

Intra-operative colloid administration increases the clearance of a post-operative fluid load

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Background: It is unknown whether an intra-operative colloid infusion alters the dynamics of a crystalloid load administered post-operatively.

Methods: Ten patients received 12.5 ml/kg of Ringer's lactate over 30 min 1–3 days before and 4 h after laparoscopic cholecystectomy, during which 10 ml/kg of a colloid solution, hydroxyethylstarch (HES 130/0.4), was infused. The total body clearance of the pre- and post-operative test infusions was taken as the ratio between the urinary excretion and the Hb-derived dilution of venous plasma over 150 min. The plasma clearance of the infused fluid was calculated using volume kinetics based on the plasma dilution alone. The pre-operative plasma clearance was compared with the post-operative plasma clearance and patients served as their own control.

Results: The urinary excretion averaged 350 ml for the pre-operative infusion and 612 ml post-operatively, which

corresponds to 46% and 68% of the pre- and post-operative infusions, respectively. The total body clearance of the crystalloid fluid was 30 ml/min before surgery and 124 ml/min after surgery ($P < 0.01$). The plasma clearance, as obtained from the plasma dilution alone, was 28 and 412 ml/min, respectively. The maximal increase in plasma volume was 410 ml pre-operatively vs. 220 ml post-operatively.

Conclusions: Infusion of a colloid solution in combination with a crystalloid during laparoscopic cholecystectomy increased the plasma clearance of a post-operative crystalloid infusion.

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LIMITED evidence-based guidelines for intra-operative fluid regimens have led to large variations in the amount of fluids administered in daily surgical practice.^{1,2} Presently, no evidence exists to recommend the use of colloids vs. crystalloids in elective surgical procedures, or to establish guidelines regarding the actual fluid volumes to administer.¹

We previously found that a 'liberal' crystalloid regimen of ~3 l of Ringer's lactate (RL) vs. a 'restrictive' regimen of ~1 l of the same fluid administered intra-operatively significantly reduced the cardiovascular endocrine surgical stress responses and improved peri-operative organ functions as well as outcome after laparoscopic cholecystectomy.³ A subsequent study showed that elimination of a crystalloid fluid load was

slightly increased 4 h after laparoscopic cholecystectomy compared with pre-operatively, and that the rate of elimination post-operatively was independent of whether the patient was randomized to a 'liberal' or a 'restrictive' intra-operative fluid regimen.⁴ In this study, volume kinetic calculations were applied, which is a mathematical approach based on serial haemoglobin measurements. Volume kinetic analysis might offer mechanistic explanations as to why various fluid regimens are followed by different outcomes, and has been extensively applied previously in surgical patients as well as in healthy volunteers to quantify the distribution and elimination of a fluid load.^{5–10}

In the present study, we use volume kinetic analysis to investigate the effects of an intra-operative fluid regimen of a combination of a crystalloid and a colloid on the capacity of patients undergoing laparoscopic cholecystectomy to eliminate a post-operative infusion of crystalloid (RL).

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Materials and methods

General procedure

Ten patients scheduled for elective laparoscopic cholecystectomy were studied prospectively between September 2006 and January 2007. Exclusion criteria were: age <18 years, weight >100 kg, American Society of Anesthesiologist's score III–IV, alcohol intake >5 U 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, haemoglobin <7 mmol/l, conversion from laparoscopic to open surgery, psychiatric illness (intake of psychiatric medication other than selective serotonin re-uptake inhibitors) and intra-operative bleeding >500 ml. The study was approved by the Regional Ethics Committee (Copenhagen, Denmark), and all subjects gave written, informed consent before inclusion.

