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Effects of propofol and dexmedetomidine with and without remifentanil on serum cytokine concentrations in healthy volunteers: a *post hoc* analysis

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Abstract

Background: Anaesthetic agents are likely to alter circulating cytokine concentrations. Because preceding studies have not been able to exclude the contribution of surgical trauma, perioperative stress, or both to circulating cytokine concentrations, the effects of anaesthesia remain unclear. The aim of this study was to quantify serum cytokines in healthy volunteers administered i.v. anaesthetic agents in the absence of surgical trauma and perioperative stress.

Methods: Serum samples obtained during previous standardised studies from healthy volunteers were compared before and 6–8 h after induction of anaesthesia with propofol (n=31), propofol/remifentanil (n=30), dexmedetomidine (n=17) or dexmedetomidine/remifentanil (n=15). Anaesthetic regimens were standardised and volunteers did not undergo any surgical intervention. Serum concentrations of interleukin (IL)2, IL4, IL6, IL10, IL17, IL18, IL21, IL22, IL23, C-X-C motif ligand 8, interferon gamma, E-selectin, L-selectin, major histocompatibility complex class I chain-polypeptide-related sequence (MIC)A, MICB, Granzyme A, and Granzyme B were quantified using a multiplexed antibody-based assay (Luminex).

Results: Samples were obtained from volunteers of either sex aged 18–70 yr. After anaesthesia with propofol alone, concentrations of IL4 (P=0.012), IL6 (P=0.027), IL21 (P=0.035), IL22 (P=0.002), C-X-C motif ligand 8 (P=0.004), MICB (P=0.046), and Granzyme A (P=0.045) increased. After anaesthesia with propofol and remifentanil, IL17 (P=0.013), interferon gamma (P=0.003), and MICA (P=0.001) decreased, but IL6 (P=0.006) and L-selectin (P=0.001) increased. After dexmedetomidine alone, IL18 (P=0.002), L-selectin (P=0.017), E-selectin (P=0.002), and Granzyme B (P=0.023) decreased. After dexmedetomidine with remifentanil no changes were observed.

Conclusions: In healthy volunteers not undergoing surgery, different i.v. anaesthesia regimens were associated with differential effects on circulating cytokines.

Keywords: cytokines; dexmedetomidine; immune response; oncology; propofol; remifentanil

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Editor's key points

- The impact of anaesthetic agents on systemic inflammation remains unclear, chiefly because samples have not been obtained from individuals receiving anaesthesia alone.
- The authors used stored samples obtained during pharmacokinetic studies of different i.v. anaesthesia agents in healthy volunteers of either sex to examine the impact of propofol or dexmedetomidine in the presence/absence of remifentanil on circulating cytokine concentrations.
- Although different individuals were recruited in these studies, this exploratory *post hoc* analysis suggests differences between i.v. anaesthesia agents on circulating cytokines.
- Amongst several limitations, no functional immune cell studies were conducted using flow cytometry.
- These data suggest that systemic inflammation after surgery is altered by anaesthetic agents directly.

During cancer surgery, the immune and inflammatory response will be altered by several factors.[12] Anaesthetics are known to influence the immune response and may have either a direct effect on circulating immune cells or an indirect effect by influencing the neuroendocrine pathway.[1] The activity and total amount of natural killer (NK) cells are, together with cytotoxic T cells, pivotal in tumour immunosurveillance.[3]

Propofol is considered to have immunological properties that might be favourable during cancer surgery.[4–9] This hypothesis is based on promotion of NK cell cytotoxicity, inhibition of cyclooxygenase, and reduction of hypoxia-inducible factor-1α.[1] Immunological effects of dexmedetomidine during cancer surgery have also been posited,[10,11] perhaps mediated by its sympatholytic, sedative, and analgesic properties. However, opiates may confer unfavourable effects on circulating cytokines during cancer surgery through the suppression of NK cell cytotoxicity and vascular endothelial growth factor-dependent angiogenesis.[2] However, putative effects of different anaesthetic regimens remain difficult to determine because of the confounding impact of surgical trauma and oncological disease.

