Pathophysiology and clinical implications of perioperative fluid management in elective surgery

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THE EIGHT ORIGINAL PAPERS ARE

1. Holte K, Jensen P, Kehlet H: Physiologic effects of intravenous fluid administration in healthy volunteers. Anesth Analg 2003; 96: 1504-9
2. Holte K, Foss NB, Svensén C, Lund C, Madsen JL, Kehlet H: Epidural anesthesia, hypotension, and changes in intravascular volume. Anesthesiology 2004; 100: 281-6
3. Holte K, Nielsen KG, Madsen JL, Kehlet H: Physiologic effects of bowel preparation. Dis Colon Rectum 2004; 47: 1397-1402
4. Holte K, Klarskov B, Christensen DS, Lund C, Nielsen KG, Bie P, Kehlet H: Liberal vs. restrictive fluid administration to improve recovery after laparoscopic cholecystectomy: A randomized, double-blind study. Ann Surg 2004; 240: 892-9
5. Holte K, Kehlet H: Fluid therapy and surgical outcomes in elective surgery: A need for reassessment in fast-track surgery. A systematic review. J Am Coll Surg 2006; 202: 971-89
6. Holte K, Foss NB, Andersen J, Valentiner L, Lund C, Bie P, Kehlet H: Liberal or restrictive fluid administration in fast-track colonic surgery: a randomized, double-blind study. Br J Anaesth 2007; 99: 500-8
7. Holte K, Kristensen BB, Valentiner L, Foss NB, Husted H, Kehlet H: Liberal vs. restrictive fluid management in knee arthroplasty: A randomized, double-blind study. Anesth Analg 2007; 105: 465-74
8. Holte K, Hahn RG, Ravn L, Bertelsen KG, Hansen S, Kehlet H: Influence of ”liberal” vs. ”restrictive” intraoperative fluid management on elimination of a postoperative fluid load. Anesthesiology 2007; 106: 75-9

Definitions and abbreviations

The terms ”liberal” vs. ”restrictive” or “high” vs. “low” fluid (internationally accepted in the medical literature), are applied in this thesis to describe studies applying two different levels of fluid administration and do not infer conclusions regarding the suitability of either regimen. However, I recognize, that these terms have contributed to confusion in the literature on fluid therapy, and whenever possible, the actual amounts of fluid administered are mentioned. In this review, I refer to fluid administration in elective surgical procedures with a negligible blood loss, unless stated otherwise. The term “fluid administration” refers to intravenous fluid administration unless stated otherwise. Whenever possible, the specific fluid type is mentioned – e.g. crystalloid, colloid etc.

Abbreviations RL - Ringer´s lactate, PONV – postoperative nausea and vomiting, ECV – extracellular volume, RCT – Randomized, controlled trial, GDM - Goal-directed fluid administration strategies by individualized flow-related parameters, ED - Esophageal Doppler, Mixed fluid – indicates intravenous administration of a combination of crystalloids and colloids, RCT – randomized, controlled trial.

INTRODUCTION

The limited knowledge of the pathophysiology and clinical implications of perioperative fluid management in elective surgical procedures precludes formation of rational guidelines(9). Previously, focus has mainly been on the choice of fluid to administer (e.g. which fluid?), and until recently scientific evidence regarding the amounts of fluid to administer was very scarce (e.g. how much fluid?). The choice of fluid to administer has been investigated in numerous randomized, controlled trials and systematic reviews primarily in critically ill patients with ambiguous results and with unclear implications for fluid management in elective surgical procedures(10-15). Case series reporting positive outcomes with high-volume fluid resuscitation primarily in trauma settings(16;17) induced a shifting paradigm in fluid administration regimens extending to elective surgery, from the ”restrictive” perioperative fluid regimens widely recommended before the 1950´s(18;19) to the propensity for ”liberal” fluid administration practiced today (figure 1)(9). However, neither the pathophysiology, functional physiology nor the clinical outcomes of such fluid administration regimens have been systematically investigated in the elective surgical setting. Thus, inadequate knowledge of the pathophysiology as well as shortage of evidence from randomized, controlled trials on clinical outcomes may be contributory factors to the large variation in perioperative fluid regimens seen in daily practice both within and between the surgical specialties (figure 2)(9) with largely unknown implications for patient recovery and outcome.

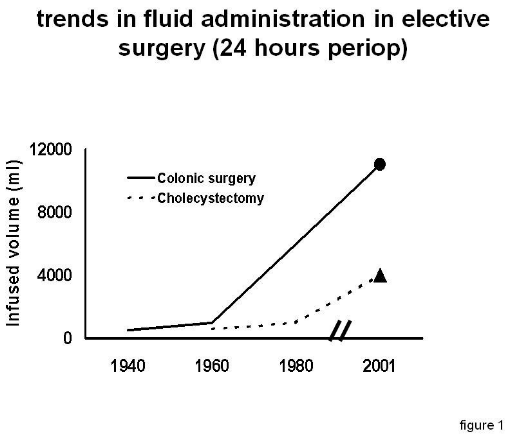

Figure 1
Data from(5;9). Data indicate approximate administered intravenous fluid volumes within 24 hours of surgery in excess of apparent losses incl. blood loss.

THE THESIS – AN OVERVIEW

The purpose of the thesis was to investigate the pathophysiology and functional outcomes of various fluid administration regimens in elective surgical procedures and describe factors of importance in perioperative fluid management. The goal was to create a rational physiologic background on which to design future randomized, clinical trials focusing on clinical outcomes aiming to produce evidence-based guidelines for rational perioperative fluid therapy. The main hypothesis of the thesis was that the ”liberal” fluid administration regimens seen in daily clinical practice may be detrimental and contribute to increased perioperative morbidity primarily due to increased functional demands of the cardiopulmonary system and gastrointestinal tract as well as decreased tissue oxygenation (impaired wound healing). The thesis consists of descriptive studies in healthy volunteers (aiming to describe normal-physiologic organ functions after a fluid (crystalloid) infusion(1) and to estimate internal fluid shifts of importance for perioperative fluid management(2;3)), descriptive and interventional studies in surgical patients (aiming to describe the additional effects of the surgical trauma on organ functions and morbidity after various levels of fluid administration(4;6-8)) and a systematic review (aiming to review the evidence of which type of fluid to administer in elective surgical procedures(5)).
Initially we described the functional physiologic effects of an intravenous fluid (crystalloid) infusion in healthy volunteers(1) and subsequently the effects of a similar fluid (crystalloid) infusion on functional physiology and outcome in a randomized, clinical trial in laparoscopic cholecystectomy(4). To further explore fluid homeostasis after laparoscopic cholecystectomy, we applied a mathematical analysis (volume kinetic analysis) describing body fluid distributions after perioperative fluid (crystalloid) infusions(8). The effects of two different volumes of fluid (mixed fluid) administration on functional physiology were studied in a randomized, controlled trial in knee arthroplastic surgery (moderately-complex surgery)(7). In major surgery, we initially described the physiologic effects of bowel preparation(3) and the influence of epidural anesthesia on internal fluid shifts(2), before conducting a randomized, clinical study investigating the functional physiology of two levels of intraoperative fluid administration (mixed fluid) in colonic surgery(6). Finally, a systematic review was conducted estimating the importance of the choice of fluid for functional physiologic as well as clinical outcomes in adult elective non-cardiac surgery(5).

typical ranges of fluid administration in various surgical specialties (24h periop)

vascular surgery – aorta	6-12 liters
colonic surgery	(2)-10 liters
laparoscopic cholecystectomy	(1)-4 liters
orthopedic surgery	(2)-7 liters
lung surgery	1-(5) liters

figure 2

Figure 2
Data from(5;9). Data indicate approximate administered intravenous fluid volumes within 24 hours of surgery in excess of apparent losses incl. blood loss. Regimens encircled by () are not commonly practiced.

