Influence of "Liberal" versus "Restrictive" Intraoperative Fluid Administration on Elimination of a Postoperative Fluid Load

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Background: Previously, the authors found "liberal" fluid administration (approximately 3 l Ringer's lactate [RL]) to improve early rehabilitation after laparoscopic cholecystectomy, suggesting functional hypovolemia to be present in patients receiving "restrictive" fluid administration (approximately 1 l RL). Because volume kinetic analysis after a volume load may distinguish between hypovolemic *versus* normovolemic states, the authors applied volume kinetic analysis after laparoscopic cholecystectomy to explain the difference in outcome between 3 and 1 l RL.

Methods: In a prospective, nonrandomized trial, the authors studied 20 patients undergoing laparoscopic cholecystectomy. Ten patients received 15 ml/kg RL (group 1) and 10 patients received 40 ml/kg RL (group 2) intraoperatively. All other aspects of perioperative management were standardized. A 12.5-ml/kg RL volume load was infused preoperatively and 4 h postoperatively. The distribution and elimination of the fluid load was estimated using volume kinetic analysis.

Results: Patient baseline demographics and intraoperative data did not differ between groups, except for intraoperative RL, having a median of 1,118 ml (range, 900–1,400 ml) in group 1 compared with a median of 2,960 ml (range, 2,000–3,960 ml) in group 2 ($P < 0.01$). There were no significant preoperative *versus* postoperative differences in the size of the body fluid space expanded by infused fluid (V), whereas the clearance constant k_r was higher postoperatively *versus* preoperatively ($P = 0.03$). The preoperative *versus* postoperative changes in volume kinetics including V were not different between the two groups.

Conclusions: Elimination of an intravenous fluid load was increased after laparoscopic cholecystectomy *per se* but not influenced by the amount of intraoperative fluid administration.

THERE is a lack of evidence-based guidelines for perioperative fluid administration,[1] with some authors advocating restrictive fluid administration *versus* others advocating goal-directed fluid administration (generally leading to more fluids administered).[1–6] We recently demonstrated that intraoperative administration of approximately 3 l *versus* approximately 1 l Ringer's lactate (RL) significantly reduced the cardiovascular surgical stress response and improved perioperative organ functions (pulmonary function, exercise capacity, and balance function), recovery, and hospital stay after laparoscopic cholecystectomy.[7] These results suggest that the low-volume regimen resulted in functional hypovolemia, thereby posing additional vasoactive hormonal activity and delayed recovery. The technique of volume kinetic analysis[8] offers a method to look closer into body fluid homeostasis, because it includes an intravenous fluid load followed by hemoglobin samples and the application of mathematical analysis to assess functional fluid spaces and fluid excretion. The method has been proven effective in distinguishing normovolemic *versus* hypovolemic conditions as well as perioperative fluid shifts.[9–12] The aim of the current study was therefore to investigate whether the previously demonstrated improved postoperative physiologic functions seen with 3 l *versus* 1 l RL could be due to avoidance of hypovolemia based on volume kinetic data.

Materials and Methods

General Procedure

In a prospective trial approved by the regional ethics committee (Copenhagen, Denmark), we studied 20 patients scheduled to undergo elective laparoscopic cholecystectomy from April 2004 through November 2005 after informed consent. Exclusion criteria were as follows: age younger than 18 yr; weight greater than 100 kg; American Society of Anesthesiologists physical status III or IV; alcohol intake greater than 5 units daily; insulin-dependent diabetes mellitus; cardiac disease except uncomplicated arterial hypertension (treatment with one drug only); renal, pulmonary, or endocrine disease; treatment with diuretics; abnormal creatinine, sodium, or potassium; hemoglobin less than 7 mM; conversion from laparoscopic to open surgery; and psychiatric illness (intake of psychiatric medication other than selective serotonin reuptake inhibitors).

Anesthesia and Perioperative Management

Laparoscopic cholecystectomy was performed in a semiambulatory setting with perioperative management and fluid regimens similar to our previous publication on fluid management in laparoscopic cholecystectomy[7] and summarized below.