To address this problem, here we analysed serum samples obtained from a cohort of healthy volunteers who received i.v. anaesthesia in the absence of surgery. Different anaesthetic regimens were administered in clinically relevant concentrations to examine the intrinsic effects of propofol and dexmedetomidine with and without remifentanil on circulating cytokine concentrations that might be relevant during oncological surgery.[12–14]

Methods

Study design

This report is an exploratory *post hoc* analysis of serum samples obtained during previously reported studies. A total of 93 volunteers were included in this serum analysis of previously published trials; 31 volunteers received propofol (study I), 30 volunteers received propofol and remifentanil (study II), 17 volunteers received dexmedetomidine (study III), and 15 volunteers received dexmedetomidine and remifentanil (study IV).[12–14] These volunteers were selected from three different trials with approval from the local Medical Ethics Review Committee (METC, University Medical Center Groningen, Groningen, the Netherlands; METC numbers: study I: NL43238.042.13, study II: NL43238.042.13, study III: 2012/400, study IV: NL61190.056.17), and registered in the ClinicalTrials.gov database (study I: NCT02043938, study II: NCT02043938, study III: NCT01879865, study IV: NCT03143972). Written informed consent was obtained before inclusion.

Study I and II—propofol with/without remifentanil

The methodology of this study has been published elsewhere.[13] Volunteers were stratified according to age, sex, and administration of remifentanil. Exclusion criteria were weight <70% or >130% of ideal body weight, pregnancy, neurological disorders, diseases involving the cardiovascular, pulmonary, gastric, or endocrinological system, recent use of psychoactive medication, or intake of >20 g of alcohol daily. Volunteers underwent four at random sessions with either propofol alone, propofol with remifentanil (2.0 ng ml^{-1} [N=9] or 4.0 ng ml^{-1}) or sevoflurane alone and sevoflurane with remifentanil. There was a minimal interval of 1 week between each session. Five volunteers were excluded from study I and six from study II because of insufficient blood collection for further analyses.

Titration of propofol was done through a step-up and followed by a step-down infusion. For propofol and remifentanil, the effect-site concentration was predicted by the pharmacokinetic–pharmacodynamic model of Schnider and Minto, respectively.[15,16] The starting dose of propofol was set to 0.5 μg ml^{-1}, followed by consecutive steps toward predicted target concentrations of 1, 1.5, 2.5, 3.5, 4.5, 6, and 7.5 μg ml^{-1}. Downward staircase steps were initiated using identical targets but in reverse order. For volunteers who received propofol and remifentanil, identical procedures were applied, albeit that 2 min before propofol was started, a 2 or 4 ng ml^{-1} was targeted and maintained throughout the study.

During sessions with propofol (with or without remifentanil) the last blood sample was obtained between 6 and 8 h after induction with propofol. During sessions with sevoflurane (with or without remifentanil) the last blood sample was obtained 45 min after induction with sevoflurane. As we consider this time interval quite short for an immunological response, but above all to compare comparable time intervals with other anaesthetics in this study, we excluded the sevoflurane data from our final results.

Study III—dexmedetomidine

The methodology of this study has been published elsewhere.[12] One volunteer was excluded because of missing data. Exclusion criteria were known intolerance to dexmedetomidine and BMI less than 18 kg/m^2 or greater than 30 kg/m^2. Women who were pregnant or nursing were also excluded. One volunteer was excluded because of insufficient blood collection for further analyses. An initial short infusion of dexmedetomidine, given at 6 μg kg^{-1} h^{-1} for 20 s, was followed by a 10 min recovery period. Thereafter, dexmedetomidine was delivered as a target-controlled infusion using the Dyck model with stepwise increasing targets of 1, 2, 3, 4, 6, and 8 ng ml^{-1}. Each target was maintained for 30 min. The maximal infusion rate was limited to 6 μg kg^{-1} h^{-1} for the first four steps; for the target of 6 and 8 ng ml^{-1}, the maximal infusion rate was increased to 10 μg kg^{-1} h^{-1}. Bispectral index was targeted between 60 and 40. Blood samples were obtained before the first infusion of dexmedetomidine and after 5 h.

