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Renal injury during hip fracture surgery: an exploratory study

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Abstract

Background: The present observational study was undertaken to identify potential markers of poor outcome, such as renal failure and mortality, after hip fracture surgery.

Methods: Forty-three patients, with a mean age of 78 years, were studied having undergone acute hip fracture surgery. Analysis included the urinary excretion of cortisol, albumin and sodium. The degree of fluid retention was evaluated based on the urinary excretion of metabolic end products. Fluid retention and the excretion of albumin and neutrophil gelatinase-associated lipocalin (NGAL) were measured repeatedly in a sub-group of 15 patients who also underwent haemodynamic monitoring. The perioperative change in serum creatinine and a 30-day mortality served as outcome measures.

Results: Although serum creatinine increased by > 25% in 21% of the patients, only a high preoperative creatinine concentration correlated with a 30-day mortality.

The subgroup analysis revealed that fluid retention was pronounced and remained essentially unchanged up to the first postoperative day. A rise in serum creatinine was always preceded by increased urinary excretion of NGAL that, in turn, was associated with preoperative fluid retention. The only perioperative event that correlated with a higher 30-day mortality was perioperative aggravation of albuminuria (67% vs 0%, $P < 0.01$), which became more common with advanced age and a low cardiac index.

Conclusions: Two different mechanisms seem to affect the kidneys during hip fracture surgery. The first elevates the serum creatinine concentration while the second increases the albuminuria. Only the second mechanism had a bearing on mortality.

Key words: acute kidney injury; albuminuria, mortality; creatinine; hip fracture, surgery

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Hip fracture repair is a surgical intervention associated with a high risk of postoperative complications. The causes of such complications are not completely known, although poor preoperative health and dehydration play a role [1].

A local quality-assurance control study at Södertälje county hospital in Sweden revealed that 23% of the 90 patients who underwent hip fracture repair between January and August 2012 had a postoperative increase in serum creatinine of > 50%, which is a sign of kidney injury [2]. The treatment program was then modified to remove any factor that could potentially harm the kidneys. No hydroxyethyl starch was allowed and a routine preoperative continuous infusion (1.5 mL^{-1} kg^{-1} h^{-1}) of 2.5% glucose with electrolytes was instituted.

A follow-up 6 months later showed a drop from 23% to only 4% in the number of patients with a rise in serum creatinine of > 50%. However, 10% of patients still had an increase in serum creatinine of 25–50%, compared to the previous value of 6%. These observations, which were reported in a local medical journal [3], stimulated a further search for relationships between surgical factors and kidney injury.

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The aim of the present observational study was to examine relationships between potential markers of poor outcome, such as kidney injury and mortality, in hip fracture patients. The hypothesis was that preoperative renal fluid retention, haemodynamic changes and/or signs of renal inflammation could be associated with this type of injury. Fifteen of these patients were further monitored with non-invasive haemodynamic recordings and an assessment of perioperative changes in biomarkers.

METHODS

Forty-three patients (25 females and 20 males), aged from 41 to 96 years (mean 78, median 81) years, were included in this prospective observational study. All patients underwent acute hip fracture surgery under spinal anaesthesia at Södertälje Hospital in Södertälje, Sweden. Ethics approval was obtained from Stockholm (dnr 2014/497-31/4; approved 2014-04-02) and informed consent was obtained from each subject.

The original intention to randomize patients to colloid and non-colloid treatment was abandoned due to increasing awareness of the negative effects of colloids, particularly with respect to kidney function [4]. Exclusion criteria were dementia, an inability to understand Swedish, and serum creatinine > 250 μmol L^{-1}. Patients agreed to participate after being informed about the purpose of the study.

Patients underwent operations within 24 hours of arriving at the Emergency Department [5] and received glucose (2.5%) with sodium (80 mmol) as a continuous infusion at 1.5 mL kg^{-1} h^{-1} from the time of diagnosis until surgery was initiated.

Spinal anaesthesia was performed with 3–4 mL of bupivacaine (5 mg mL^{-1}). Twelve operations consisted of hip replacement while the others were fixations of the fracture with a hip screw. Plasma volume support during the surgery consisted of Ringer's acetate and an infusion of 1 L of glucose (5%) was routinely initiated in the postoperative care unit. Blood loss was calculated as the sum of the visually estimated amounts present on swabs and dressings and the measured volume found in suction bottles. Data on comorbidity and 30-day mortality were obtained by reviewing the hospital medical records.

