Liberal Versus Restrictive Fluid Management in Knee Arthroplasty: A Randomized, Double-Blind Study

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BACKGROUND: There are few data describing the relationship between amount of perioperative fluid and organ function. In this study we investigated the effects of two levels of intravascular fluid administration ("liberal" versus "restrictive") in knee arthroplasty on physiological recovery as the primary outcome variable.

METHODS: In a double-blind study, 48 ASA I–III patients undergoing fast-track elective knee arthroplasty were randomized to restrictive or liberal perioperative intravascular fluid administration. Patients received a fixed rate infusion of Ringer's lactate solution with a standardized volume of colloid. All other aspects of perioperative management (including anesthesia, preoperative fluid status, and postoperative management) were standardized. Primary outcome variables included pulmonary function (spirometry), exercise capacity ("timed up and go" test), coagulation (Thrombelastograph®), postoperative hypoxemia (nocturnal pulse oximetry), postoperative ileus (defecation), and subjective patient recovery (visual analog scales). Hospital stay and complications were also noted.

RESULTS: Fluid guidelines were followed strictly in all patients. Liberal (median 4250 mL, range 3150–5200 mL) compared with restrictive (median 1740 mL, range 1100–2165 mL) intravascular fluid administration led to improved pulmonary function 6 h postoperatively, significant hypercoagulability 24–48 h postoperatively, and reduced incidence of vomiting. There were no overall differences in the other assessed perioperative physiological recovery variables (postoperative hypoxemia, exercise capacity or subjective patient recovery variables). No difference was found in hospital stay (median 4 days in both groups, not significant).

CONCLUSION: A liberal compared to a restrictive intravascular fluid regimen may lead to significant hypercoagulability and a reduction in vomiting, but without differences in other recovery variables or hospital stay after fast-track knee arthroplasty.

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There are few studies examining the relationship between intravascular perioperative fluid management and various outcomes in elective surgery (1,2). Data from randomized, clinical trials consistently indicate that 1–2 L IV fluid (predominantly crystalloid) improves outcomes such as dizziness, nausea and vomiting after minor surgery (3). However, data from major surgery are contradictory, with some studies reporting fluid restriction to reduce length of postoperative ileus and decrease postoperative complications (4–6), whereas other investigators report benefits (primarily reduced length of postoperative ileus and reduced hospital stay) of individualized, goal-directed fluid administration (1,7,8). Furthermore, in laparoscopic cholecystectomy (a moderately complex surgical procedure), a randomized trial (9) reported that administration of approximately 3 L of Ringer's lactate solution (RL) improved perioperative physiologic organ function, recovery and hospital stay compared with 1 L of RL. The lack of procedure-specific evidence-based guidelines for perioperative fluid management results in large variations of administered fluid regimens in daily practice. For example, in knee arthroplasty surgery perioperative fluid regimens may vary between 1 and 5 L of IV administered fluids (crystalloids or crystalloids/colloids) regardless of loss (2).

No randomized study has investigated the effect of various levels of intravascular fluid administration on outcome in elective orthopedic surgery. Because elective knee arthroplasty is a relatively standardized surgical trauma, we performed a randomized, controlled, double-blind trial in 48 patients scheduled for knee arthroplasty with "liberal" versus "restrictive" perioperative fluid management. Perioperative physiology and organ function (primarily pulmonary function, exercise capacity/mobilization and coagulation)

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Table 1. Protocol of Fluid Administration and Patient Management

	Restrictive fluid (N = 24)	Liberal fluid (N = 24)
Preoperatively	All patients fasting from midnight. 175 mL water drunk at 6 AM the morning of surgery	
Preload (at placement of epidural)	None	10 mL/kg RL
Fluid protocol during surgery	10 mL/kg/h RL Voluven®: 7 mL/kg	30 mL/kg/h RL Voluven®: 7 mL/kg
Postoperatively (PACU) on the day of surgery	5 mL/kg RL	5 mL/kg RL
Postoperatively (ward) on the day of surgery (0–24 h)	1 l oral intake. Free solid food intake No IV fluids on the ward without specific indication (clinical signs of dehydration or hypovolemia)	
1st postoperative day (24–48 h)	Free solid food intake. Oral fluid intake aimed at 2–2.5 liter Removal of bladder catheter	
2nd postoperative day (48–72 h)	Free solid food intake. Removal of epidural catheter	
3rd postoperative day (72–96 h)	Discharge in the morning according to departmental guidelines (sufficient pain relief on oral analgesics, mobilized to maintain daily activities, discharge to patients own home)	

were the primary outcome variables. The main hypothesis was that restrictive intravascular fluid administration may lead to an improvement in these physiologic variables.

