

Effect of Propofol on Colorectal Cancer Angiogenesis and Metastasis

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Abstract

Background: Vascular Endothelial Growth Factor (VEGF) is one of the most critical factors that stimulate angiogenesis in colorectal cancer patients. The Matrix Metalloproteinases (MMPs) are involved in the degeneration of the extracellular matrix and regulation of cell-matrix interactions. MMP-3 plays an important role in metastasis of colorectal cancer. Our aim was to investigate the effect of propofol on VEGF and MMP-3 plasma levels in colorectal cancer patients. **Methods:** Colorectal cancer patients were included. Blood samples were collected at before and after propofol infusion. VEGF and MMP-3 plasma levels were measured using Enzyme-Linked Immunosorbent Assay (ELISA). **Results:** A total of 40 colorectal cancer patients were included. The median age of patients was 53 years. Nineteen patients were male and 21 were female. Twenty-five patients were diagnosed with colon cancer and 15 were rectal cancer. The mean propofol infusion dose was 2.02 mg/kg. There were no significant variations in VEGF and MMP-3 plasma levels after propofol infusion compared with before. No side effects occurred in all the patients. **Conclusion:** Propofol might have no significant effect on VEGF and MMP-3 levels in colorectal cancer patients and further studies need to be investigated.

Keywords

Propofol, VEGF, MMP-3, Colorectal Cancer

1. Introduction

Colorectal cancer is one of the most common cancers and one of the most common cancer causes of death globally, accounting for approximately 600,000 deaths per year [1]. Although great progress has been made in the diagnosis and treatment of colorectal cancer, the outcome for these patients is still pessimistic

for prolonging the survival time and has always been challenging when metastasis occurred [2]. And paradoxically, surgical resection that is the primary treatment of colorectal cancer patients, may directly or indirectly stimulate the growth of residual tumor deposits or circulating tumor cells [3].

Angiogenesis plays an important role in tumor growth and progression in solid tumors. Vascular Endothelial Growth Factor (VEGF) is one of the most critical and specific factors that stimulate both physiological and pathological angiogenesis. Overexpression of VEGF is associated with progression of and poor prognoses for several tumors, especially colorectal cancer [4] [5] [6]. Treatment with a VEGF antagonist significantly attenuated angiogenesis and tumor progress and this treatment has been listed in NCCN guidelines as a molecular therapy for colorectal cancer [7].

The Matrix Metalloproteinases (MMPs) are a family of at least 28 zinc-dependent enzymes which are involved in the degeneration of the Extracellular Matrix (ECM) and regulation of cell-matrix interactions. ECM degradation is a necessary component of metastasis [8]. MMP-3 has been shown to induce EMT in cultured colorectal cancer cells [9] and to play an important role in the growth and/or metastatic transformation of colorectal cancer [10] [11].

Except treatment of surgeries and chemoradiotherapy, anesthetic techniques had been investigated to affect cancer development [12]. Propofol (2,6-diisopropylphenol), one of the most commonly used intravenous anaesthetic agents, also exerts a number of non-anesthetic effects, including anti-tumor activity. Propofol has been attributed with certain anti-inflammatory properties, e.g. via the reduction of inflammatory cytokines [13]. It was also shown that propofol might be able to suppress proliferation and metastasis of colorectal cancer cells [14].

The impact of propofol on VEGF and MMP-3 plasma levels in colorectal cancer patients is unknown. So our aim was to investigate the expression variation of VEGF and MMP-3 after intravenous administration of propofol in colorectal cancer patients.

2. Methods

2.1. Patients

Patients diagnosed with colorectal cancer, aged ≥ 18 were eligible for enrollment. Patients with complete or incomplete intestinal obstruction, full stomach, pregnant, allergy to propofol, a history of anesthesia in recent three months or a history of colorectal surgical resection or other type of cancer were excluded. The cases who received chemo- or radio-therapy were excluded. All patients were given informed consent. This clinical trial had been agreed by the ethics committee of hospital.

