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Original Article

Isotonic saline in elderly men: an open-labelled controlled infusion study of electrolyte balance, urine flow and kidney function

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Summary

Isotonic saline is a widely-used infusion fluid, although the associated chloride load may cause metabolic acidosis and impair kidney function in young, healthy volunteers. We wished to examine whether these effects also occurred in the elderly, and conducted a crossover study in 13 men with a mean age of 73 years (range 66–84), who each received intravenous infusions of 1.5 l of Ringer's acetate and of isotonic saline. Isotonic saline induced mild changes in plasma sodium (mean +1.5 $mmol.l^{-1}$), plasma chloride (+3 $mmol.l^{-1}$) and standard bicarbonate (−2 $mmol.l^{-1}$). Three hours after starting the infusions, 68% of the Ringer's acetate and 30% of the infused saline had been excreted ($p < 0.01$). The glomerular filtration rate increased in response to both fluids, but more after the Ringer's acetate ($p < 0.03$). Pre-infusion fluid retention, as evidenced by high urinary osmolality (> 700 $mOsmol.kg^{-1}$) and/or creatinine (> 7 $mmol.l^{-1}$), was a strong factor governing the responses to both fluid loads.

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Introduction

Isotonic saline is widely used for plasma volume expansion during anaesthesia and surgery. However, many studies suggest that a buffered Ringer's solution would be more appropriate, because saline causes mild metabolic acidosis due to its high chloride content [1]. In healthy volunteers, two l of saline infused over 1–2 h also reduced glomerular filtration rate (GFR) and renal blood flow [2, 3], probably due to vasoconstriction caused by the chloride load [4]. Retrospective studies have associated isotonic saline with the development of postoperative complications after major abdominal surgery [5, 6] and acute kidney injury in intensive care [7].

In transurethral surgery, saline is used for irrigation of the surgical field, and the irrigating medium is often absorbed by the patient [8]. In the elderly, the use of isotonic saline could be more troublesome than in younger subjects, as renal function decreases with age, and the ability to handle the excess chloride load might be impaired. However, there have been no studies of how isotonic saline is handled by elderly patients.

We undertook a study to compare the effects of isotonic saline with Ringer's acetate solution on

electrolyte balance, urine flow and kidney function in elderly patients. The hypothesis was that isotonic saline would cause as great a reduction in GFR in elderly patients as has previously been shown in animals and in young healthy volunteers.

Methods

This was an open-label, crossover study in elderly men with bladder outflow obstruction due to benign prostatic hypertrophy, which had been alleviated by an indwelling bladder catheter while awaiting surgery.

We undertook the study between December 2012 and March 2014 at the Department of Urology at Södersjukhuset in Stockholm, Sweden. The protocol was approved by the Regional Ethics Committee in Stockholm. Exclusion criteria were heart or kidney failure, and duration of catheter treatment of less than two weeks.

We administered intravenous (IV) infusions of 1.5 l of isotonic saline and of Ringer's acetate via infusion pumps over 45 min on two occasions separated by one week. The first seven patients received isotonic saline on the first occasion, while the remaining patients received Ringer's acetate first. The reason for the lack of randomisation was concern about the carry-over effects of isotonic saline [9], which were disproven after an interim analysis after the first four patients. The study would have been discontinued if we had found persistent effects of the saline infusion when the patients returned to receive Ringer's.

The infusion and sampling scheme is shown in Fig 1. The patients arrived at the hospital at 7:30 a.m. for the study, which lasted for four hours. Food and water intake after midnight had been limited to one glass-full. We inserted one 16-G venous cannula into each arm, and gave an IV injection of 10 ml of iohexol (Omnipaque® 300 mg iohexol.ml^{-1}; Nycomed Amersham, Lidingö, Sweden), immediately followed by an IV infusion of 10 ml.h^{-1} of iohexol over four h.

We calculated the clearance of iohexol, creatinine and urea for each 30 min period as the product of the substance concentration in urine and the urine volume, divided by the serum concentration measured in the middle of that period.