METHODS

After approval by the Regional Ethics Committee (Copenhagen Section, Denmark) and written informed consent, we studied 48 consecutive patients scheduled for fast-track elective primary knee arthroplasty from September 22, 2003 to September 24, 2004 in a randomized, double-blind trial. Exclusion criteria were as follows: age <50 yr, weight >110 kg, body mass index >40, inability to perform the preoperative test program, ASA class IV, insulin-dependent diabetes mellitus, severe cardiac insufficiency (New York Heart Association IV, MI <3 months), severe pulmonary insufficiency (forced expiratory volume in the first second [FEV_1] <1 L), psychiatric illness (intake of other psychiatric medication than selective serotonin reuptake inhibitors), alcohol intake >5 U daily, glucocorticoid maintenance therapy, anticoagulant treatment, contraindication to intraoperative tranexamic acid, contraindication to epidural catheter insertion, chronic opioid use, morphine intolerance, inability to give informed consent (not Danish-speaking etc.), surgery not by project surgeon, and previous participation in the study (other knee). During the study period 125 patients underwent elective knee replacement surgery. Seventy-one patients did not meet the inclusion criteria. Of the remaining 54 patients, 4 were excluded because of unavailability of the investigators, leaving 50 patients for randomization. Two patients were excluded after randomization, but before initiation of surgery (conversion of regional anesthesia to general anesthesia due to failure of spinal block and asthmatic attack immediately before surgery leading to cancellation of procedure), leading to two other patients to be randomized instead (two new numbers). All other randomized patients completed the study.

Perioperative procedures are summarized in Table 1. The day of the operation was defined as Day 0. All perioperative patient management was according to the principles of fast-track knee arthroplastic surgery with a planned maximum 5-day hospital stay, which is standard at our institution and has been described in detail elsewhere (10,11). Preoperative fluid status was standardized in all patients by ensuring that they all fasted from midnight before the operation and drank 175 mL of water at 6 AM on the morning of surgery. Upon arrival in the operating room, patients were randomized by the sealed envelope method (serially numbered, sealed, and opaque envelopes based on an externally generated computer-generated list of random numbers) to the restrictive or liberal fluid infusion group (details of the fluid regimens are shown in Table 1). The randomization code was kept separate and not known to any of the investigators until the study was completed. Double-blinding was achieved by hiding the fluid infusion bags in large opaque sacks (thus masking the volume of fluid infused) ensuring blinding of the surgeon, the patients and the investigators obtaining the data (KH, LV). The allocated fluid regimen was administered by two anesthesiologists (NBF, BK) not involved inpatient assessments. After termination of the fluid infusion, the fluid bags were discarded and the peripheral venous line closed.

All patients received a standardized combined spinal-epidural anesthesia and continuous epidural analgesia for postoperative pain management. With the patient in the lateral position (procedure side downwards) an 18-gauge × 8 cm Touhy needle was introduced at the L2–3 or L3–4 interspace. After identification of the epidural space a thin 27-G pencil-point spinal needle was carefully placed in the subarachnoid space and 12.5 mg hyperbaric bupivacaine was administered for spinal anesthesia. Subsequently, the epidural catheter was placed and tested with 3 mL 2% lidocaine with epinephrine 1:200.000 followed by

morphine (patient age <70 yr: 2 mg, ≥70 yr: 1 mg). Light sedation with propofol (0.5–2 $mg \cdot kg^{-1} \cdot h^{-1}$) was maintained throughout the procedure. Intraoperative normothermia was maintained with a Bair-Hugger® (Augustine Medical, Eden Praire, MN). Hypotension in the absence of surgical bleeding was treated with ephedrine 25 mg IM/5–10 mg IV. Fluid guidelines (Table 1) were adhered to strictly. Diuretics were not used. All patients were operated on by a senior consultant surgeon (HH). According to departmental guidelines, patients were operated on in the supine position using a tourniquet inflated 100 mm Hg above the systolic blood pressure during the procedure. A standard midline skin incision with a median parapatellar approach was used. An AGC® prosthesis was inserted (Biomet & Merck, Warsaw, IN). The prosthesis consists of three parts, which are fastened to the bone with cement (Palacos, Biomet & Merck, Warsaw, IN). Drains were not used. Tranexamic acid 10 mg/kg was administered at the end of surgery to minimize blood loss. After surgery, continuous epidural analgesia with bupivacaine 0.125% + morphine 0.05 mg/mL was maintained at 4 mL/h for 48 h. Furthermore, tenoxicam 20 mg once daily and acetaminophen 1000 mg/6 h was administered postoperatively until hospital discharge. After removal of the epidural catheter oxycodone 5 mg/6 h was administered orally until hospital discharge. Break-through pain was treated with oxycodone (tablets, 5 mg) as the first choice and ketobemidone (tablets, 5 mg) as the second choice. In the recovery room, personnel were unaware of the fluid regimen. Patients were allowed (but not forced) to drink fluids after surgery, with a maximum of 1000 mL on the day of surgery.

On the surgical ward, patients were managed according to the principles of fast-track surgery (10), with removal of the bladder catheter after 24 h and removal of the epidural catheter after 48 h, free solid food intake, enforced mobilization (patients were fully mobilized on the day of surgery and subsequently had daily training sessions with a physiotherapist) and planned discharge before or at the fifth postoperative day. Low molecular weight heparin (tinzaparin) 4500 IE SC was administered from 6 h postoperatively and once daily until hospital discharge. A laxative (Bisacodyl®) 10 mg was administered once daily from the day of operation and until hospital charge. Discharge criteria were standardized and included sufficient pain relief on oral analgesics, sufficient mobilization to maintain daily function, and patient acceptance of discharge. All patients were discharged to their own homes. Study assessments took place preoperatively, 0, 2, 6, 24, 48, and 72 h after surgery.

