Systemic and Renal Effects of Preventing Contrast Nephrotoxicity With Isotonic (0.9%) and Hypotonic (0.45%) Saline

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Introduction and objectives. Physiological and hypotonic saline solutions have been used interchangeably for preventing contrast media nephrotoxicity. No analysis of the possible differential effects of the 2 solutions on the milieu interieur or intercompartmental fluid volumes has been performed. Our aim was to study the systemic and renal effects of 2 types of saline solution regularly used to prevent contrast media nephrotoxicity in patients undergoing coronary angiography.

Methods. Changes in electrolyte levels and volume distribution were studied in 71 individuals who were randomized to receive either 0.9% isotonic saline (n=36) or 0.45% hypotonic saline (n=35) during the 12 hours before and after contrast injection (2000 mL in each period).

Results. The creatinine level was elevated equally often in the isotonic and hypotonic saline groups. Isotonic saline administration led to reductions in hemoglobin level, hematocrit, and plasma albumin level, and to increases in plasma volume, by 12.3% and 10.4% at 24 and 48 hours, respectively. These changes were significant compared with baseline measurements and compared with the group that received hypotonic saline. Neither of the 2 saline solutions resulted in a change in plasma atrial natriuretic peptide level. Plasma and urine osmolality decreased only with hypotonic saline. The increase in plasma creatinine level was similar with both isotonic and hypotonic saline.

Conclusions. During standard therapy for preventing contrast media nephrotoxicity: a) isotonic saline, but not hypotonic saline, increased plasma volume; b) this increase did not raise the atrial natriuretic peptide level; and c) no difference in the increase in serum creatinine level was observed between the 2 saline solutions. These findings provide evidence that 0.45% saline, at a dose suitable for preventing contrast media nephrotoxicity, is associated with a lower risk of volume expansion. This result is important for patients with severely impaired ventricular function.

Key words: *Contrast nephrotoxicity. Isotonic saline. Hypotonic saline. Plasma volume. Osmolality. Renal protection.*

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Efectos renales y sistémicos en la prevención de la nefrotoxicidad por contraste con sueros salino (0,9%) e hiposalino (0,45%)

Introducción y objetivos. En la prevención de nefrotoxicidad por contraste se han empleado indistintamente suero salino fisiológico o hiposalino, sin analizarse las posibles diferencias de efecto en el medio interno y la distribución compartimental de volumen. Se estudiaron los efectos renales y sistémicos de dos tipos de suero salino, empleados según pauta de prevención de nefrotoxicidad por contraste en coronariografía.

Métodos. Se estudiaron aspectos hidroelectrolíticos y de distribución de volumen en 71 individuos, aleatorizados a recibir suero salino isotónico al 0,9% (n = 36) o suero hiposalino al 0,45% (n = 35), durante las 12 h previas y las 12 h tras el contraste (2.000 ml en cada período).

Resultados. La incidencia de elevación de creatinina en el grupo salino fue igual que en el hiposalino. El suero salino causó reducción en los valores de hemoglobina, hematocrito y albúmina plasmática, y un incremento del volumen plasmático (el 12,3 y el 10,4%, a las 24 y a las 48 h); estos cambios fueron significativos con respecto al estado basal y al grupo con suero hiposalino. Sin embargo, los sueros administrados no produjeron elevación del péptido natriurético auricular. Las osmolalidades plasmática y urinaria descendieron sólo con el suero hiposalino. Las elevaciones de creatinina plasmática fueron similares con el suero salino y con el hiposalino.

Conclusiones. En una pauta preventiva estándar de la nefrotoxicidad por contraste: *a*) el suero salino, pero no el hiposalino, aumenta el volumen plasmático; *b)* este aumento no incrementa la concentración de péptido natriurético auricular, y *c)* no se ha detectado diferencias entre los sueros en la elevación de creatinina sérica. Estos resultados aportan evidencia de que el suero hiposalino, a la dosis preventiva de nefrotoxicidad por contraste, implica menos riesgo de expansión. Este dato es relevante en pacientes con función ventricular críticamente afectada.