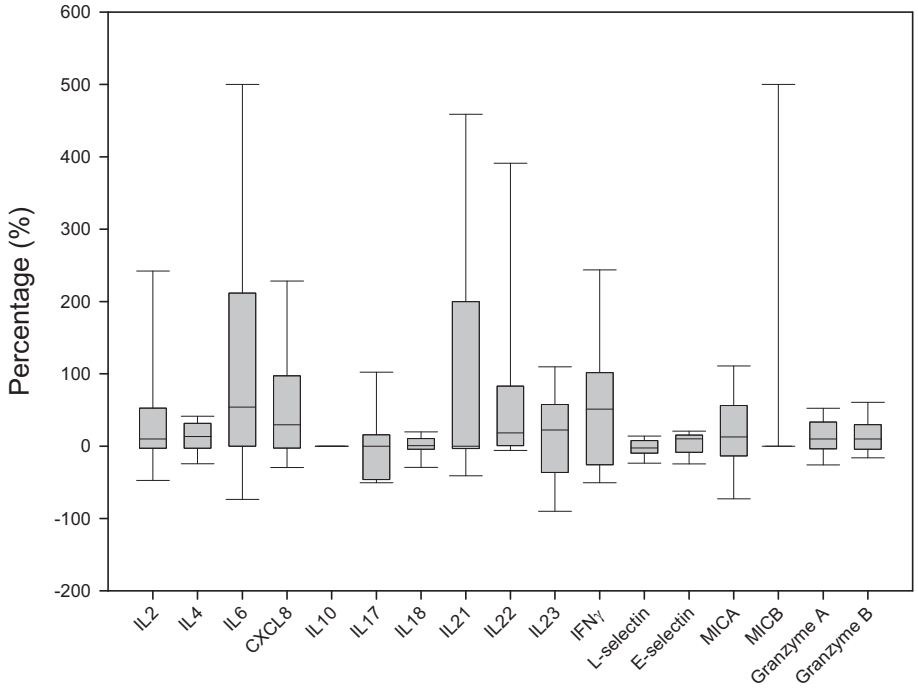

Fig 1. Study I. Propofol alone. Differences in percentages after administration of propofol alone (N=31) (T0 *vs* T1) for each measurement. The horizontal line in the boxplot indicates the median. Distribution of cytokine concentrations after propofol alone resulted in pro-inflammatory and anti-inflammatory responses with large variations between healthy volunteers. CXCL8, C-X-C motif ligand 8; IFNγ, interferon gamma; IL, interleukin; MIC, major histocompatibility complex class I chain-polypeptide-related sequence.

Study IV—dexmedetomidine and remifentanil

The methodology of this study has been published elsewhere.[14] Exclusion criteria were BMI less than 18 kg/m^2 or greater than 30 kg/m^2 weight, pregnancy (or current breast-feeding), neurological disorder, diseases involving the cardiovascular, pulmonary, gastric, or endocrinological system, recent use of psychoactive medication, or intake of >20 g of alcohol daily. In order to have comparable groups between study III and study IV, 15 volunteers from study IV were matched based on age and gender from a total of 30 volunteers. Blood samples were obtained before the first infusion of dexmedetomidine and after 5 h. Infusion of remifentanil is started at 0.5 ng ml^{-1}, remifentanil infusion will increase every 15 min to target respectively: 1.0, 1.5, 2.0, 2.5, 3.0, 4.0 ng ml^{-1}. Background infusion of dexmedetomidine was estimated between 2.0 and 3.0 ng ml^{-1} to achieve tolerance to laryngoscopy in about 50% of volunteers.

Measurements of serum cytokines and chemokines

Plasma concentrations of interleukin (IL)2, IL4, IL6, IL10, IL17, IL18, IL21, IL22, IL23, C-X-C motif ligand 8 (CXCL8), interferon gamma (IFNγ), Granzyme A, Granzyme B, E-selectin, L-selectin, major histocompatibility complex class I chain-polypeptide-related sequence (MIC)A, and MICB (see for details Supplementary Table S1 and Figure S1) were measured using commercially available Luminex kits (Human Magnetic Luminex assay, LXSAHM, Bio-Techne, Abingdon, UK) according to the manufacturer's instructions. Analysers were masked during analyses. Lower limit of detection (LOD) were, respectively, for IL2: 29.63 pg ml^{-1}, IL4: 14.61 pg ml^{-1}, IL6: 4.73 pg ml^{-1}, IL10: 4.77 pg ml^{-1}, IL17: 12.80 pg ml^{-1}, IL18: 10.12 pg ml^{-1}, IL21: 32.92 pg ml^{-1}, IL22: 13.00 pg ml^{-1}, IL23: 133.33 pg ml^{-1}, CXCL8: 5.19 pg ml^{-1}, IFNγ: 58.48 pg ml^{-1}, Granzyme A: 21.11 pg ml^{-1}, Granzyme B: 17.7 pg ml^{-1}, E-selectin: 344.44 pg ml^{-1}, L-selectin: 1921.48 pg ml^{-1}, MICA: 68.40 pg ml^{-1}, and MICB: 108.19 pg ml^{-1}.