Pulmonary Function

Pulmonary function (FEV_1, forced vital capacity [FVC], and peak expiratory flow) was measured preoperatively, 6, 24, 48, and 72 h after surgery with the patient in the sitting position as described previously (9).

Weight

The patients were weighed with standardized hospital clothing preoperatively, 6, 24, 48, and 72 h after surgery.

Exercise Capacity

Exercise capacity/degree of mobilization was evaluated preoperatively, 24, 48, and 72 h after surgery with the previously validated timed up and go (TUG) test, which measures the time (seconds) it takes the patient to raise from a chair, walk 3 m, turn and walk back to the chair, and finally sit down again (12,13).

Coagulation

Coagulation was assessed with thrombelastography (TEG®) preoperatively, immediately after induction of spinal anesthesia, 0, 2, 6, 24, 48, and 72 h postoperatively as previously validated (14,15). TEG provides an analysis of full-blood coagulation by the component variables *r* (reaction time in minutes), *k* (time for amplitude to reach 20 mm in minutes), $\propto$ (clot formation rate in degrees) and MA (clot strength, maximum amplitude in millimeters). Analyses were performed on a TEG Coagulation Analyzer 5000 machine (Hemoscope Corpe, Niles, IL) with native (non-activated) blood analyzed 4 min after sampling. Hemoglobin (Hgb) was measured at the same time points. Clinical thromboembolic complications were noted. Because of the multiple measurements involved, we predetermined that a minimum 2 of the 4 TEG parameters should be altered before we would conclude that alteration in coagulation took place.

Postoperative Hypoxemia

Postoperative hypoxemia was measured by nocturnal pulse oximetry (Nellcor N-595®, Nellcor Puritan Bennett, Pleasanton, CA) (from 23 PM to 07 AM) on the first, second, and third postoperative nights as previously described and validated (16,17). Outcome variables were mean Spo_2, minimal Spo_2, numbers of desaturations (Spo_2 <90 or decrease in Spo_2 ≥5% from baseline for a minimum of 10 s) and time spent with an Spo_2 <90%. Data were subsequently downloaded from the monitor, analyzed, and reported as median of each patient's mean for summary statistics. Oxygen treatment was not given postoperatively.

Postoperative Ileus

Time to defecation was noted.

Recovery Variables

Self-reported registrations of pain, nausea, appetite, general well-being, thirst, headache, dizziness, and drowsiness were evaluated using a 100-mm visual analog scale (0 = no symptom, 100 = worst symptom possible) before surgery, 6, 24, 48, and 72 h after surgery as previously described (9). Numbers of vomiting episodes were registered at the same time points (1, 2, 3, 4 or >4 episodes). Fatigue was evaluated on a

Table 2. Patient Demographics

	Restrictive fluid (N = 24)	Liberal fluid (N = 24)	*P*
Sex (F/M)	11/13	14/10	0.56
Age (yr)	71.5 (58–80)	71.5 (55–83)	0.97
Weight preop	83 (54–98)	88 (61–106)	0.11
BMI (kg/m^2)	27.6 (20–38)	29.6 (24–40)	0.18
ASA class I/II/III	7/10/7	7/13/4	0.55
Preop cardiovascular disease (yes/no)	15/9	13/11	0.77
Preoperative Hgb (mmol/l)	8.4 (6.8–9.8)	8.5 (7.0–9.4)	0.84
Smoking (package-years)	1.5 (0–38)	0 (0–46)	0.39

Table 3. Intraoperative Data

	Restrictive fluid (N = 24)	Liberal fluid (N = 24)	*P* (N = 24)
Duration of surgery (min)	67 (41–127)	70 (51–125)	0.46
Duration of anesthesia (min)	104 (76–163)	115 (71–164)	0.34
Propofol (mg)	228 (0–775)	285 (0–1252)	0.24
Systolic pressure (average)	120 (100–150)	130 (100–190)	0.14
Heart rate (average)	70 (55–80)	70 (60–110)	0.08
Systolic pressure <90 mm Hg (min)	0 (0–0)	0 (0–0)	1.00
Ephedrine (total dose mg)	0 (0–50)	0 (0–50)	0.80
Ephedrine (patients requiring)	11	11	1.00
Intraoperative RL (mL)	815 (500–980)	3275 (2400–4000)	<0.01
Intraoperative colloid (mL)	500 (325–700)	500 (450–700)	0.15
RL (PACU) (mL)	400 (250–500)	425 (300–500)	0.16
Total IV fluid (intraop + PACU) (mL)	1740 (1100–2165)	4250 (3150–5200)	<0.01
Blood loss (mL)	0 (0–150)	0 (0–500)	0.06
Blood transfusion before 3rd postop day (mL)	0 (0–0)	0 (0–0)	1.00
Diuresis intraoperatively (mL)	450 (0–950)	950 (20–1800)	<0.01
Time spent in PACU (min)	100 (30–570)	108 (45–405)	0.35
Systolic pressure PACU (mm Hg average)	130 (100–170)	135 (110–160)	0.23
Heart rate (average)	70 (50–90)	70 (50–100)	0.58

10-point fatigue scale (1 = no fatigue and 10 = worst fatigue imaginable) before surgery, 24, 48, and 72 h after surgery (18).