We also used the blood samples taken in the middle of each urine collection for calculation of the strong ion difference, which was calculated as the sum of the plasma concentrations of sodium and potassium, minus the plasma chloride concentration [3]. Moreover, we took a sample of blood every five min to measure the haemoglobin (Hb) concentration, and the plasma volume expansion calculated based on the fractional dilution of the blood Hb concentration. This was given by 100 $([Hb_o - Hb_n]/Hb_n)/(1 - Hct_o)$, where Hb_o and Hct_o were the Hb concentration and the haematocrit at baseline, respectively, and Hb_n was the blood Hb at an arbitrary later time, with the result as a percentage.

We also analysed the first and last urine samples for neutrophil gelatinase-associated lipocalin (NGAL), an indicator of renal tubular interstitial inflammation [10], and alpha-1-microglobulin (protein HC), which is a marker of tubular damage. We only measured the osmolality of the first urine sample. The first and last blood samples were analysed for C-reactive protein as the measure of inflammation, and syndecan-1 as an index of endothelial glycocalyx breakdown [11].

All electrolyte, creatinine, urea, NGAL and Hb concentrations were measured within 24 h at the clinical chemistry laboratory at Karolinska Hospital in Stockholm, Sweden. The samples used for determination of the iohexol concentration were stored at −80 °C until analysed with high-pressure liquid chromatography, with a coefficient of variation (CV) of 2% after dilution to 1:2 (serum) and 1:50 (urine). C-reactive protein and alpha-1-microglobulin were measured on a Cobas c701 (Roche Diagnostics, Rotkreutz, Switzerland) and syndecan-1 quantified by an ELISA kit (Diaclone, Besancon Cedex, France).

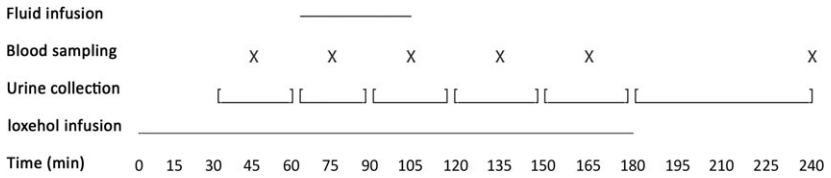

Figure 1 The infusion and sampling scheme.

Creatinine and osmotically active particles are excreted at a fairly constant rate. Therefore, reduced excretion of water can be indicated by a raised urinary creatinine concentration and urinary osmolality [12–14]. Pre-infusion fluid retention was diagnosed when the creatinine concentration in the urine collected before the infusions started was > 7.0 $mmol.l^{-1}$ and/or the osmolality was > 700 $mOsmol.kg^{-1}$. These cut-offs were chosen to divide the subjects into two groups of equal size, and to yield the best possible agreement between the two markers. Here, they agreed in 76% of the experiments.

We reported results showing normal distribution as the mean (SD), and evaluated changes using the paired *t*-test. We analysed differences between subgroups by one-way or two-way ANOVA. Correlations between parameters were studied by simple linear regression analysis, where r = correlation coefficient. Data with a skewed distribution were presented as the median (IQR[range]), and comparisons between subgroups were made using the Mann–Whitney test or, occasionally, by two-way ANOVA after logarithm-transformation of the data. Changes were studied by Wilcoxon's matched-pair test.

The study was powered to detect a difference in iohexol clearance, which was used to calculate the GFR, of 10% at the end of the two infusions. This difference was relevant based on previous work [2, 4]. The iohexol clearance has previously been associated with a standard deviation of 11% [15], and we assumed a GFR of 70 $ml.min^{-1}$ in the study population. This would require 12 patients with a power of 90% and alpha = 0.05.

One baseline plasma chloride value was an extreme outlier (eight SD from the mean) and was replaced by the mean value for the group. We considered $p < 0.05$ to be statistically significant.

Results

Data on demographics, morbidity and medications are shown in Table 1. No serious complications occurred. One patient's infusion (Ringer's acetate) was not studied because blood could not be efficiently sampled.

