

Propofol/Remifentanil Vs Desflurane/Fentanyl in Open Hemicolectomy Surgery

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Abstract

In a prospective, randomized, parallel-group study the aim was to compare TIVA (total intravenous anesthesia) with propofol / remifentanil and anesthesia with desflurane / fentanyl in open hemicolectomy surgery. 10 patients were randomly assigned each group. The primary endpoint hemodynamic stability was evaluated as number of dose-adjustments due to responses to surgery (hypertension, tachycardia, somatic or autonomic responses). Catecholamine levels, recovery times after anesthesia, postoperative variables and costs were also evaluated. There were no significant differences between the two groups in number of dose-adjustment due to responses to surgery ($P = 0.88$). One min after skin incision arterial noradrenaline levels were 59 ± 14 pg/ml in the TIVA-group and 262 ± 87 pg / ml in the desflurane-group ($P < 0.01$). Corresponding adrenaline levels were 16 ± 3 and 38 ± 12 pg/ml ($P < 0.05$), respectively. Recovery times after anesthesia were not significantly different between the two groups. In the TIVA-group we found significant increased use of opioids ($P = 0.034$), a trend towards increased use of epidural analgesia ($P = 0.06$) and about 30% higher costs ($P = 0.03$). We conclude that hemodynamic stability is not different between the two types of anesthesia in patients undergoing open hemicolectomy. TIVA reduces catecholamine levels and increases postoperative analgesic demands and costs.

Keywords: Abdominal surgery; Catecholamines; Desflurane; Fentanyl; Propofol; Remifentanil

Introduction

TIVA (total intravenous anesthesia) with propofol/remifentanil is well documented with regard to effect, tolerability and safety [1]. Propofol has rapid onset and clearance [2] and inhibits postoperative nausea and vomiting [3]. Remifentanil has rapid onset, followed by rapid recovery, due to degradation by non-specific blood and tissue esterases [4]. Recovery is relatively independent of doses, duration of the infusion and liver and kidney function. Thus, it can be administered in high doses during surgery, without delaying postoperative recovery.

The role of TIVA with propofol/remifentanil is well established in ambulatory- and minor surgery, whereas its role in major surgery, such as open abdominal surgery, is not established. Remifentanil has been shown to increase immediate postoperative pain levels after major abdominal surgery [5] and to increase the demand for postoperative analgesia [6]. In addition to analgesia, amnesia, and sleep, general anesthesia should also inhibit somatic, autonomic and hemodynamic responses to surgical trauma. Hemodynamic stability is important because tachycardia, hypertension and hypotension increase risk for perioperative cardiac complications [7,8]. Remifentanil reduces the response to pain stimuli and dose-dependently reduces systemic blood pressure and heart rate [9-11]. Propofol also affects the cardiovascular system, predominantly by peripheral vasodilation [3].

Today balanced anesthesia with a volatile agent and an opioid is mainly used in major abdominal surgery. Desflurane is often used to maintain anesthesia, because recovery and extubation are faster than for other volatile agents [12,13]. It is often combined with bolus injections of fentanyl. Different opioids (including remifentanil) have been investigated in combination with volatile agents for different surgical procedures. As far as we are aware of, there are only three studies [14-16] reporting a comparison between TIVA and balanced anesthesia with a volatile agent and opioids in abdominal surgery. [14] compared TIVA and anesthesia with sevoflurane/fentanyl in gynecological laparoscopic surgery and found reduced recovery time and time to extubation in the TIVA-group. In contrast [15], found

faster recovery time and time to extubation after desflurane / fentanyl based anesthesia than after TIVA in open abdominal prostatectomy surgery. No perioperative data were presented. They also found higher perioperative costs in the TIVA-group than in the desflurane-group [16]. Compared propofol / remifentanil with sevoflurane/remifentanil in elective abdominal and urological operations lasting over 3.5 hours and found minimal shorter time to extubation in the TIVA group, whereas other per- and postoperative parameters did not differ. Costs were not evaluated [16]. None of these studies evaluated catecholamine levels.