Anaesthesia and peri-operative management

Laparoscopic cholecystectomy was performed in a semi-ambulatory setting in a public hospital with peri-operative management (except for fluids as detailed below) similar to our previous publications in laparoscopic cholecystectomy,^{3,4} and summarized as follows:

Pre-operative fluid status was standardized in all patients, ensuring that all fasted from midnight and drank 175 ml water in the morning of surgery, which took place between 9:00 and 12:00 hours. All patients received an intra-operative infusion of 12.5 ml/kg RL (composition: Na⁺ 130 mmol/l, K⁺

4 mmol/l, chloride 109 mmol/l, lactate 28 mmol/l, and calcium 1.4 mmol/l) and 10 ml/kg hydroxyethyl starch (HES 130/0.4; Voluven[®], Fresenius Kabi, Bad Homburg, Germany) (protocol infusion). Fluid guidelines were followed strictly. The intra-operative fluids were infused simultaneously at a constant rate over 1.5 h, starting immediately before induction of anaesthesia. All patients received a similar general anaesthesia with remifentanyl, propofol and muscle relaxants for tracheal intubation (Table 1). The laparoscopic technique and multimodal pain management were applied as described previously¹¹, 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 ephedrine 10 mg intravenously (i.v.). Diuretics were not used. In the recovery room, pain treatment was standardized with sufentanil (first choice) and morphine. On demand, anti-emetic treatment was standardized and consisted of ondansetron 4 mg i.v. once (first choice) and thereafter 0.625 mg droperidol (second 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 haemoglobin measurements

All patients received two infusions of RL (test infusions), the first pre- and the second post-operatively. The first infusion took place between 1 and 3 days before surgery, and the second 4 h after surgery. A cannula was placed in each cubital vein for fluid infusion and blood sampling. After voiding

Table 1

Patient demographics.

	Colloid+RL group, present study	RL group, previous study ⁴
Sex (F/M)	8/2	6/4
Age (year)	44 (25–66)	41 (26–75)
BMI (kg/m ²)	26 (21–33)	27 (22–31)
ASA class I/II	10/0	10/0
Amount of crystalloid infused intra-operatively (ml)	1140 (900–1700)	1118 (900–1400)
Amount of colloid infused intra-operatively (ml)	755 (600–1000)	0
Duration of surgery (min)	65 (31–137)	73 (48–149)
Duration of anaesthesia (min)	97 (62–168)	112 (88–193)
Intra-operative blood loss (ml)	10 (0–100)	0 (0–20)
Propofol (mg)	609 (330–992)	748 (387–1490)
Remifentanyl (mg)	4.7 (1.6–10.3)	4.7 (4–11)
Post-operative fluid intake (ml)	895 (450–1100)	N/A
RL infused for volume kinetic analysis (ml) (infused twice)	951 (742–1187)	932 (750–1140)

RL, Ringer's lactate.

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 haemoglobin concentration (mmol/l). Before the fluid infusion, a baseline haemoglobin sample was collected in triplicate. Two hours before the post-operative infusion, duplicate 1 ml blood samples were collected for haemoglobin analysis every 20 min for the remaining 2 h until the beginning of the post-operative infusion. A total of 47 ml blood was drawn during each infusion for the haemoglobin analysis and replaced with 47 ml saline. Twelve millilitres of blood was drawn for the sampling 2 h before the post-operative infusion and was replaced by saline. Urinary excretion was measured from the beginning of the infusions until the end of the blood sampling (0–150 min). The patients were allowed to void at any time during the blood sampling and all patients voided at 150 min.

Kinetic analysis

The distribution of fluid given by i.v. infusion was analysed using a one-volume kinetic model as described and used previously in several studies in both healthy volunteers and surgical patients.^{4–10} 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. 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 , and their respective standard deviations were obtained using nonlinear least-squares regression (modified Gauss–Newton method). The mathematical solution to the equation shown above was then fitted to the dilution–time profiles for the whole group of pre- and post-operative infusions, respectively, in two separate analyses. Calculations were performed using Matlab version 4.2 (Math Works Inc., Natick, MA).