Preoperative fluid status was standardized in all patients (fasting from midnight, drinking 175 ml water on the morning of surgery and scheduled morning proce-

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Table 1. Patient Demographics

	15 ml/kg RL	40 ml/kg RL	*P* Value
Sex, F/M	6/4	9/1	0.17
Age, yr	41 (26–75)	50 (29–73)	0.20
BMI, kg/m2	27 (22–31)	26 (19–31)	0.76
ASA physical status I/II	10/0	8/2	0.17
Preoperative creatinine, μM	74 (60–89)	76 (56–96)	0.65
Amount fluid infused intraoperatively, ml	1,118 (900–1400)	2,960 (2,000–3,960)	< 0.01
Duration of surgery, min	73 (48–149)	72 (42–151)	0.76
Duration of anesthesia, min	112 (88–193)	122 (69–215)	0.68
Intraoperative blood loss, ml	0 (0–20)	0 (0–200)	0.97
Propofol, mg	748 (387–1,490)	738 (408–1,588)	0.82
Remifentanil, mg	4.7 (4–11)	5.2 (3–14)	0.94
Fluid infused for volume kinetic analysis	932 (750–1,140)	918 (618–1,240)	0.73

ASA = American Society of Anesthesiologists; BMI = Body mass index; RL = Ringer's lactate.

dures). Ten patients received an intraoperative infusion of 15 ml/kg (group 1) and 10 patients received an intraoperative infusion of 40 ml/kg (group 2) RL (composition: 130 mM Na^+, 4 mM K^+, 109 mM chloride, 28 mM lactate, 1.4 mM calcium) (protocol infusion). The amount of RL was infused at a constant rate over 1.5 h, starting immediately before induction of anesthesia. All patients received a similar general anesthesia with remifentanil, propofol, and muscle relaxants for tracheal intubation (table 1). The laparoscopic technique and multimodal pain management were applied as described previously[13] with ketorolac (30 mg), ondansetron (4 mg), and sufentanil (0.3–0.5 μg/kg) administered at the end of surgery. Hypotension was treated with 10 mg intravenous ephedrine. Fluid guidelines (table 1) were followed strictly, as reported previously.[7] Diuretics were not used. In the recovery room, pain treatment was standardized with sufentanil (first choice) and morphine. On-demand antiemetic treatment was standardized and consisted of 4 mg intravenous ondansetron once (first choice). Patients were allowed (but not forced) to drink fluids after surgery without restrictions. Fluid was ingested from standard cups, and the amount was registered 0–4 h after surgery (until the second test, fluid infusion).

Fluid Infusions and Hemoglobin Measurements

All patients received two infusions of RL (test infusions), the first preoperatively and the second postoperatively. The first infusion took place between 1 and 5 days before surgery, and the second occurred 4 h postoperatively. A cannula was placed in each cubital vein for fluid infusion and blood sampling. After voiding and 30 min of rest, 12.5 ml/kg RL (test infusion) was infused at a constant rate over 30 min. Venous blood samples were collected in duplicate for every 5 min during the first 60 min, and thereafter every 10 min until 150 min with subsequent measurement of blood hemoglobin concentration (in millimolars). Before the fluid infusion, a baseline hemoglobin sample was collected in triplicate.

A total of 11.5 ml blood was drawn for the hemoglobin analysis and replaced with 11.5 ml saline.

Volume Kinetic Analysis. The distribution of fluid given by intravenous infusion was analyzed using a one-volume kinetic model as described and validated previously in several studies in both healthy volunteers and surgical patients.[8,11,12,14-16] The fluid is given at a rate k_i and becomes distributed in an expandable space with a volume (v), which the fluid space strives to maintain at an ideal (target) volume (V). Fluid leaves the space at a basal rate, representing perspiration and baseline diuresis (k_b, fixed at 0.5 ml/min), and at a controlled rate proportional by a clearance constant (k_r) to the deviation from the target volume. Therefore, V is an indicator of the distribution, k_r indicates the elimination rate, and $T_{1/2}$ indicates the half-time of the infused fluid. The following differential equation describes the volume expansion in this model:

$$\frac{dv}{dt} = k_i - k_b - k_r \frac{v - V}{V}.$$

The best estimates of the two unknowns in this model, V and k_r, were obtained by using nonlinear least-squares regression (modified Gauss-Newton method). The mathematical solution to the equation shown above was fitted to the individual dilution–time profiles. Calculations were performed by using Matlab version 4.2 (Math Works Inc., Notich, MA).