Our objective was to compare TIVA with propofol / remifentanil and desflurane / fentanyl anesthesia in open hemicolectomy surgery. This is a relative homogenous surgical procedure, with regard to surgical trauma and duration of surgery. We hypothesized that type of anesthesia influences perioperative hemodynamic stability, catecholamine levels, recovery characteristics, postoperative characteristics, including analgesic demand, and costs.

Materials and Methods

We included 20 patients (all non-smokers) scheduled for open hemicolectomy due to colon cancer in a prospective, randomized, parallel-group study at Oslo University Hospital, Ullevål. Patients in American Association of Anesthesiologists (ASA) classification 1-3 were included. Exclusion criteria were pregnancy, abuse of drugs or alcohol, routine use of sedative drugs, previous malignant hyperthermia, known hypersensitivity for opioids, severe

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cardiovascular or pulmonary impairment, psychiatric disorders or participation in another pharmacological research project. All patients gave their informed consent and the study was in accordance with the Helsinki Declaration. The regional ethical committee approved the study.

Experimental procedure

Patients were included one day before surgery. Randomization was performed by opening a sealed envelope. After fasting over night they were premedicated with paracetamol (1-2 g) and diazepam (5-10 mg) \approx one hour before surgery. In the operating room, two cannulas were placed in large superficial veins for infusions. A catheter was inserted in a. radialis for blood pressure recordings and blood sampling. Standard monitoring was used, with continuous monitoring of the electrocardiogram, arterial blood pressure, peripheral oxygen saturation, end-tidal carbon dioxide (CO₂) partial pressure and bispectral index (BIS) (Aspect Medical System, Spacelabs Medical, model A1050 software 1.21, Aspect, WA, USA). Before anesthesia Ringer acetate (5 ml / kg) was administered and an epidural catheter introduced (Th₆₋₁₀). After adequate preoxygenation, tracheal intubation was performed, facilitated by cisatracurium (0.15 mg / kg iv). In the TIVA-group (n=10) anesthesia was induced by remifentanyl (0.1-0.5 μ g / kg/min iv) and propofol (1.0-1.5 mg / kg iv). Maintenance was provided by remifentanyl (0.2-0.7 μ g / kg/min iv) and propofol (3-10 mg / kg/t iv). In the desflurane-group (n=10) anesthesia was induced by pentobarbital (4-5 mg / kg iv) and fentanyl (0.2-0.3 mg iv). Maintenance of anesthesia was provided by fentanyl (0.1-0.2 mg iv) and desflurane (0.8-1.0 MAC - minimal alveolar concentration). Patients were ventilated in a pressure-controlled mode by a ventilator with 40-60 % oxygen in air with a fresh gas flow of 0.7-1.5 l / min (Draeger Primus, Draeger Medical, Lübeck, Germany). Ventilation was adjusted to obtain end-tidal CO₂ partial pressure within a range of 4.5-6.0 kPa. Epidural analgesia (bupivacain 1 mg/ml, fentanyl 2 μ g/ml and adrenaline 2 μ g/ml) started \approx one hour before end of surgery after giving a bolus of 4 ml bupivacain (5 mg/ml). Droperidol (1.25 mg iv) was given at end of surgery. Supplementation of cisatracurium was given as required. Neuromuscular blockade was antagonized with neostigmine (2.5 mg) and glucopyrrolate (0.5 mg). In both groups fentanyl (0.05-0.3 mg iv) was given at end of surgery. During the last 30 min of surgery it was allowed to reduce infusion rates of remifentanyl and propofol and delivery of desflurane according to clinical needs. After the last skin suture, all drugs were discontinued. Patients were treated according to common practice and followed until 07.00 the next day. To treat postoperative pain ketobemidone was used as rescue medication.

Catecholamine analysis

Arterial samples for catecholamine analysis (TIVA-group: n = 8, desflurane-group: n = 4) were obtained 1) before anesthesia, 2) after induction of anesthesia, 3) one min after skin incision and 4) one min after colectomy. Blood was immediately mixed with glutathione and EGTA (ethylene glycol tetra-acetic acid) in prechilled glass tubes, put on ice and centrifuged at 4°C within one hour. Plasmas were frozen at -80°C. Plasma catecholamines were measured by a radioenzymatic technique according to [17], as previously reported [18]. The same technician performed the assay on all samples.