2.2. Anaesthesia Management

The anaesthesia techniques were standardised. No patient received pre-anaesthetic

medication. Anaesthesia was induced after establishing routine monitoring, including electrocardiogram, non-invasive blood pressure, pulse blood oxygen saturation (SPO₂), and the Bispectral Index (BIS). All the patients received central venous puncture and catheterization. Propofol was administered with a speed of 1 mg/kg/h until the target BIS value of 50 was achieved (Orchestra® Base Primea; Fresenius Vial, Brezins, France).

2.3. Blood Sampling and Processing

To be eligible for entry into this study, venous blood samples were collected in heparin-containing tubes before and after inducing anesthesia through central venous catheter. The samples were processed within 6 h of collection, and the plasma fraction stored in aliquots at -80°C until the assay was performed.

2.4. VEGF Measurement

VEGF levels were measured using a VEGF enzyme-linked immunosorbent assay (ELISA) kit (Invitrogen, Massachusetts, USA). VEGF measurements were performed according to the manufacturer's instructions and quality control was ensured. VEGF concentrations are reported as picograms per milliliter (pg/ml).

2.5. MMP-3 Measurement

Plasma levels of total MMP-3 were determined in duplicate using commercially available Enzyme-Linked Immunosorbent Assay (ELISA) (R&D Systems) according to the manufacturer's instructions. MMP-3 concentrations are reported as nanograms per milliliter (ng/ml).

2.6. Statistical Methods

All statistical analyses were carried out with SPSS version 17 (SPSS Inc, Chicago, IL, USA). Numerical variables with a normal distribution were presented as the mean ± standard deviation (SD), and those with a non-normal distribution as the median and interquartile range. A paired t-test or Wilcoxon signed-ranks test was used to compare pre-anesthesia and post-anesthesia index. A P value < 0.05 was considered statistically significant.

3. Results

3.1. Patient Characteristics

A total of 40 colorectal cancer patients fulfilled inclusion criteria were enrolled in the study after providing informed written consent. The median age of patients was 53 years. Nineteen patients were male and 21 were female. Twenty-five patients were diagnosed with colon cancer and 15 were rectal cancer. Twenty-three patients with primary colorectal cancer were diagnosed at stage II, 14 patients at stage III and three patients with stage IV.

The mean propofol dose was 2.02 mg/kg. There were no side effects occurred in all patients, like allergy reactions, severe hypoxemia or other situations need

emergency measures. Other baseline data had been shown in **Table 1**.

3.2. Hemodynamic Index

The mean blood pressure, SpO₂ and hear rate of all the colorectal cancer patients were significantly decreased post-anesthesia compared with pre-anesthesia (**Table 2**).

3.3. Serum Expression VEGF and MMP-3 before and Post Anesthesia

The serological VEGF levels in colorectal cancer patients before anesthesia were 188.70 ± 22.92 pg/ml compared to that after anesthesia measured as 191.30 ± 22.66 pg/ml, indicating no significant variation in VEGF expression.

The serological MMP-3 levels in colorectal cancer patients before anesthesia were 22.81 ± 5.11 ng/ml compared to that after anesthesia measured as 23.13 ± 4.48 ng/ml, indicating no significant variation in MMP-3 expression.

Table 1. Demographic and clinical characteristics of the study population.

Items	
Age, years (mean \pm SD)	53.38 \pm 8.16
Sex (n)	
Male	19 (47.5%)
Female	21 (52.5%)
BMI (kg/m ²)	24.15 \pm 2.37
Preoperative chemoradiotherapy (n)	0
Type of cancer (n)	
Colon cancer	25 (62.5%)
Rectal cancer	15 (37.5%)
Cancer stage (n)	
Stage II	23 (57.5%)
Stage III	14 (35%)
Stage IV	3 (7.5%)
Propofol (mg/kg)	2.02 \pm 0.22

Table 2. Hemodynamic index and serum levels of VEGF and MMP-3 pre- and post-anesthesia.

