Prospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(4) 1–7

DOI: 10.1177/0300060520918420
journals.sagepub.com/home/imr
SAGE

Effect of anesthetic technique on serum vascular endothelial growth factor C and prostaglandin E2 levels in women undergoing surgery for uterine leiomyomas

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Abstract

Objective: Angiogenesis is essential for growth and recurrence of uterine leiomyomas, and angiogenesis is mediated by vascular endothelial growth factor C (VEGF-C) and prostaglandin E2 (PGE_2). This study investigated whether spinal anesthesia (SA) with continuous postoperative epidural analgesia attenuates postoperative changes in these angiogenic factors compared with general anesthesia (GA) with patient-controlled intravenous analgesia.

Methods: Forty-four women with uterine leiomyomas undergoing abdominal myomectomy were randomized to receive either standard SA or GA. Blood samples were taken before anesthesia and at 48 hours after surgery for measuring serum VEGF-C and PGE_2 levels, which were analyzed by using enzyme-linked immunosorbent assays. Visual analog scale pain scores were used to evaluate postoperative pain.

Results: Serum VEGF-C and PGE_2 levels were not significantly different preoperatively between the SA and GA groups, but they were decreased in each group at 48 hours after surgery compared with preoperatively. The change in pre- and postoperative VEGF-C levels was smaller in the GA group than in the SA group.

Conclusions: Removal of uterine leiomyomas by surgery can reduce serum VEGF-C and PGE_2 levels. The anesthetic technique affects serum VEGF-C levels, which are associated with angiogenesis in surgery for leiomyomas.

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Keywords
Analgesia, anesthesia, leiomyoma, tumor, vascular endothelial growth factor, prostaglandin

Date received: 27 October 2019; accepted: 9 March 2020

Introduction

Uterine leiomyoma is the most common benign tumor of the uterus and it is also the most common tumor in women.[1,2] Similar to many other types of tumors, uterine leiomyomas require an independent blood supply to enlarge. This process of angiogenesis is mediated by vascular endothelial growth factor C (VEGF-C) and prostaglandin E2 (PGE_2). Several studies have shown that VEGF-C levels are high in patients with uterine leiomyomas[3,4] Additionally, VEGF-C is related to occurrence and growth of uterine leiomyomas because it is capable of promoting angiogenesis, mitogenic activity, and vascular permeability-enhancing activity.[5,6] Some studies have also suggested that suppression of prostaglandin synthesis via cyclooxygenase type-2 (COX-2) enzyme inhibition reduces the incidence of some tumors.[7,8]

Currently, the effect of the anesthetic technique on some angiogenesis factors in patients with benign tumors is unknown. Therefore, this study aimed to determine the effect of the anesthetic technique on changes in postoperative serum VEGF-C and PGE_2 levels. We also aimed to examine the potential effect of the anesthetic technique on recurrence and growth of leiomyomas after surgery of abdominal myomectomy.

Materials and methods

Subjects

Women with leiomyomas requiring abdominal myomectomy were included in this prospective, randomized study from May 2015 to April 2016 and divided into two groups. In one group, women had spinal anesthesia (SA) with continuous postoperative epidural analgesia. In the other group, women had general anesthesia (GA) with patient-controlled intravenous analgesia.

Inclusion criteria were patients with leiomyomas requiring abdominal myomectomy, those aged 18 to 65 years, and those with American Society of Anesthesiologists (ASA) physical status I or II. Exclusion criteria were patients who had a history of surgery within the preceding 2 weeks, those with a history of blood transfusion and a history of coronary artery disease, and those with any contraindication to SA or opioid analgesia. Patients were randomly assigned to either the SA group or GA group.

The study protocol was approved by the Research Ethics Committee of General Hospital of Ningxia Medical University (2015-183) and registered in the international trial register Clinicaltrials.gov (NCT02829333). Written informed consent for participation was obtained from all patients.