Endpoints

The primary endpoint was defined as number of dose adjustments due responses to surgery from 10 min after start of surgery to end of surgery. The first 10 min of surgery was used to determine a stable

level of anesthesia. Responses to surgery was defined as either 1) episodes of hypertension (systolic blood pressure > 150 mmHg > 1 min), 2) episodes of increased heart rate (heart rate > 90 slag / min > 1 min), 3) somatic responses (movements, swallowing, eye opening or grimacing) or 4) autonomic responses (lacrymation, sweating). In the TIVA-group these responses were treated with stepwise increases in remifentanyl by 0.1 μ g / kg/min. In addition, propofol (10-20 mg iv) as a bolus might be given. In the desflurane-group, these responses were treated with stepwise increases in end expiratory concentrations. In addition, fentanyl (0.1-0.2 mg iv) as a bolus might be given.

Secondary endpoints were:

- Hypotension (systolic blood pressure < 80 mmHg > 1 min). In the TIVA-group hypotension was treated with 100-200 ml Ringer acetate, stepwise reductions by 50% per min in the remifentanyl infusion or vasopressors. In the desflurane-group hypotension was treated with 100-200 ml Ringer acetate, stepwise reductions in end expiratory concentrations or vasopressors.
- Bradycardia (heart rate < 40 beats/min > 1 min). Episodes were treated with atropin iv.
- Consumption of anesthetic- and vasoactive drugs during surgery.
- Recovery characteristics after anesthesia. Time from end of surgery until: 1) spontaneous and adequate respiration (respiration frequency > 8 breaths/min), 2) response to verbal stimuli (opening of eyes or movement of limbs), 3) extubation, 4) full orientation (able to state name and date of birth).
- Postoperative variables. Length of stay at the intensive care unit (ICU), consumption of drugs and iv fluids.
- Costs. Costs due to drugs per- and postoperatively and one infusion set peroperatively was calculated for each patient. Blood products and iv fluids were not included, because they depend more on the surgical procedure than of type of anesthesia. Costs for oxygen, bupivacain, paracetamol, disposables (cannulae, orotracheal tubes and infusion lines), staff (physician and nurses) and other overhead costs (e.g. anesthesia machines and monitoring) were not included.

Consumption of desflurane was calculated by weighing the amount of desflurane used. Before induction of anesthesia the vaporizer (Tec 6, Datex Ohmeda, Steeton, West Yorkshire, UK) was filled completely. After end of surgery, a bottle of desflurane that was weighed on a precision weighing machine (Sartorius AG, model BA 4100S, Göttingen, Germany), was used to completely fill the vaporizer. Thereafter, the bottle of desflurane was weighed again. Conversion from g to ml was obtained by using the specific weight of desflurane (1.465 g / ml).

Statistics

Data are presented as mean \pm standard error of the mean (SEM). Normally distributed data were analyzed by t-test (single variables between groups), ANOVA test with Holm-Sidak method (changes over time within groups) or MANOVA test (data over time between groups). Data not normally-distributed, according to the Kolmogorov-Smirnov test, were analyzed with Mann-Whitney rank sum test or Friedman test with Dunnett` post-hoc test. Proportions were analyzed with z-test. Statistical analyses were performed by the programs Statistica and Sigmapstat. All statistical tests were two-sided. A *P* value < 0.05 was considered significant.

Results

Group characteristics are given in (Table 1). There were no significant differences between the two groups for any variables. No serious complications were seen. Perioperative drug requirements are given in (Table 2). There were no significant differences between the two groups, except that more fentanyl was used in the desflurane-group ($P < 0.001$).

There were no significant difference between the TIVA-group and the desflurane-group in number of dose adjustments due responses to surgery from 10 min after start of surgery to end of surgery (0.8 ± 0.4 vs 0.7 ± 0.2 , $P = 0.88$) or in episodes of hypotension (1.8 ± 0.3 vs 1.6 ± 0.6 , $P = 0.31$). No episodes of bradycardia were seen in either group.