Clinical Outcomes

We recorded time to discharge, readmissions within 30 days, and complications within 30 days (or during the primary hospital admission). Major complications were defined as

1. Cardiovascular:
   a. ischemia: myocardial infarction as verified by chest pain, electrocardiogram (ECG) signs, and increased enzymes, or angina defined as symptoms of angina with appropriate ECG-changes, or
   b. arrhythmia defined as ECG-verified cardiac arrhythmia requiring treatment
2. Respiratory:
   a. pneumonia: temperature >38.5°C, clinical signs of pneumonia and positive radiograph
3. Thromboembolic:
   a. thrombosis/embolus: clinical signs of thrombosis and positive scintigraphy,
4. Infectious:
   a. wound infection requiring drainage.

Statistics

Data were analyzed using an intention-to-treat basis using nonparametric statistical methods with data presented as median (range). $P < 0.05$ was considered significant. Continuous data were compared with Mann–Whitney or Wilcoxon's test. Categorical data were compared using Fisher's exact test. Outcome assessments including multiple measurements were analyzed with summary measures to avoid multiple comparisons, and thus visual analog scales were analyzed by comparing the area under the curve (AUC).

Calculation of sample size was based on the hypothesis that restrictive fluid administration may lead to an improvement in pulmonary function. A previous study (19) found a reduction in pulmonary function

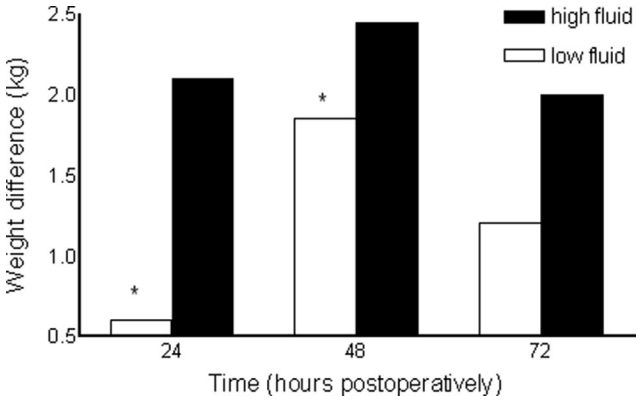

Figure 1. Postoperative weight gain after liberal versus restrictive fluid administration. *$P < 0.05$. Median values presented.

Table 4. Postoperative Data

	Restrictive fluid (N = 24)	Liberal fluid (N = 24)	*P* (N = 24)
Postoperative oral fluid intake (day of operation) (mL)	1025 (400–1450)	1100 (575–1375)	0.50
Total amount of fluid administered (mL) (day of operation. IV and oral)	2928 (1850–4005)	5475 (4675–6675)	<0.01
Fluid balance day 0* (mL)	1246 (200–2880)	2288 (105–4825)	<0.01
Total amount of fluid administered (mL) 1st postop day (IV and oral)	1963 (600–3125)	1900 (850–3125)	0.68
Total amount of fluid administered (mL) 2nd postop day (IV and oral)	2100 (1300–2900)	1900 (600–2200)	0.20
Diuresis 0–24 h postop (mL)	1063 (500–2650)	2000 (750–4150)	<0.01
Additional opioid intake† (mg)	10 (0–40)	10 (0–40)	0.35
Bowel movement (days)	3 (1–7)	3 (1–6)	0.52
Hospital stay (days)	4 (3–18)	4 (3–5)	0.25
Hospital stay (incl. readmission)	4 (3–18)	4 (3–8)	0.45

Values presented as median (range). Summary data for hemodynamic values reported as medians of the means for summary statistics.

RL = Ringer's lactate solution; PACU = postanesthesia care unit; BMI = body mass index; Hgb = hemoglobin.

* Fluid balance: Input (IV and oral fluids) − output (diuresis, blood loss, vomiting).

† administration of opioid in excess of standard (all patients received oxycodone 5 mg/6 h after removal of epidural catheter and no other standard opioid was administered). Composition of RL: Na^+ 130 mmol/l, K^+ 4 mmol/l, chloride 109 mmol/l, lactate 28 mmol/l, calcium 1.4 mmol/l.

(FVC) after laparoscopic cholecystectomy from 3.8 to 2.3 (40%) (SD 0.8). We considered a reduction in the decrease in postoperative pulmonary function (FVC) by 50% (from a 40% to a 20% reduction) clinically relevant. With a power to detect a minimal relevant difference between the two groups of 80% and a level of significance of 0.05, 21 patients were needed in each group. To counter for potential patient exclusion after randomization, we decided to include 24 patients in each group. The CONSORT guidelines (20) were followed for the report of this trial.

RESULTS

Patient demographics are shown in Table 2. Duration of anesthesia, surgery, and administration of propofol did not differ between the groups (Table 3). Patients in the restrictive group received median 1740 mL (range 1100–2165 mL) IV fluid intraoperatively and in the postanesthesia care unit compared with median 4250 mL (range 3150–5200 mL) in the liberal group ($P < 0.01$) (Table 3). On the day of surgery, two patients in the restrictive group each had 1000 mL crystalloid infused in addition to the protocol (erroneously ordered by physicians not involved in the study on unclear indication). One patient (restrictive group) had 500 mL colloid infused on the first postoperative day on suspicion of hypovolemia. On the second postoperative day, one patient in the liberal group had 500 mL crystalloid infused (unknown indication), one patient had 1000 mL crystalloid infused during surgery for capsular rupture (liberal group), and one patient (restrictive group) with persistent vomiting was given 1000 mL crystalloid IV. Apart from these patients, no additional IV fluid was administered in the study period and fluid guidelines were followed strictly in all patients. All patients were included in the analysis.