The hemoglobin-derived plasma dilution was used to indicate the dilution of V. The reference equation for this relation is

$$\frac{v - V}{V} = \frac{Hb_o/Hb - 1}{1 - Hct_o},$$

where Hct is the hematocrit, Hb is the hemoglobin concentration in venous blood at any time (t), and Hb_o is the hemoglobin concentration at baseline. A correction was made for the losses of hemoglobin by blood sampling.[11] The half-life ($T_{1/2}$), which is a secondary param-

Table 2. Volume Kinetic Analysis

	15 ml/kg RL		40 ml/kg RL	
	Preop	Postop	Preop	Postop
V, l	7.2 (4.7–10.5)	6.1 (3.8–12.9)	5.0 (2.9–13.7)	6.2 (2.4–11.0)
k_r, ml/min	123 (18–270)	181 (43–536)*	148 (26–290)	270 (14–630)*
$T_{1/2}$, min	34 (19–365)	17 (8–97)	41 (10–173)	20 (4–321)
Plasma dilution, 30 min	0.102 (0.068–0.127)	0.102 (0.084–0.118)	0.108 (0.09–0.116)	0.081 (0.069–0.092)

Volume kinetic analysis after infusion of 12.5 ml/kg Ringer's lactate (RL) preoperatively and 4 h postoperatively with an intraoperative fluid administration of 15 ml/kg or 40 ml/kg RL.

* $P < 0.05$ compared with preoperatively.

eter in this model, was calculated individually for each patient as $0.693 \times V/k_r$.

Statistics

A formal power analysis could not be performed because of a lack of data with a similar setup and procedure. The number of subjects studied was therefore chosen arbitrarily but was suggested to be approximately 20 patients to detect a difference by 30 ml/min in k_r and by 1.5 l in V between groups with a power of 90% at the level of $P < 0.05$, based on findings in hip surgery.[12] Data were analyzed using nonparametric statistical methods and presented as median (range). The Wilcoxon signed rank test for paired observations was used to describe differences before *versus* after surgery. For comparing data between the groups (high *vs.* low intraoperative fluid administration), the Mann-Whitney test was used. Categorical data were analyzed using the Fisher exact test. $P < 0.05$ was considered significant.

Results

Patient demographics are shown in table 1. Duration of anesthesia and surgery and administration of propofol and remifentanil did not differ between the groups (table 1). Patients in the "restrictive" group received a median of 1,118 ml (range, 900–1,400 ml) RL compared with a median of 2,960 ml (range, 2,000–3,960 ml) RL intraoperatively in the "liberal" group ($P < 0.01$) (table 1). Postoperative oral intake was equal in both groups (375 [70–750] ml) in the restrictive group *versus* 450 (150–1050) ml in the liberal group; not significant) and patients receiving liberal *versus* restrictive fluid management had a weight gain of 1.5 *versus* 0.6 kg 4 h postoperatively ($P = 0.01$). Fluid guidelines were followed strictly in all patients, and no intravenous fluids apart from those mentioned above were administered.

Volume Kinetic Analysis

Volume kinetic parameters are depicted in table 2. There were no significant differences in V or $T_{1/2}$ preoperatively *versus* postoperatively, but a higher k_r (indicating a more rapid elimination) for the fluid load adminis-

tered after surgery than for the one given before surgery was found ($P = 0.03$). There were no statistically significant differences in volume kinetics between the two groups ($P > 0.05$).

Computer simulations based on the kinetic data presented in table 2 represented the individual plasma dilution–time curves reasonably well (fig. 1). A comparison between the simulated curves representing the four series of infusion (the test infusions in patients receiving 15 *vs.* 40 ml/kg RL intraoperatively, respectively) illustrates the slightly more rapid elimination after surgery, regardless of intraoperative fluid regimen (fig. 2).