Statistics

Results are presented as means with standard deviation. Differences in percentage (T0 *vs* T1) are presented as medians with inter-quartile range (IQR) for each measurement and are also displayed in figures. The first measurement (T0) was statistically considered as the preliminary measurement. To determine the effect of different anaesthetics on cytokine concentrations, changes were analysed with a paired sample *t*-test (normal distribution) or Wilcoxon rank test (skewed distribution). If measurements were below the LOD, the LOD of the respective cytokine was used and if more than one-third of the outcomes were under the LOD, the exact percentage was given in the results section. The Th1/Th2 ratio, as measured by IFNγ (Th1 response) and IL4 (Th2 response) was calculated for each regimen. No formal power calculation was carried out. For statistical analyses we used the Statistical Package for Social Sciences: SPSS version 20.0.0 (SPSS Inc., Chicago, IL, USA).

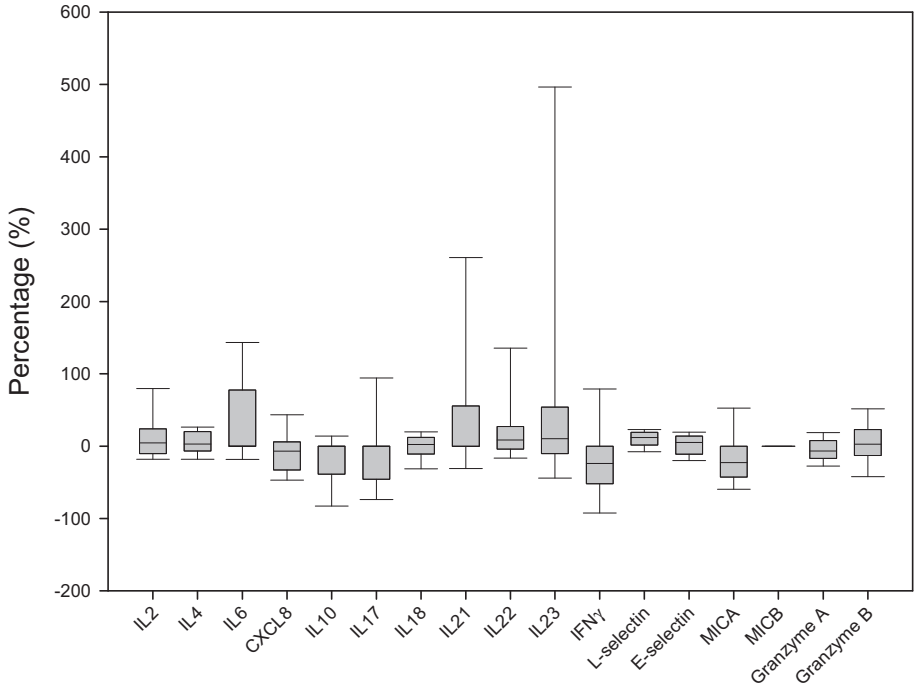

Fig 2. Study II. Propofol and remifentanil. Differences in percentages after administration of propofol with remifentanil (N=30) (T0 *vs* T1) for each measurement. The horizontal line in the boxplot indicates the median. Variations between cytokine concentrations were less pronounced compared with propofol alone. Instead of primary elevated concentrations, the addition of remifentanil also caused decreasing cytokine concentrations. CXCL8, C-X-C motif ligand 8; IFNγ, interferon gamma; IL, interleukin; MIC, major histocompatibility complex class I chain-polypeptide-related sequence.

Results

Study I: propofol alone

A total of 31 (15 male/16 female) volunteers received propofol alone according to a step upward technique until a target concentration of 7.5 μg ml^{-1} was reached (age ranges: 18–35 yr [*n*=11], 35–50 yr [*n*=7], 50–70 yr [*n*=13]). The median duration of propofol infusion was 231 min (IQR: 126–284). Measurements of IL10, IL17, and MICB were less than the LOD. Cytokine concentrations increased after anaesthesia with propofol alone (Fig. 1). None of the Th1 cytokines (IFNγ, IL2) increased, in contrast to Th2 cytokines IL4 (*P*=0.012) and IL6 (*P*=0.027). For Th17 cytokines, IL21 (*P*=0.035) and IL22 (*P*=0.002) increased. CXCL8 (*P*=0.004), MICB (*P*=0.046), and Granzyme A (*P*=0.045) (cytotoxic response) also increased (Supplementary Table S1). The Th1/Th2 ratio remained unchanged (*P*=0.290).

