Clinical research

Propofol but not sevoflurane decreases circulating levels of sEGFR and sE-selectin after colorectal cancer surgery

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Abstract

Introduction: Surgery and anaesthesia may affect the outcomes of cancer. The aim of the study was to evaluate the effect of propofol or sevoflurane on cancer biomarkers such as interleukins, adhesion molecules, and EGFR.
Material and methods: Eighty patients scheduled for colorectal cancer surgery were randomised to either propofol or sevoflurane anaesthesia. Blood samples for interleukin (IL)-6, IL-8, IL-10, tumor necrosis factor α (TNF-α), interferon α (IFN-α), soluble intracellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), sE-selectin, and sEGFR measurements were obtained before induction of anaesthesia, at the end of surgery, and 72 h postoperatively.
Results: Complete samples were obtained from 71 patients. Demographic data and anaesthesia/surgery-related data were similar between the two groups. There were significant differences produced by sevoflurane vs. propofol on the sE-selectin (median (IQR) 57.1 (59.2) vs. 42.7 (22.9) ng/ml, $p = 0.011$) and sEGFR (median (IQR) 49905.7 (22673.5) vs. 25.657.2 (13842.1) ng/ml, $p < 0.001$) concentrations postoperatively, while sEGFR plasma levels also showed a significant difference during surgery (median (IQR) 32964.5 (14402.5) vs. 25567.0 (13315.4) ng/ml, $p = 0.04$). IL-10 levels were significantly higher in the propofol group postoperatively (median (IQR) 13.7 (18.5) vs. 14.9 (66.6) pg/ml, $p = 0.05$).
Conclusions: Given the role of EGFR and adhesion molecules on tumour progression and the generation of metastases, the inhibitory effect of propofol observed in this study might prove useful in the future. Further studies in larger populations investigating the effect of anaesthetic agents on these biomarkers are warranted.

Key words: adhesion molecules, biomarkers, colorectal cancer, epidermal growth factor receptor, anaesthesia, propofol.

Introduction

While surgical resection of a tumour and lymph nodes is the most effective method of treatment for cancer, the perioperative period itself

may play a pivotal role in tumour promotion and the development of metastases [1, 2]. Surgical stress and general anaesthesia induce the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) [3]. This causes, in turn, a release in tumour-derived soluble factors, pro-inflammatory cytokines, and adhesion molecules, which can ultimately lead to suppression in cell-mediated immunity (CMI). A dysregulated balance between proinflammatory/anti-inflammatory and Th1/Th2 cytokines [4–6], suppression of NK cell activity by multiple pathways [7–9], or a decrease in cytotoxic T-cell activity [6] are all proposed mechanisms of the influence of surgery and anaesthesia on immune function and carcinogenicity.

Several studies suggest that cell adhesion molecules such as intracellular adhesion molecules-1 (ICAM-1) and vascular cell adhesion molecules-1 (VCAM-1), members of the immunoglobulin superfamily, or E-selectin, a type-I transmembrane glycoprotein, are involved in cancer progression and metastases [10, 11]. c forms of ICAM (sICAM-1), and VCAM (sVCAM-1) have been previously identified [12]. E-selectin occurs on the surface of endothelial cells and is shed from them during damage or activation by pro-inflammatory factors and is involved in tumour neoangiogenesis. Malignant cells detached from the primary tumour penetrate into blood or lymph vessels, survive in the circulation, and are then arrested in the capillary endothelium of distant organs, extravasate and grow as a secondary lesion [13]. Therefore, sICAM-1, sVCAM-1, and sE-selectin interactions between endothelial and cancer cells seem to be crucial for the development of metastases.

The endothelial growth factor receptor (EGFR) pathway also plays a central role in colorectal cancer development and progression. EGFR overexpression has been associated with tumour grade (poor differentiation) [14] and reduced survival [15, 16] in some studies. There are, however, no comparative studies on the influence of different anaesthetic agents on adhesion molecules and EGFR kinetics in the perioperative period.

The aim of the study was to evaluate the effect of propofol or sevoflurane-based anaesthesia on cancer biomarkers such as interleukins, adhesion molecules, and EGFR.

