British Journal of Anaesthesia **113** (S1): i49–i55 (2014)
Advance Access publication 25 June 2014 · doi:10.1093/bja/aeu148

BJA

Effect of thoracic epidural anaesthesia on serum vascular endothelial growth factor C and cytokines in patients undergoing anaesthesia and surgery for colon cancer

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Editor's key points

- It has previously been shown that propofol–paravertebral anaesthetic technique reduces postoperative increases in angiogenesis factors in breast cancer.
- This prospective, randomized, trial evaluated the effect of propofol-epidural technique on serum VEGF expression versus standard GA.
- Propofol-epidural technique reduces postoperative serum expression of angiogenesis markers in colorectal cancer surgery.

Background. Serum vascular endothelial growth factor-C (VEGF-C), transforming growth factor-β (TGF-β), and interleukin (IL)-6 promote angiogenesis and metastases in colon cancer. We hypothesized that patients who received propofol–epidural anaesthesia (PEA) would exhibit decreases in VEGF-C, TGF-β, and IL-6 and an increase in IL-10 compared with patients who received general anaesthesia (GA).

Methods. Colon cancer surgery patients were randomly assigned to the PEA (n=20) or GA (n=20) group. Serum VEGF-C, TGF-β, IL-6, and IL-10 levels before surgery and 24 h after surgery were measured.

Results. Patients who received PEA showed decreases in VEGF-C [526 (261) *vs* 834 (304) pg ml^{-1}, P=0.001], TGF-β (P=0.027), and IL-6 (P=0.007) and an increase in IL-10 (P=0.001) 24 h after surgery compared with patients subjected to GA. The visual analogue scale scores at rest and during coughing at 2 and 24 h after operation were significantly lower in PEA patients ($P<0.05$).

Conclusions. PEA reduces serum concentrations of factors associated with angiogenesis during colon cancer surgery.

Clinical trial registration. ChiCTR-TRC-13003146 (www.chictr.org).

Keywords: anaesthesia, general; anaesthetic techniques, epidural; cancer, colorectal; surgery, colorectal

Accepted for publication: 8 March 2014

Colon cancer is one of the five most prevalent cancers in the adult population.[1] Metastasis and recurrence after cancer surgery are major factors that affect survival. The reported rate of recurrence for colorectal cancer is 8–25%.[2] Local metastasis or recurrence largely depends on the balance between immune surveillance and the tumour's ability to spread.[3 4]

Angiogenesis can facilitate the delivery of oxygen, nutrients, and growth factors to tumour cells.[5] Tumour angiogenesis plays an essential role in the growth, invasion, and metastatic spread of solid neoplasms. A number of molecular factors can stimulate and maintain angiogenesis. Vascular endothelial growth factor-C (VEGF-C) is an important factor for the promotion of tumour angiogenesis.[6 7]

Regional anaesthesia has been postulated to have an effect on cancer outcome. Thoracic epidural anaesthesia and analgesia have commonly been used for the management of intra- and postoperative pain during colon cancer surgery. Because epidural anaesthesia blocks the afferent neural input, intra- and postoperative neuroendocrine stress responses can be decreased.[8] Thus, the use of epidural anaesthesia may protect patients from postoperative tumour metastasis or recurrence. Studies on the outcome of colon cancer have been both positive and negative.[9–12]

Propofol may attenuate cancer cell migration, proliferation, and metastasis *in vitro*.[13] Propofol also has cyclooxygenase (COX)-2 inhibitory activity.[14] As such, we hypothesized that patients who receive propofol–epidural anaesthesia (PEA) would exhibit decreases in angiogenic factors compared with those who receive general anaesthesia (GA) and sufentanil analgesia. A similar study evaluated propofol-paravertebral anaesthesia *vs* GA alone in breast cancer patients and previously found VEGF increases after GA.[15]

The primary endpoint was the change in perioperative VEGF-C concentration. Secondary endpoints included levels

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of transforming growth factor-β (TGF-β), interleukin (IL)-6, and IL-10 and also postoperative visual analogue scale (VAS) pain scores.

Methods

This randomized trial (ChiCTR.org ID ChiCTR-TRC-13003146) was conducted after approval from the Cancer Hospital, Fudan University Institutional Human Ethics Committee (Shanghai, China). After obtaining written informed consent, 40 ASA I–III patients aged 21–81 yr who underwent open colon cancer surgery were included in the trial. Patients with general contraindications for epidural anaesthesia, recent history (8 weeks) of chemotherapy or radiation, or any contraindication to the administration of midazolam, sufentanil, propofol, or sevoflurane were excluded.