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

$$\frac{v - V}{V} = \frac{\text{Hb}_0/\text{Hb} - 1}{1 - \text{Hct}_0}$$

where Hct_0 is the haematocrit at baseline, Hb is the haemoglobin concentration in venous blood at any time (t) and Hb_0 is the Hb concentration at baseline. A correction was made for the losses of haemoglobin by blood sampling.⁵

The results were expressed as the following types of output: (1) the total body clearance of the crystalloid fluid was obtained for each test infusion separately as the urinary excretion divided by the area under the plasma dilution–time curve between 0 and 150 min, as calculated by the linear trapezoid method, after setting dilution <0 to 0. (2) The half-life of the infused fluid in plasma was calculated for each series of test infusions as $0.693 \times V/k_r$. (3) The plasma volume expansion for each group was estimated as the Hb-derived plasma dilution plus one, which was multiplied by the expected plasma volume at baseline (body weight $\times 7\% \times (1 - \text{Hct}_0)$). (4) A complementary aspect on the fluid distribution was yielded at the end of the experiment by applying simple mass balance principles on the distribution of the infused crystalloid, using the fact that infused volume must be accounted for either in the plasma, in extravascular tissues or in the urine.

Statistics

Data were presented as median (range). Wilcoxon's signed rank test for paired observations was used to describe differences before vs. after surgery. $P < 0.05$ was considered significant.

Results

Patient demographics are shown in Table 1. All patients were discharged at the day of surgery. Fluid guidelines were followed strictly in all patients and no i.v. fluids apart from those mentioned above were administered.

The crude Hb values obtained for the two experiments are given in Fig. 1. The baseline Hb level for the second test infusion (7.55 mmol/l, range 6.13–8.56) was lower than the first baseline value (8.17, range 6.76–9.52; $P < 0.01$).

The Hb values collected during 2 h before the second infusion were intended to provide the

half-life of the colloid fluid, but these were not sufficiently consistent to warrant analysis.

Urinary excretion

The urinary excretion during the 150-min test infusions was 350 (220–775) ml before surgery and 612 (175–1240) ml after surgery, which corresponded to 46% (23–92) and 68% (15–114) of the infused fluid volumes ($P > 0.05$).

The total body clearance of the infused fluid, which was obtained as the ratio between the urinary excretion and the plasma dilution over time, amounted to 30 (9–143) ml/min for the pre-operative infusion and to 124 (11–992) ml/min for the post-operative infusion ($P < 0.01$).

Volume kinetics

The individual plasma dilution–time profiles for the pre- and post-operative series of test infusions, respectively, are shown in Fig. 2, together with the

optimal curve-fit for the two pooled series of data as given by least-squares regression. The baseline plasma dilution was apparently restored much faster after the post-operative infusion, the kinetic analysis showing a clearance constant k_r of 28 ml/min for the pre-operative infusion and 412 ml/min for the post-operative one (Table 2), which corresponded to half-lives in the plasma of 172 and 7 min, respectively.

The modelled maximum increase in plasma volume was twice as large at the end of the pre-operative compared with the post-operative infusion (Fig. 3) and corresponded to 43% and 23% of the infused fluid volumes, respectively.

Mass balance

Mass balance calculations showed that 30% of the infused fluid volume resided extravascularly at the end of both experimental periods. The difference between the pre- and the post-operative test infusions was that 25% of the remaining fluid was to be found in the plasma after the pre-operative infu-

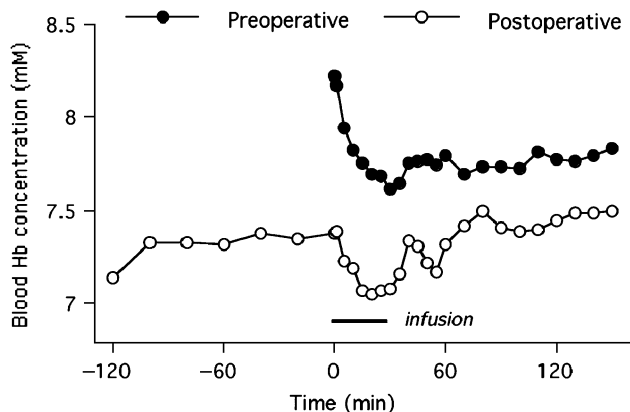


Fig. 1. Crude Hb concentration (mean) during and after. The two test infusions of 15 ml/kg of Ringer's lactate.

Table 2

Result of the volume kinetic analysis.

	Pre-operative	Post-operative
V (l)	6.9 (1.47)	4.2 (3.81)
k_r (ml/min)	28 (21.1)	412 (188)
$T_{1/2}$ (min)	172	7
Maximum increase in plasma volume (ml)	410	220

V, is the expandable body fluid space; k_r , is the clearance constant, $T_{1/2}$, is the context half-life.