Material and methods

The study was approved by the Research and Ethics Committee of Attikon University Hospital (approval date 5/12/2010), National and Kapodistrian University of Athens and was performed in accordance with the Helsinki Declaration (revised 2000).

Eighty patients scheduled for colorectal cancer surgery were consecutively enrolled in this prospective, randomised, single-centre study. Written, informed consent was obtained by all patients. Sealed envelope randomisation was used using a computer-generated random list allocating patients to the propofol or sevoflurane group. Inclusion criteria comprised adults ≥ 18 years old, ASA class I–III, without known allergies to the study drugs, or severe cardiac (NYHA class > 3), respiratory, or metabolic (including diabetes) disease. Patients with body mass index (BMI) > 35 kg/m^2, distant metastasis, or having received chemotherapy or radiotherapy prior to surgery were excluded. Immunodepressed patients or patients receiving immunosuppressive therapy, using steroid therapy, with history of alcohol abuse, or with renal or hepatic insufficiency were also excluded. All patients underwent open colorectal surgery with tumour resection (right/left colectomy, low anterior resection, or abdominoperineal resection with rectal amputation).

Patients were not premedicated. On arrival in the operating room an infusion of Ringer's lactate solution was started. An arterial line was inserted, and blood was withdrawn for baseline laboratory measurements. The line was maintained postoperatively until the end of blood withdrawals. Intraoperative monitoring included ECG, heart rate (HR), pulse oximetry (SpO_2), capnography, end-tidal concentration of sevoflurane, and core temperature using a nasopharyngeal thermocouple probe. Depth of anaesthesia was monitored using bispectral index to achieve values between 40 and 55 (BIS, Vista; Aspect Medical System, Newton MA, USA).

All patients received a bolus dose of propofol 1.5 to 2 mg/kg for anaesthesia induction. Fentanyl was administered at 1 µg/kg. Tracheal intubation was facilitated with rocuronium 0.6 mg/kg. In the propofol group, maintenance of anaesthesia was achieved with propofol target controlled infusion TCI using the Marsh model at a Cp target of 3–5 ng/ml following BIS values. In the sevoflurane group, maintenance was accomplished with sevoflurane 1 MAC in an O_2/air mixture. The lungs were ventilated with volume control ventilation (6–8 ml/kg of ideal body weight) (Dräger Prius, Germany). During surgery, fentanyl was administered for analgesia at the anaesthesiologists' discretion depending on the patients' analgesic needs assessed by changes in HR, blood pressure (BP) (more than 25% above baseline value), pupil size, sweating, and lacrimation. We chose to not insert an epidural catheter for intra and postoperative analgesia because of the known anti-inflammatory and immunologic effects of local anaesthetics [1], which could result in a bias factor, mitigating the effect of propofol or sevoflurane.

At the end of surgery, neuromuscular blockade was antagonised with neostigmine 0.05 mg/kg

given with atropine 20 mg/kg. Postoperative analgesia was achieved using patient-controlled analgesia (PCA) with morphine boluses of 1 mg and an 8-min lockout period, with the aim of maintaining a pain score of less than 3 on a 10-point visual analogue scale (VAS). Intravenous morphine 0.15 mg/kg was administered 40 min before the end of surgery. In addition, intravenous paracetamol 1 g was administered every 8 h; the first dose was administered 30 min before the end of surgery. Postoperative nausea and vomiting (PONV) were treated by intravenous ondansetron 4 mg.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and HR were recorded every minute during induction and every 5 min after tracheal intubation, until the end of surgery. Hypotension (defined as a decrease of mean arterial BP by 25% of the baseline value) was treated with an increased infusion rate of crystalloid solution and intravenous boluses of phenylephrine. Bradycardia (defined as a decrease in HR by 25%) was treated with intravenous boluses of ephedrine.

Total morphine consumption, and nausea/vomitus requiring antiemetic administration were recorded.