There was a significantly larger weight gain in the liberal compared to the restrictive group until 72 h postoperatively (Fig. 1). Intraoperative hemodynamic data did not differ between the groups (Table 3). Intraoperative diuresis and 24 h total diuresis was significantly larger in the liberal versus the restrictive group (Tables 3 and 4). Postoperative fluid intake and management including opioid administration did not differ between groups (Table 4).

Patients were discharged at median Day 4 in both groups (Table 4). Four patients had postoperative complications: One pneumonia (restrictive group), two with rupture of joint capsule requiring surgery, one of them was readmitted (liberal group), and one patient with a wound defect requiring operation (readmitted) (liberal group). Additionally two patients (liberal group) were readmitted under observation for deep venous thrombosis and peptic ulcer (not found).

Pulmonary Function

Pulmonary function did not differ between the groups preoperatively. There was a significant decrease in FVC 6 h postoperatively in the restrictive compared to the liberal group (Fig. 1). No difference in FEV_1 or peak flow (Fig. 2) was seen at any time point between the groups.

Exercise Capacity

No differences in exercise capacity (TUG test) were found pre- or postoperatively between groups (Fig. 3).

Recovery Variables

Vomiting was significantly reduced in the liberal compared to the restrictive group (median AUC values 30 (restrictive group) versus 0 (liberal group), $P < 0.05$). The actual episodes of vomiting were median 2 (0–9) in the restrictive group versus 0 (0–14) in the liberal group. We found no differences between the

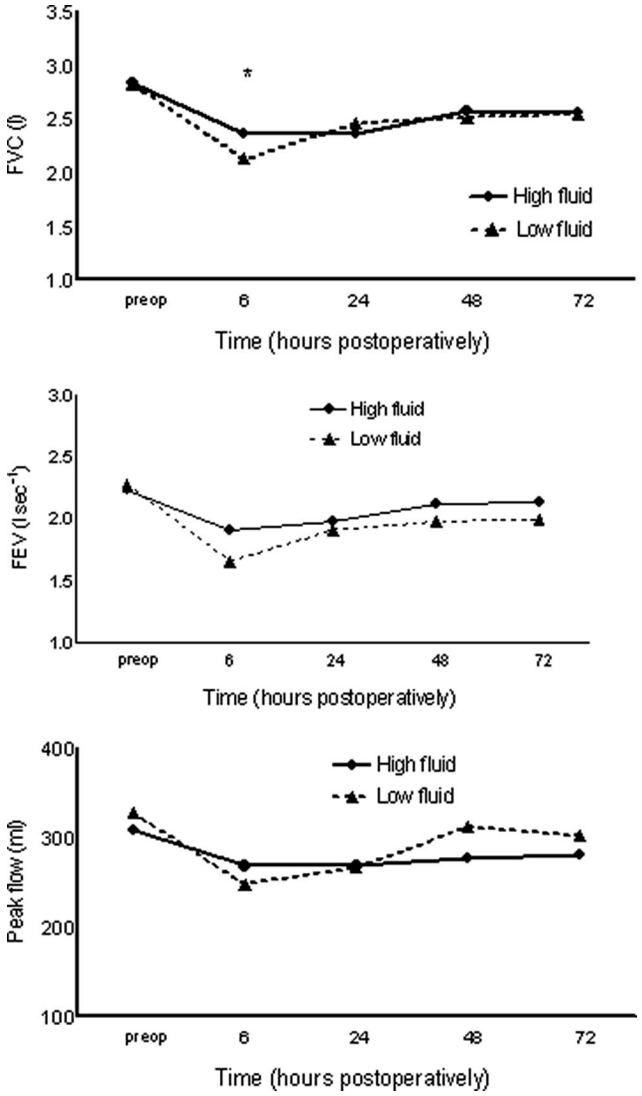

Figure 2. Effect of liberal versus restrictive fluid administration on pulmonary function after knee arthroplasty. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s. No difference in actual values between the groups was found at any time points. $^*P < 0.05$ difference from baseline compared between groups (Mann–Whitney). Median values presented.

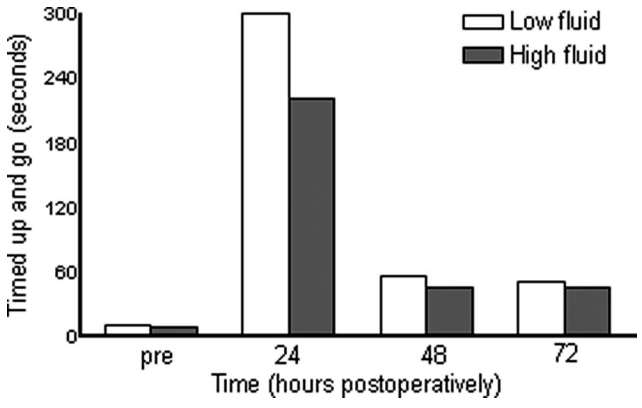

Figure 3. Effect of liberal versus restrictive fluid administration on exercise capacity (timed up and go [TUG] test) after arthroplasty. Median values presented.