Discussion

In summary, we found that the clearance constant (k_r) describing the elimination of an intravenous volume load
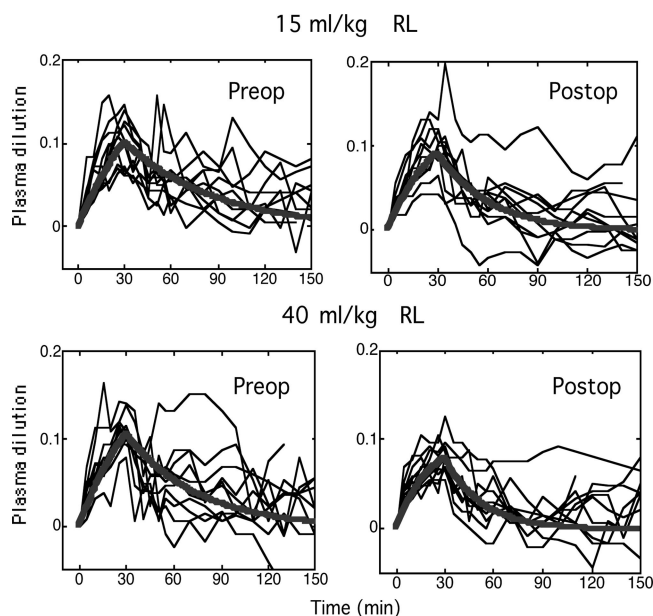

Fig. 1. The fractional plasma dilution based on hemoglobin in individual patients (*thin lines*) and the computer-generated curve based on the median kinetic parameters (*thick line*) during and after a 30-min infusion of 12.5 ml/kg Ringer's lactate (RL) before surgery (*left panels*) and after surgery (*right panels*) depending on whether the intraoperative fluid regimen consisted of 15 ml/kg RL (*top*) or 40 ml/kg RL (*bottom*).
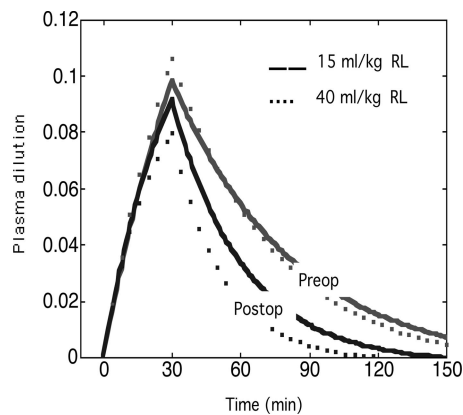
Fig. 2. Superpositioned computer-generated curves from figure 1 highlight the slightly more rapid elimination of infused fluid after surgery. RL = Ringer's lactate.

was increased after a postoperative compared with a preoperative volume load, whereas the distribution (V) of an intravenous fluid load was not altered. The half-life of the infused fluid, as indicated by the ratio of these parameters, tended to be lower after surgery, but this difference did not reach statistical significance. However, these changes in volume kinetics were not influenced by a liberal *versus* restrictive intraoperative fluid regimen.

The volume kinetic models were based on the assumption that the body strives to maintain volume homeostasis of fluid spaces.[17] Infused crystalloid fluids usually distribute over a central and a remote functional body fluid space, which obtain sizes that correlate reasonably well to the plasma and interstitial volumes. However, because the distribution of fluid between them requires as much as 25–30 min to be completed,[9,11] the two spaces become difficult to distinguish when the renal elimination is very prompt.[16] In our patients, fluid was excreted efficiently both before and after surgery, and the central space and the parts of the remote space, probably the ones that most readily exchanged fluid with the plasma, then mingled into a single fluid space. Hence, we are unable to discriminate between the two spaces. Historic controls indicate that the fluid elimination would be much slower during the actual surgical procedure, because previous studies have found a significantly decreased clearance of infused crystalloid fluid (k_r) during several types of anesthesia (epidural, spinal, isoflurane, and propofol)[11,18–21] and surgery,[10,11] including laparoscopic cholecystectomy.[14] A difference also becomes apparent from the collected urine, which amounted to 5–10% of the infused volume within 2.5 h of thyroidectomy[11] and 5% within 60 min of laparoscopic cholecystectomy.[14] In contrast, the urinary excretion collected in the patients studied here averaged 65% of the volume load, which is similar to what has been found after 2 h of a crystalloid infusion in healthy, young female volunteers.[16] The decreased urinary excretion during and immediately after surgery is in accord with