Fluid retention was present in six of the patients before the infusions of Ringer's acetate. All of these subjects as well as two other patients had fluid retention before receiving saline.

Table 1 Baseline characteristics, morbidity and medication taken in the studied patients. Values are mean (SD).

Parameter	Result
Subjects in final analysis; men	13
Age; years	72 (4)
Body weight; kg	82.0 (7.1)
Body mass index; $kg.m^{-2}$	26.4 (2.9)
Morbidity, incidence	
Infravesical obstruction	12
Hypertension	8
Hyperlipidemia	5
Diabetes type 2	3
Prostate cancer	2
Medication, frequency*	
Antihyperlipidemics	5
Calcium antagonists	4
ACE inhibitors	3
ANG II antagonists	3
Beta blockers	2
Oral antidiabetics	3

*Diuretics had been prescribed to two patients, but were discontinued before the study. ACE, angiotensin converting enzyme; ANG II, angiotensin II.

Only the saline infusion increased the plasma sodium concentration by the end of the infusion ($p < 0.04$) and 30 min later ($p < 0.02$, Fig. 2a).

Changes in the plasma potassium concentration were small (Fig. 2b).

Both infusions raised plasma chloride, but changes were greater for saline at the end of infusion, and during the subsequent hour (each point in time $p < 0.001$; Fig. 2c). Saline induced a minor but statistically significant reduction in standard bicarbonate, that persisted throughout the experiment (Fig. 2d).

The mean (SD) of the strong ion difference was 40.5 (1.9) at baseline. A lower strong ion difference for saline than for Ringer's was found when the infusions had just ended, falling to 38.3 (2.2) vs. 39.9 (1.3) $mmol.l^{-1}$; $p < 0.04$.

Pre-infusion fluid retention was associated with lower plasma sodium during the study (141.2 (2.0) vs 143.5 (2.6) $mmol.l^{-1}$; $p < 0.03$). A difference of about 2 $mmol.l^{-1}$ was present at baseline ($p < 0.02$). The strong ion difference was also lower among those with fluid retention, with a mean of 39.0 (1.4) vs 40.4 (1.9); $p < 0.03$.