PERIOPERATIVE FLUID ADMINISTRATION – PATHOPHYSIOLOGY

SURGICAL STRESS RESPONSE AND THE FLUID PHASES

The physiologic stress response to surgery induces inflammation, catabolism and fluid retention initiated by afferent neural stimuli as well as by inflammatory factors arising from the area of injury(20-22). The fluid retention is a consequence of sodium and water retention with ADH, aldosterone and the renin-angiotensin II system as the principal endocrine mediators(21;22). Plasma concentrations of ADH, aldosterone and renin-angiotensin-II are decreased after saline infusions in unoperated and operated (aldosterone) subjects, suggesting a functional feed-back mechanism to be present(9;23;24). However, the classic stress hormones (cortisol, glucagon, ephinephrine) and inflammatory mediators released in response to surgery also induce fluid retention per se(25;26). The magnitude of the surgical stress response and subsequent impairments in physiologic organ functions including fluid elimination is proportional to the degree of surgical trauma(27). Vascular permeability is increased proportional to the size of injury (surgery), inducing distribution of fluid from the intravascular to the interstitial space, thus promoting hypovolemia(28). At the same time the perioperative patient has a propensity for fluid retention, since administered fluids are not readily excreted, which may predispose to postoperative fluid overload (assessed by weight gain) caused by fluid accumulation in peripheral tissues(29). It was previously thought that surgery elicited an obligatory decrease in functional (i.e. exchangeable) ECV necessitating intravenous crystalloid infusions to maintain internal body fluid homeostasis(30), findings since contradicted by others(31) and attributed by several investigators to inadequacy in methodological (isotope) techniques(31;32). The distinction between minor and major surgical procedures relies predominantly on the profound stress activation and impaired capillary permeability causing internal fluid shifts seen in the latter.
Distribution and elimination of fluid – volume kinetic analysis

In volume kinetic analysis the distribution and elimination of an infused fluid volume is estimated by application of mathematical analysis based on the fractional dilution of blood by repeated hemoglobin concentration measurements(33;34). The concept is based on the assumption that the body strives to maintain volume homeostasis of the internal fluid spaces (compartments), in which an infused amount of fluid (crystalloid or colloid) aims to maintain an ideal (target) volume. The infused fluid then leaves the initially occupied volume at a rate proportional to the deviation from that target volume(33-35). Infused crystalloid usually distribute in a central and a remote functional body fluid space, with sizes reasonably well correlating to (but not representing) the plasma and interstitial compartments(33;34). This method has been proven effective in distinguishing normo- vs. hypovolemic conditions as well as perioperative fluid shifts(36-40). Elimination of infused crystalloid is significantly decreased during anesthesia(41;42) and surgery(37;38). The method offers an alternative way to investigate internal fluid shifts and the distribution and elimination of an intravenous fluid load in the perioperative setting.

CARDIAC FUNCTION/EXERCISE CAPACITY

Both hypovolemia and fluid overload may lead to insufficient cardiovascular function promoting organ dysfunction caused by inadequate peripheral perfusion/oxygen supply(9;43;44). Furthermore, fluid overload may theoretically increase cardiac demands contributing to ischemia, arrhythmia or cardiac failure (pulmonary edema)(9), but this has not been systematically investigated. Exercise capacity may be viewed as an indicator of functional cardiovascular capacity, and has previously been evaluated perioperatively by submaximal exercise tests on treadmill (colonic surgery(45;46) and laparoscopic cholecystectomy(47)), 6-minute walking test (colonic surgery)(48) and "timed up and go"-test (knee arthroplasty, hip fractures)(49). Furthermore, decreased orthostatic function may correlate to PONV50 and postoperative fatigue(51) as well as to dizziness hindering mobilization.

HYPOXEMIA

The pathogenesis of late postoperative hypoxemia is multifactorial and includes endocrine-metabolic stress activation, pulmonary dysfunction and sleep disturbances(52;53). Late nocturnal postoperative hypoxemia (constant and episodic) have been described with a maximum on the 2nd and 3rd postoperative nights, which may be associated with cardiovascular and cerebral dysfunction(52). Theoretically, both hypovolemia and fluid overload may influence late postoperative hypoxemia by impairing peripheral circulation and promoting extravascular fluid accumulation, respectively, but has not previously been studied specifically.

PULMONARY FUNCTION

The obligatory decrease in pulmonary function after surgery may theoretically be amplified by fluid overload predisposing to pneumonia and respiratory failure(9), however this has not previously been investigated specifically. Spirometry is the commonly accepted measurement to asses perioperative pulmonary function(54), however it should be noted that decrease in pulmonary function may not be directly related to incidence of pulmonary complications(55). Retrospective studies in patients undergoing pneumonectomy and esophagectomy have reported correlations between the amounts of administered fluid perioperatively and postoperative respiratory complications, with increased amounts of intravenous fluid administration leading to increased complication rates(9;56-58).

GASTROINTESTINAL FUNCTION

The surgical trauma causes an obligatory impairment in gastrointestinal motility(59;60), which may theoretically be amplified both by hypovolemia (decreased splanchnic circulation)(61) and fluid overload (decreased motility caused by fluid accumulation in the gastrointestinal wall and surrounding tissue)(9;62). Gastrointestinal motility has been evaluated postoperatively by transit of radiopaque markers(63) and 111indium-scintigraphy(64). The combined functional outcome of normalization of food intake together with restoration of bowel function may be most relevant in assessment of postoperative ileus(59).

COAGULATION

Surgery induces hypercoagulation which may predispose to clinical thromboembolic complications(27;65). Choice of perioperative fluid management may potentially influence coagulation and earlier findings in both healthy volunteers and surgical patients find crystalloid administration (independent of type) to promote hypercoagulation(9;66;67), while colloids (primarily high-molecular weight starches) promote a decrease in coagulation(67). Thrombelastography provides a computerized functional bed-side analysis of coagulation, evaluating speed of clotting and maximal clot strength(68). Despite the increased use in clinical settings and applications in various types of surgery, thrombelastography has been criticized of not being validated and standardized in accordance with international standards in the field(69). Thrombelastography is a global non-specific full blood test compared to analytical coagulation tests, however it may be argued that for fluid administration purposes whole blood coagulation properties may be more relevant than deficiencies in individual components of the coagulation cascade. Associations between thrombelastography values and clinical thromboembolic outcome have only been suggested in a few studies(70-72) and need further establishment in clinical trials.

RENAL FUNCTION

There is no generally accepted definition of postoperative acute renal failure, and since the clinical relevance of raised creatinine levels in postoperative patients has not been determined(73) the most clinically relevant definition of postoperative renal failure may be the need of dialysis(73). ADH, aldosterone and angiotensin-II are among the principal mediators of the surgically induced fluid retention resulting in a decrease in diuresis, a common trigger for fluid administration in clinical practice (figure 3). Although intraoperative diuresis is increased in response to fluid administration(74), intraoperative diuresis per se does not seem to predict postoperative renal failure (defined as need of dialysis) in elective surgical patients(75). However, further studies in this area are needed.