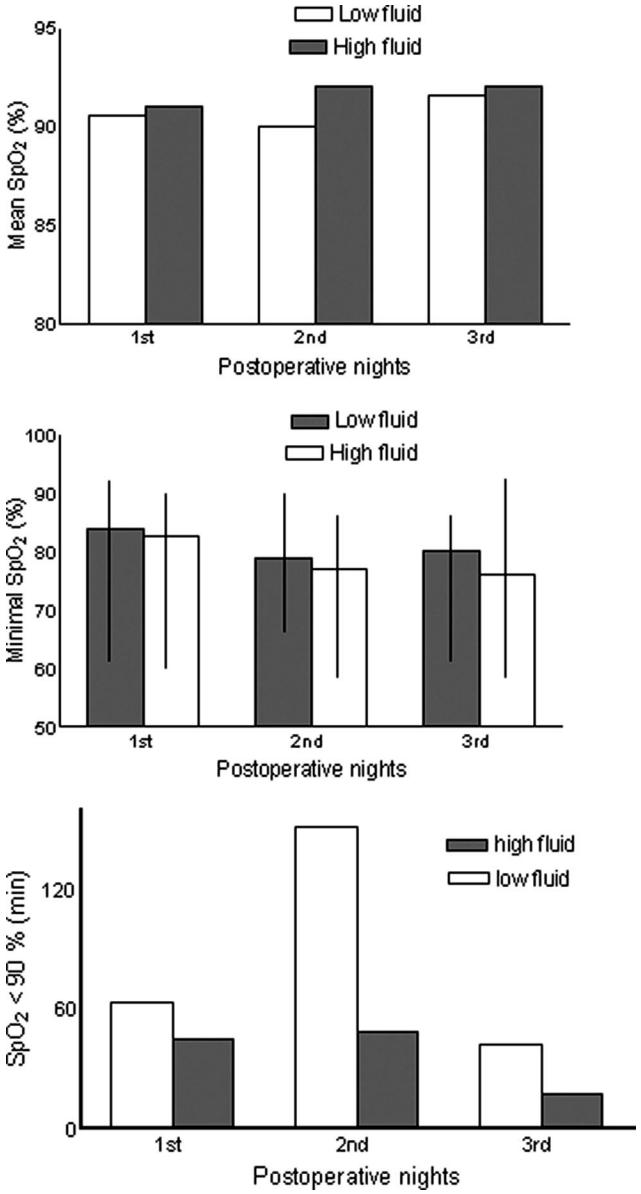

Figure 4. Effect of liberal versus restrictive fluid administration on nocturnal oxygenation variables. Spo_2: Oxygen saturation. Median values of mean Spo_2, median values of minimal Spo_2 (presented with bars indicating range) and median time (min) <90% presented.

groups in pain, nausea, appetite, general well-being, thirst, headache, dizziness, drowsiness or fatigue either pre or postoperatively (data not shown).

Postoperative Ileus

Length of postoperative ileus did not differ between the groups (time to defecation median 3 days in both groups, Table 4).

Postoperative Hypoxemia

No differences in mean Spo_2, minimal Spo_2, number of desaturations, or time spent with Spo_2 <90% were found between groups (Fig. 4).

Coagulation (TEG)

The TEG analysis showed a pattern of reduced coagulation in the restrictive group during surgery

Table 5. Coagulation (Thrombelastography)

