmission and neuronal NOS in rats.[36,37] NO plays a significant part in the regulation of vascular tonus. Halothane, isoflurane, enflurane, and sevoflurane have been shown to reduce the level of endothelium-dependent relaxants.[38,39] In the study of Blaise, halothane was found to slowly, but remarkably suppress the relaxation induced by exogenous NO.[40] Halothane has been shown to attenuate the hemodynamic changes caused by NOS inhibitor, whereas isoflurane has been shown to have a lower effect in this aspect compared with the halothane.[41] Wei et al. reported that isoflurane prevented changes in the arterial blood pressure and cerebral vascular resistance induced by NOS inhibitors.[42]

Tschaikovsky et al. reported that halothane, enflurane, isoflurane, sevoflurane, and desflurane reduced nitrite production in a doze and time dependent fashion,[11] and observed a higher amount of nitrite production due to combined usage of LPS + TNF-α compared with the sole usage. Boost et al. showed that desflurane increased NO release from alveolar macrophages.[6]

In this study, NO showed a decrease at the end of the operation among the low flow group which was still present at 24 h postoperatively, whereas NO exhibited a reduction at the end of the operation but started to rise again at 24 h postoperatively.

Present study results suggest that desflurane, similar to other volatile anesthetics, reduces NO release. This conclusion was not consistent with the study of Boost et al. which has shown that desflurane increased NO release.[6] This inconsistency may be arising from the difference between the times of measurement, because in our study, NO level at 24 h postoperatively approached the basal value in the low flow group.

Delogu et al. conducted a study with propofol–fentanyl and sevoflurane in which they found an increase in IL-10 level and a decrease in NO level postoperatively; no correlation was reported between the changes.[7] In the present investigation we were unable to demonstrate any relationship between circulating IL-10 and NO in both groups tested.

In conclusion, in this study desflurane by itself increased the plasma level of IL-10 in patients. However, the rate of desflurane flow did not change the IL-10 level. Desflurane by itself decreased NO levels in patients. Moreover, the rate of desflurane flow changed NO levels. In addition, no relationship linked the increase in circulating IL-10 with altered NO production. Those results suggest that iNOS is influenced by factors other than IL-10 as well.

Conflicts of interest

The author declares no conflicts of interest.

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