TISSUE OXYGENATION

Both fluid overload(76) and hypovolemia(77) may impair tissue oxygenation with negative implications for wound healing(78) and possibly wound complications(79) including anastomotic leakage(80). In one study during cardiac surgery, plasma volume expansion to achieve maximal ventricular stroke volume assessed by esophageal Doppler (discussed in detail later) led to improved perfusion of the gastrointestinal mucosa and a significant decrease in major postoperative complications (major infections, stroke, paralytic ileus, respiratory failure and death)(81). Tissue perfusion has been monitored perioperatively by various methods including intestinal tonometry(82), laser Doppler flowmetry(83), microdialysis(84), near-infrared spectroscopy (muscle tissue saturation)(85), transcutaneous oxygen tension(86), muscle pH electrodes(87) and subcutaneously placed Clark-type electrodes(88). However, most of the above methods are invasive and thus not readily applicable in clinical practice(89). The clinical implications are thus unclear, and neither administration of fluids or vasopressors according to optimize transcutaneous oxygen measurements(86) or gastric tonometry(90;91) has lead to improvements in clinical outcome.

RECOVERY

Pain, PONV, dizziness and drowsiness have been found to independently predict hospital stay after ambulatory surgery(92) and to potentially be influenced by fluid adminstration(93). Objective computerized evaluation of balance function has been used in clinical studies finding impairments in balance function after anesthesia (general and regional)(94-96). Postoperative fatigue may be influenced by physiological as well as psychological factors, contributes to delayed recovery(97;98) and has been evaluated in both minor and major surgical procedures with a 10-point ordinal scale(97). Visual analogue scales are extensively validated for assessment of postoperative pain(99) and has furthermore been applied to evaluate subjective discomfort in surgical patients (such as nausea, drowsiness, thirst, well-being and appetite)(100-102). The pathogenesis of PONV is multifactorial(103) including both the types of surgery (increased risk with laparoscopy) and anesthesia (decreased risk with propofol) as well as patient demographic data (increased risk as female and non-smoker)(104;105). Multiple RCTs, reviews and guidelines to optimize PONV management have been published(104-107) generally finding ondansetron, dexamethasone, droperidol and propofol-based anesthesia the most effective agents in both treatment and prophylaxis(106;107). Fluid homeostasis and peripheral circulation may theoretically influence PONV and preoperative orthostatic dysfunction has been associated with PONV(50). Initial reports that supplemental perioperative oxygen administration decreased PONV(108;109) have not been confirmed in subsequent clinical trials(110-114).

common indications for intravenous fluid substitution in elective surgery

- **preoperative fluid deficits**
- **control hemodynamics under anesthesia**
- **maintain high CVP**
- **control hemodynamics postoperatively**
- **avoid blood transfusion**
- **avoid postoperative renal failure**
- **no enteral nutrition postoperatively**
- **prevention of hypotension with regional anesthesia/analgesia**

figure 3

PERIOPERATIVE ISSUES INFLUENCING FLUID MANAGEMENT

PREOPERATIVE ISSUES

Fasting – guidelines To minimize preoperative dehydration derived from fasting, commonly accepted guidelines generally allow clear fluid intake until two hours before surgery(115;116). The fluid loss from equivalent preoperative fasting regimens has been estimated to 0,5 liter(117), however there is a lack of studies describing preoperative fluid status.

Oral carbohydrates Preoperative oral hydration with carbohydrate-rich beverage reduces postoperative insulin-resistance(118) and improves preoperative well-being(100), but with varying reports regarding effects on postoperative outcome, varying from none(101) to reduced PONV in laparoscopic cholecystectomy(119) and to reduced hospital stay and earlier gut function in one report in colonic surgery(120).

Bowel preparation The physiologic effects of bowel preparation have not previously been described in a standardized setting. We therefore investigated in detail the physiologic effects of bowel preparation with bisacodyl and sodium phosphate in 12 "elderly" healthy volunteers (median age 63 years) with standardized oral fluid and food intake(3). Bowel preparation led to a significant decrease in exercise capacity (median 9 %) and weight (median 1.2 kg) while no differences in plasma or extracellular volumes, orthostatic tolerance and balance function were seen(3). Two liters crystalloid has previously been found to improve (but not alleviate) orthostatic tolerance during bowel preparation with sodium picosulphate(121), and in patients scheduled for laparoscopic surgery bowel preparation with bisacodyl and polyethylene glycol resulted in relative hypovolemia correctable by 1500 ml crystalloid infusion(122). The functional hypovolemia resulting from preoperative bowel preparation may be pronounced in elderly patients with a decreased capacity for oral intake(123). A recent study concluded that only half of patients undergoing elective abdominal surgery with bowel preparation responded to intraoperative crystalloid administration with an increase in cardiac output, a variation possibly attributable to differences in preoperative fluid status(124). Thus, knowledge of preoperative fluid status is a prerequisite for adequately intraoperative fluid management, informations largely missing in the literature. The lack of benefit of bowel preparation in colorectal surgery has been documented in several large randomized, controlled trials and meta-analyses(125;126). Despite of this, a recent survey documented, that preoperative bowel preparation is still used in more than 85% of cases in colonic surgery(127).

In summary, bowel preparation leads to a decrease in functional cardiovascular capacity probably attributed to dehydration and with implications for subsequent intra- and postoperative cardiovascular dysfunction and fluid management. In elderly patients undergoing preoperative bowel preparation, 2-3 liters supplemental intravenous crystalloid should be administered preoperatively. In clinical trials investigating outcomes of fluid administration, use of bowel preparation may influence the results and should be avoided and the degree of preoperative dehydration should be sought standardized and described, for example by weighing the patients or by applying non-invasive flow-related measurement techniques(128) (discussed below).

INTRAOPERATIVE ISSUES

Anesthesia

Regional anesthesia (spinal or epidural) is the preferred anesthetic technique in lower body orthopedic procedures, primarily due to the decrease in blood loss and improved perioperative morbidity(27;129). Furthermore combined general and thoracic epidural anesthesia with local anesthetics continued for a minimum of 24 hours postoperatively is recommended in major abdominal surgery primarily due to the improved dynamic analgesia which is a prerequisite for optimal postoperative recovery(130;131). The most common side effect of epidural or spinal anesthesia is hypotension, caused by arterial and venous vasodilation(132) prompting fluid infusions or administration of vasopressors(133). Neither treatment with intravenous fluids (crystalloids, colloids or hypertonic solutions) or vasopressors may eliminate the incidence of hypotension(133) as documented in several RCTs and a meta-analysis in spinal anesthesia for cesarean section(134). Furthermore, fluid administered on this indication is a common contributory factor to postoperative fluid overload(9;133). The hemodynamic effects of low levels of spinal/epidural anesthesia (T8 or below) are usually moderate due to compensatory upper body vasoconstriction, as opposed to a high thoracic blockade potentially resulting in decreased cardiac output and hypotension by the reduced preload and impaired sympathetic cardiac drive(135). Previous observations have suggested a movement of fluid from the interstitial to the intravascular space with experimentally induced hypovolemia(136) and in hypotensive, but not normotensive patients after epidural anesthesia(137;138). A potential, endogenous increase in plasma volume after neuraxial blockade may have implications for choosing the optimal regimen to treat hypotension (i.e. fluids or vasopressors). In order to describe the intravascular consequences of epidural anesthesia, we induced thoracic epidural anesthesia (T7-T10) with 10 ml bupivacaine 0,5% in 12 healthy volunteers and administered fluid (7 ml/kg colloid) or a vasopressor (ephedrine 0,2 mg/kg) after 90 minutes with plasma volume and volume kinetic analysis-derived values being the primary outcome parameters(2). Blood pressure was decreased with epidural anesthesia, but plasma volume (125I-albumin) did not change per se after thoracic epidural or vasopressor treatment but increased with colloid administration. Volume kinetic analysis showed that the infused colloid appeared initially to be located in a central compartment suggesting compensatory peripheral vasoconstriction. In summary, we may conclude that thoracic epidural anesthesia did not induce intravascular fluid expansion. Thus, vasopressors may be preferred to alleviate epidurally-induced hypotension in particular in patients at high risk of adverse reactions to perioperative fluid overload (such as elderly patients with cardiopulmonary comorbidity).