Palabras clave: *Nefrotoxicidad por contraste. Salino isotónico. Hiposalino. Volumen plasmático. Osmolalidad. Protección renal.*

ABBREVIATIONS

ANP: atrial natriuretic peptide
ARF: acute renal failure
CN: contrast nephrotoxicity
EF: ejection fraction
PCr: plasma creatinine
RF: renal failure

INTRODUCTION

Contrast Nephrotoxicity (CN) remains an important complication in cardiac and vascular imaging studies. Although the renal effects are usually reversible, the development of acute renal failure (ARF) is associated with longer hospital stays, need for dialysis, and mortality. Traditionally, contrast ARF has been defined as plasma creatinine (PCr) elevations of 25% or more in the 48 hours after administration of intravenous contrast.[1,2] It follows from this definition that most cases of CN are subclinical and have little effect on the subsequent disease course. However, in certain cases, it can represent a major complication. Incidence varies according to series, and can be as high as 10%.[1-7]

The pathogenesis of CN has not been sufficiently well established, but a main role has been attributed to medullary ischemia with associated decreased renal blood flow and to imbalances between vasodilator and vasoconstrictor factors.[1,2,5-9] Several approaches have been used for prevention aimed at increasing blood flow, inducing vasodilation, and increasing diuresis. A list—not to be considered exhaustive—of the agents used includes dopamine, fenoldopam, mannitol, atrial natriuretic peptide (ANP), theophyllines, calcium channel blockers, and N-acetylcysteine.[1,10-21] While measures for expansion of circulating volume remain the most widely used and reliable method for preventing CN, the actual effect is often masked by the concomitant use of the other treatments mentioned. Both isotonic saline solution (0.9%) and hypotonic saline solution (0.45%) have been used indistinctly as prophylaxis against CN, but no comparative studies have been done on the efficacy or on possible differences in the cardiorenal and hemodynamic effects.[11,12,22-26]

In clinical practice with cardiac patients, use of these salines is unlikely to be indistinct and there will be significant qualitative differences between the 2. Intuitively, one might think that hypotonic saline is preferable in individuals at risk of severe systolic dysfunction. To our knowledge, only 1 prospective randomized study has been published that analyzes the possible differences between the 2 solutions,[27] and only with respect to preventing ARF. The findings of that study showed greater efficacy for isotonic saline compared to hypotonic saline in terms of the incidence of cases of ARF. However, although that study was performed in a large number of patients, it did not provide in-depth data on the differences in the effect of the 2 salines on the milieu interieur or how the fluid was distributed to different compartments, information which might help to clarify some of the underlying pathophysiological aspects.

Building on what is currently known, the aim of the present study was to determine the renal and systemic effects of isotonic and hypotonic saline, beyond mere renal protection. A specific aspect of the study consisted of analyzing the hypothesis, which can be predicted but which has often been put forward but never submitted to formal examination, that hypotonic saline is the treatment of choice when it is desirable to decrease the risk of vascular expansion. A further aspect consisted of providing measures of the degree of expansion obtained with the normal administration regimens of each saline.

METHODS

Patients

The study was performed in an invasive cardiology unit of a teaching hospital. Seventy-four adult patients admitted to the cardiology service were included. These patients underwent elective coronary angiography. The study design was comparative, prospective, and randomized, in which patients were assigned to isotonic saline or hypotonic saline. Exclusion criteria were applied to ensure a homogeneous study population. These criteria were as follows: changes in PCr ≥0.5 mg/dL in the 24 hours prior to the test, advanced renal failure, or dialysis (stage 4 and 5 of the National Kidney Foundation classification[28]), pregnancy, contrast allergy, severe clinical heart disease, and/or ejection fraction (EF) <30%, acute myocardial infarction in the previous 2 weeks or hemodynamic instability necessitating inotropic support, uncontrolled hypertension, liver disease, chronic

obstructive pulmonary disease, N-acetylcysteine or need for intercurrent serum therapy, and significant concomitant disease, such as malignant tumors, uncontrolled diabetes mellitus, hypothyroidism, or hyperthyroidism. Diuretic therapy was suspended 48 hours before the contrast study. Baseline renal failure was defined as PCr values ≥1.4 mg/dL and hypertension as blood pressure >140/90 mm Hg.

Study Protocol

The protocol was approved by the institutional review board and ethics committees. All patients received an explanation of the aims and nature of the study. Informed consent was obtained in writing before their participation and the findings were treated in accordance with current legislation concerning data protection.