the known activation of stress hormones prompting fluid retention. That urinary excretion increases 4 h after surgery in laparoscopic cholecystectomy to a level comparable to that of unoperated healthy volunteers may indicate that the surgically induced fluid retention is diminished at that time point in this particular small operation. Because of the relatively efficient elimination of infused fluid, convergence to stable parameter values was usually not obtained for the two-volume model, or else they became estimated with poor precision. Therefore, we chose to present all of the experiments according to the one-volume model. Postoperative volume kinetics have been studied only twice, and never before with intraindividual studies of a preoperative and postoperative volume load. One study in elderly patients with hip fractures found fluid excretion to be decreased by approximately 50% on the first postoperative day (k_r decreased from 166 ml/min to 85 ml/min compared with matched volunteers).[12] This prolonged fluid retention is in accord with the major stress hormone activation in conjunction with this emergency procedure opposed to our current results in laparoscopic cholecystectomy. However, interpretation in such patients is difficult because of unknown fluid balance due to preoperative, intraoperative, and postoperative interventions. On the contrary, on the second day after abdominal hysterectomy, volume kinetic variables of a 2.5% glucose solution load were in the normal range (k_r approximately 130 ml/min) compared with previous results in healthy volunteers.[22,23] These findings correlate well with our current study in that the trauma of abdominal hysterectomy on the second postoperative day is comparable to that of laparoscopic cholecystectomy 4 h postoperatively.

In the current study with identical volume loads administered preoperatively and postoperatively, elimination of the fluid load was effective (table 2) and not influenced by the intraoperative fluid regimen, although the second (postoperative) fluid load was eliminated more effectively than the first one (fig. 2), which corroborates a previous study in volunteers.[15]

The volume kinetic model has previously been proven sensitive to detect even moderate hypovolemia by a decrease in V indicating a central distribution of fluid caused in part by peripheral vasoconstriction.[24] Therefore, our results do not suggest the presence of hypovolemia 4 h after laparoscopic cholecystectomy with approximately 1 l *versus* approximately 3 l RL administered intraoperatively. One of the incitements for this study was to look further into our previous findings where the same perioperative fluid regimens (intraoperative administration of 40 ml/kg compared with 15 ml/kg RL) resulted in reduced vasoactive hormonal responses and improved postoperative organ functions, recovery, and shortened hospital stay with 40 ml/kg RL.[7] Another study in gynecologic laparoscopy confirmed these findings, reporting decreased nausea and

vomiting with 30 ml/kg *versus* 10 ml/kg RL administered intraoperatively.[25] However, the current volume kinetic analysis could not explain the differences in functional outcome between the two fluid regimens,[7,25] and mechanisms other than those studied in the current study must therefore be sought. Such mechanisms may include the role of extravascular volume expansion or organ function, although previous theories on posttraumatic "third space" expansion are debatable.[26] Although the current volume kinetic analysis did not explain mechanisms for altered outcome by different interoperative fluid regimens, the data comparing a preoperative *versus* a postoperative volume load clearly demonstrate that even a minor surgical injury such a laparoscopic cholecystectomy alters postoperative volume kinetics significantly. These findings, may be valuable in our further understanding of posttraumatic fluid homeostasis where previous tracer studies on "third space" are inconclusive.[26] Therefore, future volume kinetic analyses should be performed in major procedures and should also explore potential differences between administration of colloid *versus* crystalloid or pharmacologic modifiers of endothelial function and capillary permeability.

In summary, we found that elimination of an intravenous fluid load was significantly enhanced by surgery but not altered with intraoperative administration of approximately 3 l *versus* approximately 1 l RL in laparoscopic cholecystectomy.

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