Laparoscopic vs. open surgery The hemodynamic changes induced by pneumoperitoneum may have implications for perioperative fluid administration(139), but have not been investigated specifically with regards to fluid administration regimens in clinical studies.

POSTOPERATIVE ISSUES

Recent data from various surgical specialties show that a multimodal revision of principles for perioperative management (e.g. fast-track surgery) may improve outcome (reviewed in detail elsewhere)(130;140;141) with implications also for perioperative fluid management130. The combination of improved postoperative organ functions(46) (in particular postoperative ileus)(64) and strict guidelines for postoperative management (removal of nasogastric tubes, institution of early oral nutrition and mobilization and intravenous fluids administered only on specific indications) has resulted in a decrease in perioperative intravenous fluid administration in fast-track surgical programmes(142-145). However, the specific importance of the perioperative fluid administration regimens on perioperative physiology and clinical outcome in fast-track surgery has not been addressed until the present studies(6;7). Additionally, a standardized and optimized perioperative management protocol is a prerequisite in accurately evaluating the influence of a single intervention (such as perioperative fluid administration) on the perioperative course(146).

Table 1

Clinical outcome	Physiological outcome	Methods og evaluation
Mobilization/exercise capacity	Cardiac function	Walking and treadmill tests Orthostatic function
Pneumonia	Pulmonary function CT atelectasis	Spirometry
Sufficient oral nutrition	Ileus	Scintigraphy Transit, defecation
Renal failure	Renal function	Need for therapy (monitoring/dialysis etc.)
Wound infection (incl. anastomotic leakage) Cerebral dysfunction Myocardial ischemia/infarction	Tissue pO2 /spO2	Subcutaneous tonometry Oximetry
Thrombosis	Coagulation	Individual coagulation factors Thrombelastography
Discharge criteria	PONV Balance function	Visual analogue scales Computerized balance measurements
Convalescence	Mobilization	Ability to perform usual activities

STRATEGIES IN PERIOPERATIVE FLUID MANAGEMENT

Routine cardiovascular monitoring such as blood pressure, heart rate, urine output (figure 3) are not reliable predictors of intravascular fluid status and thus not rational to guide perioperative fluid therapy(44;89) (table 1). Strategies in perioperative fluid management based on predefined target values (achieved by combinations of inotropes and fluid infusions) of such pressure-derived variables (primarily central venous and estimated left atrial pressures) were developed in the 1970´s(9). While significant mortality reductions in high-risk patients (control group mortality > 20%) was found with such hemodynamic optimization providing it was initiated before organ failure and the hemodynamic goals were met(147), no benefits in patient populations with a baseline mortality rate less than 15% could be demonstrated(147). Clinical trials in elective surgical patients targeting predefined pressure-derived variables obtained by pulmonary artery catheter have largely been disappointing(148;149). The disappointing results from the above trials may not be surprising since both central venous and capillary wedge pressures are poor markers of intravascular volume, primarily due to non-linear variations in vascular compliance(150;151). In that context, individualized fluid administration guided by individualized (as opposed to predefined) flow-related variables seems rational(43;44). Goal-directed fluid administration strategies (GDM) are based on the assumption that fluid resuscitation to maximize oxygen delivery (estimated by individualized flow-related parameters) may improve outcome(89). The only GDM strategy sufficiently evaluated in clinical trials consists of colloid infusions guided by cardiac filling pressures obtained via a transesophageal Doppler (ED), however other techniques are available(89;152). Fluid management guided by ED usually results in more fluid (~1-2 liters including some colloid) being administered(44). In randomized, clinical trials assessing intraoperative fluid administration, two fluid administration strategies have been evaluated: Fluid administration based on predetermined rates of infusion ("fixed-infusion rate strategy") and GDM. With fixed-infusion rate strategies, infusion rates of intravenous fluids have been determined based on general estimations of perioperative fluid losses. In minor and moderately sized surgery this is the only strategy evaluated in RCTs. In major surgery, both of the above strategies have been evaluated. Recent controversy centers on advantages of fluid "restriction" vs. advantages of GDM(44;153-157) (discussed further below).

FLUID MANAGEMENT IN ELECTIVE SURGERY – CLINICAL STUDIES
Literature

A Medline search (1966-May 1st 2007) was performed in order to identify all randomized, clinical trials published in English-language journals comparing different amounts of intravenous fluid administered for fluid replacement purposes pre- intra- and postoperatively in elective non-cardiac surgery. Trials in pediatric surgery and cesarean section were excluded, as well as trials with no clinical or physiological (e.g. parameters reflecting organ functions) outcomes reported beyond the intraoperative period. The search string was similar to our recent systematic review(5) and consisted of the free text terms "crystalloid*", "colloid*", "fluid therapy", "hyperton*", "surgery", and the medical subject headings "Fluid therapy", "Surgical Procedures, Operative" and "Colloids". All of the above search criteria regarding fluids and surgery were combined. Additional studies were identified from review articles and articles cited in original papers. We arbitrarily divided the studies into minor (estimated duration of surgery ~ 30 min and potentially outpatient surgery), intermediate (estimated duration of surgery ~ 1 hour) and major surgery (estimated duration of surgery > 1 hour).
Table 2 shows all RCTs included according to the above criteria.

MINOR SURGERY

In minor surgery, perioperative fluid shifts are small and organ dysfunctions minor. The clinically relevant outcomes in this patient category include feasibility of same-day discharge and convalescence (return to work or daily activities), with pain, nausea, vomiting, drowsiness, dizziness and well-being as limiting factors(92;158). Dehydration caused by preoperative fasting accounts for the majority of fluid deficits in these procedures. It is well documented from our two recent systematic reviews(5;159) that fluid substitution aiming to correct preoperative dehydration (1-2 liters primarily crystalloid vs. no fluid) may improve drowsiness and dizziness as well as PONV (table 2). In adults, as opposed to children(160), a mandatory postoperative fluid intake (150 ml) does not influence PONV(161). Several uncontrolled pro- and retrospective studies have reported fluid restriction (~500 ml. vs. ~1000-1500 ml total) to reduce urinary retention after hernia and anal surgery(9;162;163), which, however is not confirmed in the available RCTs comparing ~500 vs. 1000-1300 ml crystalloid(164;165).