Outcome measures were compared with preoperative measurements of several biomarkers. Two urine samples were taken from all 43 patients just before surgery. Urine colour was assessed immediately by holding a 10 ml tube of urine next to a colour scale [6] (available at www.hydrationcheck.com). The colours used have been assigned RGB codes [7]. One urine tube was used to measure albumin excretion (a sign of glomerular damage), as well as the concentration of metabolic waste products (which can be used to quantify the degree of dehydration-induced renal water conservation) [7, 8].

The urinary albumin and albumin/creatinine ratio were measured on a DCA Vantage Analyser (Siemens Healthcare Diagnostics). Micro-albuminaemia was defined as an albumin/creatinine ratio of 2.5–25 mg $mmol^{-1}$ and macro-albuminaemia as a ratio > 25 mg $mmol^{-1}$ [9, 10]. The urine-specific gravity was determined using Multistix®10 SG reagent strips and a Clinitek Status®+ Analyser (Siemens Healthcare Diagnostics).

The second tube was sent to the certified clinical chemistry laboratory at Karolinska University Hospital in Stockholm, Sweden, within 24 hours for analysis of osmolality, as well as cortisol and creatinine concentrations.

The preoperative serum sodium and potassium concentrations were also measured.

The arterial pressure was measured every 5 min during the surgery and in the postoperative care unit by an automatic non-invasive monitor (BeneView T1 or T8, Mindray, Shenzhen, PR of China). Hypotension was defined as a systolic pressure of ≤ 80 mm Hg for > 5 min in the perioperative period. Lower arterial pressures were routinely treated with a vasoconstrictor, administered as an intravenous infusion (phenylephrine) or injection (ephedrine), at the discretion of the attending anaesthetist.

The results were compared with the change in serum creatinine concentration from admission to the hospital to the day after the surgery and with a 30-day mortality.

SUBGROUP STUDY

In a subgroup of 15 patients, haemodynamics were monitored continuously during the surgery while perioperative changes in several biomarkers were compared with the postoperative change in serum creatinine and with a 30-day mortality.

The mean arterial pressure (MAP) and cardiac index (CI) were measured continuously during the surgery with a Nexfin device (BMEYE, Amsterdam, NL), which is based on a non-invasive photoplethysmographic technology [11].

Urine was sampled on three occasions. The first sample was the same as for the large group. A second sample was taken at the end of the surgery and a third on the morning of the first postoperative day.

Measurements on all three occasions also included neutrophil gelatinase-associated lipocalin (NGAL), an indicator of tubule-interstitial inflammation [12, 13]. The lower limit for detection of NGAL was 35 μg L^{-1}. All NGAL/creatinine ratios that did not exceed the lower limit of detection for NGAL were set to 2.0 to prevent these ratios from being higher than those of samples in which NGAL was actually detectable.

The urine was also used for an assessment of urine colour and for a measurement of the urine-specific weight, osmolality and creatinine.

FLUID RETENTION INDEX (FRI)

Analysis of urine for metabolic waste products that appear in higher concentrations when the kidneys conserve water has previously been used to diagnose dehydration in elite sports [6, 14, 15], recreational physical exercise [7], and the preoperative patient condition [1, 15, 16]. The use of a composite index for fluid retention based on several markers of renal water conservation has the benefit of reducing confounding influences such as diet, disease and medication, which typically change only one of the markers. The urine colour is due to end products from the fairly stable breakdown of erythrocytes, and darkens with progressive dehydration. The specific gravity of the urine also increases, as do creatinine concentrations and its osmolality.

Specific gravity has been the most stable urinary marker in previous studies of dehydration where the deficit in body fluid volume was known. The ranges of colour, osmolality and creatinine concentrations have been published for subjects aged 17–69 years, and each range paralleled the specific gravity scale [7]. These ranges were assigned a score, where a higher value indicated more severe dehydration (Fig. 1).

The mean of the four scores is termed the fluid retention index (FRI) as fluid may be retained for reasons other than dehydration in hospitalized patients. An index value of ≥ 4.0 corresponds to the degree of renal water conservation that accompanies dehydration amounting to 3% of one's body weight (specific gravity ≥ 1.02, creatinine ≥ 12 mmol L^{-1}, colour ≥ 4 and osmolality ≥ 600 mOsmol kg^{-1}) [7].

The composition of the index was then checked for outliers, which were determined by calculating the standard deviation (SD) for the mean of the four scores. An outlier typically raised the SD to > 1.0. The individual scores were then reviewed and any single outlier was omitted, followed by recalculation of the index. The new value was accepted if the SD was ≤ 1.0, whereas the index was discarded as a failure if the SD still exceeded 1.0 [7].