Study II: propofol with remifentanil

A total of 30 (14 male/16 female) volunteers (age ranges: 18–35 yr [*n*=11], 35–50 yr [*n*=7], and 50–70 yr [*n*=12]) received propofol/remifentanil infusion for a median 209 min (IQR: 128–308). Measurements of IL6, CXCL8, IL10, IL17, IL21, INFγ, MICA, and MICB were less than the LOD. Cytokine concentrations after 6–8 h were lower than those measured from volunteers who received propofol alone (Fig. 2). In contrast to study I, serum concentrations of IFNγ (*P*=0.003), IL17 (*P*=0.013), and MICA (*P*=0.001) were lower. IL6 (*P*=0.006) and L-selectin (*P*=0.001) increased between T0 and T1 in study II (Table 1). The addition of remifentanil was associated with a lower Th1/Th2 ratio (T0 0.651 *vs* T1 0.43; *P*=0.001).

Study III: dexmedetomidine alone

A total of 17 (nine male/eight female) volunteers (age ranges: 18–34 yr [*n*=7]; 35–54 yr [*n*=6]; 55–72 yr [*n*=5]), received dexmedetomidine alone up to 8 ng ml^{-1} for a median duration of 220 min (IQR: 40–220). Measured concentrations of IL6, CXCL8, IL10, IL17, IL21, INFγ, MICA, and MICB were less than the LOD. Most other cytokines decreased after dexmedetomidine infusion (Fig. 3), compared with T0 (Table 2). The Th1/Th2 ratio remained unchanged after dexmedetomidine infusion (*P*=0.838).

Study IV: dexmedetomidine with remifentanil

In study IV, 15 (nine male/six female) volunteers (age ranges: 18–35 yr [*n*=6], 35–50 yr [*n*=6], 50–70 yr [*n*=3]) received an infusion of dexmedetomidine combined with remifentanil in concentrations up to 4.0 ng ml^{-1} for a median duration 180 min (IQR:48–225). Measurements of IL6, IL10, IL17, IL21, INFγ, and MICB were less than the LOD. In this study only INFγ (3.92%) and MICB (1.03%) were increased on T1 (not significant) (Fig. 4). There were no differences in serum cytokine concentrations between T0 and T1 (Table 2).

Table 1 Plasma concentrations of interleukin (IL)2, IL4, IL6, C-X-C motif ligand 8 (CXCL8), IL10, IL17, IL18, IL21, IL22, IL23, interferon gamma (IFNγ), L-selectin, E-selectin, major histocompatibility complex class I chain-polypeptide-related sequence (MIC)A, MICB, Granzyme A, and Granzyme B (median with IQR) on T0 and after anaesthesia with propofol (study I) and propofol/remifentanil (study II). IQR, inter-quartile range.

(pg ml^{-1})	Study I (propofol alone)			Study II (propofol with remifentanil)		
	T0 (IQR)	T1 (IQR)	P	T0 (IQR)	T1 (IQR)	P
IL2	97 (106)	103 (87)	0.142	129 (83)	131 (51)	0.336
IL4	96 (25)	100 (22)	0.012	105 (32)	116 (28)	0.882
IL6	2 (4)	4 (4)	0.027	5 (2)	5 (0)	0.006
CXCL8	7 (8)	9 (4)	0.004	7 (10)	5 (8)	0.848
IL10	5 (0)	5 (0)	0.317	5 (0)	5 (3)	0.059
IL17	13 (1)	13 (2)	0.434	13 (2)	13 (3)	0.013
IL18	197 (139)	185 (135)	0.991	210 (156)	200 (127)	0.894
IL21	27 (19)	33 (11)	0.035	33 (10)	33 (0)	0.108
IL22	30 (39)	40 (27)	0.002	57 (24)	58 (16)	0.082
IL23	411 (499)	523 (567)	0.092	469 (551)	497 (425)	0.284
IFNγ	58 (44)	63 (43)	0.141	61 (51)	56 (13)	0.003
L-selectin	329 686 (77 774)	333 489 (74 137)	0.341	333 623 (86 137)	367 713 (91 155)	0.001
E-selectin	18 120 (9173)	18 370 (8936)	0.594	21 947 (8875)	20 693 (12 897)	0.572
MICA	84 (63)	105 (91)	0.198	105 (85)	68 (36)	0.001
MICB	108 (0)	108 (0)	0.046	108 (0)	108 (0)	0.465
Granzyme A	97 (38)	106 (52)	0.045	107 (44)	106 (39)	0.116
Granzyme B	52 (25)	58 (21)	0.202	62 (24)	69 (22)	0.538

