Recovery Profiles of General Anesthesia and Spinal Anesthesia for Chemotherapeutic Perfusion with Circulatory Block (Stop-Flow Perfusion)

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BACKGROUND: Chemotherapeutic stop-flow perfusion is a new investigational treatment for locally advanced cancers that is usually performed under general anesthesia (GA), and, less frequently, under spinal anesthesia (SA). We designed this clinical trial to compare the clinical profiles of GA and SA for stop-flow perfusion.

METHODS: Anesthesia and recovery times, scores on visual analog scales for postoperative pain, and postoperative nausea and vomiting, and admission to the postanesthesia care unit were measured in 40 cancer patients who randomly received either GA with propofol, nitrous oxide/sevoflurane, and fentanyl, or SA with bupivacaine hydrochloride for lower limb or pelvic stop-flow perfusion.

RESULTS: GA and SA did not differ in times to achieve home readiness or patient satisfaction. Compared with GA, SA significantly ($P < 0.05$) reduced anesthesia times (34 vs 16 min), postoperative visual analog scale scores for pain (5 vs 0) and nausea (8 vs 2), and the number of admissions to the postanesthesia care unit (9 vs 0).

CONCLUSIONS: For stop-flow perfusion, GA and SA are both effective, but SA provides faster recovery, superior analgesia, and less postoperative nausea and vomiting in the immediate postoperative period.

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Systemic chemotherapy often has a limited therapeutic effect on locally advanced cancers because anticancer drugs are highly toxic (1) and can be given only at low, hence not quite effective, doses (2). Hypothetically, a better therapeutic effect may be achieved by delivering larger doses of drugs directly in the arterial supply to cancers. In recent years, different techniques have been developed, such as stop-flow perfusion, that are aimed at delivering larger local concentrations of chemotherapeutic drugs and enhancing their cytotoxic effects by hypoxia. Our hospital is conducting a phase III trial on stop-flow perfusion for cancers in the pelvis (i.e., colorectal cancers) and in the limbs (i.e., skin melanomas and soft tissue sarcomas) (3–6).

Stop-flow perfusion is an invasive procedure that involves temporary vascular isolation of the pelvis or limbs by pneumatic balloons and then surgical insertion of stop-flow perfusion catheters. Hence, stop-flow perfusion requires immobilization of the patient, and is performed most frequently under general anesthesia (GA) (2,4,7–14). We recently reported a pilot use of spinal anesthesia (SA) indicating that SA is safe, effective, and a potentially, the anesthesia of choice for stop-flow perfusion (15). In the present study, we systematically compared GA and SA for stop-flow perfusion in terms of times of anesthesia, postoperative recovery, and patient satisfaction.

METHODS

After obtaining IRB approval at the Department of Anesthesiology of Padova University, Italy, and written informed consent, 40 consecutive patients with ASA physical status I–III were enrolled in a stop-flow perfusion phase III trial for unresectable or metastatized cancers in the lower limbs or pelvis. Inclusion criteria and technical details for stop-flow perfusion have been reported elsewhere (15). Before stop-flow perfusion, patients had diagnostic work-up and blood testing, including a coagulation panel. Patients were assigned to the GA group or the SA group for stop-flow perfusion by using a computer-generated random table.

After overnight fasting, a 18–16-gauge IV line was placed in the arm and an infusion of saline solution established. Before anesthesia, patients were premedicated by IV administration of cephazoline 2 g, midazolam 0.05 mg/kg, atropine 0.01 mg/kg, and sodium

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chloride solution 0.9% 8–10 mL/kg. All patients had heart rate and hemoglobin oxygen saturation measured continuously and arterial blood pressure at 5-min intervals. GA patients also had inspiratory and expiratory end-tidal gas concentrations (oxygen, carbon dioxide, nitrous oxide, and sevoflurane), bispectral index (BIS Monitor, Aspect Medical System Inc., Newton, MA), the adductor pollicis train-of-four ratio (TOFR) (TOF-watch Organon Teknik, Ireland), and urine flow monitored.

In the GA group, anesthesia was induced with IV propofol 2–3 mg/kg and IV fentanyl 1–2 μg/kg and maintained with nitrous oxide 70% in oxygen with a gas flow of 3–4 L/min. During stop-flow perfusion, sevoflurane was delivered at concentrations (between 0.8% and 1.2%) to maintain a target bispectral index value of 50 and fentanyl 1–2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ was administered IV for analgesic purposes. IV boluses of vecuronium were given before stop-flow perfusion to facilitate tracheal intubation (0.1 mg/kg) and during stop-flow perfusion to maintain neuromuscular block (TOFR >0.5) (0.03 mg/kg). In the SA group, anesthesia was performed with the patient in the sitting position. After skin infiltration with lidocaine 1%, a Sprotte 25-gauge needle (Sprotte–Kanüle, Pajunk, Germany) was inserted at either the L1–2 interspace for pelvic stop-flow perfusion or at the L2–3 interspace for limb stop-flow perfusion. After a free flow of cerebrospinal fluid was obtained, 15 mg of hyperbaric bupivacaine 1% was injected, and the patient was positioned supine. In case of passive or active aspiration of blood, the procedure was interrupted and repeated at another interspace. The patient was evaluated for the onset of sensory and motor block (i.e., complete inability to feel cold stimulus by diethyl ether and to move legs).