STATISTICS

No power analysis was made since this exploratory study searched for correlations between parameters. The results were presented as the median and interquartile range, and differences studied by the Mann-Whitney U test. Differences in incidences were determined by a contingency table analysis. Correlations between parameters were established by a simple linear or stepwise multiple regression analysis, where parameters were logarithm-transformed if their distribution was skewed. $P < 0.05$ was considered statistically significant.

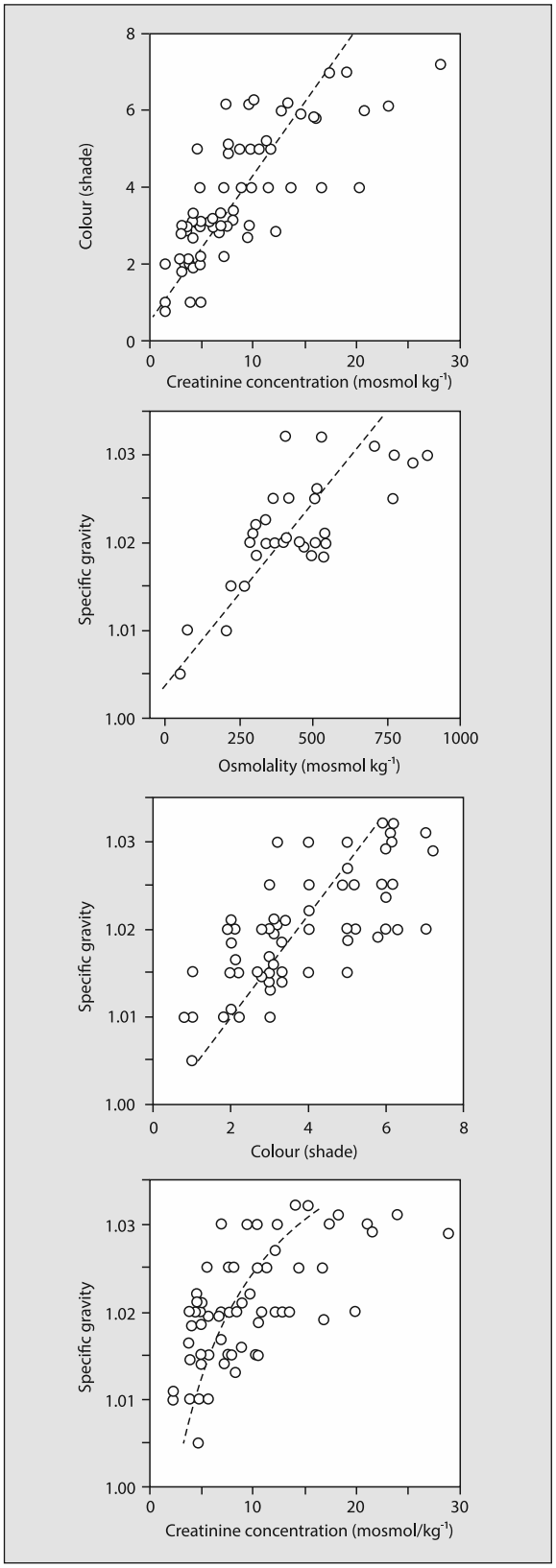

Figure 1. Correlations between the four urinary markers used to calculate the Fluid Retention Index (FRI). The data shown are all measurements from all 43 patients, except for osmolality, which were obtained from only 33 patients

Table 1. Demographics and selected biochemical parameters that were measured before, during and after hip fracture surgery