Inflammatory cytokine and adhesion molecule measurements

Blood samples (7 ml) were taken from the arterial line before induction of anaesthesia (T1) at the end of surgery (T2) and 72 h postoperatively (T3). Blood sampling was performed from the arterial line only, which was not heparinised. The first 5 ml of blood was discarded, and the next 7 ml was collected for interleukin and other biomarker assays. Blood samples were centrifuged at 2500 rpm for 10 min; the supernatant serum was withdrawn and stored at –80°C until processed. Serum levels of interleukin (IL)-6, IL-8, IL-10, tumor necrosis factor α (TNF-α), interferon (IFN)-α, IFN-γ, IL-12, IL-2, IL-1b, IL-12 (p40), IL-12 (p70), sICAM-1, sVCAM-1, sE-Selectin, and sEGFR were measured in all three time instances. Serum concentrations of the cytokines were determined with the Milliplex High-Sensitivity Cytokine/Chemokine Kit multiplex assay (Millipore Corp, Billerica, MA, USA), according to the manufacturer's instructions. Serum concentrations of sICAM-1, sVCAM-1, and sE-selectin analysis were determined using MAP Human Cardiovascular Disease Kit multiplex assay (Millipore Corp, Billerica, MA, USA), while sEGFR analysis was performed on the Luminex 200 platform (Luminex Corp, Austin, TX, USA) according to the manufacturer's instructions.

We hypothesised that colorectal surgery for cancer leads to the release of pro-inflammatory interleukins and that propofol would lead to a lower concentration of pro-inflammatory cytokines and adhesion molecules than sevoflurane anaesthesia. The primary outcome of the study was sEGFR concentration. Secondary outcomes were variation in other adhesion molecules and biomarkers concentrations. The sample size was calculated from a pilot study (n = 5 patients in each group). Concentrations of sEGFR showed a mean difference of 18332.3 ng/ml between the two groups. For a type 1 (a) error of 0.05 and a type 2 (b) error of 0.02, we calculated a sample size of 35 patients per group. On the basis of our previous experience, we decided to enrol at least 40 per group to account for attrition bias or technical reasons for exclusion or missing data.

Statistical analyses

Normally distributed continuous data were analysed using the independent-samples t-test, while categorical variables were compared using Fisher's exact test. The Shapiro-Wilk test was performed to test for normal distribution of continuous variables. Comparisons between biomarker concentrations at different timepoints, among each treatment group, were undertaken using the Wilcoxon signed-rank test; data were not normally distributed, and the results are given as median and interquartile range (IQR).

Between-group comparison of biomarker concentrations over time was performed using linear mixed model for repeated measures analysis. To this end, an unstructured covariance matrix was implemented, using time and group allocation as fixed factors. The interaction between the group and time variable was also examined.

Data were expressed either as mean (SD), median (interquartile range), or percentage (%). Significance was set at $p < 0.05$ unless otherwise mentioned, and all p-values were two-tailed. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 24 (IBM Corp., Armonk, NY, USA).

Results

Eighty patients were randomly assigned to receive either sevoflurane (40 patients) or propofol anaesthesia (40 patients). No patient was excluded from the analyses; however, 36 and 35 patients in the sevoflurane and propofol group, respectively, had complete biomarker concentration measurements for all three time points (Figure 1), so they were included in the analysis.

Participants' characteristics by treatment group are presented in Table I. No difference was observed in demographic or surgical variables among groups. Duration of surgery and anaesthesia did not differ among groups. Variations of more than 25% in systolic blood pressure and heart rate