Anesthesia

In the SA group, SA was used for surgery and epidural catheterization was used for postoperative analgesia. Using a standard technique, the L3–4 (between the third lumbar and fourth lumbar vertebrae) interspaces were used for SA. After success of lumbar puncture, 3 mL of 0.5% bupivacaine was intrathecally administrated.

Before SA, a thoracic epidural catheter was placed between T11 and T12 for postoperative epidural analgesia, with 5 mL of 2% lidocaine as a test dose. A bolus dose of 8 mL of 0.2% ropivacaine was administered after surgery and then maintained at a rate of 5 mL/hour by an epidural infusion pump. Catheters were removed approximately 48 hours after surgery.

In the GA group, induction of anesthesia was performed with midazolam (0.05–0.10 mg/kg), propofol (1.0–1.5 mg/kg), cisatracurium (0.15–0.20 mg/kg), and fentanyl (2–4 μg/kg). This was followed by preoxygenation for at least 3 minutes. When a laryngeal mask airway was properly placed, GA was maintained with isoflurane (0.5–0.8 minimal alveolar concentration) and continuous infusion of propofol (3–5 mg/kg/hour) and remifentanil (0.2–0.4 μg/kg/minutes). Patients received a bolus of sufentanil 0.1 μg/kg and patient-controlled intravenous analgesia was used for postoperative analgesia (with sufentanil 2 μg/kg plus 100 mL normal saline). The rate of continuous intravenous infusion was 2 mL/hour and the lockout time was 15 minutes.

Monitoring indicators

Static pain was assessed by using the visual analog scale (VAS) pain score (0 = no pain, 10 = the worst imaginable pain).[9] The VAS pain score was assessed at 2, 4, 8, 12, 24, and 48 hours after surgery by the anesthetist. Blood samples were taken before anesthesia and at 48 hours after surgery for serum VEGF-C and PGE_2 level measurement.

Blood samples were centrifuged at 1500 $\times g$ and the products were stored at −80°C for analysis. Serum VEGF-C and PGE_2 concentrations were analyzed by using the Quantikine Enzyme Immunoassay System (R&D Systems Inc., Minneapolis, MN, USA) in accordance with the manufacturer's instructions. Enzyme-linked immunosorbent assays were prepared for angiogenic factors. The calibration standards were assayed at the same time as the samples to allow the operator to produce a standard curve of optical density versus VEGF-C and PGE_2 levels. VEGF-C and PGE_2 concentrations in the samples were then determined by comparing the optical density of the samples with the standard curve.

Statistical analysis

Data are reported as mean ± standard deviation. The independent samples *t*-test was used to compare between-group differences. The paired samples *t*-test was used to compare within-group differences for serum VEGF-C and PGE_2 levels. The VAS pain scores were tested by the Mann–Whitney U test and data are expressed as median (25%–75% interquartile range). Statistical analysis was performed using IBM SPSS Statistics v20.0 (IBM Corporation, Armonk, NY, USA). $P < 0.05$ was considered as statistically significant.

Results

Forty-four patients were eligible for this study and all of the patients completed the study according to the experimental program. Twenty-two patients were assigned to each of the SA group and the GA group. Age, ASA physical status, weight and height, characteristics of leiomyomas, and surgical factors were not significantly different between the two groups (Table 1).

There was no significant difference in preoperative serum VEGF-C concentrations between the two groups (Table 2). Serum VEGF-C concentrations were decreased 48 hours after surgery compared with before surgery in the GA group ($P < 0.0001$). VEGF-C concentrations were also decreased after surgery compared

Table 1. Patients' characteristics.