	All patients (N = 43)	Substudy (N = 15)
DEMOGRAPHICS		
Age (years)	80 (73–86)	83 (76–89)
Body weight (kg)	60 (36–90)	70 (67–79)
Males/females	20/23	8/7
Morbidity (N %)		
Hypertension	15 (35%)	4 (31%)
Atrial fibrillation	6 (14%)	3 (20%)
Heart failure	7 (16%)	3 (20%)
Diabetes mellitus	6 (14%)	4 (31%)
Stroke	8 (19%)	3 (20%)
Cancer	7 (16%)	3 (20%)
Respiratory insufficiency	5 (12%)	1 (8%)
BEFORE SURGERY		
Serum creatinine (μmol L^{-1})	73 (59–93)	89 (69–112)
Serum sodium (mmol L^{-1})	137 (136–39)	137 (136–139)
Serum potassium (mmol L^{-1})	4.1 (3.8–4.2)	3.9 (3.7–4.2)
Urinary cortisol excretion (nmol $mmol^{-1}$ of creatinine)	36 (13–188)	24 (8–172)
Urinary albumin excretion (mg $mmol^{-1}$ of creatinine)	7 (4–20)	6 (4–22)
Fluid retention index (FRI)	4.0 (3.3–5.0)	3.3 (3.0–4.3)
DURING SURGERY		
Cardiac index (L min^{-1} m^{-2})	–	1.8 (1.3–2.2)
Mean arterial pressure (mm Hg)*	–	85 (76–96)
Surgical bleeding (mL)	275 (150–400)	400 (200–775)
Operating time (min)	66 (36–90)	88 (75–101)
Hypotension** (N, %)	15 (35%)	5 (33%)
DAY AFTER SURGERY		
Serum creatinine (μmol L^{-1})	77 (59–98)	88 (72–16)
Increase 25–50%	8 (19%)	4 (27%)
Increase ≥ 50%	1 (2%)	1 (7%)
Mortality within 30 days	6 (14%)	4 (27%)

*as obtained by Nexfin hemodynamic monitor
**defined as systolic arterial pressure of 80 mm Hg during > 5 min

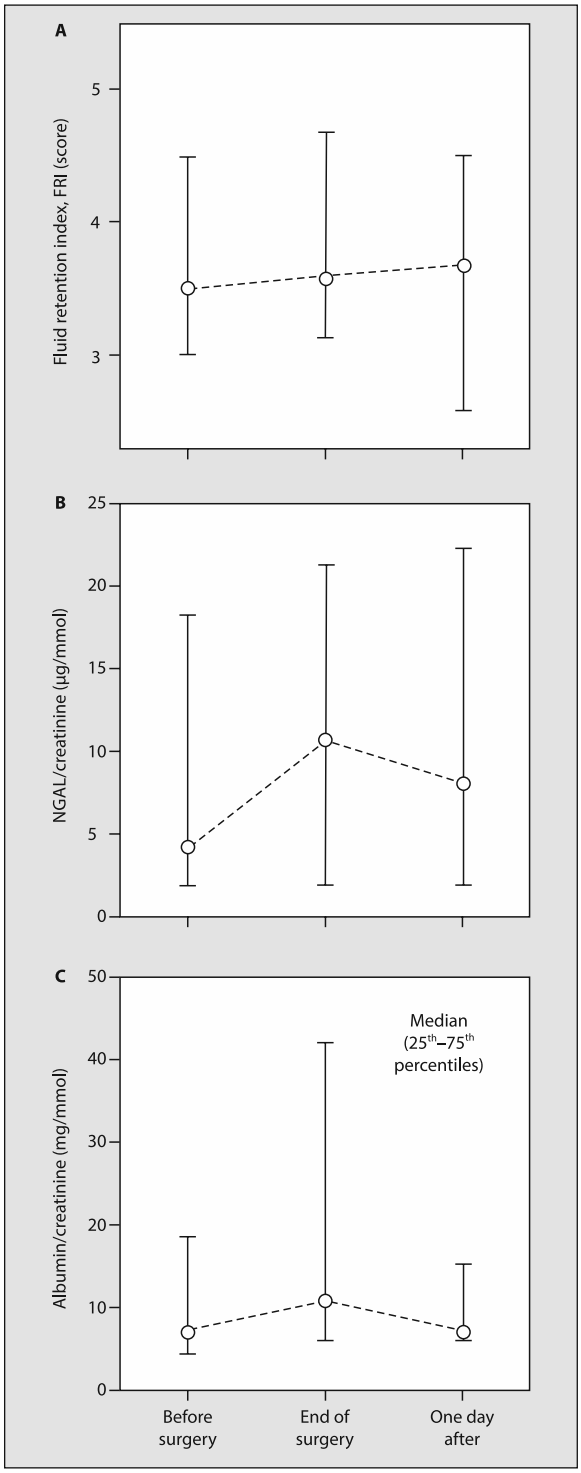

Figure 2. Fluid retention index (**A**), NGAL excretion (**B**) and albuminuria (**C**) measured before, at the end of, and the day after acute hip fracture surgery in a subgroup of 15 patients. FRI is shown only for the 12 patients for who had no outlier scores in their series of three FRI scores

RESULTS

Demographics and selected biochemical data are shown in Table 1.