Once a subject had been included by the treating physicians, each type of saline was assigned randomly by a different investigator who was blinded to the clinical data. Participants received 2000 mL of 0.9% saline ([Na] 154 mEq/L) or hypotonic saline at 0.45% ([Na] 77 mEq/l) for the 12 hours prior to intravenous administration and for 12 hours afterwards. The oral fluid intake was similar in the 2 groups (1200-1500 mL/24 hours). The contrast medium used was nonionic with low osmolality (iodixanol, Visipaque 320, Nycomed Imaging A.S., 290 mOsm/kg).

Weight and vital signs were measured at baseline. The laboratory tests were done at 8 o'clock in the morning of the catheterization day, and 24 and 48 hours afterwards, and included hemoglobin, hematocrit, uric acid, total protein and blood albumin, transtubular potassium concentration gradient, fractional and total sodium loss, blood urea nitrogen, electrolytes, and blood and urine osmolality. As an additional marker of the state of expansion, ANP in blood was measured by radioimmunoassay,[29] before administration of saline and 24 hours after catheterization. The interassay and intra-assay variations in this method were 3.3% and 2.4%, respectively. The ejection fraction (EF) was measured during catheterization and, in cases in which ventriculography was not performed, it was calculated from 2-dimensional echocardiography done in the preceding 60 days. Blood pressure, intake, and diuresis were measured in the 3 test periods. The increase in plasma volume was calculated using the W van Beaumont formula.[30] Fractional sodium excretion and the transtubular potassium concentration gradient were calculated using conventional formulas.

Statistical Analysis

The Kolmogorov-Smirnov test with the Lilliefors correction was used to determine whether the distribution could be considered normal. The analysis included intragroup variation (that is, the statistical significance of differences between baseline and the measurement at 24 and 48 hours) and the interaction with the type of saline in time (whether the differences between baseline and 24 hours or baseline and 48 hours were different according to saline type). For the comparison of the 2 groups analyzed, the χ^2 test was used with the Fisher exact test for qualitative variables and the Student *t* test for the comparison of means of quantitative variables. When a normal distribution could not be assumed, the Mann-Whitney *U* test was used to compare the 2 groups. For comparison of variables before and after administration of contrast, the Student *t* test was used for paired observations and ANOVA for repeated measurements, applying the Bonferroni method. The ANOVA analysis considered the significance of the changes in a variable over time (24 and 48 hours), whether or not differences existed according to saline type and possible interactions. The comparison between 2 qualitative variables was done using the χ^2 test. A *P* value less than .05 was considered significant.

RESULTS

Seveny-one patients with measurements before and after catheterization completed the study, 36 in the isotonic saline group and 35 in the hypotonic saline group. Three of the subjects initially included were discarded from the analysis, 2 because the measurements after catheterization were missing, and 1 due to significant bleeding at the site of arterial puncture, with associated hemodynamic instability. The baseline characteristics are shown in Table 1. No differences were observed between the 2 groups in the baseline values of the different demographic, laboratory, and clinical variables (which included age, sex, serum creatinine, blood pressure, EF, water intake, and urine volume) as well as the number of individuals with diabetes mellitus, hypertension, renal failure, or dose of intravenous contrast administered.

The incidence of CN, defined as 25% or greater increase in PCr, in the isotonic saline group and in the hypotonic group was 5/37 (13.5%) versus 4/34 (11.7%) and 3/37 (8.1%) versus 1/34 (2.9%) at 24 hours and 48 hours, respectively; these differences were not statistically significant. The mean (SD) PCr tended to decrease in both the isotonic and hypotonic saline groups: 24 h, –0.046 (0.004) and –0.079 (0.005); 48 h, –0.008 (0.001), and –0.007 (0.003) (no comparisons were statistically significant). An analysis of the results in general did not reveal different rates of CN with respect to age, sex, diabetes mellitus, hypertension, or severity of previous renal failure. Likewise, there was no significant relationship with EF, and in the isotonic saline group, there were only 2 patients with EF <60%.