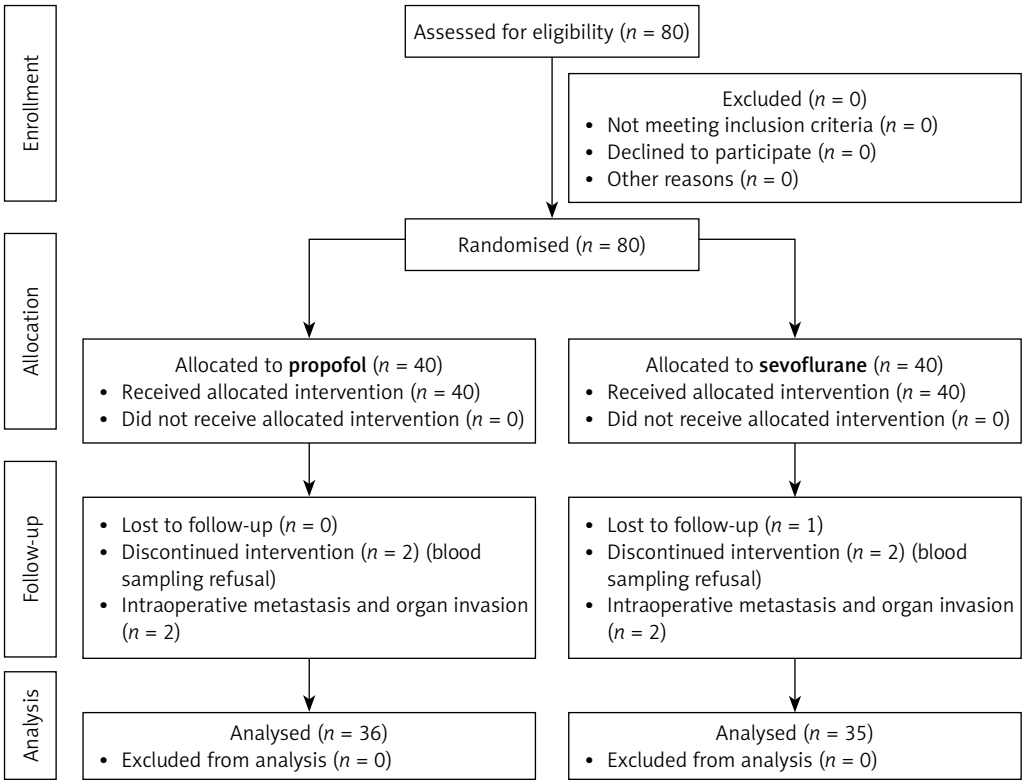

Figure 1. Flow diagram of the study

were significantly more frequent among patients assigned to the propofol group ($p < 0.05$). However, participants in the sevoflurane group required greater doses of crystalloids ($p < 0.001$).

Serum levels of IL-1b, IL-2, IL-12 (p40), IL-12 (p70), and IFN-γ were, in the majority of measurements, below the detection limits of the essay and thus were not included in the analysis. IL-6, IL-8, IL10, TNF-α, IFN-α, sICAM-1, sVCAM-1, sE-selectin, and sEGFR were measured and are hereby presented (Tables II and III).

Concentrations of measured biomarkers and mediators were not normally distributed and so are presented as medians (IQR), and non-parametric tests were performed. Pre-operative concentrations were similar in the two groups for all biomarkers. sEGFR kinetics were significantly different between the two groups intra- and postoperatively ($p = 0.04$ and $p = 0.001$, respectively). sEGFR was higher in the sevoflurane group. sE-selectin levels were higher in the sevoflurane group postoperatively ($p = 0.011$), while IL-10 levels were lower in the same group ($p = 0.05$) at 72 h postoperatively.

The mixed model for repeated measures analysis for each biomarker is presented in Table III. The intercept corresponds to the predicted value of the outcomes for the dependent variable if the independent variables are 0. Group is the predicted influence of the sevoflurane group on the outcome variable. Both group and time were used as fixed factors of the model, and the parameter estimates were assessed with the Restricted Maximum Likelihood method (REML). We observed a significant influence of time in sE-selectin, sICAM-1, IL-10, IL-6, and sEGFR levels, while group allocation was significant only for sE-selectin and sEGFR levels. The interaction between group and time was significant only for sEGFR.

Discussion

Our study population showed no differences in demographic data with the exception of consumption of crystalloids, which was higher in the sevoflurane group. The propofol group showed higher variation of blood pressure and heart rate. Our findings indicate that there were significant differences produced by propofol or sevoflurane on the sE-selectin and sEGFR concentrations postoperatively, while sEGFR plasma levels showed a significant difference during surgery as well. A significant effect of time, not influenced by type of anaesthetic, was observed in sICAM-1, IL-6, and IL-10 levels although IL-10 levels were significantly higher in the propofol group postoperatively.

In the past 15 years, data have emerged on a possible role of anaesthetic agents in the balance between pro- and anti-inflammatory responses to surgery [1, 17, 18], which may influence cancerogenicity and tumour growth, and thus have an impact on long-term postoperative outcome in cancer patients [19–21].