Fluid retention index (FRI). The relationship between renal water conservation, as indicated by urine colour and gravity, agreed well with the chart evaluated for younger healthy people [7]. However, the excretion of creatinine and osmolality were lower and needed to be scored one step higher on the scale to match the two other markers (Table 2). After calculating the FRI, three scores were recalculated due to outliers while another three were discarded due to a persistent SD value > 1.0.

Twenty patients (50%) then scored ≥ 4.0 before the surgery, which is the cut-off for dehydration [7]. Although

Table 2. Scheme for calculating the Fluid Retention Index (FRI), which is the mean of the fluid retention scores for four urinary markers

Fluid retention score	1	2	3	4	5	6
Specific gravity	≤ 1.005	1.010	1.015	1.020	1.025	1.030
Colour (shade)	1	2	3	4	5	6
Creatinine (mmol L^{-1})	< 4		4–7	7–12	12–17	> 17
Osmolality (mOsmol kg^{-1})	< 250		250–400	400–600	600–800	> 800

the FRI decreased with the urinary sodium/creatinine ratio (r = –0.70, $P < 0.001$), there was no statistically significant correlation between the FRI and the urinary cortisol/creatinine ratio.

In the sub-study, the FRI did not improve during the perioperative period. At the end of surgery, 40% of the patients could be classified as being dehydrated (FRI ≥ 4.0); this value increased to 47% on the first postoperative day (Fig. 2A).

Hypotension. Patients who became hypotensive during the surgery did not differ with respect to the preoperative FRI, serum creatinine or mortality.

In the sub-study, hypotension correlated with postoperative nausea and/or confusion (80% vs. 20%; $P < 0.04$) and with aggravation of the albuminuria from before to after the surgery (median +77% vs. –47%; $P < 0.02$).

Albuminuria. Urinary excretion of albumin was common. By definition, 66% had micro-albuminuria and 24% macro-albuminuria [9, 10]. The levels in six patients reached the maximum detectable albumin concentration (300 mg L^{-1}).

In the sub-study, 9 patients (60%) had an increase in albumin excretion during surgery. Indeed, the albuminuria in six of these patients (40%) more than doubled (Fig. 2C). Although the increase was greater in patients with greater age (r = 0.73, $P < 0.003$) and in those with CI < 2 L min^{-1} m^{-2} ($P < 0.05$; Mann-Whitney test), it did not correlate with the FRI, NGAL or serum creatinine.

NGAL. This parameter was only measured in the sub-study. At the end of surgery, 8 patients (53%) had an increase of > 20% in NGAL from baseline (Fig. 2B). These patients had a higher FRI than the others at that time, with medians of 4.7 *vs.* 2.7 ($P < 0.03$). In the morning after the surgery, two patients showed further elevations of NGAL.

All 8 patients who developed an increase in NGAL during surgery showed an elevation of serum creatinine on the next day. This did not occur in any of the patients who did not show an increase in NGAL during surgery.

Mortality. Overall, 6 patients died within one month (14%). Although the serum creatinine before surgery was higher in non-survivors (median, 93 [80–185] µmol L^{-1}) than in the others (71 [59–90] µmol L^{-1}; Mann-Whitney test $P < 0.02$), no greater change occurred in serum creatinine in response to surgery. Mortality did not correlate with age, with the FRI or the preoperative cortisol or albumin excretions, or with the surgical blood loss. However, the 6 patients who had an increase in albuminuria from before surgery to the first postoperative day in the sub-study had a higher likelihood of dying within one month (67% vs. 0%, $P < 0.01$).

DISCUSSION

The present work represents a follow-up on a quality assurance-based finding of the frequent elevation of serum creatinine after hip fracture surgery at our hospital. Although elevations of > 25% still occurred in 21% of the patients, the rise was less pronounced than before the institution of the preoperative hydration protocol and the exclusion of hydroxyethyl starch. Despite the small size and the exploratory character of the study, several findings are of potential interest to the anaesthetist.

The results suggest that two mechanisms may affect the kidneys during hip fracture surgery. The first of these elevates the serum creatinine concentration. In the present study, any postoperative increase in serum creatinine was preceded by an elevation of NGAL during the surgical procedure. This NGAL elevation was, in turn, associated with a high FRI, which could be due to dehydration or to other factors that promote fluid retention. Before surgery, almost half the patients with high NGAL had excretion above the baseline, and the further and more marked increase observed during the operation suggests that kidney injury could mostly be related to events occurring in close association with the surgery (Fig. 2B).