No significant differences were observed between the groups in heart rate, invasive blood pressures or BIS either before anesthesia or during surgery. From before anesthesia to 10 min after start of surgery a significant reduction in heart rate was observed in the TIVA-group (17 ± 4 beats/min, $P < 0.001$), but not in the desflurane-group ($P = 0.23$) (Figure 1). There was also a significant reduction both in systolic and diastolic blood pressure from before anesthesia to 10 min after start of surgery (both groups $P < 0.001$). The reduction in systolic blood pressure was significantly greater in the TIVA-group (58 ± 5 vs 27 ± 9 mmHg, $P = 0.011$). A trend towards a greater reduction in diastolic blood pressure was also found in the TIVA-group (34 ± 5 vs 25 ± 4 mmHg, $P = 0.17$).

	TIVA-group	Desflurane-group	P-value
ASA-classification (1-4)	2.3±0.2	2.6±0.2	0.27
Age (years)	73±3	75±6	0.20
Height (cm)	174±3	170±3	0.34
Weight (kg)	75±5	71±4	0.20
Sex (male/female)	7/3	3/7	0.37
Previous abdominal surgery	5/10	3/10	0.65
Right hemicolectomy	5/10	7/10	0.65
Duration of surgery (min)	149±17	118±9	0.15
Duration of anesthesia (min)	195±21	165±11	0.21
Peroperative bleeding (ml)	410±130	310±90	0.73
Peroperative fluid balance (ml)	3110±200	3240±270	0.70

Data are given in mean ± SEM. ASA: American Association of Anesthesiologists, TIVA: total intravenous anesthesia

Table 1: Group characteristics.

	TIVA-group	Desflurane-group	P-value
Remifentanyl (mg)	3.68±0.52	-	-
Propofol (mg)	933±148	-	-
Fentanyl (mg)	0.18±0.03	0.47±0.03	<0.001
Pentobarbital (mg)	-	260±30	-
Desflurane (ml)	-	113±17	-
Cisatracurium (mg)	15±2	13±1	0.71
EDA (ml)	7.6±1.1	6.2±0.9	0.35

Data are given in mean ± SEM
EDA: epidural analgesia, TIVA: total intravenous anesthesia

Table 2: Perioperative drug requirements.

	TIVA-group	Desflurane-group	P-value
Length of stay ICU (hours)	8.8±1.3	6.3±2.3	0.62
Fluid balance (ml)	3050±370	3200±360	0.83
Total bleeding (ml)	410±120	310±100	0.73
Ketobemidone (mg)	10.0±2.7	3.0±1.3	0.034
EDA (ml)	142±0	109±13	0.06
Metoclopramide (mg)	8±4	5±3	0.50

Data are given in mean ± SEM. EDA: epidural analgesia, ICU: intensive care unit, TIVA: total intravenous anesthesia

Table 3: Postoperative characteristics during the study period.

Arterial catecholamine levels were not significantly different between the two groups before anesthesia. Noradrenaline levels were consistently lower in the TIVA-group than in the desflurane group, both after induction of anesthesia and at the two time points during surgery (Figure 2). The same trend was also seen for adrenaline levels, although significant only at one min after skin incision. One min after skin incision arterial noradrenaline levels were 59 ± 14 pg/ml in the TIVA-group vs 262 ± 87 pg/ml in the desflurane-group ($P < 0.01$). Corresponding adrenaline levels were 16 ± 3 and 38 ± 12 pg/ml ($P < 0.05$), respectively.

With regard to recovery characteristics, we found a trend towards reduced time for response to verbal stimuli in the TIVA-group ($P = 0.07$). There were no significant difference in time from end of surgery until spontaneous and adequate respiration ($P = 0.52$), time to extubation ($P = 0.26$) or time to full orientation ($P = 0.28$).