Table I. Demographics and surgery-related variables

Parameter	Sevoflurane (n = 36)	Propofol (n = 35)
Age, mean (SD)	66.4 (8.8)	65.4 (10.5)
Males, *n* (%)	23 (63.9)	21 (60)
BMI, mean (SD)	27.7 (3.7)	28.5 (5.3)
Cancer localisation, *n* (%):		
Right colon	8 (22.2)	7 (20)
Transverse colon	0 (0.0)	1 (2.9)
Left colon	3 (8.3)	6 (17.1)
Sigmoid	14 (38.9)	8 (22.9)
Rectum	11 (30.6)	13 (37.1)
Operation, *n* (%):		
Right colectomy	6 (16.7)	6 (17.1)
Right extended colectomy	0 (0.0)	3 (8.6)
Sigmoidectomy	16 (44.4)	12 (34.3)
Low anterior resection	5 (13.9)	9 (25.7)
Abdominoperineal resection	9 (25.0)	5 (14.3)
Dukes score, *n* (%):		
1	3 (8.3)	5 (14.3)
2	24 (66.7)	17 (48.6)
3	6 (16.7)	12 (34.3)
4	3 (8.3)	1 (2.9)
ASA score, *n* (%):		
Sevoflurane (I/II/III)	12 (33.3)/19 (52.8)/5 (13.9)	
Propofol (I/II/III)	12 (34.3)/22 (62.9)/1 (2.9)	
Smoking, *n* (%)	18 (50)	12 (34.3)
Fentanyl administered, mean (SD) [µg]	111 (31.8)	118 (24.5)
Phenylephrine use, mean (SD) [mg]	1.0 (0.27)	1.04 (0.35)
Ephedrine use, mean (SD) [mg]	9.8 (7.13)	11.5 (7.9)
Variation of SBP > 25%, *n* (%)	8 (22.2)	29 (82.9)[b]
Variation of HR > 25%, *n* (%)	17 (47.2)	28 (80)[b]
Crystalloids, mean (SD) [ml]	2544.2 (834)	1909 (578)[a]
Colloids, mean (SD) [ml]	733 (313)	669 (253.2)
Morphine consumption, mean (SD) [mg]	28 (6.7)	31 (5.6)
Blood loss, mean (SD) [ml]	215 (45)	230 (36)
Surgery time, mean (SD) [min]	162.3 (57)	169.7 (61.2)
Anaesthesia time, mean (SD) [mim]	196.4 (56.4)	198.7 (65)

[a]Significant difference among groups at $p < 0.001$ in the two-sided t-test; [b]Significant difference in categorical variables among groups at $p < 0.05$, using χ^2 tests, SD – standard deviation, BMI – body mass index, ASA – American Society of Anaesthesiology, SBP – systolic blood pressure, HR – heart rate.

Table II. Biomarker concentrations and between-group analysis

Parameter	Sevoflurane (*n* = 36)	Propofol (*n* = 35)	*P*-value
sE-selectin [ng/ml]:			
Preoperative	48.2 (35.0)	41.7 (28.3)	0.140
End of surgery	39.7 (28.7)	38.3 (14.2)	0.148
POD#3	57.1 (59.2)	42.7 (22.9)	0.011
sVCAM-1 [ng/ml]:			
Preoperative	780.6 (571.4)	830.9 (310.3)	0.584
End of surgery	710.9 (336.0)	791.4 (236.7)	0.399
POD#3	798.8 (540.5)	701.5 (625.5)	0.357
sICAM-1 [ng/ml]:			
Preoperative	172.9 (320.5)	147.8 (55.6)	0.434
End of surgery	125.4 (106.8)	109.5 (53.4)	0.633
POD#3	204.6 (174.4)	175.0 (84.7)	0.660
IL-6 [pg/ml]:			
Preoperative	3.8 (31.9)	3.7 (11.8)	0.854
End of surgery	55.6 (58.9)	53 (171.9)	0.911
POD#3	31.01 (122.8)	37.1 (118.8)	0.241
IL-8 [pg/ml]:			
Preoperative	29.0 (54.6)	21.0 (13.8)	0.938
End of surgery	29.8 (155.7)	56.5 (120.2)	0.299
POD#3	29.5 (122.3)	40 (50.2)	0.985
IL-10 [pg/ml]:			
Preoperative	8.38 (9.8)	2.5 (2.33)	0.411
End of surgery	15.8 (29.9)	20.5 (107.4)	0.244
POD#3	13.7 (18.5)	14.9 (66.6)	0.050
TNF-α [pg/ml]:			
Preoperative	17.5 (36.4)	11.5 (8.5)	0.676
End of surgery	19.0 (39.5)	13.1 (9.4)	0.800
POD#3	23.4 (48.9)	13.6 (26.7)	0.544
IFN-α [pg/ml]:			
Preoperative	32.7 (127.1)	3.2 (10.8)	0.409
End of surgery	26.7 (87.7)	3.2 (25.6)	0.615
POD#3	3.2 (77.4)	3.2 (29.8)	0.650
sEGFR [ng/ml]:			
Preoperative	22716.5 (12151.1)	20702.2 (6253)	0.382
End of surgery	32964.5 (14402.5)	25567.0 (13315.4)	0.040
POD#3	49905.7 (22673.5)	25.657.2 (13842.1)	< 0.001