The patients were randomly assigned to receive PEA or GA according to a computer-generated random numbers table. In the PEA group, using the paramedian approach, an epidural catheter was inserted under sterile conditions through the T_{9-12} interspace using the 'loss-of-resistance' technique. The catheter was advanced 4 cm cephalad. When the aspiration test results for blood and cerebrospinal fluid were negative, a test dose with lidocaine 1% (3 ml) was injected through the catheter. GA was induced by propofol plasma target-controlled infusion (TCI; a target plasma concentration of 3.5–4 μg ml^{-1}) using Marsh pharmacokinetic and Graseby 3500 TCI pump, and an i.v. midazolam 0.03 mg kg^{-1}, sufentanil 0.3 μg kg^{-1}, and cisatracurium 0.2 mg kg^{-1}. Anaesthesia was maintained with the TCI of propofol (a mean plasma concentration of 2.9 μg ml^{-1}). The loading dose of 0.375% ropivacaine was 6–8 ml, depending on the height and weight of the patient. Ropivacaine at 5 ml h^{-1} was then infused using a microinfusion pump for the duration of surgery. The analgesic agent was composed of ropivacaine 0.15% and sufentanil 0.5 μg ml^{-1}. Patients received patient-controlled analgesia with a continuous infusion of 4 ml h^{-1} and a 2 ml bolus on request with a 15 min lockout time. Analgesic regiments were supplied during 72 h.

The GA group had induction of balanced GA with midazolam 0.03 mg kg^{-1}, sufentanil 0.3 μg kg^{-1}, propofol 1–2 mg kg^{-1}, and cisatracurium 0.2 mg kg^{-1}. Anaesthesia was maintained with 1.0–1.5 minimum alveolar concentration sevoflurane. Intraoperative analgesia consisted of fentanyl 0.2–0.4 μg kg^{-1} h^{-1}. Room temperature was adjusted to 22–25°C. Oesophageal temperature was monitored and maintained above 36°C throughout the operation. Patients in the GA group received patient-controlled i.v. analgesia with sufentanil (1 μg ml^{-1}, with a bolus 2 ml, lockout time of 15 min, and background infusion rate of 2.5 ml h^{-1}). The analgesia was maintained for 72 h. Pain intensity was assessed using a 10 cm VAS at rest and during coughing at 2, 24, and 48 h after operation.

Venous blood was withdrawn before the operation and 24 h after operation. Samples were centrifuged at 4000 *g*. Thereafter, the serum was stored at −20°C for future measurement. Enzyme-linked immunosorbent assays were prepared for VEGF-C (Immuno-Biological Laboratories Co., Ltd, Japan) and TGF-β1 (DRG Instruments GmbH, Germany). Plasma levels of IL-6 and IL-10 were measured with commercially available quantitative sandwich enzyme-linked immunosorbent assay kits (Quantikine; R&D Systems, Minneapolis, MN, USA).

Previously published studies on VEGF suggested that its standard deviation (SD) *in vivo* is in the order of 200 pg ml^{-1}.[16 17] Fifteen patients would be required to detect a reduction of 1 standard deviation, 200 pg ml^{-1}, with an α-value of 0.05 and a power of 0.8. To compensate for potential dropouts, we enrolled 20 patients. The data were compared using an independent group *t*-test for parametric data and a Mann–Whitney *U*-test for non-parametric data. Differences in VAS scores were assessed using repeated-measures analysis of variance and corrected with a Tukey *post hoc* test. Categorical data were assessed using Fisher's exact test. The data are presented as mean (SD). $P<0.05$ was considered statistically significant.

Results

All patients completed the study according to the protocol. All procedures were performed by the same team of anaesthetists and surgeons (Fig. 1).

The groups were similar with respect to the mean age, body weight, height, male/female ratio, functional status, anaemia, albumin, diabetes mellitus, β-blocker, COX-2 inhibitor, and statin therapy (Table 1). Intraoperative blood transfusion, blood loss, time of surgery, and tumour stage were similar in both groups (Table 2). The consumption of intraoperative sufentanil was significantly higher in the GA group than that in the PEA group [51 (5.5) *vs* 20 (3.2) μg, $P<0.001$] (Table 2).

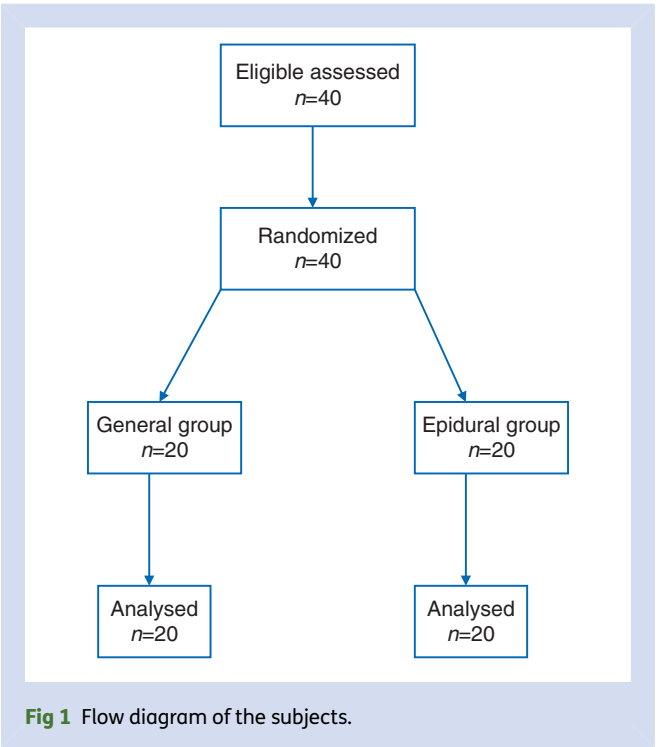

Fig 1 Flow diagram of the subjects.