INTERMEDIATE (MODERATELY COMPLEX) SURGERY

With the above definition intermediate surgery covers procedures such as laparoscopic cholecystectomy, laparoscopic fundoplication, hysterectomy, knee and hip arthroplasty and peripheral vascular surgery. Only two RCTs of fluid management exist in this category.
Laparoscopic cholecystectomy is one of the most commonly performed surgical procedures, and may be performed on an outpatient basis with a short convalescence (<1 week)(166). A multi-modal regimen to improve recovery after laparoscopic cholecystectomy including optimized analgesia, preoperative dexamethasone(167;168), and short recommendations for convalescence ensures same-day patient discharge, normalization of organ functions after 2-3 days(47) and return to work within one week after surgery(166). Clinically relevant outcomes include feasibility of same-day discharge and factors influencing the convalescence period include pain, nausea and well-being(92;166;169). In a double-blind, randomized, clinical trial in 48 patients undergoing laparoscopic cholecystectomy in the above setting, we found that intraoperative administration of 40 ml kg-1 (~3 liters) vs. 15 ml kg-1 (~1 liter) RL led to significant improvements in pulmonary function, exercise capacity, balance function and subjective recovery measures (nausea, general well-being, thirst, dizziness, drowsiness and fatigue) together with a significantly reduced cardiovascular hormonal response assessed by changes in hormones influencing fluid homeostasis (reductions in aldosterone, ADH and AT-II) and a shortened hospital stay(4). This was the first study reporting functional physiologic outcomes with two levels of intraoperative fluid administration within a fast-track setting. The decrease in pulmonary function differed from our findings in a prospective, double-blind, cross-over randomized study in 12 healthy volunteers, mimicking the perioperative set-up for laparoscopic cholecystectomy, but without surgery being performed, where infusion of 40 ml kg-1 (~ 3 liters) RL over 3 hours led to a significant although small (~5-7%) decrease in pulmonary function and in addition a significant weight gain lasting 24 hours, but without effects on exercise capacity and balance function(1). Previous studies with infusions of ~ 1-2 liters saline in healthy volunteers resulted in a similar decreases in pulmonary function(170;171), while infusion of ~1 liter saline in patients with left ventricular dysfunction reduced alveolar-capillary membrane function, increased airway obstruction and reduced pulmonary diffusion capacity(172;173), as opposed to healthy subjects(173). However, it seems that upon addition of surgery, patients receiving ~1 liter vs. ~3 liters RL intraoperatively were functional hypovolemic (as seen by the impaired physiologic and clinical outcomes together with the increased cardiovascular hormonal response indicating the presence of a physiologic feedback mechanism). These findings may explain the improved outcomes found in patients receiving ~3 liters RL intraoperatively despite a weight gain of 2,2 kg 4 hours postoperatively(4). Thus, the existence of a critical period intraoperatively where volume substitution is beneficial may be hypothesized, suggesting a potential importance of the timing of fluid administration even in patients without apparent signs of hypovolemia. Obviously, since we only investigated 40 ml kg-1 vs. 15 ml kg-1 RL, a dose-response relationship was not determined. In a study mixing patients undergoing gynecologic laparoscopy or laparoscopic cholecystectomy, intraoperative administration of 1700 ml vs. 1100 ml crystalloid was found to decrease PONV(88) as well (included in table 2(5)). Theoretically, patient positioning may affect fluid dynamics, with the 10 degrees head-up positioning used in our study in laparoscopic cholecystectomy leading to decreased preload and theoretically increased fluid requirements(4). However, patients in the studies in gynecologic laparoscopy were positioned app. 10 degrees head-down and with re-

ported similar beneficial effects of additional crystalloid administration (~1800 vs. ~200 ml)(174). Furthermore, the hemodynamic effects of pneumoperitoneum per se in the applied range (<12 mmHg) are usually moderate and transient(139). In summary, the same volume of RL causing adverse physiologic effects in healthy volunteers improved outcome in laparoscopic cholecystectomy, thus indicating increased fluid requirements with the addition of surgical trauma.
To further characterize the physiologic effects of 40 ml kg-1 vs. 15 ml kg-1 RL in laparoscopic cholecystectomy, we applied the volume kinetic analysis model described previously, infusing a crystalloid load of 12.5 ml kg-1 RL pre- and 4 hours postoperatively and with intraoperative fluid administration consisting of 15 ml kg-1 vs. 40 ml kg-1 RL administered in the same setting as described above(4;8). We found that distribution and elimination of this crystalloid load was not altered by the level of intraoperative fluid administration but was eliminated more rapidly after than before surgery. The rapid elimination postoperatively is similar to previous findings in hysterectomy patients(40), but in contrast to the slower postoperative elimination after hip fracture surgery(39), in accordance with the larger fluid retention induced by the more pronounced stress reaction seen after the latter. In summary, volume kinetic analysis indicated no presence of either hypo- or hypervolemia 4 hours after laparoscopic cholecystectomy. However, this does not exclude the presence of intraoperative functional hypovolemia correctable by fluid infusions as indicated by the activation of cardiovascular stress hormones in patients receiving ~1 liter RL intraoperatively(4).
In summary, we may conclude that < 1 liter RL deteriorates functional and clinical outcomes in laparoscopic cholecystectomy and that ~3 liters RL improves outcome. These findings may be extrapolated to similar types of surgery such as laparoscopic fundoplication and hysterectomy and are in accordance with the studies in minor procedures where administration of >1 l crystalloid improved outcome compared with <1 l crystalloid(5;159). However, since we only studied patients without cardiopulmonary disease, further evaluation is needed in patients with cardiopulmonary morbidity to allow general recommendations.
Knee arthroplasty may be considered a moderately complex surgical procedure, but with a substantial reduction of the surgical stress activation when performed during regional anesthesia(129). Multimodal rehabilitation according to the principles of fast-track surgery with early nutrition, enforced mobilization and epidural analgesia have resulted in hospital stays of ~4 days(175). One of the major determinants of convalescence and hospital stay in this patient group is mobilization/ability to participate in physiotherapy. To characterize the effects of fluid administration in knee arthroplasty, we conducted a randomized, double-blind study in 48 patients within the fast-track rehabilitation program described above(175). Intraoperative fluid infusions were planned according to a predetermined fixed rate based on estimated fluid losses in a ”liberal” vs. a ”restrictive” group, both within commonly administered fluid volume ranges practiced in this type of surgery. We found that ”liberal” (4250 ml total, including 500 ml colloid) compared to ”restrictive” (total 1740 ml including 500 ml colloid) intraoperative RL-based fluid administration resulted in significant hypercoagulability, while no over-all differences in functional recovery (pulmonary function, exercise capacity, nocturnal hypoxemia and ileus) could be demonstrated.
Moderate hypercoagulation (assessed primarily with thrombelastography) with crystalloid infusions have been described in healthy volunteers(176) as well as in surgical patients(177-179) possibly due to imbalance between pro- and anticoagulatory factors after crystalloid infusions(180). However, the clinical implications of this hypercoagulability are unclear, since only one randomized study reported crystalloid-induced hypercoagulation to correlate with clinical thromboembolic complications(72) (table 2). The previously reported hypocoagulability with colloid administration may be of minimal clinical relevance with the newer colloid preparations(67).

In summary, despite inducing hypercoagulability, over-all functional outcomes were not changed with ”liberal” vs. ”restrictive” fluid management in knee arthroplasty within a multi-modal rehabilitation concept. As opposed to our previous study in laparoscopic cholecystectomy, the patients were twice the age (72 yr vs. 36 yr) and ~50% had significant cardiovascular comorbidities, indicating the safety of a ”liberal” fluid management (~4 liters) in elderly patients during regional anesthesia in the presence of cardiovascular disease when participating in a fast-track rehabilitation program.

MAJOR SURGERY

In major surgery, the combination of internal fluid shifts and fluid retention resulting in extravascular fluid accumulation and postoperative organ dysfunctions complicates perioperative fluid management. Colonic surgery is a commonly performed procedure in this category. Postoperative ileus, which is also a determinant of hospital stay(59), together with pulmonary function/hypoxemia and cardiovascular exercise capacity are relevant physiologic outcomes. Clinically relevant outcomes with regards to fluid administration include cardiopulmonary and wound healing complications including anastomotic leakage and thromboembolic complications (discussed above).