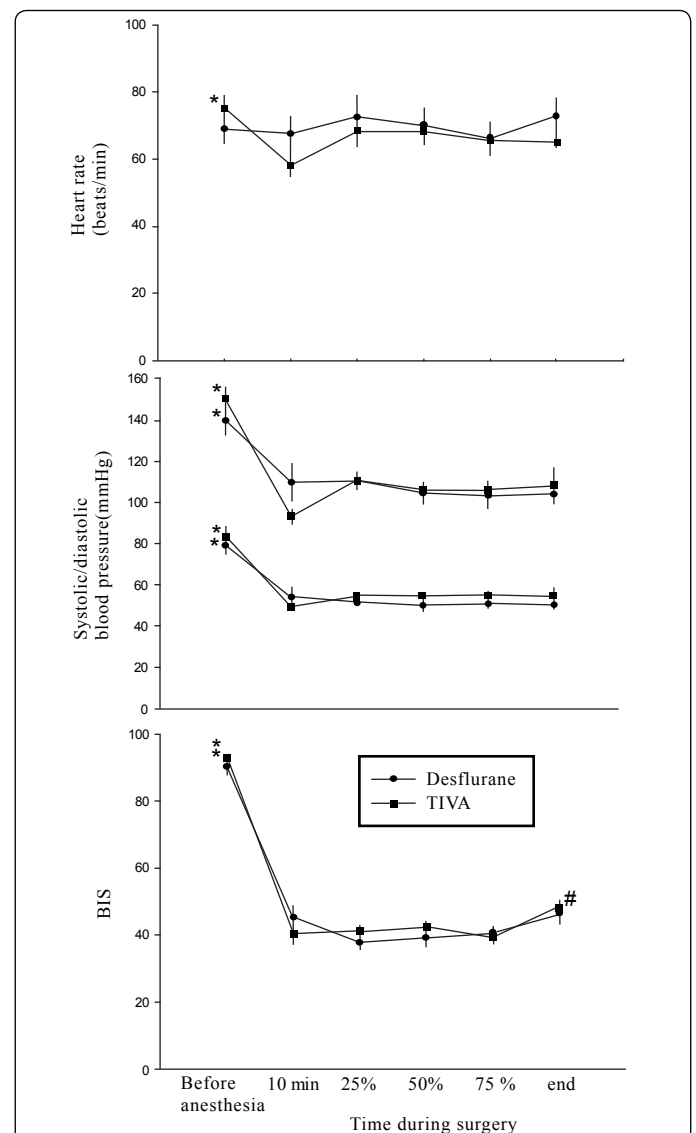
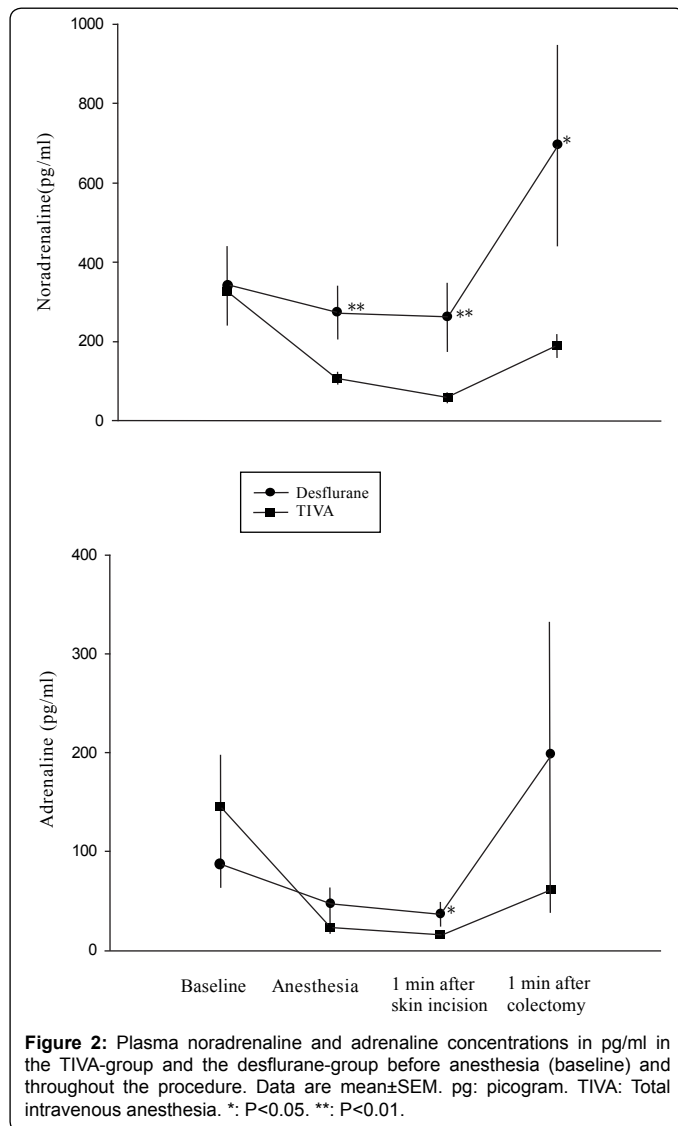