The main findings concerning the aim of the study are shown in Table 2. The baseline values of the variables shown in this table were as follows in the isotonic and

TABLE 1. **Comparison of the Baseline Characteristics of the Patients According to Treatment**[a]

Characteristics	Isotonic (0.9%) (n=36)	Hypotonic (0.45%) (n=35)	*P*
Age, mean, (SD), y	64 (10)	68 (10)	.094[b]
Sex (M/F), n	26/10	22/13	.454[c]
Weight, mean (SD), kg	70.3 (14)	66.6 (13)	.218[d]
Hypertension, n (%)	21 (58.3)	20 (57.1)	1.000[c]
Blood pressure, mean (SD), mm Hg			
Systolic	118.7 (13.6)	124.7 (20.9)	.474[d]
Diastolic	70 (9.2)	68.7 (12.9)	.286[d]
Serum creatinine, mg/dL	1.59 (1.37)	1.57 (1.38)	.763[b]
PCr ≥1.4, n (%)	9 (25)	9 (25.7)	1.000[c]
Diabetes Mellitus, n (%)	5 (13.9)	9 (25.7)	.245[c]
Ejection fraction, mean (SD), %	58.6 (14.7)	60.7 (12.1)	.525[d]
Hematocrit, mean (SD), %	41.3 (5.3)	38.7 (4.1)	.025[d]
Plasma sodium, mean (SD), mEq/L	139.3 (2.5)	138.4 (2.8)	.151[d]
Diuresis, mean (SD), mL	2.014 (681)	1.927 (754)	.615[d]
Iodine contrast dose, mean (SD), mL	184.7 (83.5)	195.1 (81)	.439[b]

[a]PCr indicates plasma creatinine.
The continuous variables are presented as means (SD).
[b]Mann-Whitney *U* test for comparison of 2 independent samples. None of the variables analyzed showed any group differences.
[c]χ^2 test with Fisher exact statistic.
[d]*t* test for comparison of means from 2 independent samples.

hypotonic saline groups, respectively: hemoglobin, 13.8 (1.8) and 13.1 (1.6) g/dL; hematocrit 41.1% (6.2%) and 39.2% (5%); plasma volume 58.6% (5.2%) and 61.2% (4.1%); albumin, 3.8 (0.4) and 3.8 (0.4) g/dL; uric acid, 6.7 (1.9) and 6 (1.4) mg/dL; plasma sodium, 139 (2.3) and 138.6 (2.7) mEq/L; plasma potassium, 4.4 (0.4) and 4.3 (0.4) mEq/L; systolic blood pressure, 117.4 (13.6) and 120.8 (20.6) mm Hg; diastolic blood pressure, 69.3 (9) and 65.5 (11.8) mm Hg; diuresis, 2.089 (652) and 1.941 (743) mL; ANP, 1.6 (0.5) and 1.7 (0.5) fmol/mL.

The administration of isotonic saline led to a significant decrease in the plasma levels of hemoglobin, hematocrit, and albumin after 24 and 48 hours compared to baseline and to the other group (Table 2). In the hypotonic saline group, no significant changes in hemoglobin, albumin, and hematocrit were observed. The only statistically significant decreases occurred for plasma urea nitrogen and uric acid, although to a lesser extent than was the case for isotonic saline. In the isotonic saline group, an increase was documented in plasma volume (24 h, +12.3% [1.1%]; 48 h, +10.4% [0.8%]; both with $P<.05$ compared to baseline), whereas in the hypotonic group, the plasma volume remained unchanged (0.1% [0.2%] and 5.6% [0.3%]; with no statistically significant differences compared to baseline). This variation in plasma volume was significant after 24 hours and between groups ($P<.05$) (Table 2). Of particular interest was the fact that ANP values did not vary for either treatment (no significant differences between groups or within each group) (Figure 1).

At 24 and 48 hours after performing the coronary angiography, systolic blood pressure increased significantly in the isotonic saline group but not in the hypotonic group (means; 8.3 [1.1] and 0.6 [0.3] mm Hg; $P<.05$ and not significant, respectively, compared to baseline) (Table 2). The increase in diastolic blood pressure was similar and showed no difference between groups.

During the 24 hours after administration of the contrast medium, diuresis increased similarly in both groups ($P<.01$ with respect to baseline; no significant group differences) (Table 2). However, the urine osmolality decreased markedly in the hypotonic group, both at 24 hours and at 48 hours ($P<.01$ and $P<.05$, respectively). There was also an increase in fractional and total sodium excretion at 24 hours and 48 hours—an increase which was greater in the isotonic group although this difference was only statistically significant in both groups at 24 hours (Table 3). The group comparison did not show significant differences (Table 3). The plasma sodium and osmolality were lower at 24 hours in the hypotonic group ($P<.05$).