Chemotherapeutic stop-flow perfusion was performed as described elsewhere for 20 min (5,15). Before insertion of stop-flow perfusion catheters, and in the SA group at least 1 h apart from the administration of SA, sodium heparin (150–200 UI/kg) was given IV. Crystalloids or colloids were administered IV at approximately 10 $mL \cdot kg^{-1} \cdot h^{-1}$ and their total volume depended on the duration of the procedure, hemodynamic stability, and the actual loss of fluids (i.e., blood, urine, and fluids in the extracorporeal circuit). Atropine 0.5 mg was given IV in case of bradycardia (i.e., ≤40 bpm), and colloids or crystalloids and IV etilefrine 2 mg in case of significant hypotension (i.e., systolic arterial blood pressure below 90 mm Hg or 50 mm Hg below baseline). Dexamethasone 4 mg was administered IV before ending stop-flow perfusion as prophylaxis for postoperative nausea and vomiting (PONV). After completion of stop-flow perfusion, chemotherapeutics were filtrated from the blood of the extracorporeal circuit. IV protamine sulfate was given in doses to neutralize approximately half the heparin in the stop-flow perfusion circuit, and IV neostigmine 2 mg along with atropine 0.01 mg/kg to reverse vecuronium when TOFR values were between 0.5 and 0.8. IV ketorolac 30 mg was administered just before the end of stop-flow perfusion. Once suitable conditions were reached (TOFR >0.8, respiratory rate <24, and tidal volume >5 mL/kg), the trachea was extubated and patients were evaluated for appropriate transfer to the postanesthesia care unit (PACU) or to the ward.

Table 1. Demographics, ASA Status, Length of Stop-Flow Perfusion and of Hospital Stay in Patients Undergoing General Anesthesia (GA) or Spinal Anesthesia (SA) for Stop-Flow Perfusion

Patients	GA group	SA group
Male/female gender (*n*)	9/11	12/8
Age (yr)	62.6 ± 10.7	65.5 ± 16.8
Weight (kg)	69.5 ± 12.7	65.2 ± 9.3
ASA physical status (I/II/III) (*n*)	7/9/4	5/8/7
Stop-flow perfusion duration (min)	185 ± 18	171 ± 27
Hospital stay (d)	9.1 ± 6.3	7.15 ± 3.4

Data are expressed as means ± SD.

Group gender data have been compared by χ^2 test, all other data by Student's *t*-test.

Arterial blood pressure, heart rate, and oxygenation were monitored postoperatively in all patients, level of consciousness in GA patients, pain, and sphincter, motor (i.e., Bromage scale) (15) and sensory (i.e., pinprick test) functions in SA patients. These variables were assessed until normalization, continuously in the PACU and every 15 min in the ward. Ketorolac 30 mg IV was administered every 8 h as prophylaxis for postoperative pain. In addition, fentanyl 1–2 μg/kg, ketorolac 30 mg, or paracetamol 1 g was administered when needed for severe (visual analog scale [VAS] score >7), moderate (VAS score >3 <7), or mild (VAS score <3) pain, respectively, and IV granisetron 3 mg for nausea and vomiting.

PACU admission required the patient to have unstable cardiovascular (mean arterial blood pressure <70 or >105 mm Hg) or respiratory status (hemoglobin oxygen saturation <95% or >95% with oxygen supplementation) or altered level of consciousness 10 min after the end of the procedure. Ward admission required the patients to be awake and alert, with stable vital signs, and free of PONV or bleeding. Residual spinal block (i.e., Bromage score ≤3) was allowed at the time of transfer to hospital ward.