Figure 1: Heart frequency, systolic/diastolic blood pressure and BIS before anesthesia and during surgery (10 min after start of surgery, at 25, 50, 75 % duration of surgery and at end of surgery) in the TIVA-group and desflurane-group. Data are mean±SEM. BIS: Bispectral index. TIVA: Total intravenous anesthesia. *: $P < 0.001$ vs all times during surgery, #: $P < 0.05$ vs other time points during surgery.



There were no significant differences between the two groups in length of stay in ICU, fluid balance, total bleeding or in consumption of antiemetic drugs (Table 3). A significant higher requirement of ketobemidone ($P = 0.034$) and a trend towards increased consumption of epidural analgesia ($P = 0.06$) were observed in the TIVA-group.

Perioperative costs during surgery and total costs during the whole observation period were significantly higher in the TIVA-group than in the desflurane-group (perioperative costs 430 ± 52 vs 293 ± 25 NOK, total costs 632 ± 63 vs 455 ± 42 NOK, for both: $P = 0.03$). A trend towards higher postoperative costs was also found in the TIVA-group ($P = 0.13$).

Discussion

Both types of anesthesia studied are safe and effective and produce stable hemodynamic conditions during open hemicolectomy surgery. Lower levels of catecholamines, increased use of postoperative analgesia and higher costs in the TIVA-group were found, with no differences in recovery characteristics or other postoperative variables.

The primary endpoint, defined as number of dose adjustments due responses to surgery from 10 min after start of surgery to end of surgery, was not statistically different between the two groups. In this interval hemodynamic variables were not significantly different. As far as we are aware of, this is the first study in which hemodynamic stability during TIVA with propofol/ remifentanil has been compared with opioid potentiated desflurane anesthesia during open abdominal surgery and related to catecholamine levels [15]. Compared TIVA (propofol / remifentanil) and desflurane/ fentanyl based anesthesia during open prostatectomy surgery, but no perioperative data were presented [14], compared TIVA (propofol / remifentanil) with sevoflurane / fentanyl during gynecological laparoscopic surgery and found significantly lower perioperative heart rate in the TIVA group than in the sevoflurane / fentanyl group. However, no objective measures for depth of anesthesia were used to guide their administration of anesthetics [14]. Under BIS guidance, [16] compared propofol / remifentanil with sevoflurane / remifentanil in elective abdominal and urological operations lasting over 3.5 hours and found comparable perioperative hemodynamics in the two groups.

During induction of anesthesia we observed a reduction in heart rate in the TIVA-group, but not in the desflurane-group. Systemic blood pressure also declined more in the TIVA-group than in the desflurane-group. These findings are in accordance with the lower levels of catecholamines found in the TIVA-group. Arterial plasma catecholamines may be used as markers of overall sympathetic activity. Noradrenaline in plasma is derived from sympathetic nerves and adrenaline is derived from the adrenal gland [19]. The hemodynamic data are also in accordance with previous studies showing transient cardiovascular stimulation during desflurane anesthesia in humans [20,21]. This aspect might be of importance for induction of anesthesia in elderly people with cardiovascular diseases.