The primary parameters V and k_r are given as the best estimate (standard deviation) for the 10 pooled curves. The standard deviation thus contains all errors due to curve fitting and intergroup differences.

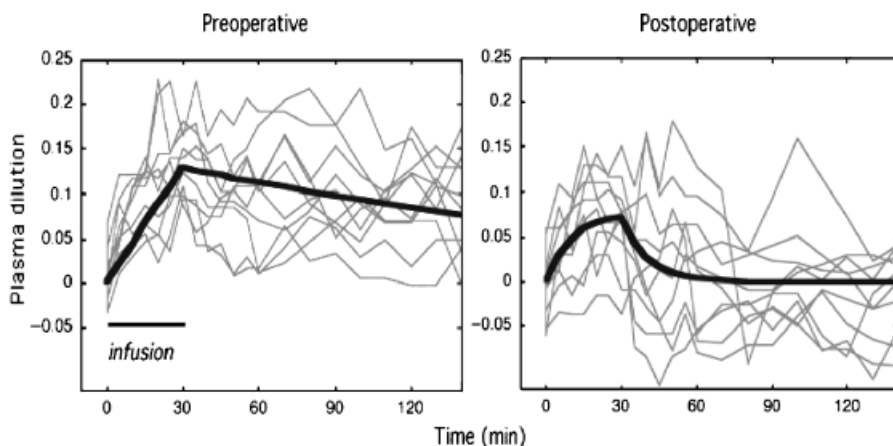


Fig. 2. Individual plasma dilution-time curves (thin lines) and the modelled curve based on the pooled data (thick line) for the pre- and post-operative crystalloid infusions.

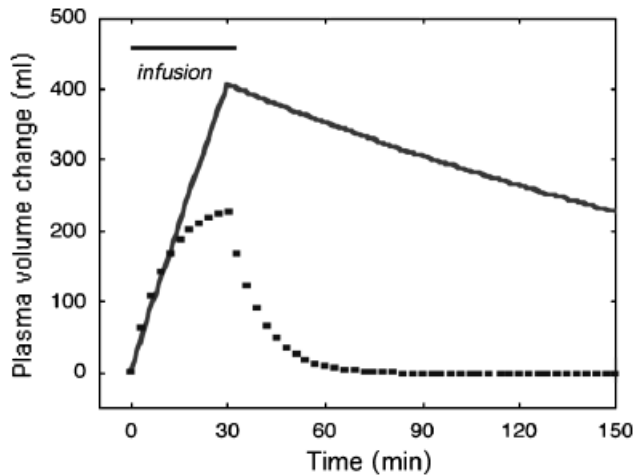


Fig. 3. Plasma volume change during the pre-operative (solid line) and post-operative (broken line) test infusion of Ringer's lactate. The baseline plasma volume was estimated to be 3.15 l.

sion, while all had been excreted via the urine after the post-operative infusion.

Discussion

The calculations show that the total body clearance of a post-operative infusion of RL was increased by approximately four times and the plasma clearance increased 15 times after laparoscopic cholecystectomy when a colloid solution had been administered intra-operatively. The very high clearance of RL after surgery almost abolished the plasma dilution and, hence, the plasma volume expansion resulting from the infusion. Moreover, the slight plasma volume expansion that could be found lasted only for about 30 min. This result was unexpected and differs markedly from a previous study by our group in which only RL and no HES was infused during cholecystectomy.⁴

We used two approaches when calculating the clearances (Fig. 2). The first and simpler approach was based on the ratio between the measured urinary excretion and the area under the plasma dilution-time profile, and could be applied here because urinary excretion is the only important route of elimination. This clearance represents the elimination of fluid from the whole body. An obvious limitation to these calculations is the lack of bladder catheters for urinary sampling; however, the included patients had no prior urological problems. The second and more complex way of calculating the clearance of infused fluid from the plasma was to apply volume kinetics to the data on