Data are expressed as median (IQR); between-group comparisons performed using the Wilcoxon signed-rank test.

Table III. Linear mixed models for repeated measures

Variables	Covariates	Denominator d*f*	*F*	*P*-value
sE-selectin	Intercept	37.090	254.324	< 0.001
	Group	37.090	7.855	0.008
	Time	34.514	9.253	0.001
	Group * Time	34.514	2.169	0.130
sVCAM-1	Intercept	36.103	347.331	< 0.001
	Group	36.103	0.193	0.663
	Time	34.238	0.893	0.419
	Group * Time	34.238	0.568	0.572
sICAM-1	Intercept	37.193	91.288	< 0.001
	Group	37.193	1.161	0.288
	Time	34.389	4.204	0.023
	Group * Time	34.389	0.682	0.512
IL-6	Intercept	28.375	2.671	0.113
	Group	28.375	1.997	0.169
	Time	32.309	11.840	< 0.001
	Group * Time	32.309	1.243	0.302
IL-8	Intercept	39.922	20.529	< 0.001
	Group	39.922	0.202	0.655
	Time	38.377	2.989	0.062
	Group * Time	38.377	0.779	0.527
IL-10	Intercept	39.307	25.645	< 0.001
	Group	39.307	3.358	0.067
	Time	34.491	7.830	0.002
	Group * Time	34.491	3.122	0.057
TNF-α	Intercept	37.665	30.253	< 0.001
	Group	37.665	1.315	0.259
	Time	34.188	2.920	0.067
	Group * Time	34.188	2.021	0.148
IFN-α	Intercept	28.841	31.393	< 0.001
	Group	28.841	1.172	0.288
	Time	19.012	0.557	0.582
	Group * Time	19.012	0.006	0.994
sEGFR	Intercept	39.199	541.502	< 0.001
	Group	39.199	23.907	< 0.001
	Time	37.441	29.442	< 0.001
	Group * Time	37.441	19.188	< 0.001

The intercept corresponds to the predicted value of the outcomes for the dependent variable if the independent variables are 0. Group is the predicted influence of the sevoflurane group on the outcome variable. Repeated measure is time. Both group and time were used as fixed factors of the model and the parameter estimates were assessed with the Restricted Maximum Likelihood method (REML).

Increased concentrations of IL-6 promote tumour growth, affect tumour cell differentiation, and protect cells from apoptosis [22, 23], while IL-10 suppresses pro-inflammatory interleukins and favours antitumour immunity [24] in cancer patients. Deegan *et al.* [25] reported a significant increase in IL-10 concentration postoperatively in propofol-paravertebral anaesthesia vs. sevoflurane-opioid anaesthesia for breast cancer surgery. Additionally, other authors have made a strong point regarding the anti-inflammatory properties of propofol. It decreases pro-inflammatory cytokines, inhibits COX-2 and PGE2 functions, and increases cytotoxic T-lymphocyte (CTL) activity [26–28]. Moreover, it does not affect the Th1/Th2 ratio, so surgery-induced immunosuppression is attenuated [1, 6]. Our study confirms the results of Deegan *et al.* because we observed an increase of IL-10 in the propofol group postoperatively. We also observed a significant effect of time and thus surgery in the IL-6 plasma concentrations; however, this increase did not differ among groups.