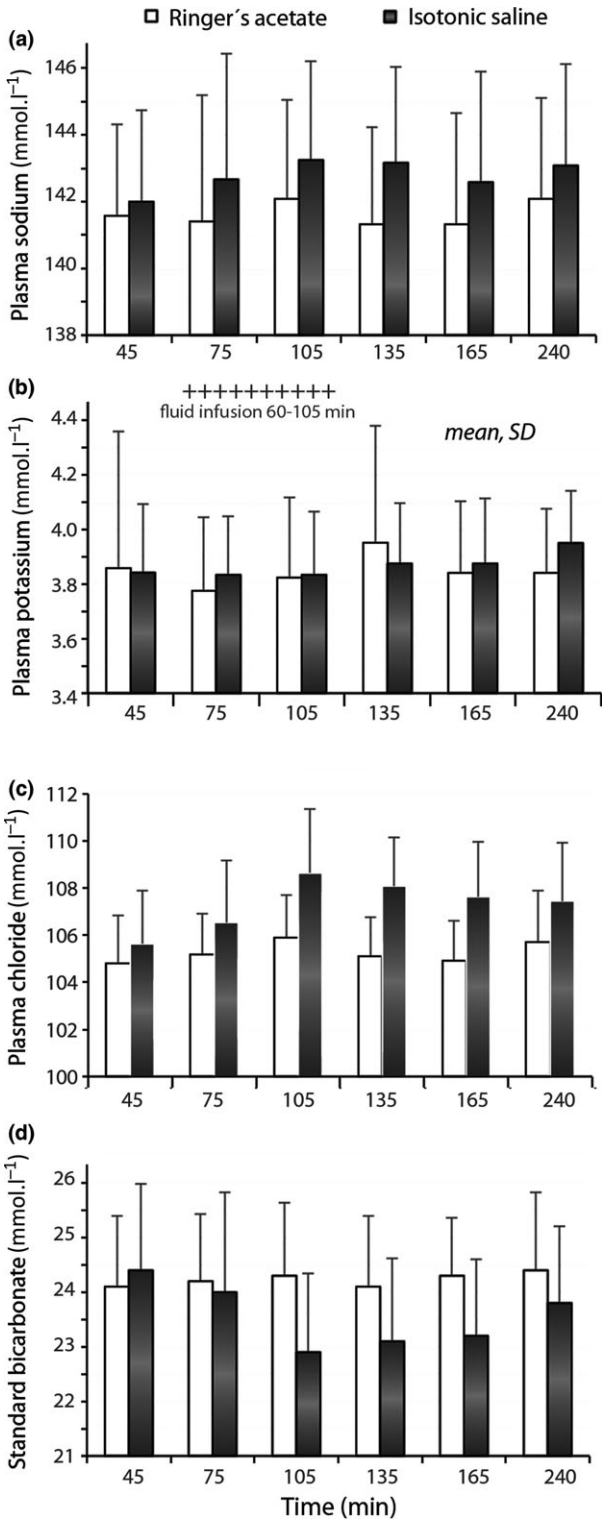

Figure 2 Plasma electrolytes and the standard bicarbonate concentration in whole blood. Ringer's acetate (open boxes) and isotonic saline (filled boxes) was infused between 60 min and 105 min. The box represents the mean and the error bars and the SD.

The total urinary excretion was lower during the infusion of isotonic saline, when compared with Ringer's acetate ($p < 0.01$; Table 2). Urine flow was consistently higher during the Ringer's acetate experiment (Fig. 3a), but the difference was also dependent on pre-infusion fluid retention (Fig. 3b, c). Both the use of saline ($p < 0.04$) and pre-infusion fluid retention ($p < 0.001$) independently reduced the urine volume ($p = 0.07$). The effect of pre-infusion fluid retention on urinary excretion was mirrored in a greater plasma volume expansion over time ($p < 0.02$; Fig. 4).

Chloride excretion was similar after the two infusions, regardless of the larger amount administered with the saline (Fig. 5a). Chloride flow closely followed the urinary excretion (Fig. 5b), which means that chloride excretion was dependent on pre-infusion fluid retention (Table 2).

There were strong linear correlations between the iohexol, creatinine and urea clearances at baseline; the correlation coefficient varied between 0.77 and 0.90. Both fluids significantly increased the iohexol clearance, the overall rise being 16%, but the magnitude of the response depended on fluid retention ($p < 0.03$) and the choice of fluid ($p < 0.04$). For patients without fluid retention, the median increase was 17% for Ringer's acetate, and 5% for saline. In those with fluid retention, the corresponding values were 101% and 11%, respectively. The iohexol clearance at baseline was 20% lower in patients with fluid retention, but variability was considerable, with a clearance of 56 (25) $ml.min^{-1}$ vs 68 (13) $ml.min^{-1}$, $p = 0.13$.

Changes in the creatinine and urea clearances were small (Fig. 6b, c). In patients with pre-infusion fluid retention, creatinine clearance increased transiently at the end of infusion to 141 (65) $ml.min^{-1}$ while those without retention cleared 89 (17) $ml.min^{-1}$ ($p < 0.02$). Urea clearance was consistently lower when patients received saline, with a mean (SD) of 55 (16) $ml.min^{-1}$ vs 68 (14) $ml.min^{-1}$; $p < 0.04$).

There were no significant changes in inflammatory markers (Table 3). Alpha-1-microglobulin was detectable in only 27% of the urine samples taken before and after the experiments; there was an increase after the infusion in only one patient.

Syndecan-1 was lower at baseline in patients with pre-infusion fluid retention, 23 (12–32 [2–79]) $ng.ml^{-1}$,

Table 2 Urinary and chloride excretion from the start of the fluid infusion until the end of the study three hours later (60–240 min), depending on the presence of pre-infusion fluid retention. Values are median (IQR [range]).