With regard to potassium, at 24 hours both the transtubular concentration gradient and the potassium concentration in urine decreased with both types of saline. No other relevant changes were detected (Table 3).

In order to investigate whether systolic function influenced the differences between the 2 types of saline, the data were stratified according to whether EF was ≥60% or <60%. After stratification, in the isotonic saline group, hematocrit decreased equally in individuals with EF <60% and those with EF ≥60%; in contrast, no significant changes in the hypotonic group were observed in either of the 2 EF strata (Table 4). In the population of patients with EF <60%, the group comparison was statistically significant for plasma volume, total sodium

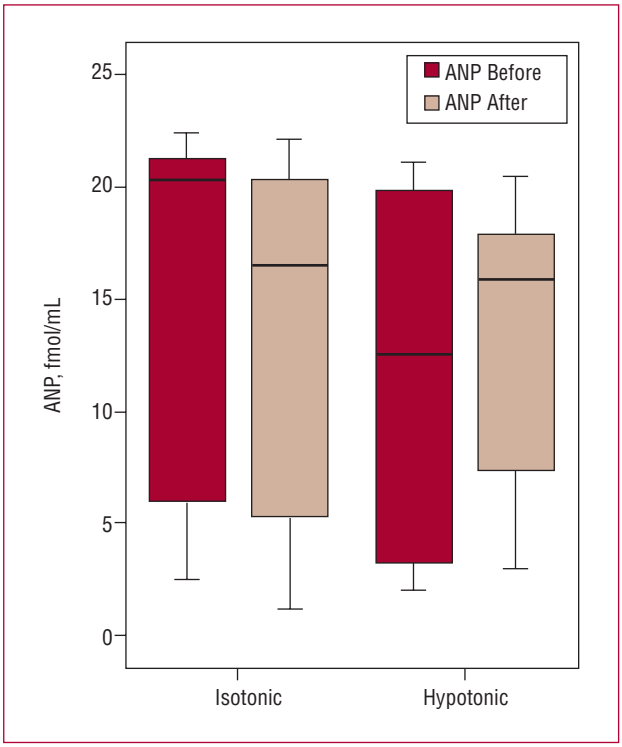

Figure 1. Levels of atrial natriuretic peptide (ANP) presented as a box-plot, at baseline and 24 hours after treatment with isotonic saline solution or hypotonic saline solution. No significant differences were found between any of the conditions. ANP before indicates atrial natriuretic peptide (ANP) before volume expansion prior to catheterization; PNA after, atrial natriuretic peptide after volume expansion after catheterization

excretion and urine sodium, and osmolality (P<.05) (Table 4). Table 4 shows the full group comparison data.

Extending the analysis according to whether renal failure (PCr >1.4 mg/dL) was present or not, it was observed that at 24 hours the changes in hematocrit and plasma volume behaved in a similar fashion to that shown in Table 4, although the effect was greater in patients with prior renal failure in the case of patients with EF <60% who received isotonic saline. The total sodium excretion was also greater after administration of isotonic saline than with hypotonic saline, but the difference was only statistically significant in the subgroup with EF <60% and renal failure (P<.05).

DISCUSSION

Our findings provide data for the first time on the differences in the effect of water and electrolyte management and the degree of expansion reached with the same standard dose of the 2 saline solutions used most frequently in preventative treatment of CN. Thus, this study differs from those published previously on the subject in that it does not focus on the actual prevention but rather on the comparative effect of the solutions on a series of variables not analyzed in previous studies. The conclusions obtained may also answer some outstanding questions when choosing between different saline solutions for patients who are scheduled for cardiac catheterization.