Physiological recovery

Multimodal perioperative management according to the principles of fast-track surgery including epidural analgesia with local anesthetics, early enteral nutrition, no naso-gastric tubes and drains and enforced mobilization(181) have resulted in improved physiologic organ functions(46), decreased complication rates(143) and hospital stay of 2-4 days after colonic surgery(181). In this setting we conducted a randomized, double-blind study in 32 patients undergoing elective colonic surgery comparing ”restrictive” (total 1640 ml) vs. ”liberal” (total 5050 ml) intraoperative administration of RL (including 500 ml colloid in each group)(6). Fluids were administered according to a predetermined fixed rate based on estimated fluid losses in a ”liberal” vs. a ”restrictive” group, both within commonly administered fluid volume ranges in daily practice(5). Bowel preparation was not used(125). We found that ”restrictive” fluid administration significantly improved pulmonary function and late postoperative hypoxemia, while no differences in ileus, exercise capacity, orthostatic tolerance or other recovery parameters were demonstrated. In contrast, the cardiovascular hormonal response (renin, aldosterone and angiotensin II) was significantly reduced with ”liberal” fluid administration. The reduced cardiovascular hormonal response seen with the ”liberal” fluid group suggests a physiologic feed-back mechanism to be active, hypothesizing functional hypovolemia to be present intraoperatively in the ”restrictive” fluid administration group. In that context we noted, although not a primary outcome, that three patients in the ”restrictive” group vs. none in the ”liberal” group had anastomotic leakage. The improvement in nocturnal hypoxemia in colonic surgery with ”restrictive” fluid therapy opposed our findings in

knee arthroplasty where no differences between the two fluid administration regimens were seen. This may indicate the presence of fluid accumulation in the extracellular phase in colonic surgery. However, our findings suggest that a ”liberal” (total ~6 liters on the day of surgery including oral intake) compared with a ”restrictive” (~2,6 liters) fluid regimen may not deteriorate functional outcomes after fast-track colonic surgery. However, a ”restrictive” fluid regimen without a sufficient pre- and early intraoperative volume load may theoretically predispose to increased morbidity, which needs evaluation in larger trials.
The influence of perioperative fluid administration on postoperative ileus has been evaluated in six RCTs (table 2): Two RCTs reported decreased postoperative ileus with “fluid restriction”(62;182), while another trial found no influence of fluid management on postoperative ileus(183). Applying GDM with ED strategies, two studies found postoperative ileus to be slightly decreased (1-2 days) in the intervention groups(184;185), while no difference was found in the third study(186) (table 2). When discussing these studies it is however important to note the exact volume and timing of the administered fluid, rather than rely on terms such as “restrictive” or “liberal”. The actual volumes administered in these GDM studies (in both groups)(184;185) approximated the “liberal” regimen in our study in colonic surgery(6). However, the timing of the fluid administration differed, with a substantial part of the fluid in the GDM studies being administered immediately before/during the start of surgery.

Clinical outcomes

Wound healing

In a randomized, clinical trial in 253 patients undergoing colonic surgery, ”liberal” (~5,7 liters) vs. ”restrictive” (~3,1 liters) intraoperative crystalloid administration (fixed-infusion rate strategy) did not affect wound healing/wound infection rates(187), despite the improved tissue oxygen tension found in the ”liberal” fluid administration group in a subset from this study(88) (table 2). Postoperative fluid management guided by subcutaneous tonometry (5,7 vs. 4,6 liters crystalloid) has earlier been found to improve collagen accumulation in wounds(188) while in major abdominal surgery, a colloid-based (~6 liters) vs. a crystalloid based (~12 liters) fluid regimen improved tissue oxygen tension(189). While the optimal fluid management to reduce postoperative wound infections is unclear, other perioperative interventions influencing the postoperative wound infection rate such as oxygen administration(190;191) (although debated)(192) and maintenance of intraoperative normothermia(193) should also be controlled.

Major complications and hospital stay

Four RCTs applying fixed-infusion rate strategies assessed the influence of various fluid administration regimens on postoperative complications and hospital stay in major surgery, but not including fast-track protocols: In one RCT in colorectal surgery, administration of 3 vs. 5 liters mixed crystalloid/colloid on the day of surgery led to a significant decrease in major complications, primarily cardiopulmonary (7% versus 24%) and tissue-healing complications (16% versus 31%) (194). These results were confirmed in another RCT in 152 patients undergoing mixed major abdominal surgery, where ~3,6 vs. ~5,9 liters crystalloid led to a decrease in postoperative complications (13 vs. 23 patients with complications) and hospital stay (8 vs. 9 days)(182). In the RCT mentioned above with 253 patients undergoing colonic surgery, no difference in hospital stay with ~6 vs. ~3 liters crystalloid (7 days in both groups) was found(187), but lack of specific information on organ functions, ileus, care regimens etc. hinders more detailed interpretation. And in the most recent trial, postoperative “fluid restriction” (minimizing intravenous crystalloid administration to ~2 vs. ~2,7 liters the first days postoperatively) did not influence hospital stay or ileus(183). Four RCTs applying GDM with ED assessed hospital stay: Three studies found a reduction in hospital stay in the intervention groups (5, 7 and 10 vs. 7, 9 and 11,5 days)(184;185;195), while GDM did not affect hospital stay in the fourth study (11 vs. 12 days)(186). However, both in cardiac and hip fracture surgery, GDM-based fluid strategies have decreased major postoperative complications(81;196) as well as improved postoperative mobilization and hospital stay(197;198) (or readiness to discharge(199)). The benefits of GDM has been attributed to avoidance of gut mucosal hypoperfusion (improvements in gastric pHi)(81), although guiding fluid therapy according to optimize pHi has not been found to improve outcome(90;91). Since the difference in actual volumes administered is 1-1,5 liters between the groups with GDM, it is unlikely that the observed outcome differences may be attributed to a volume effect or an effect of colloid per se. However, the timing of fluid administration – targeting volume at a critical time point intraoperatively with patients potentially susceptible to hypovolemia combined with the individualized approach may be of significant importance, and deserves further study.
Unfortunately, in most of the above studies type of surgery, choice of fluid, use of diuretics, use of preoperative bowel preparation and perioperative management were not standardized(182;187;194), all of which may hinder precise interpretation and evaluation of the outcome differences presented. As an example the improvement to tolerate solid diet in 3 vs. 5 days with EDM(184) may be of limited relevance in a fast-track regimen where solid diet is tolerated on the day of operation regardless of ”liberal” or ”restrictive” fluid administration6. Furthermore, it is important to look at the actual volumes of fluid administered and not just adhere to the terms “liberal” or “restrictive”, since in most available studies a large overlap between the two groups are seen, blurring interpretation(194). Furthermore, fluid administration regimens classified as being in the “liberal” group by some authors are considered in the “restrictive” group by others, regardless that the actual administered volumes are the same(6;194).
In summary, EDM may improve outcome in major surgery, but need more rigorous evaluation in settings with standardized surgical procedures and optimized perioperative management. Briefly, available data in elective major abdominal surgery indicate that administration of >5 liters fluid (primarily crystalloid) without specific indications may increase morbidity while administration of < 2,0 liters may not be recommended due to a potential risk of hypovolemia. However, there is very limited data from studies with 24 h postoperative fluid administration. Summarizing, fluid overload as well as functional hypovolemia should be avoided, but the currently available techniques to assess normovolemia are insufficient, although ED assessment of stroke volume may be most thoroughly evaluated at this time.