Although a preoperative elevation of serum creatinine was associated with increased mortality, no statistically significant link was found between the perioperative change and mortality. This finding agrees with results from our larger study where, despite an overall 30-day mortality of 10%, all patients who showed a postoperative increase of serum creatinine by > 50% were alive 6 months later, and had by then also arrived at their preoperative level [3]. Hence, while serum creatinine is routinely measured after hip surgery, perioperative elevations seem to resolve spontaneously without affecting one's survival.

The second mechanism was expressed by an aggravated perioperative albuminuria and statistically associated with old age and low cardiac index, which was not the case for NGAL and serum creatinine. Albuminuria is a sign of glo-

merular damage of inflammatory origin and has long-term prognostic value in cardiovascular and metabolic disease, such as heart failure, hypertension and diabetes [10]. In the present study, increasing albuminuria was the only perioperative event that was statistically related to a higher 30-day mortality. Why increasing albuminuria occurred is unclear, but renal vascular inflammation due to poor circulation is one possible mechanism.

Although micro- and macro-albuminuria was present in nearly all (90%) patients before the operation, only an increased degree during the surgery and the early postoperative period seemed to be of pathophysiological importance. Hence, the situation was the opposite to that of creatinine which could be statistically related to mortality only when the preoperative concentration was elevated. The hypothesis of a double mechanism for kidney injury is interesting and will soon be challenged in a larger study at our hospital.

Urine sampling can be used to assess how intensively the kidneys retain fluid, which is a key sign of dehydration. Renal water conservation in the form of a high fluid retention index (FRI) was common, despite taking precautions like minimum-delay surgery and preoperative fluid administration. Our patients had an average FRI of 4.0, which can be compared to 2.8 in patients awaiting elective abdominal surgery [8] and 2.7 in healthy volunteers just before and 3.55 after a 90-min recreational physical exercise [7]. The FRI did not decrease during the surgical procedure, although fluid administration was not restrictive (mean 2.2 L during the surgery).

One problem with the FRI in the surgical setting is that concentrated urine may arise due to dehydration-induced and to trauma-induced fluid retention. There was no statistical correlation between the FRI and the preoperative urinary cortisol/creatinine ratio, which is often used as a marker of "stress". However, the low sodium excretion in patients with high FRI is consistent with the action of a renal sodium-sparing mechanism like aldosterone, which is released in response to insufficient renal perfusion.

Dehydration is difficult to diagnose in the elderly and reliable clinical signs are hard to find. Whole-body bioimpedance reveals that severe body fluid deficits are common in patients awaiting hip fracture surgery [17]. A previous report has shown that patients who underwent operations while in a state of fluid retention/dehydration suffered almost four times as many postoperative complications when compared to those who were euhydrated [1]. In the present study, severe dehydration was probably prevented by minimum-delay surgery and preoperative fluid administration. Although complications were not recorded systematically, notes about nausea, vomiting and confusion were taken by the research staff in the sub-study.

An apparent limitation of the present study is the small number of patients used to investigate the relatively complex course of hip fracture surgery. Several interesting associations did not quite pass the 5% significance limit. While these related to the role of arterial hypotension, none involved the key outcome measures (kidney injury and mortality). The most accepted criterion for arterial hypotension is that the arterial (or only systolic) pressure has fallen by 30% from the preoperative value [18]. In the present study, a more specific target value was chosen because autoregulation of the renal blood flow holds that perfusion of the kidneys is unchanged down to this pressure. A systolic pressure of ≤ 80 mm Hg is also often used clinically to indicate the need for administration of a vasoconstrictor, which was also frequently used here to combat low arterial pressures. Given this definition, hypotension did not elevate NGAL or serum creatinine, but it could aggravate the albuminuria and thereby impair a prognosis.

The FRI value would be somewhat lower (about 3.5) without the correction made in this study. However, the urine-specific weight and the urine colour are the most consistent markers of dehydration when the body fluid volume has been altered by physical exercise [7]. The low muscle mass in this patient group and the age-dependent difficulty to raise urinary osmolality makes this correction reasonable.

CONCLUSIONS

The study suggests that two mechanisms seem to affect the kidneys during hip fracture surgery. The first elevates the serum creatinine concentration and is statistically linked to with preoperative fluid retention and increased perioperative secretion of NGAL. The second mechanism aggravated the albuminuria and was associated with old age and a low cardiac index. Only the second mechanism elevated the 30-day mortality.

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3. The authors declare no conflict of interest.

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