Discussion

The aim of this study was to examine the impact of propofol and dexmedetomidine with and without remifentanil on circulating cytokine concentrations in healthy volunteers in the absence of a surgical injury. Our data suggest that i.v. anaesthesia alone impacts on serum cytokine concentrations.

We observed that after anaesthesia with propofol alone, circulating cytokines were elevated. A Th2 response was indicated by increased concentrations of IL4 and IL6.

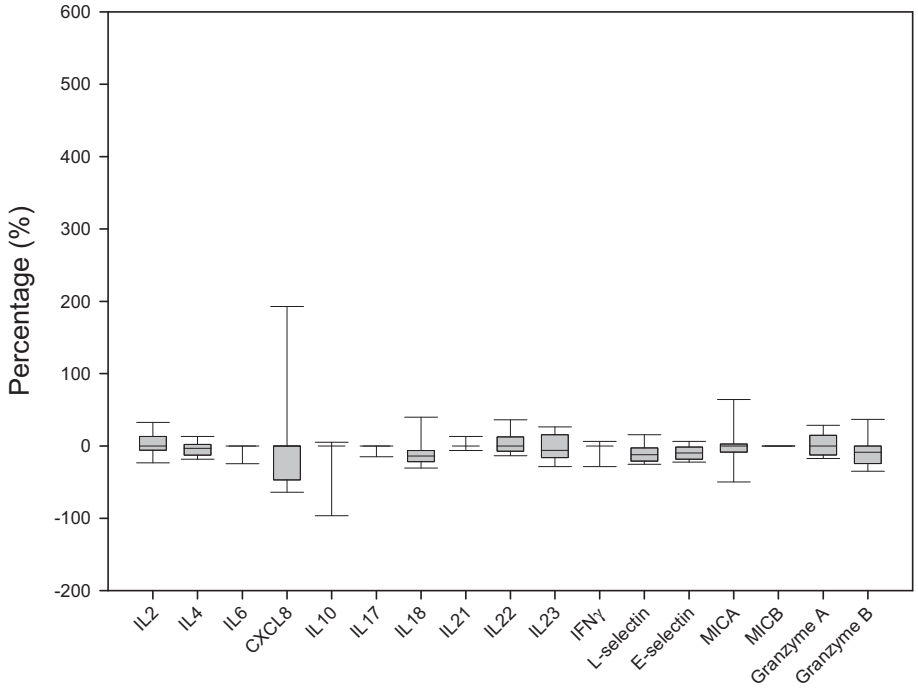

Fig 3. Study III. Dexmedetomidine alone. Differences in percentages after administration of dexmedetomidine (N=17) (T0 *vs* T1) for each measurement. The horizontal line in the boxplot indicates the median. Differences in percentages were much less pronounced compared with healthy volunteers who underwent anaesthesia with propofol alone. CXCL8, C-X-C motif ligand 8; IFNγ, interferon gamma; IL, interleukin; MIC, major histocompatibility complex class I chain-polypeptide-related sequence.

Table 2 Plasma concentrations of interleukin (IL)2, IL4, IL6, C-X-C motif ligand 8 (CXCL8), IL10, IL17, IL18, IL21, IL22, IL23, interferon gamma (IFNγ), L-selectin, E-selectin, major histocompatibility complex class I chain-polypeptide-related sequence (MIC)A, MICB, Granzyme A, and Granzyme B (median with IQR) on T0 and T1 after anaesthesia with dexmedetomidine (study III) and dexmedetomidine/remifentanil (study IV). IQR, inter-quartile range.