With regard to the 2 populations, the 2 groups were well balanced. The homogeneity observed in a series of variables such as age, sex, diabetes mellitus, hypertension, prior kidney failure, or ejection fraction is to be expected given that this is a population of uncomplicated patients who underwent elective angiography. The incidence of CN was within the range expected for this type of sample,[1-7] and the lack of differences between the 2 solutions was also to be expected given that, even though some series report advantages of isotonic saline, these, although statistically significant, are only of marginal clinical relevance.[27] In any case, the study did not aim to look for differences between the salines in terms of renal protection. Such an endpoint would have needed a much larger series, although given the homogeneity of the

TABLE 2. **Variation in Clinical Variables, According to Absolute Values of Variables (I), Between Time 0—Prior to the First Expansion—and at 24 hours and 24 hours After Catheterization**[a]

	Isotonic Group			Hypotonic Group			*P*		
	0 h	24 h	48 h	0 h	24 h	48 h	Type	Time	Interaction
Hemoglobin, g/dL	13.8	12.9	12.7	13.1	13.1	12.7	.648	.002	.033
Hematocrit, %	41.1	38.4	38.5	39.2	39.4	37.8	.710	.004	.048
Increase in plasma volume, %	–	12.3	10.4	–	0.1	5.6	.096	.030	.015
Albumin, g/dL	3.8	3.6	3.7	3.8	3.7	3.6	.760	.042	.050
Uric acid, mg/dL	6.7	5.9	5.9	6	5.4	5.5	.394	.000	.413
Plasma sodium, mEq/L	139	139	138.4	138.6	138.3	138.6	.575	.698	.520
Plasma potassium, mEq/L	4.4	4.3	4.4	4.3	4.2	4.1	.060	.043	.186
Systolic blood pressure, mm Hg	117.4	130.7	121.2	120.8	123.2	120.8	.754	.013	.126
Diastolic blood pressure, mm Hg	69.3	71.9	68.6	65.5	70.8	69.5	.573	.108	.454
Diuresis, mL	2089	2919	2220	1941	2623	2033	.278	.000	.886

[a]Means and levels of significance associated with the corresponding ANOVA. The Greenhouse-Geisser correction was used when necessary. The data given correspond to the baseline values and values at 24 hours and 48 hours.
Standard deviations have been omitted to facilitate presentation of the Table.

TABLE 3. **Variation in Clinical Variables (II), Between Time 0—Prior to the First Expansion—and at 24 hours and 24 hours After Catheterization**[a]

	Isotonic Group			Hypotonic Group			*P*		
	0 h	24 h	48 h	0 h	24 h	48 h	Type	Time	Interaction
FE Na, %	1.1	1.9	1.3	0.7	1.42	0.8	.632	.001	.547
Total E Na, mEq/L	86.3	167.9	107.3	83.8	145.9	80.6	.538	<.001	.292
UNa, mEq/L	40	63.3	49.1	45.7	58.8	41.7	.252	<.001	.214
UK, mEq/L	31	26	23.5	30	20.1	21.6	.352	.010	.880
TTPCG	5.7	4.8	4.4	5.9	5.5	4.7	.171	.030	.625
UOsm, mOSm/L	360.9	372.5	359.2	388.3	281.3	314.3	.009	.030	.214

[a]Total E Na indicates total sodium excretion in urine; FE Na, fractional excretion of sodium in urine; TTPCG, transtubular potassium concentration gradient; UK, urine potassium; UNa, urine sodium; UOsm, urine osmolality.
The data given correspond to the baseline values and values at 24 hours and 48 hours. Standard deviations have been omitted to facilitate presentation of the Table. Values are expressed as variation with respect to baseline.

TABLE 4. **Variation in Clinical Variables at 24 Hours According to Ejection Fraction**[a]

	Isotonic Group		Hypotonic Group		*P*[b]	
	EF <60 (n=17)	FE >60 (n=19)	FE <60 (n=14)	FE >60 (n=21)	FE <60	EF >60
Hematocrit, %	–2.5[c]	–2.8[d]	+2.1	–0.5	NS	NS
Plasma volume, %	+11.9	+13.1	–7.9	+2.8	.001	NS
Plasma Na, mEq/L	+1.3	–1.2	–0.08	–1.05	NS	NS
Urine Na, mEq/L	+24.7[c]	+15.4[d]	+12.2	+12.9[d]	.029	NS
Total E Na, mEq/L	+125[c]	+68.8[d]	+41	+83.2[c]	.004	NS
POsm, mOSm/L	+2.7	–8.2	+1.5	–2.9	NS	NS
UOsm, mOSm/L	–10.6	–29	–79.6[d]	–86.1	.042	NS

[a]Total E Na indicates total urinary sodium excretion; EF, ejection fraction; UOsm, urine osmolality; POsm, plasma osmolality.
[b]*P* between groups.
[c]*P*<.01 intragroup.
[d]*P*<.05 intragroup.