Anesthesia times included preoperative preparation and postoperative times. Preparation time was measured in the GA group from the start of administration of oxygen to the beginning of mechanical ventilation, and in the SA group from patient positioning to the onset of the anesthetic block. Postoperative time was measured in both groups from stop-flow perfusion completion (positioning of the compressive dressing) to admission to the ward or to the PACU. Ten minutes after ending of anesthesia patients were asked to rate pain and PONV by using a VAS ranging from 0 (none) to 10 (worst) and were asked to answer the following question: "How

Table 2. Anesthesia and Recovery Times, Postoperative Complaints and Satisfaction in Patients Undergoing General Anesthesia (GA) or Spinal Anesthesia (SA) for Stop-Flow Perfusion

	GA group	SA group	*P*
Anesthesia preparation time	11 ± 3.8	16 ± 2.5	<0.05
Anesthesia postoperative time	23.4 ± 5.6	—	—
Overall anesthesia time	34.3 ± 8.4	16 ± 2.5	<0.05
Admission to PACU	9	0	<0.05
Patient satisfaction (yes/no)	14/6	18/2	0.11
Anxiolytic therapy	—	9	—
Sedative therapy during stop-flow perfusion	—	3	—
Perioperative hypotension	4	7	0.29
Perioperative bradycardia	0	1	0.31
Postoperative pain (VAS >3)	5	0	<0.05
PONV (VAS >3)	8	2	<0.05

VAS values were determined at 10 min after ending of stop-flow perfusion.

Group mean times are expressed as min ± SD; all other data are numbers of patients ± SD.

Group times were compared by Student's *t*-test; all others by χ^2 test.

PACU = postanesthesia care unit; PONV = postoperative nausea and vomiting; VAS = visual analog scale.

would rate your satisfaction with the anesthesia provided (satisfied or dissatisfied)?"

Gender group differences were analyzed for statistical significance by χ^2 statistics; all other demographic and outcome data by Student's *t*-test. Significance was taken as $P < 0.05$ in all cases.

RESULTS

Patient demographic data, duration of stop-flow perfusion, hospital stay, and patient satisfaction were not different between groups (Tables 1 and 2).

Mean preoperative preparation time was significantly longer in the SA group, whereas postoperative time was longer in the GA group (Table 2). After completion of stop-flow perfusion, all SA patients were admitted to the ward. Nine of 20 GA patients were admitted to the PACU ($P < 0.05$) (Table 2). In the GA group, patients who needed the PACU were significantly ($P < 0.05$) older than those who did not (72 ± 4 vs 54 ± 7, mean years of age ± SD).

Moderate hypotension and bradycardia were observed shortly after anesthesia induction and promptly treated by fluid infusion or atropine. No major hemodynamic alteration was recorded during stop-flow perfusion in either group (Table 2).

In the immediate postoperative period, pain and PONV of moderate intensity (VAS score 3–7) occurred significantly in more GA than in SA patients ($P < 0.05$) (Table 2). No patient reported severe (VAS score >7) pain or PONV, and there was no patient complication that could be related to GA or SA, neither during nor after stop-flow perfusion.

DISCUSSION

Stop-flow perfusion is a new aggressive chemotherapy in which the therapeutic effects of high local concentrations of anticancer drugs are enhanced by hypoxia. SA and GA for stop-flow perfusion were similarly well tolerated and appreciated by our patients. SA with bupivacaine, however, was superior to GA with sevoflurane in reducing anesthesia time, PONV, and the number of admissions to the PACU.

Reportedly, stop-flow perfusion has been associated with serious complications, such as deep venous thrombosis, pulmonary embolism, arterial vascular lesions (5,11), and with some deaths (2). In our patients, GA and SA both allowed completion of stop-flow perfusion with some side effects but without complications. Hypotension, with or without bradycardia, is a well-known occurrence of GA and SA and was easily controlled by the infusion of colloids.

GA with sevoflurane provided rapid awakening, and recovery of orientation and ability to respond to commands (16,17). However, older patients receiving GA and those in whom stop-flow perfusion lasted longer had a slower recovery of consciousness and needed admission to the PACU for oxygen supplementation and monitoring of level of consciousness (16). SA patients had a residual sensory-motor block of the lower limbs that turned out to be an advantage in terms of pain control rather than a limitation for ward admission. In addition, groin hematomas, because of the loosening of the compression from leg movements, were observed in two patients in the GA group but not in any SA patient.

No patient complained of severe pain (VAS score >7). However, after stop-flow perfusion moderate (VAS score 3–7), pain and PONV were reported more often in GA patients than in SA patients. Pain was generally referred to the perfusion area, but also to the site of percutaneous puncture and was exacerbated by compression. Because, after stop-flow perfusion, anticancer drugs were filtrated from blood in the extracorporeal circuit, PONV was probably related to GA (18). Paracetamol and granisetron were always effective in treating postoperative pain and PONV.

The overall duration of the procedure, including preoperative and postoperative times, was significantly longer in the GA group. Although the preparation time was significantly longer in the SA group, no additional time was required at the end of the procedure. However,

preparation was shorter in the GA group, but a considerable amount of time was required at the end of GA because patients required extubation and evaluation in the first 10 min before transfer to the ward or the PACU. The increase in PACU admission after GA makes it less advantageous compared with SA.

In conclusion, GA and SA are both effective for stop-flow perfusion, but SA provides faster recovery, superior analgesia, and less PONV in the immediate postoperative period.

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