Endothelium and cell adhesion molecules are engaged in tumour invasion. Cancer cell-leukocyte-platelet complexes adhere to the endothelium, extravasate, and migrate beyond the circulation. Increased expression of cell adhesion molecules in neoplastic disease is associated with cancer progression and poor prognosis [29, 30]. Numerous studies have reported a significant relationship between the levels of sICAM-1, sVCAM-1, and the disease stage [31, 32]. High levels of sICAM-1 and sE-selectin, present on the surface of active endothelial cells in colorectal cancer patients, have been found in patients with distant metastases [32]. It is believed that the main role of selectins in cancer growth is their involvement in the formation of metastases. In a study by Korniluk *et al.* [33] a significant correlation of the level of soluble E-selectin with primary tumour size and the presence of metastases was observed. Conversely, low expression of E-selectin was associated with a considerable reduction of the number of metastases and circulating cancer cells in mice, which suggests that the lack of selectins prevents the cells from leaving blood vessels [34]. During surgery, an increase of cell adhesion molecules is expected. In fact, mechanical manipulation of the tumour as well as the surgical stress response induces inflammatory molecules and thus expression and presentation of ICAM-1 and VCAM-1, which are already higher in cancer patients than in normal individuals [11]. However, the role of anaesthetic drugs on the expression and circulating levels of these adhesion molecules has not yet been elucidated. In a timely review, Kim [1] shed light on the possible mechanisms of involvement of anaesthetic drugs in tumour growth and metastases. It has been found that sevoflurane promotes proliferation, migration, and invasion of oestrogen receptor (OR)-positive breast-cancer cells, as well as proliferation and migration of ER-negative cells [35]. Volatile anaesthetics are associated with increased HIF-1a levels and increased proliferation and migration of prostate cancer cells, an action inhibited by propofol [36]. Given these data on sevoflurane and inhalational anaesthesia, the observed small but significant increase of sE-selectin in the sevoflurane group postoperatively may reflect its effect on tumour proliferation and progression.

EGFR overexpression has been linked to tumour progression and poor survival in various malignancies [37], but its clinical significance in colorectal cancer is uncertain [14–16, 38, 39]. The EGFR pathway has been a target for therapy by the use of monoclonal anti-EGFR antibodies, which act by preventing the activation of signal transduction pathways. The effectiveness of anti-EGFR drugs such as cetuximab has been confirmed by phase II and III trials [39]. The exact mechanisms by which these drugs target EGFR and thus colorectal cancer cells have not been yet fully understood [40]. It is, however, interesting that EGFR overexpression was inhibited by propofol in our study but not by sevoflurane in a highly significant manner. There is paucity in literature regarding the effect of anaesthetic drugs on adhesion molecules and EGFR; consequently, it could be interesting to further investigate the mechanisms by which different anaesthetic agents might play a role in circulating concentrations of these factors.

Our study presents potential limitations. The number of patients recruited to our study was small but similar to other studies on the subject. In order to reduce bias from other perioperative factors we did not perform epidural anaesthesia for intra- and postoperative analgesia. All operations were open surgeries for colorectal cancer. Due to the short time interval for postoperative follow-up, we did not evaluate the incidence of recurrence of cancer. Therefore, our study lacks of any information on long-term outcome that would be useful to clarify whether the effect of propofol on circulating EGFR and sE-selectin levels might affect patient prognosis. Further studies in a larger population investigating the effect of anaesthetic agents on these biomarkers are warranted.

In conclusion, in our study population consisting of colorectal cancer patients undergoing surgery we found a significant decrease of sE-selectin and sEGFR concentrations in the propofol group. Levels of anti-inflammatory IL-10 were also higher in the propofol group postoperatively. Given the role of EGFR and adhesion molecules in tumour progression and the generation of metastases,

the inhibitory effect of propofol observed in this study might prove useful in the future.

Conflict of interest

The authors declare no conflict of interest.

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