	Preop	Spinal	0 h	2 h	6 h	24 h	48 h	72 h
r (min)								
Low fluid	12 (1.3–31.2)	16.3 (3.3–32.1)†	19.9 (2.0–51.7)*†	18.4 (0.9–55.0)	12.2 (2.3–28.2)	15.3 (0.5–39.6)	9.0 (1.3–47.9)*†	6.6 (1.3–22.4)
High fluid	13.4 (1.6–25.9)	14.4 (3.6–20.4)	12.1 (4.3–36.2)	13.2 (1.9–40.4)	12.6 (1.8–23.3)	6.3 (1.5–26.5)	3.7 (1.1–21.7)	5.3 (0.6–38.5)
k (min)								
Low fluid	5.5 (1.3–15.5)	6.6 (1.1–11.3)	7.9 (2.9–30.3)*†	8.3 (1.8–21.1)	5.0 (1.3–15.6)	6.8 (1.3–21.5)*	3.3 (1.3–31.5)†	1.9 (1.3–16.6)
High fluid	5.0 (0.9–42.0)	4.0 (1.3–9.0)	3.5 (1.4–15.8)	4.7 (1.7–16.8)	4.7 (1.5–13.2)	2.4 (1.3–17.4)	2.0 (0.8–13.0)	1.8 (0.8–16.8)
Alfa (degree)								
Low fluid	36.1 (18.6–73.1)	31.7 (18.4–71.8)†	26.7 (5.7–53.6)*	26.0 (10.0–66.0)	39.1 (13.0–71.6)	31.4 (12.3–71.9)*	50.6 (6.4–73.2)	65.5 (18.0–74.9)
High fluid	41.6 (14.6–76.8)	42.8 (19.8–72.6)	41.8 (12.7–70.3)	39.6 (12.1–67.0)	40.8 (17.9–68.7)	62.0 (16.1–71.5)	63.4 (16.1–75.5)	68.5 (18.1–80.1)
MA (mm)								
Low fluid	60.5 (25.6–84.0)	55.3 (41.4–92.4)	49.7 (32.0–68.7)*	56.2 (33.2–93.0)	58.3 (31.5–73.5)	55.4 (21.0–72.3)*†	72.9 (23.5–93.3)	76.6 (20.6–86.0)
High fluid	61.2 (48.7–79.4)	61.5 (47.1–79.8)	58.4 (5.8–78.5)	58.9 (29.9—-74.8)	59.9 (44.2–74.2)	70.7 (48.4–81.2)	72.0 (33.6–83.0)	76.8 (13.3–87.8)
Hgb (mmol/l)								
Low fluid	8.4 (6.8–9.8)	8.6 (6.5–10.0)†	7.1 (6.1–8.6)*†	7.6 (6.5–9.0)	7.8 (6.4–9.2)	7.4 (6.0–9.1)	6.8 (5.6–8.8)	6.9 (5.2–8.9)
High fluid	8.5 (7.0–9.4)	8.1 (7.1–9.1)	6.8 (6.0–7.8)	7.6 (6.6–8.3)	7.4 (6.4–8.5)	7.2 (5.6–8.9)	7.1 (5.7–8.6)	7.0 (5.3–8.3)

* $p < 0.05$ between groups.

† $P < 0.05$ difference from baseline compared between groups. Values presented as median (range). To convert from mmol/L to g/dL divide by 0.62.

(significant prolongation of *r*-time and *k*-time and a significant reduction in ∝-angle and MA). However, significant hypercoagulation was present in the liberal Group 24 and 48 h postoperatively with significantly shortened *k* and *r* times and increase in ∝ and MA values, respectively (Table 5). Hgb values only differed at the end of surgery, at which time a significant decrease in the liberal group was seen (Table 5). No clinical thromboembolic complications were noted.

DISCUSSION

Liberal (median 4250 mL) compared to restrictive (median 1740 mL) intraoperative fluid administration led to improved pulmonary function 6 h postoperatively, significant hypercoagulability 24–48 h postoperatively, and reduced incidence of vomiting. There were no overall differences in the other assessed perioperative physiological recovery variables (postoperative hypoxemia, exercise capacity or subjective patient recovery variables).

In *minor (ambulatory) surgery* fluid substitution to correct preoperative dehydration (1–2 L vs no fluid) may improve some variables of recovery (drowsiness, dizziness, nausea, and vomiting) (3,21,22). In *moderately complex surgical procedures* (e.g., laparoscopic cholecystectomy), the only randomized study found intraoperative administration of 40 mL/kg (approximately 3 L) compared with 15 mL/kg (approximately 1 L) RL to reduce the cardiovascular hormonal responses (antidiuretic hormone, aldosterone and angiotensin II), improve perioperative organ function (pulmonary function, exercise capacity and balance function), improve recovery (nausea, dizziness, drowsiness, general well-being) and reduce hospital stay (9). In *major surgical procedures* two main strategies in perioperative fluid management have been investigated in randomized studies: Infusion of predetermined rates of fluid (e.g., liberal versus restrictive fluid management) and "goal-directed"/individualized fluid therapy. Three randomized clinical trials (4,5,23) have assessed liberal versus restrictive fluid management in major surgery, with two studies (4,5) reporting restrictive (approximately 3–3.6 L) versus liberal (approximately 5–5.9 L) fluid management to decrease postoperative complications, whereas in the third (and largest) study (23) including 256 patients, approximately 5.7 vs 3.1 L crystalloid did not affect wound healing or hospital stay. The apparent differences in outcomes among these studies are difficult to evaluate, because information on both pre- and postoperative care including fluid and pain management (epidural) and bowel preparation is not available and comparable among the trials. Furthermore, a mixture of intraabdominal procedures (5) versus colorectal surgery (4) and colonic surgery (23) was studied, which may not be comparable in terms of pathophysiology. Individualized fluid therapy consisting primarily of colloid infusions guided by cardiac filling pressures (esophageal Doppler), has been found beneficial in several (1,7,8,24–26) but not all (27) randomized trials in various types of surgery (primarily decreased length of postoperative ileus and hospital stay), generally administering approximately 0.5–1.5 L more fluid to the intervention group. A potentially new method of guiding perioperative fluid therapy would be according to the principles of volume kinetic analysis, which, in many experimental and clinical studies, has been found to reflect distribution of infused fluid volumes (28–30).

We deliberately designed our fluid administration regimens to reflect daily fluid administration practices as documented in the literature regarding knee/hip arthroplasty (2), and to deliver the same amount of colloid, making the difference between the two volume regimens to consist of crystalloid. In this context, we recently (31) conducted a systematic review of 80 randomized trials in elective noncardiac surgery. Unfortunately, no conclusions on the administration of colloids versus crystalloids in elective surgery could be made with the presently available data, mainly because of lack of standardization and measurements of relevant clinical/physiological end points in the available literature.