71 subjects studied, it is unlikely that, even with a sample size twice or 3-times as big, larger differences would have been seen.

The findings concerning the specific aim of the study can be summarized in 2 main points: isotonic saline expanded the circulating volume more than hypotonic saline and was associated with a different pattern of urinary elimination of water and electrolytes. The data on plasma volume, as well as plasma sodium, which decreased with hypotonic saline and remained constant with isotonic saline, illustrate the different distribution to different compartments of the 2 solutions, with inflow of the free water in the hypotonic saline into the intracellular compartment in the case of hypotonic saline. Of particular interest was the fact that our data provided actual numbers for the changes obtained with a maneuver—preventative expansion with saline—which has been used empirically for decades. For example, quantitatively, the increases in plasma volume reached with isotonic saline solution after 24 hours were around 300 mL. Whether or not this change is significant or not depends on the prior state of ventricular function. It is extremely interesting to note that this increase was insufficient to increase secretion of ANP, indicating that pressure and volume changes in the right atrium were not large enough to induce such an increase. Of additional interest was the fact that these latter results provided evidence, previously unavailable, to indicate that the effect of salines on the composition of urine and, predictably, the protective effect, are independent of increased ANP.

The results obtained have direct clinical consequences. The data indicate that the 2 types of saline can be used interchangeably in the prevention of CN. However, evidence is provided, based on a real measurement, that would support the preference for hypotonic saline in situations in which it is desired to avoid expansion of circulating volume. Although the increase in plasma volume with saline solution was not particularly large, this might be crucial in patients with borderline cardiac function. In a simple application, isotonic saline would be preferable in patients with low blood pressure in whom problems of volume overload are not foreseen. Less importantly, though still with practical implications, the laboratory blood and urine tests are a useful guide for interpreting the biochemistry of these patients in the days after catheterization; these findings will vary

according to the type of saline used. The changes observed are consistent with the different quantities of free water in each saline and the urine dilution effect with hypotonic saline.

Of particular interest, and bearing in mind that the patients with cardiorenal failure are increasingly numerous, is the fact that the data obtained in subjects with EF <60% and prior renal failure indicate that the maximum increase in plasma volume occurred in this subgroup, an observation which indicates a greater difficulty for redistribution or elimination of the infused fluid. These results are similar to those reported by Koomans et al,[21] who found that, in contrast to healthy subjects, rapidly infused saline solution (25 mL/kg in 30 minutes) to patients with severe renal failure was preferentially distributed to the intravascular compartment with a significant increase in the ratio of blood volume/extracellular volume at 2 hours after infusion. In the study by Merten et al,[32] the authors recommended the administration of a sodium bicarbonate solution for preventing NC but, given that this was distributed to the extracellular space, its use, as in the case of isotonic saline solution, could be problematic in patients with poor tolerance of expansion. In a more general sense, it is important to highlight that in these 2 studies the differences between isotonic and hypotonic saline and between saline and bicarbonate were not particularly relevant in terms of preventing CN.[27,32]

One limitation of this study was the relatively small number of patients included. Here we would like to point out once again that the primary objective of the protocol was not to determine the superiority of one saline or the other in the prevention of CN but rather to investigate the mechanisms; for this end, a sufficient number of patients were included. Another limitation is the lack of patients with a critical degree of heart or kidney failure. Thus, although the volume changes observed may be extrapolated to any patient who was not in a marked edematous state, it would be useful to carry out a similar study in individuals with myocardial dysfunction and/or severe renal failure, to obtain an evidence-based confirmation. A more definitive demonstration of the protective superiority of one of the types of saline commonly used, such as 0.9% or 0.45% saline, or bicarbonate would require much larger groups than those included in this study.

Taken together, the study provides necessary and previously unavailable information, which shows differences between isotonic saline and hypotonic solution in the distribution to different compartments and the water and electrolyte balance of urine. The degree of intravascular volume expansion produced by isotonic saline was quantified—a statistically significant difference but not one large enough to stimulate release of ANP. In general, these data support the possibility that hypotonic saline is the saline of choice in patients with worse myocardial function.

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