	Ringer's acetate	Isotonic saline	*p*-value
Urinary excretion			
All patients; ml	1022 (876–1494 [244–2574])	450 (319–1239 [178–1968])	$p < 0.01$
Excreted/infused; %	68 (58–100 [16–172])	30 (21–83 [12–131])	
No fluid retention, ml	1494 (953–2057 [394–2574])	1256 (1055–1581 [523–1968])	$p = 0.71$
Excreted/infused; %	100 (64–137 [26–172])	84 (70–105 [35–131])	
Fluid retention; ml	996 (798–1044 [244–1080])	338 (267–408 [178–512])	$p < 0.03$
Excreted/infused; %	66 (53–70 [16–72])	23 (18–27 [12–34])	
Chloride excretion			
All patients; mmol	94 (72–159 [26–282])	75 (44–157 [32–240])	$p = 0.38$
Excreted/infused; %	48 (33–82 [13–145])	32 (19–68 [14–104])	$p = 0.23$
No fluid retention; mmol	154 (73–210 [38–282])	159 (133–188 [88–240])	$p = 0.86$
Excreted/infused; %	79 (30–101 [20–145])	69 (38–81 [38–104])	$p = 1.0$
Fluid retention; mmol	77 (71–116 [26–120])	48 (39–72 [32–76])	$p = 0.07$
Excreted/infused; %	40 (37–59 [13–62])	21 (17–31 [14–33])	$p < 0.04$

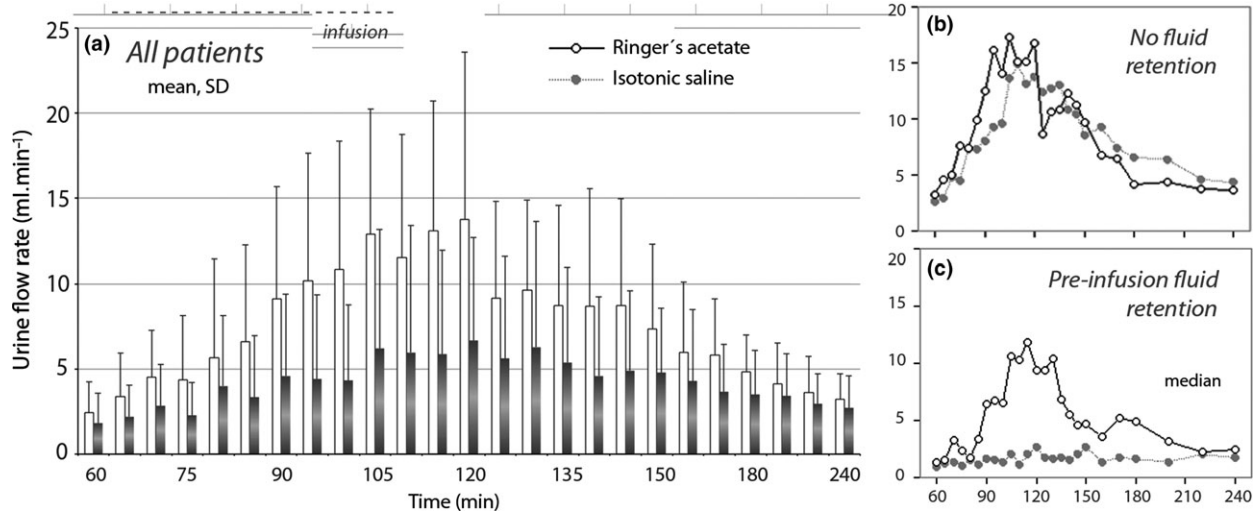

Figure 3 Urinary excretion in all patients (a) and in those without (b) and with (c) pre-infusion fluid retention. Ringer's acetate (open boxes) and isotonic saline (dark boxes) was infused between 60 min and 105 min. Values are mean (SD) (a) and medians (b and c).

compared with those without retention, where it was 65 (36–107 [4–129]) ng.ml^{-1} ($p < 0.01$). The urinary NGAL/creatinine ratio was also lower in these patients, 39 (28–71 [11–214]) μg.mmol^{-1} vs 111 (45–177 [18–803] μg.mmol^{-1}; $p < 0.05$), while there were no such differences with regard to C-reactive protein and alpha-1-microglobulin.