The main positive finding of this study was the reduced incidence of vomiting and the hypercoagulability associated with liberal fluid administration. The suggestion that crystalloid administration may lead to hypercoagulation is not new, although it has not been investigated in a randomized, clinical trial comparing different levels of fluid administration (2). We found impaired coagulation in the low volume compared with the high volume group intraoperatively; however, the underlying mechanisms for these changes remain unclear. Furthermore, we found relative hypercoagulation present in the high volume group 24–48 h postoperatively. The clinical implications of these findings are unclear. Our results support earlier findings in both healthy volunteers and surgical patients that crystalloid administration (independent of type) leads to hypercoagulation (2,14,32,33). Furthermore, in the only randomized, clinical trial, in 60 patients undergoing major abdominal surgery randomized to no IV fluids during or after the operation versus 1 L of crystalloid/h intraoperatively followed by 2–3 L of dextrose-saline per day postoperatively, the incidence of postoperative deep venous thrombosis, together with an increased hypercoagulability (34), was found to be significantly higher in the patients receiving IV fluids (30% vs 7%). The mechanism of this hypercoagulation may be an imbalance between pro- and anticoagulant factors [with antithrombin III being the most important (35)]. Thus, assessments of antithrombin-III could have helped explain our findings.

Several of the drugs used perioperatively in the present study affect coagulation parameters as evaluated by TEG: Low molecular heparin may induce changes in TEG by an increase in k- and r-time (36), whereas the effects of aspirin in analgesic doses on TEG are inconclusive (15). However, the procoagulant effect of hemodilution *in vitro* has not been found to be inhibited by aspirin (37). The decrease in fibrinolysis by tranexamic acid may appear as a slower decline in MA over time (38). Colloids, primarily high molecular weight hydroxyethyl starches (HES) have been found to decrease coagulation perioperatively (33). The new low molecular weight HES used in this study (HES 130/0.4) influences coagulation markedly less (39,40) and was administered in carefully controlled similar doses to patients in both groups. Therefore, rigorous care was taken to standardize the administration of all perioperative interventions (including low molecular heparin, aspirin and tranexamic acid) to minimize confounding effects on the TEG measurements. We cannot exclude that the high fluid volume may have interfered with kinetics of the low molecular weight heparin, although our Hgb data indicated significant volume expansion in the high volume group to be present only intraoperatively, and at all other time points there were no differences between groups in Hgb data. We did not measure single factors of the coagulation system, as this has only limited importance when assessing the influence of different intravascular volume replacement regimens on the coagulation process. Hypercoagulability is normally seen after surgery and may last up to a week after major surgical procedures (41,42). A correlation has been shown between the TEG MA and postoperative thrombotic complications (43). The changes in this study were in the same magnitude as reported in pregnancy (15,44). In our small-size study, we noted no clinical thromboembolic complications. Thus, further large-scale studies describing the TEG parameters together with clinical assessments of thrombosis are needed before recommendations can be made.

The demonstrated reduction in pulmonary function with the low volume group seen only 6 h postoperatively may be difficult to explain, but was also found in our previous study in laparoscopic cholecystectomy (9). The decreased incidence of vomiting in the high volume group may possibly have affected the pulmonary function testing in favor of the patients receiving the high volume administration.

We found no difference in functional exercise capacity or degree of mobilization. Because in our evaluation, the TUG test was a walking test, firm conclusions on cardiovascular exercise capacity cannot be made. Because of the type of surgery performed, exercise testing on a treadmill [which has been found to be influenced by perioperative fluid administration regimens (9)] was not feasible.

Knee arthroplasty is a moderately complex surgical procedure, and thus not comparable in terms of fluid physiology with major surgical procedures, where surgically stress-induced fluid shifts may influence the need for fluid replacement. The results from this study may not be directly compared with those results obtained in major surgical procedures (see above). In general, data on fluid management in minor surgical procedures may not apply to major surgery, because the relevant physiology and outcomes differ. Furthermore, in contrast to the other available studies, the present study was conducted with spinal-epidural anesthesia. It cannot be excluded that fluid requirements may differ between anesthetics that are primarily regional or neuraxial and general anesthesia (2,45). Finally, determination of sample-size may to some extent be arbitrary. We cannot exclude that our calculated sample-size based on results from laparoscopic surgery during general anesthesia may have underestimated the number of patients required in the study to see differences in the outcome variables.

In order to evaluate the precise effects of administration of a certain amount of fluid, it is imperative that postoperative management be standardized. Recent data (10,11) have demonstrated that a multimodal revision of principles for postoperative care may improve outcome after various types of surgical procedures, including knee and hip arthroplasty (e.g., fast-track surgery), which is also of relevance in determining the optimal amount of fluid to be administered. Thus, procedure-specific studies focusing on

both pathophysiology and clinical outcomes within standardized postoperative rehabilitation programs are needed in order to determine the optimal intravascular volume replacement in order to improve perioperative outcome.

In summary, liberal fluid administration induced hypercoagulability and reduced vomiting when compared with restrictive fluid administration during knee arthroplasty. However, overall functional recovery and hospital stay were not dependent on the amount of fluid administered during this procedure.

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