(pg ml^{-1})	Study III (dexmedetomidine alone)			Study IV (dexmedetomidine with remifentanil)		
	T0 (IQR)	T1 (IQR)	P	T0 (IQR)	T1 (IQR)	P
IL2	81 (102)	116 (103)	0.552	99 (87)	70 (71)	0.066
IL4	109 (33)	102 (13)	0.053	106 (48)	95 (43)	0.181
IL6	5 (0)	5 (0)	0.180	5 (3)	2 (4)	0.594
CXCL8	6 (6)	5 (4)	0.441	11 (9)	10 (10)	0.792
IL10	5 (0)	5 (0)	0.269	5 (2)	5 (3)	0.398
IL17	13 (0)	13 (0)	0.317	13 (0)	13 (4)	0.893
IL18	275 (194)	248 (155)	0.002	219 (57)	228 (108)	0.140
IL21	33 (0)	33 (0)	0.655	33 (18)	26 (16)	0.480
IL22	48 (11)	48 (12)	0.642	33 (30)	26 (20)	0.311
IL23	530 (314)	530 (265)	0.351	563 (182)	523 (244)	0.362
IFNγ	58 (0)	58 (0)	0.285	58 (5)	58 (8)	0.600
L-selectin	401304 (148394)	385 320 (110 610)	0.017	286 133 (115 186)	273 977 (46 304)	0.211
E-selectin	21 644 (6409)	18 127 (5050)	0.002	20 378 (6625)	19 363 (7804)	0.233
MICA	68 (14)	68 (0)	0.779	68 (43)	71 (33)	0.279
MICB	108 (0)	108 (0)	1.000	108 (0)	108 (0)	0.785
Granzyme A	92 (20)	92 (30)	0.846	116 (41)	125 (58)	0.374
Granzyme B	59 (32)	56 (34)	0.023	43 (45)	35 (19)	0.069

Furthermore, a Th17 response was observed by increased concentrations of IL21 and IL22, while a cytotoxic response was suggested by changes in Granzyme A. Although conducted in different volunteers, the addition of remifentanil to propofol appeared to reduce circulating concentrations of cytokines mediating the Th17 (IL17) and Th1 responses (IFNγ). By contrast, cytokines involved in the Th2 response (IL6) and L-selectin increased. Moreover, the Th1/Th2 ratio decreased and

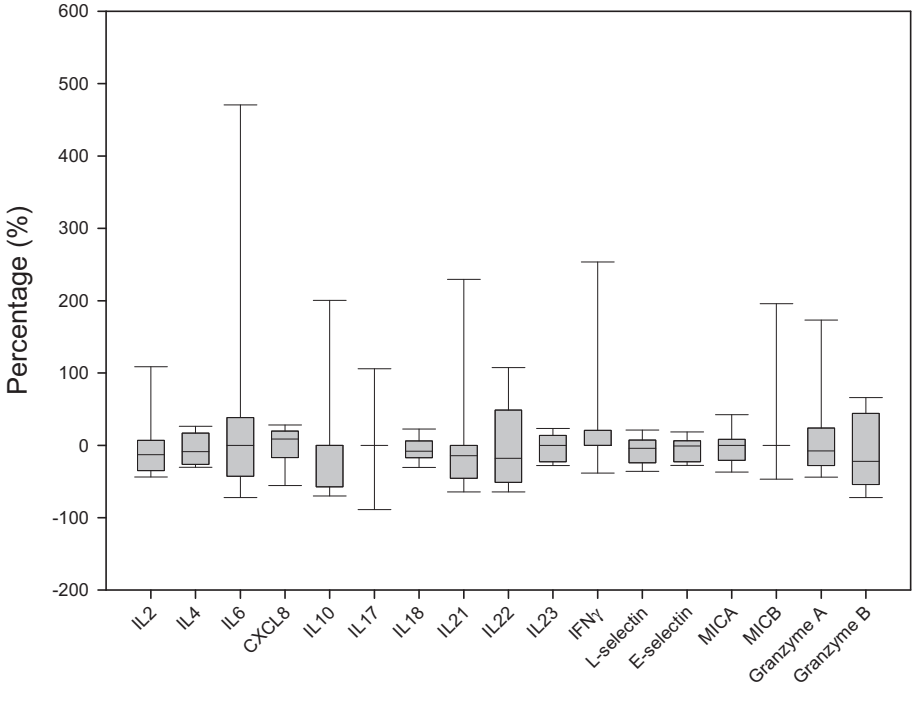

Fig 4. Study IV. Dexmedetomidine and remifentanil. Differences in percentages after administration of dexmedetomidine with remifentanil (N=16) (T0 *vs* T1) for each measurement. The horizontal line in the boxplot indicates the median. Although none of the measurements was significantly different, in comparison with dexmedetomidine alone there is more variation in cytokine concentrations with the addition of remifentanil. CXCL8, C-X-C motif ligand 8; IFNγ, interferon gamma; IL, interleukin; MIC, major histocompatibility complex class I chain-polypeptide-related sequence.

was characterised by low concentrations of IFNγ which can depress NK cell activity.[17] After dexmedetomidine alone, IL18, L-selectin, E-selectin, and the cytotoxic protease Granzyme B were decreased. After dexmedetomidine with remifentanil no changes were observed, although variations between cytokines were larger compared with dexmedetomidine alone.