Table 2. Volume-based strategies in RCT reporting functional and/or clinical outcomes						
	Procedure (no patients)	Fluid strategy	IV fluids intraop	24h postop fluid status	Intraop blood loss	Outcomes
Minor surgery						
Holte 2002[159] and Holte 2006[5]	We recently conducted two systematic reviews of the available 26 randomized trials of fluid administration to compensate for dehydration in minor surgery. In summary, > 1 L (primarily crystalloid) improved recovery as estimated by reductions in drowsiness, dizziness and PONV. Data do not support choice of one fluid over another.					
Intermediate surgery						
Holte 2004[4]	Lap chole (48)	FI intraop	1. Low: 998 ml 2. High: 2928 ml	1. WG: 0,75 kg 2. WG: 1,4 kg (4h postop)	1. 0 ml 2. 0 ml	Exercise capacity ↑, pulmonary function ↑, recovery ↑, PONV ↓ hospital stay ↓ (group 2)
Holte 2006[7]	Knee arthroplasty (48)	FI intraop	1. Low: 1740 ml 2. High: 4250 ml	1. WG: 0,6 kg 2. WG: 2,1 kg	1. 0 ml 2. 0 ml	Coagulation ↑ (group 2), pulmonary function -, exercise capacity -, hypoxemia -
Major surgery						
Janvrin 1980[72]	Abdominal (60)	FI intra- and postop	1. High: ~1 L/h intraop + 2-3 L/day postop 2. Low: No IV fluids	Not mentioned	Not mentioned	Coagulation ↓, thrombosis ↓ (group 2)
Priano 1993[74]	Radical neck (24)	FI intraop	1. Low: 3578 ml 2. High: 7431 ml	Not mentioned	1. 908 ml 2. 732 ml	Renal function -
Cassell 1996[208]	Open chole (45)	FI postop	1. High 1: 1 L cryst + 1,5 L dextrose/24h postop 2. High 2: 1 L cryst/24h postop 3. Low: No IV fluids postop IO status not mentioned	Not mentioned	Not mentioned	Renal function -, PONV -, urinary retention -
Sanders 2001[121]	Colon (41)	FI preop during bowel prep	Preoperatively: 1. High: 2 L fluid 2. Low: No fluid IO not mentioned	Not mentioned	Not mentioned	Weight loss ↓, postural hypotension ↓, renal function ↑ (group 1)
Conway 2002[186]	Bowel resections (57)	GDM with ED intraop	1. 4516 ml (colloid: 1958 ml) (ED) 2. 3770 ml (colloid: 1325 ml)	Not mentioned	Not mentioned	Hospital stay -, ileus -, complications -, mortality -
Gan 2002[184]	Mixed abdominal (100)	GDM with ED intraop	1. 5252 ml (colloid: 847 ml) (ED) 2. 4657 ml (colloid: 282 ml)	Not mentioned	1. 703 ml 2. 624 ml	Hospital stay ↓, PONV ↓, ileus ↓ (group 1), complications -
Lobo 2002[62]	Colonic (20)	FI postop	1. High: ~> 3 L IV/day postop 2. Low: ~< 2 L IV/day postop	Not mentioned	Not mentioned	Ileus ↓, hospital stay ↓, gastric emptying ↑ (group 2)
Brandstrup 2003[194]	Colorectal (141)	FI intra- and postop	Until 24 hours postoperatively: 1. Low: Total 2740 ml cryst + colloid 2. High: Total 5388 ml cryst + colloid	1. WG: 0,5 kg 2. WG: 2,8 kg	1. 400 ml 2. 500 ml	Major complications ↓, minor complications ↓ (group 1), mortality -
Nisanevich 2005[182]	Mixed abdominal (152)	FI intraop	1. Low: 1408 ml 2. High: 3878 ml	1. WG: 0,5 kg 2. WG: 1,9 kg	1. 400 ml 2. 440 ml	Complications, ileus, hospital stay ↓ (group 1)
Kabon 2005[187] + Arkilic 2003[88] (subset)	Colorectal (256)	FI intraop	1. Low: 3,1 L 2. High: 5,7 L	Not mentioned	1. 333 ml 2. 322 ml	Wound infection, wound healing, ileus, nausea vomiting, hospital stay – Tissue oxygen tension ↑ (group 2) in subset[88]
Wakeling 2005[185]	Colorectal (128)	GDM with ED intraop	1. 5000 ml (colloid 2000 ml) (ED) 2. 4500 ml (colloid 1400 ml)	Not mentioned	1. 500 ml 2. 500 ml	Hospital stay, ileus, complications ↓ (group 1)
Noblett 2006[195]	Colorectal (108)	GDM with ED intraop	1. 3638 ml (colloid 1340 ml) (ED) 2. 3834 ml (colloid 1209 ml)	Not mentioned	1. 250 ml 2. 475 ml	Hospital stay, complications ↓ (group 1)
MacKay 2006[183]	Colorectal (80)	FI postop	Not mentioned	1. Low: 2 L (WG: –0,5 kg) 2. High: 2,75 L (WG: + 1 kg) (day of surgery adm)	Not mentioned	Hospital stay -, ileus -
Holte 2007[6]	Colonic (32)	FI intraop	1. Low: 1640 ml 2. High: 5050 ml	1. Low: WG: –0,2 kg 2. High: WG: 2 kg	1. 200 ml 2. 305 ml	Pulm function ↑, late postop hypoxemia ↓ (group 1), hospital stay -

Table 2

ED: Esophageal Doppler. FI: Fluid administration administered at a fixed infusion rate. GDM: Goal-directed fluid administration strategies by individualized flow-related parameters. High vs. low: Terms to denominate the two groups in studies with fixed-infusion rate regimens. PONV: Postoperative nausea and vomiting. WG: Weight gain. IO: Intraoperatively. L: Liter(s)

If not stated otherwise, fluid management consisted of intravenous crystalloid infusion. 24 postop fluid status: Fluid status 24 h from the start of surgery. ↓: Decrease in parameter, ↑: Increase in parameter, -: No difference in parameter

DIFFERENT TYPES OF FLUID SOLUTIONS

The importance of choice of fluid on surgical outcome has been evaluated in several RCTs and meta-analyses. The theoretic advantage of colloids vs. crystalloids is the improved intravascular volume expansion(200) with the potential of minimizing the total infused fluid volumes. Several meta-analyses based on RCTs predominantly performed in critically ill patients(10;11;201) have failed to find reductions in mortality with colloids compared to crystalloids for volume resuscitation. The majority of studies focused on critically ill and trauma patients, and the results are not applicable for elective surgical procedures. Another meta-analysis found no difference between various colloids(15) or on the use of hypertonic vs. (near)-isotonic solutions(13) on outcomes (primarily mortality). The negative effects of albumin shown in a meta-analysis(202) and the subsequent lack of effect in a large RCT(203) suggests that albumin as a volume substitute may not be indicated in elective surgery, but evidence to compare albumin vs. synthetic colloids is limited in this setting. Regarding the choice of crystalloids, some authors advocate the use of "balanced" electrolyte solutions which are formulated to have a neutral pH and concentrations of electrolyte ions similar to those of human plasma (such as RL) based on reports that infusion of large amounts (> 5 liters) isotonic saline leads to a hyperchloremic metabolic acidosis(204), although with uncertain effects on clinical outcomes(205;206).