Items	Pre-anesthesia	Post-anesthesia	P value
Mean blood pressure, mmHg (mean \pm SD)	90.73 \pm 10.01	74.10 \pm 7.60	<0.001
SpO ₂ , % (mean \pm SD)	98.58 \pm 1.26	92.58 \pm 1.75	<0.001
Heart rate, n/minute (mean \pm SD)	79.50 \pm 9.32	65.63 \pm 7.84	<0.001
VEGF, pg/ml (mean \pm SD)	188.70 \pm 22.92	191.30 \pm 22.66	0.473
MMP-3, ng/ml (mean \pm SD)	22.81 \pm 5.11	23.13 \pm 4.48	0.190

4. Discussion

In this study, we have not detected any statistical difference in expression of VEGF and MMP-3 plasma levels in colorectal cancer patients after propofol infusion.

Propofol, an extensively used intravenous anesthetic agent during cancer resection surgery, has been confirmed to execute anti-tumor effect on multiple cancers, including Colorectal Cancer (CRC). It had been demonstrated that propofol could inhibit CRC cell proliferation, migration and invasion by up-regulating miR-124-3p.1 and down-regulating AKT3 [14]. Wound healing assay and migration assay demonstrated that propofol has the ability to inhibit epithelial-mesenchymal transition that induced by IL-13 in RKO and SW480 cells through up-regulation of miR-361 and miR-135b and thereafter leads to the inhibition of IL-13/STAT6/ZEB1 signaling pathway [15]. Propofol exposure repressed the NMDAR-CAMKII-ERK pathway to inactivate HIF1 α and therefore reduced aerobic glycolysis in colorectal cancer cells and in an *in vivo* xenograft model [16]. And furthermore, propofol promoted cell apoptosis and inhibited cell proliferation in both Colo205 and SW620 cells, through the down-regulation of HOXA11-AS and up-regulation of let-7i [17].

However, sometimes conflicting data have been published in clinical settings. A retrospective cohort study showed that propofol anesthesia for colorectal cancer surgery is associated with better survival irrespective of tumor-node-metastasis stage compared with desflurane [18]. A clinical study showed there was no significant difference in colorectal cancer patients' immune function with propofol anesthesia compared with sevoflurane [19]. And there were also clinical studies showed that anesthesia with propofol and anesthesia with sevoflurane induced similar inflammatory responses during colorectal cancer surgery [13] [20]. So a Sweden study had been conducting a randomised controlled trial of cancer survival after propofol- or sevoflurane-based anesthesia for cancer surgery, which may give us more information [21].

It has been demonstrated that minimally invasive colorectal resection may increase plasma MMP-3 levels directly via surgical trauma or indirectly due to surgery-associated elevations in TNF- α and IL1. Plasma MMP-3 levels remained significantly elevated from baseline for 4 weeks after minimally invasive colorectal resection for CRC [11]. Increased MMP-3 levels may promote metastases or the growth of residual cancer. But there was little study about the effect of propofol in expression of VEGF and MMP-3 plasma levels in colorectal cancer patients.

And in this study there were no significant differences either. This may be due to the difference of total amount and duration of propofol injected into patients. The total amount might not be enough to cause measurable differences of expression of VEGF and MMP-3, as well as the duration between two blood sample collected was too close. We should follow up these patients longer and detect more times after propofol infusion, and it might be some new findings. Other limitations are that most of our patients were T2 stage, and the sample size is

rather small. So we should enroll more different stages of colorectal patients in the future.

Other intravenous drugs like lidocaine may decrease the chance of tumor metastasis in colorectal cancer patients [22] [23]. So we might combine different anesthetic drugs to optimizing the anesthetic schemes.

Even though, no significant difference had been detected in expression of VEGF and MMP-3 in colorectal cancer patients after propofol infusion in this study, we could not say that propofol has no benefits on colorectal cancer patients. Further studies are needed to clarify the role of anesthesia, especially propofol in cancer recurrence in colorectal cancer patients.

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Conflicts of Interest

The authors declare that there is no conflict of interests in this study.

Author Contributions

Yubo Li designed the study, collected and analyzed the data and wrote the manuscript. Yanna Pi enrolled the patients, collected and analyzed the data and wrote the manuscript. All authors reviewed the final version of this manuscript and agreed to its submission.

Availability of Data and Material

Data is available from the authors upon reasonable request.

Ethics Approval

The study was approved by the Ethics Committee.

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