Discussion

Isotonic saline is the most widely used infusion fluid in Europe [16], despite reports of potential harm [3, 5–7, 17]. These warnings are not supported by the present study. Infusion of 1.5 l of isotonic saline in elderly male patients resulted in changes in fluid balance that were quite similar to those caused by Ringer's acetate. The small changes in plasma ionic concentrations agreed with the composition of the fluids. Plasma chloride and standard bicarbonate, which were of greatest concern, differed only by three mmol.l^{-1} between the fluids (Fig. 2).

The GFR was inferred from the renal clearance of a constant-rate infusion of iohexol. It increased after both infusions, which is contrary to our study hypothesis, and also contrary to previous findings of a

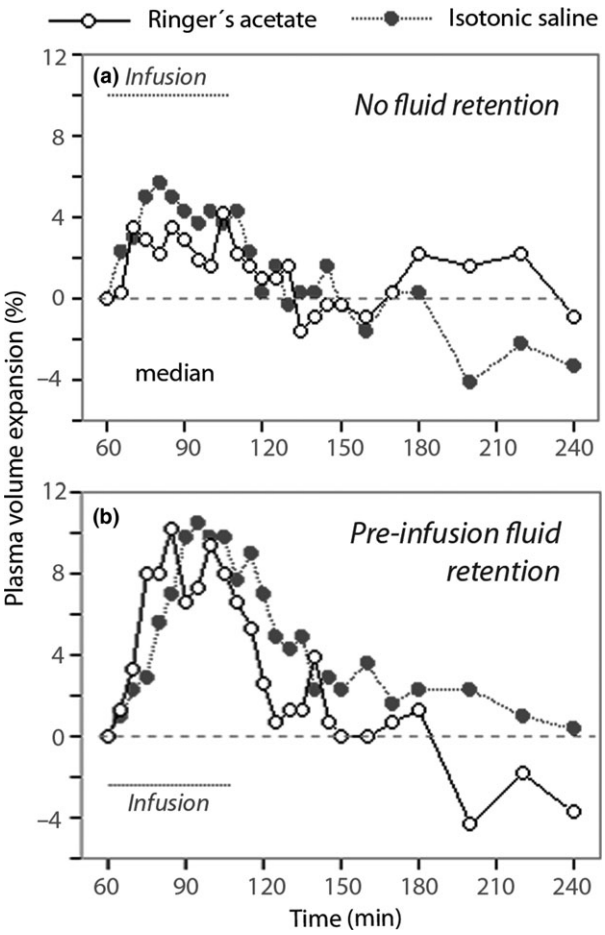

Figure 4 Plasma volume expansion estimated from the haemodilution in patients without (a) and with (b) pre-infusion fluid retention. Open circles = Ringer's acetate; Closed circles = isotonic saline. Data are mean values.