Since the results from available meta-analyses thus may not be applicable in elective surgical procedures, we decided to conduct a systematic review of RCTs assessing the types of fluid (e.g. crystalloids, colloids and hypertonic solutions) and the amounts of fluid (discussed above) administered perioperatively for fluid resuscitation purposes on surgical outcome in elective non-cardiac surgical procedures. 80 RCTs in elective non-cardiac surgery were included(5). In summary, the evidence from available randomized studies does not allow evidence-based recommendations of choice of one type of fluid over another(5) for the following main reasons: 1. Lack of assessments of clinically relevant functional outcomes in existing trials. 2. Studies were generally small, and not adequately powered to demonstrate differences in major morbidity. 3. Perioperative management, in particular in the postoperative period was not standardized and/or described. 4. Fluid in addition to the protocol was administered according to various trigger mechanisms (figure 3), rendering interpretation of the actually administered amounts of fluid difficult. 5. Studies were generally not continued into the postoperative period. 6. Various types of surgery with different pathophysiology were analyzed together. A formal meta-analysis based on the available studies is not clinically relevant, since no outcomes are reported with the required consistency for inclusion into such analysis.

In summary, recommendations on the optimal type of fluid to administer in elective surgical procedures cannot be made based on the available evidence. Studies with standardized surgery and perioperative management with functional physiologic and relevant clinical outcomes according to each procedure are needed to evaluate the importance of choice of fluid in elective surgical procedures.

2. METHODOLOGICAL CONSIDERATIONS

GENERAL DESIGN

Care was taken to assure randomization, double-blinding and consecutive patient enrolling in the three randomized, clinical studies. In particular, the double-blinding is important, since it is well known that unblinded studies may overestimate a treatment effect of about 20%(207). Patients were studied within the evidence-based perioperative management programmes used in daily clinical practice in our department, thus being clinically representative for patients scheduled for these procedures. The studies were explorative in nature, since both the descriptive and clinical studies were among the first in the respective fields. Postoperative management is currently a major determinant of recovery(130), and standardization of perioperative management, with emphasis on the updated postoperative management protocols, is a prerequisite to obtain valid results examining a single intervention (in this context fluid management) on functional physiologic recovery or outcome(130).

OUTCOME PARAMETERS

The outcome parameters and evaluation methods chosen were specifically aimed at reflecting functional recovery (discussed in details above).

FLUID ADMINISTRATION REGIMENS

The goal of perioperative fluid administration is to achieve functional normovolemia indicated by optimal functional and clinical recovery. While there is general agreement that both fluid overload and hypovolemia should be avoided(44), the necessary volumes and monitoring equipment by which to achieve functional normovolemia have not been defined. We chose the fixed-infusion rate strategy for volume replacement in the clinical studies, since this reflects common daily practice both in Denmark and internationally. It may be argued that fixed-dose regimens may not be optimal since individual patient characteristics are not accounted for. Nevertheless, such information is necessary to provide background information to be used in conjunction with GDM approaches to reach final recommendations. While the GDM approach may seem rational, the reductions in morbidity have not been determined in a fast-track surgical setting and need further evaluations. RL was used consistently in the studies in an attempt to avoid the hyperchloremic acidosis described with isotonic saline, in particular in patients receiving high volumes (~5 liters). With the perioperative relevant volumes of crystalloid (< 5 liters) administered, the slight hyperchloremic acidosis induced with isotonic saline is probably not of clinical relevance, thus the results from our studies with RL may be transferable to settings in which isotonic saline is administered(206). To focus exclusively on the volumes of fluid administered, volume differences between groups in the RCTs consisted solely of crystalloids, and a fixed standardized amount of colloid was added to both groups. Diuretics were not used. Specific algorithms guided replacement of blood loss.

In summary, all studies aimed to investigate basic pathophysiology of perioperative fluid administration and fluid shifts and were thus conducted in a controlled environment. Clinical outcomes were not primary effect parameters and further studies will be needed (discussed below).

DIRECTIONS FOR FUTURE RESEARCH

In minor surgery 1-2 liters of crystalloid administration improves functionally relevant outcomes and may be recommended without further evidence. However the role of colloids for early recovery should be explored.

In both intermediate and major surgery, there is a need for randomized, clinical trials evaluating functional physiologic outcomes as well as large-sized trials with clinical end-points such as complications with fixed-infusion rate as well as GDM strategies. Both types of studies need to be procedure-specific and to look at clinically relevant functional outcomes and morbidity in a standardized perioperative setting. The influence of fluid administration on tissue oxygenation, in particular intestinal oxygenation and blood supply in conjunction with construction of an anastomosis needs investigation. The influence of laparoscopic vs. open surgery on rational fluid administration also needs evaluation. Further clarification of the benefits of GDM strategies in standardized surgery with standardized perioperative management and with functional physiologic outcomes is required. To optimize interpretation, fluid administration protocols need to include the postoperative period (at least 1-2 days) and for this reason development of GDM devices acceptable to the wake patient are necessary (the presently available ED probes are suitable only in sedated patients). Very importantly, further research into methods to determine optimal fluid status (normovolemia/tissue oxygenation) is needed, in particular non-invasive methods with a potential for postoperative use. Since colloids compared to crystalloids have a favorable profile of obtaining intravascular expansion while reducing extravascular fluid accumulation, use of colloid vs. crystalloid-based volume replacement strategies seem rational, or various combinations of the two. Once more evidence from various elective procedures are collected, rational studies in emergency procedures where fluid administration is more complex due to the superimposed hypovolemia, sepsis and capillary leak syndrome may be designed.

SUMMARY

The purpose of this thesis was to describe pathophysiological aspects of perioperative fluid administration and create a rational background for future, clinical outcome studies.

In laparoscopic cholecystectomy, we have found ”liberal” crystalloid administration (~3 liters) to improve perioperative physiology and clinical outcome(4), which has implication for fluid management in other laparoscopic procedures such as laparoscopic fundoplication, laparoscopic repair of ventral hernia, hysterectomy etc, where 2-3 liters crystalloid should be administered based on the present evidence. That equal amounts of fluid caused adverse physiologic effects in healthy volunteers(1) indicates that addition of the surgical trauma per se increases fluid requirements. Volume kinetic analysis applied 4 hours postoperatively was not able to detect the presence of either overhydration or hypovolemia regardless of the administered fluid volume intraoperatively(8). In knee arthroplasty a ~4 vs. ~2 liters crystalloid-based fluid regimen lead to significant hypercoagulability (although with unknown clinical implications), but no over-all differences in functional recovery(7). Dehydration caused by bowel preparation leads to functional hypovolemia(3) and the deficits should be corrected, in particular in elderly patients, where preoperative intravenous fluid substitution of ~ 2-3 liters crystalloid is recommended. We did not find thoracic epidural anesthesia to be accompanied by intravascular fluid mobilization(2). In major (colonic) surgery with a standardized multimodal rehabilitation regimen, over-all functional recovery was not affected with a ”liberal” (~5 liters) vs. “restrictive” 1,5 liter crystalloid-based regimen6, however based on three anastomotic leakages in the “restrictive” group, it may be hypothesized that a too ”restrictive” fluid administration strategy could be detrimental in patients with anastomoses and need further evaluation. A systematic review concluded that present evidence does not allow final recommendations on which type of fluid to administer in elective surgery(6). Based on the current evidence, administration of > 5 liters intravenous fluis without specific indication in major surgical procedures should be avoided, while administration of < 1,5 liters in patients with anastomoses may not be recommended, an issue needing clarification in large-scale clinical studies. Finally, we have demonstrated that the conduction of double-blinded randomized trials on fluid management with postoperative outcomes is feasible.

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