plasma dilution alone. This analysis could be based only on the pooled data from each series of experiments, which is due to the variability of some curves and the frequent occurrence of a negative dilution (i.e. haemoconcentration) during the post-operative experiments. The plasma clearance for the pre-operative infusions was virtually identical to the total body clearance (28 and 30 ml/min, respectively), which indicates that the volume kinetic analysis captured the elimination well. However, the plasma clearance for the post-operative infusion was much higher than the total body clearance (412 vs. 124 ml/min). Most of this difference can be accounted for by frequent occurrence of a negative dilution, which, in the absence of profuse diuresis, suggests that some of the fluid has accumulated in peripheral tissues and was not at balance with, or did not equilibrate freely with, the plasma. This also shows that the short half-life calculated for the post-operative series of infusions (7 min) represents the context-sensitive, apparent half-life rather than providing a true figure for how much fluid remained in the body after a certain period of time.

In our previous study of laparoscopic cholecystectomy, ~31 or ~11 RL but no colloid was administered during the surgery.⁴ The 'low'-volume group (11 RL) from our previous study differs from the group in our present study only in terms of the intra-operative colloid and therefore mimics a 'control' group. The elimination constants, k_v , for this 'no colloid' group were 123 ml/min for the pre-operative infusion and 181 ml/min post-operatively.⁴ Comparatively, the k_r -values for the present 'colloid group' are 28 ml/min before surgery and 412 ml/min after surgery.

The fact that elimination of one fluid load will be faster if preceded by another fluid load has been demonstrated previously.⁸ What we have seen, though, is that the speed of elimination apparently is additionally influenced by the kind of fluid given in the preceding fluid load (i.e. intra-operative colloid). Many studies show that most colloids, like the one used here, have plasma volume-expanding abilities¹² superior to crystalloids,^{13,14} and it appears that the initial increased plasma volume expansion caused by the colloid infusion made the following elimination of the post-operative fluid load considerably faster compared with when a colloid had not been given intra-operatively.

The basic assumption of volume kinetic models is that, during an infusion of fluid, the body will

strive to maintain an ideal (target) volume of its fluid spaces^{15,16} by distributing the infused crystalloid fluid over a central and a peripheral functional fluid space. Excess fluid (deviation from the target volume) will be cleared as mentioned above. The clearance of crystalloid fluid is usually between 70 and 120 ml/min in healthy volunteers^{7,8} but only between 5 and 20 ml/min during anaesthesia and surgery^{5,17} including laparoscopic cholecystectomy.⁶ The one-volume model, which was applied here, is based on rapid equilibration between the plasma volume and parts of the interstitial fluid space that are easily expanded. The expandable body fluid space, V , typically is of a size corresponding to 150–200% of the plasma volume.

The negative plasma dilution seen after many of the present post-operative infusions posed a special problem for the kinetic analysis. Because a clearance cannot be negative, the total body clearance was calculated by setting all negative dilutions to zero. In contrast, the plasma clearance was obtained by analysing the pooled data, which means that a positive but very high clearance is obtained as long as the sum of all dilutions yields positive values. Although we believe that the latter approach is most correct, one must remember that the post-operative curves also include a slow restitution of the plasma dilution caused by the colloid fluid infused during surgery. Even if no RL had been infused, the plasma dilution should have displayed a slightly decreasing curve, although we could not see such a pattern on the Hgb samples collected during the 2 h before the second test infusion.

A plausible explanation as to why more of the infused fluid was excreted during the post-operative experiment is that the Hgb level was lower at that time, which, in the absence of marked blood loss, suggested that the patients were slightly hypervolaemic when the second series of test infusions started.¹⁸ The Hgb baseline shifts 3–5% downward as a result of anaesthesia⁶, but most of the drug vasodilatation may have been resolved 4 h after the surgery. On average, the patients received 1140 ml crystalloid and 755 ml colloid during surgery and drank 895 ml of water before the second test infusion. This explanation fits well with volume kinetic theory in which each expansion of the plasma volume from its ideal target volume speeds up elimination.

In summary, the administration of a colloid solution during laparoscopic cholecystectomy im-

paired the plasma volume expansion from a post-operative infusion of crystalloid. This was caused by a higher clearance of the infused fluid both from plasma and from the whole body. Further studies of volume kinetics with peri-operative colloid administration are warranted.

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