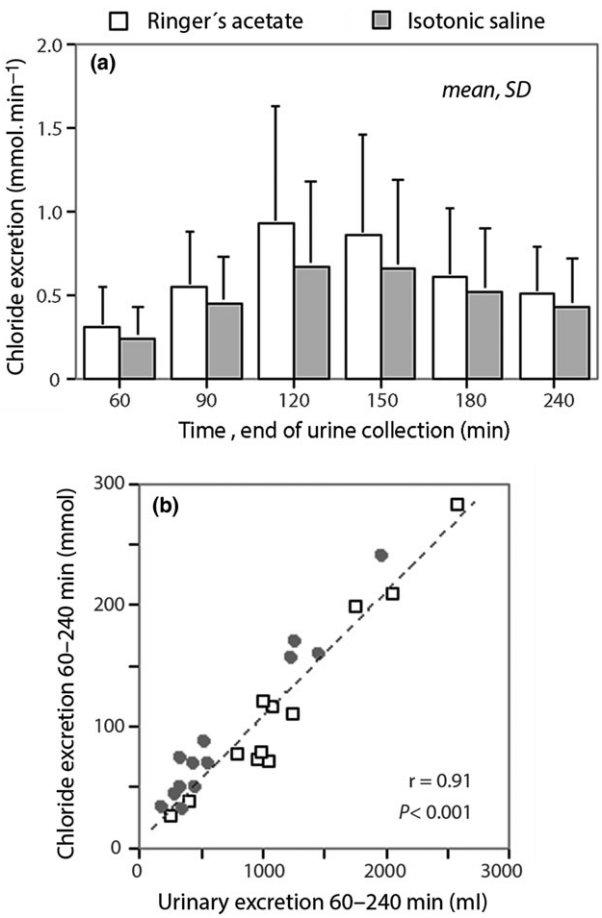

Figure 5 Excretion of chloride ions over time, given as the mean and SD (a). Close relationship between total urinary excretion and chloride excretion in individual experiments (b). Open circles = Ringer's acetate; Closed circles = isotonic saline.

reduction of 10–15% after saline [2, 4]. Although our study confirmed that the urine output was lower with isotonic saline compared with the buffered Ringer's solution [3, 17, 18], the difference was more dependent on pre-infusion fluid retention than on the choice of fluid. Patients with fluid retention excreted three times more fluid when receiving Ringer's acetate compared with saline (Table 2), while there was virtually no increase in urine flow in response to isotonic saline. In contrast, patients without fluid retention excreted almost the same volume after receiving these fluids. The inverse effect was recorded for the plasma volume expansion. Here, patients with pre-infusion fluid retention had twice as much volume expansion as the others.

Concerns have been raised about the capacity of the body to excrete a surplus chloride load, which is the key factor in why isotonic saline causes acidosis and reduces renal blood flow. In patients undergoing kidney transplantation, one week was required for plasma chloride to return to baseline [9]. In the present study, excretion was far more effective. One-third of the chloride load in the saline group and half in the Ringer's acetate group had been excreted within three hours after the infusions were initiated.

There was a strong overall correlation between urine volume and chloride excretion, so strong that the chloride content of the fluid hardly mattered. Therefore, the smaller fraction of the chloride load that was excreted after the saline infusion can be explained

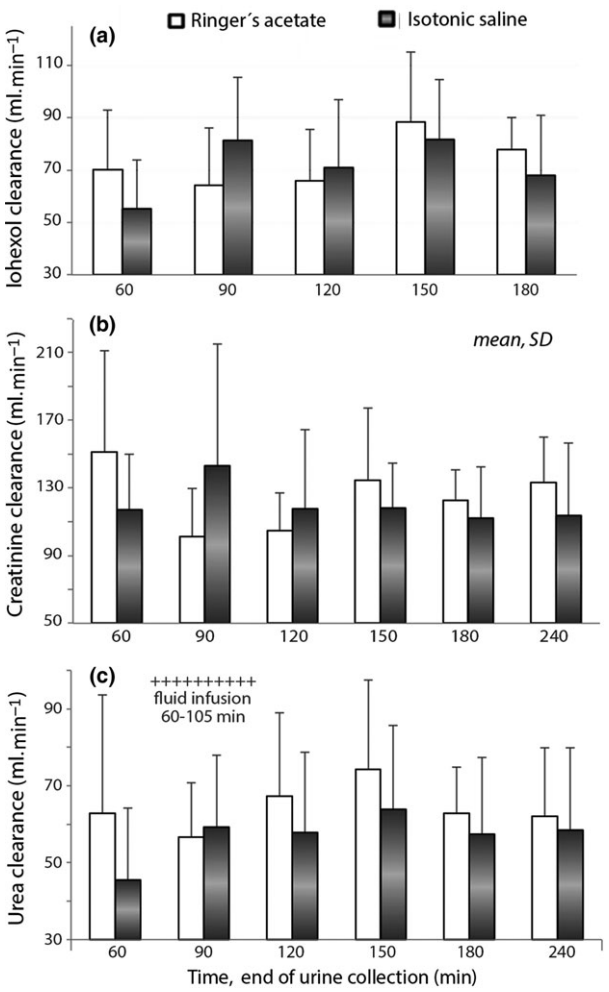

Figure 6 Renal clearances of iohexol (a), creatinine (b) and urea (c) measured over 30-min periods when 1.5 l of Ringer's acetate (open boxes) and isotonic saline (closed boxes were infused between 60 min and 105 min). Values are mean (SD).