Characteristic	GA group (n = 22)	SA group (n = 22)	*P* value
Age (years)	47 ± 7	45 ± 6	0.190
Height (cm)	160 ± 5	161 ± 4	0.467
Weight (kg)	66 ± 12	64 ± 9	0.440
ASA grade	–	–	0.741
I	15	16	–
II	7	6	–
Duration of surgery (minutes)	70 ± 24	65 ± 24	0.495
Hb (g/L)	121 ± 17	127 ± 21	0.232
Hct (%)	37 ± 4	37 ± 6	0.957
Number of leiomyomas	–	–	0.763
Single	11	10	–
Multiple	11	12	–
Menstrual cycle	–	–	0.635
No menopause	2	3	–
Menopause	20	19	
Operation	–	–	0.353
Myomectomy	7	10	–
Hysterectomy	15	12	–
Blood loss (mL)	249 ± 176	197 ± 47	0.188

Data are shown as mean ± standard deviation or number. GA group, general anesthesia with patient-controlled intravenous analgesia; SA group, spinal anesthesia with postoperative continuous epidural analgesia; ASA, American Society of Anesthesiologists; Hb, preoperative hemoglobin; Hct, preoperative hematocrit.

Table 2. VEGF-C levels preoperatively and postoperatively.

	GA group (n = 22)	SA group (n = 22)	*P* value
VEGF-C preoperatively (pg/mL)	373 ± 41	367 ± 37	0.615
VEGF-C postoperatively 48 h (pg/mL)	289 ± 38	196 ± 41	0.0001
Difference between pre- and postoperative VEGF-C levels (pg/mL)	84 ± 19	171 ± 39	0.0001

Data are shown as mean ± standard deviation. GA group, general anesthesia with patient-controlled intravenous analgesia; SA group, spinal anesthesia with postoperative continuous epidural analgesia.

with before surgery in the SA group ($P < 0.0001$). The change in pre- and postoperative VEGF-C concentrations was significantly lower in the GA group than in the SA ($P < 0.0001$).

Serum PGE_2 concentrations were significantly decreased after surgery compared with before surgery in patients in the GA group and in those in the SA group (both $P < 0.0001$) (Table 3). There was no significant difference in the change in PGE_2 concentrations between pre- and postoperatively between the two groups.

The static VAS pain scores are shown in Table 4. Static VAS pain scores were significantly lower in the SA group at 2, 4, 8, 12, 24, and 48 hours after surgery compared with the GA group (all $P < 0.0001$).

Table 3. PGE_2 levels preoperatively and postoperatively.

	GA group (n = 22)	SA group (n = 22)	*P* value
PGE_2 preoperatively (pg/mL)	384 ± 21	378 ± 34	0.615
PGE_2 postoperatively 48 h (pg/mL)	263 ± 39	259 ± 39	0.776
Difference between pre- and postoperative PGE_2 levels (pg/mL)	121 ± 52	119 ± 47	0.848

Data are shown as mean ± standard deviation. GA group, general anesthesia with patient-controlled intravenous analgesia; SA group, spinal anesthesia with postoperative continuous epidural analgesia.

Table 4. Static VAS pain scores.

Pain measure (hours)	GA group (n = 22)	SA group (n = 22)	*P* value
2	5 (3–6)	1 (0–1)	0.0001
4	5 (4–6)	1 (0–1)	0.0001
8	5 (3–6)	1 (0–2)	0.0001
12	4 (3–5)	1.5 (0–2)	0.0001
24	3 (2–4)	0 (0–1)	0.0001
48	2 (1–2)	0 (0–0)	0.0001

Data are shown as median (25%–75% interquartile range). VAS, visual analog scale; GA group, general anesthesia with patient-controlled intravenous analgesia; SA group, spinal anesthesia with postoperative continuous epidural analgesia.

Discussion

This study showed that removal of leiomyomas reduced serum VEGF-C and PGE_2 concentrations at 48 hours after surgery. This was probably due to a reduction in production of serum VEGF-C levels from leiomyomas, which strongly express VEGF. Chen et al.[10] found that serum VEGF concentrations were significantly decreased at 48 hours after hysterectomy compared with before hysterectomy, which is consistent with our results.