We observed increased concentrations of IL21 and Granzyme A after propofol infusion. Granzyme is a cytotoxic protease that kills cells by apoptosis and is found in the granules of NK cells and cytotoxic T cells. Elevated concentrations of Granzyme B have been reported to be a prognostic marker for cancer free survival in colorectal patients.[18] IL21 is a crucial cytokine in the up-regulation of the Th1 response, which contributes via a shift towards cellular immunity in controlling the immune response of tumours.[19] In our study, we found a decreased Th1/Th2 ratio when propofol was combined with remifentanil, which was mainly determined by a reduced concentration of IFNγ.

Several studies have reported that dexmedetomidine reduces concentrations of pro-inflammatory cytokines (IL1, IL6, TNF-α, and IFNγ), and cortisol concentrations and perioperative opioid use.[20–22] In this study, administration of dexmedetomidine decreased concentrations of IL18, L-selectin, E-selectin, and Granzyme B. A reduced activation of the immune system also has less favourable consequences when it comes to NK cell activation. With a significant lower concentration of adhesion molecules (L and E-selectin), the recruitment of NK cells might also be reduced. The cytokine profile after addition of remifentanil to dexmedetomidine was in contrast to that observed after the addition of remifentanil to propofol. However, because we did not measure cytokine concentrations after remifentanil alone, we are not able to draw any conclusion about the effect of remifentanil.

A comparable study to ours also analysed the effect of propofol and dexmedetomidine in healthy volunteers on circulating cytokines.[23] They concluded that dexmedetomidine seemed to have immunosuppressive effects whereas propofol seemed to induce mixed pro- and anti-inflammatory effects. These conclusions are consistent with our findings, although the duration of infusion and timepoints for collection of the last blood sample differed. Moreover, our study also examined the addition of remifentanil to both anaesthetics, as would be done in daily practice. In a study that combined dexmedetomidine with propofol, the authors concluded that dexmedetomidine reduces the perioperative immunosuppression and favours the immune function in terms of improved proportions of NK cells and T lymphocytes.[10]

Our small retrospectively designed study has several important limitations. First, we used blood samples from two separate studies in which the different timepoints for blood sampling had been determined primarily for pharmacokinetic analyses. Second, since the last blood sample was obtained after 45 min for sevoflurane (8 h for propofol and 6 h for dexmedetomidine), we could not consider the effect of this inhalation agent. Third, we did not perform any flow cytometric analyses, particularly to determine NK cell activity, since these samples were already collected and stored. A strength of the study was that we measured circulating cytokines after anaesthesia in healthy volunteers, which avoided the influence of oncological disease and the surgical stimulus. The results in this study therefore provide more insight into the intrinsic effect of the anaesthetic on the inflammatory response, but cannot be extrapolated to patients in whom the perioperative immune response is primarily affected by the surgical insult and oncological disease. In the absence of acute inflammation, some of our results were below the LODs for this assay and none were more than one-third above the LOD of the detection limit.

In conclusion, propofol appeared to be associated with increased expression of cytokines related to the activation of NK cells, but was also associated with pro-inflammatory cytokine release. Volunteers receiving dexmedetomidine primarily exhibited an anti-inflammatory cytokine profile. The addition of remifentanil to propofol did not appear to produce a cytokine profile believed to be beneficial for antitumour immune responses, given the observed decrease in Th1/Th2 ratios. Our data further support the hypothesis that the choice of anaesthetic agent may impact on the perioperative inflammatory response. Differences between combined anaesthetic agents revealed by our study emphasise the need for prospective adequately powered clinical trials.

Authors' contributions

Data analysis, writing up the first draft of the paper: DJB
Study design: MvM, PH, MMRFS
Made corrections in the first draft of the paper: MvM, PH, WA, MMRFS
Data collection: RMJ
Laboratory measurements: RMJ, WA
Illustrations: WA

Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.05.039.

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