by the smaller urinary excretion. Although the degree of pre-infusion fluid retention affected the chloride excretion, these elderly patients would invariably have excreted their chloride loads by the next morning.

We have shown that renal water conservation profoundly affected many results, which has not previously been appreciated. The responses to the fluids with regard to strong ion difference, urinary excretion, chloride excretion and renal function were all dependent on pre-infusion fluid retention. Interestingly, two inflammatory markers also differed depending on fluid retention. Plasma concentrations of syndecan-1 and the urinary excretion of NGAL were both lower in patients with retention. The clinical implication of these differences is unclear, although our NGAL data were lower than those reported by Chowdhury et al. [3]. Two previous studies of elderly hospital patients showed that fluid retention worsens outcome [19, 20]. Pre-operative patients with concentrated urine eliminate Ringer's acetate more slowly [21], which supports the present findings.

Table 3 Markers of inflammation in blood and urine before and after the infusions. Values are median (IQR [range]). No statistical differences were demonstrated.

	Ringer's acetate	Isotonic saline
Serum C-reactive protein (mg.l^{-1})		
Before	2.7 (0.8–6.1 [0.6–7.1])	1.8 (1.0–4.2 [0.6–6.8])
After	2.6 (0.8–5.8 [0.6–7.2])	1.8 (0.9–4.1 [0.6–6.5])
Serum Syndecan-1 (ng.ml^{-1})		
Before	31 (19–67 [2–109])	32 (12–74 [14–129])
After	29 (20–66 [4–93])	38 (10–77 [1–119])
Urine NGAL/creatinine (μg.mmol^{-1}), urine		
Before	60 (35–154 [26–641])	44 (21–95 [11–803])
After	81 (48–142 [10–1170])	51 (12–96 [7–217])

Analysis of urine concentrations for various metabolic waste products, which appear in higher concentrations when the kidneys conserve water, has been used to diagnose dehydration in sports medicine [12, 13]. The urinary creatinine concentration and the urinary osmolality show a 10-fold variation in healthy humans [14], and this can be attributed to how the kidneys are set to excrete or conserve water. The urine analysis used here indicates fluid retention due to any cause, but a deficit of extracellular fluid is most likely to be involved, as we excluded patients with cardiac and renal failure. Confounding effects of excessive salt intake or an extremely small or large muscle mass can be estimated by a gross discrepancy in the two urinary biomarkers [14], but this was not observed in the present study.

The strength of our study is that repeated measurements of several fluid-balance parameters allowed for good time-resolution for the resultant changes. The limitations are that all subjects were elderly men, and the results may not be valid in other patient groups, or during anaesthesia and surgery. Moreover, the results may not be transferable to infusion of larger amounts of fluid, or to the very rapid accidental absorption of

isotonic saline that sometimes occurs during transurethral surgery [8]. Here, all patients received the same fluid volume twice in an open crossover fashion. Half of them were given saline first due to ethical concerns raised by a report of slow chloride elimination in patients with impaired kidney function [9].

In conclusion, the study showed limited differences in fluid balance and renal function when 1.5 l of Ringer's acetate or isotonic saline was infused in elderly men. Glomerular filtration rate increased in response to both fluids, albeit more after infusion of Ringer's acetate. Pre-infusion fluid retention was an important factor governing the responses.

Acknowledgements

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Competing interests

This project was funded by the Stockholm City Council and the Kleberg Foundation. No competing interests declared.

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