Although the precise causes of leiomyomas are unknown, some growth factors, such as VEGF, transforming growth factor, basic fibroblast growth factor, epidermal growth factor, platelet-derived growth factor, and insulin-like growth factor, play an important role in occurrence and growth of leiomyomas.[11] Growth factors are secreted by proteins, which modulate cell growth and proliferation.[11] Several studies have shown[11–13] that angiogenesis is a prerequisite for tumor growth. VEGF-C is a major factor that promotes angiogenesis, and mitogenic and vascular permeability-enhancing activities, and is specific to endothelial cells. In this study, we showed that VEGF-C concentrations were more decreased in the SA group than in the GA group for surgery of leiomyomas. Therefore, taking into consideration the functions of VEGF-C, the SA technique may reduce the risk of recurrence and growth of leiomyomas. Relatively high VEGF-C concentrations for several hours are unlikely to change the prognosis of leiomyomas. However, our finding that the anesthetic technique may alter VEGF-C concentrations suggests that altering serum VEGF-C conditions may promote tumor micro-recurrence or micro-growth.

In our study, all participants received abdominal myomectomy, and therefore, they had comparable levels of surgical trauma. Inoue et al.[14] reported that VEGF protein levels were increased after trauma and surgery *in vivo*. This finding suggests a direct association between the stress response and VEGF levels. Because regional anesthesia is thought to be beneficial because it attenuates the stress response, this could explain why serum VEGF-C

concentrations were much lower at 48 hours after surgery in the SA group than in the GA group. Our findings show that there is a direct association between the anesthetic technique and serum VEGF-C concentrations. Our findings also suggest that the risk of recurrence and growth of leiomyomas after surgery may decrease in patients with SA and epidural analgesia. The VAS pain scores were significantly lower in patients in the SA group than in those in the GA group. Additionally, SA not only reduced the surgical stress response to myomectomy, but also provided superior analgesia compared with GA, which is similar to another study.[15] O'Riain et al.[16] found that serum VEGF-C levels were not significantly different after surgery compared with before surgery. Additionally, there was no association between VEGF levels and surgery within the first 24 hours for mastectomy with axillary node clearance. This difference in results between studies may be due to the difference in when blood samples were taken because our blood samples were taken at 48 hours after surgery.

PGE_2 is produced by the action of prostaglandin synthetase and COX on arachidonic acid, which is released from membrane phospholipids. Enhancing angiogenesis is an important biological activity of PGE_2.[16] Additionally, PGE_2 may be related to induction of cell proliferation and inhibition of cell apoptosis.[17] Xiaoping et al.[18] showed high COX-2 expression in uterine fibroids, while it facilitated increased expression of PGE_2. Leahy et al.[19] suggested that use of COX-2 inhibitors may reduce the incidence of breast cancer. These authors found that removal of leiomyomas reduced serum PGE_2 concentrations, but there was no direct association between the anesthetic technique and serum PGE_2 concentrations.

There are limitations to this study. Although we found an association between the anesthetic technique and angiogenic factors in patients with uterine leiomyomas, we could not conclude that the anesthetic technique affects recurrence of uterine leiomyomas after abdominal myomectomy. This is because we did not have any follow-up details of these patients. Furthermore, our study was a single-center trial and the sample size was small. Prospective, multicenter, randomized, controlled, clinical trials are required to evaluate this hypothesis.

In summary, this prospective, randomized study shows that removal of leiomyomas reduces serum VEGF-C and PGE_2 concentrations at 48 hours after surgery. Additionally, SA with postoperative continuous epidural analgesia results in lower serum VEGF-C concentrations for abdominal myomectomy compared with GA with patient-controlled intravenous analgesia. The anesthetic technique affects serum VEGF-C concentrations, which might be associated with angiogenesis in surgery for leiomyomas.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

The study was supported by the National Natural Science Foundation of China (grant number: 81660198) and the Key R&D Program of Ningxia (grant number: 2016KJHM59).

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