During recovery from anesthesia we observed a trend towards reduced time for response to verbal stimuli in the TIVA group. There were no significant differences in time until spontaneous and adequate respiration, time to extubation or time to full orientation. In gynecological laparoscopic surgery [14] found reduced recovery time and time to extubation in TIVA anesthesia compared to sevoflurane/fentanyl based anesthesia. In contrast, [15] found faster recovery time and time to extubation after desflurane / fentanyl based anesthesia than after TIVA anesthesia in open abdominal prostatectomy surgery. Aspects such as when the epidural analgesia was started perioperatively (≈ 1 hour before end of surgery in our study), additional drugs given (droperidol 1.25 mg in our study) and criteria for how and when anesthesia should be reduced and stopped probably explain the different results. In the present study administration of the anesthetics could be reduced at the end of the surgical procedure based on the clinic / BIS and stopped when the last suture had been performed.

Postoperatively, we found higher use of the rescue medication ketobemidone and a trend towards increased consumption of epidural analgesia ($P = 0.06$) in the TIVA-group compared to the desflurane-group. These findings are in accordance with previous data showing that intraoperative administration of remifentanil increases postoperative pain and morphine requirements [6]. Increased requirements for postoperative analgesia are also in accordance with data presented by Hansen et al. [5]. They found that remifentanil ($0.4 \mu\text{g} / \text{kg} / \text{min}$), in addition to general and epidural anesthesia, increased pain levels and requirements for postoperative analgesia in the immediate postoperative period after major abdominal surgery.

We found approximately 30% higher costs in the TIVA-group compared to the desflurane-group. This is in accordance with findings during open abdominal prostatectomy surgery, where over 60% higher costs were found in the TIVA-group compared to desflurane/fentanyl based anesthesia [15]. Higher costs in the TIVA-group were not compensated for by shorter stay at ICU or reduced consumption of antiemetic drugs. Dolk et al. [22] also found significant lower costs for desflurane anesthesia than for TIVA during ambulatory knee arthroscopy. Increased costs are important today as economical analysis of different anesthesiological regimen is mandatory in the present hospital climate of cost reductions.

A general limitation of many studies in which anesthesiological methods have been evaluated with regard to hemodynamic stability, recovery characteristics and costs is that the criteria for administration of drugs are relatively vague (increased heart rate and blood pressure perioperatively). Objective measures on depth of anesthesia have not been used and studies have often been performed on short lasting and little pain provoking day surgical interventions. In the present study patients scheduled for open hemicolectomy due to ca. coli were included and BIS, an objective measure on depth of anesthesia, was used to guide administration of the anesthetics.

An obvious limitation of the present study is that only 10 patients were included in each group. However, we included only patients scheduled for open hemicolectomy, which is relative homogenous population, with regard to surgical trauma and duration of surgery. In many studies different types of patients have been included. Power calculations show a power of 0.805 to find a difference of 0.9 dose adjustments between the two groups with the observed standard deviation (0.675) and α of 0.05. Thus, the statistical power is adequate to exclude a large difference between the two groups. However, we can not exclude small differences in some variables.

A potential limitation of our study is that patients were not followed over the exact same time interval. All patients were operated during early day-time and followed until 07.00 the next morning. Observation times were 17.6 ± 0.5 hours in the TIVA group and 17.4 ± 0.6 hours in the desflurane group ($P = 0.79$). Thus, this aspect should not affect the results.

Another potential limitation is the use of different opioids in combination with propofol and desflurane. Ideally, remifentanyl should have been used in both groups. However, we chose to compare TIVA (propofol / remifentanyl) with the standard regimen used in Scandinavia for major abdominal surgery; fentanyl potentiated desflurane anesthesia. Propofol, instead of pentobarbital, could have been used during induction of anesthesia in the desflurane-group. However, pentobarbital is the common hypnotic used during induction in this setting in Scandinavia. Pentobarbital, or its metabolites, have no analgesic effects and the drug is short acting. Thus, it can hardly influence our main findings.

Peroperative hemodynamic stability during TIVA with remifentanyl / propofol and anesthesia with fentanyl / desflurane is not different in patients undergoing open hemicolectomy. Based on lower requirements for postoperative analgesia and reduced costs we conclude that BIS guided desflurane anesthesia is superior to TIVA in this type of surgery.

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