DOES TWO INTRAVENOUS IRON FORMULATIONS INDUCE DIFFERENT ACUTE EFFECTS IN NON-DIALYSIS CHRONIC KIDNEY DISEASE PATIENTS?

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BACKGROUND AND AIM

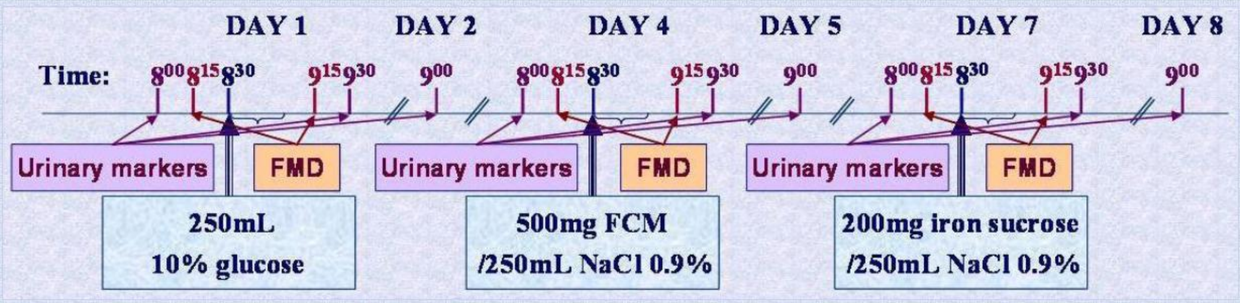
Concerns about potential nephrotoxicity and endothelial dysfunction after intravenous (IV) iron[1,2] - that is commonly prescribed in chronic kidney disease (CKD) patients[3] - were raised, but pharmacological and experimental data showed marked differences among iron formulations[4].

Since direct comparisons in clinical settings are rather scarce, we investigated the acute changes in endothelial and kidney functions during the first 24 hours after single IV infusions of iron sucrose (IS) and ferric carboxymaltose (FCM) in non-dialysis CKD patients.

METHODS

STUDY DESIGN: Prospective, crossover.

The effects of infusions containing 500mg FCM in 250mL 0.9% saline solution, 200mg IS in 250mL 0.9% saline solution and 250mL 10% glucose were compared. The infusions were administered over 30 minutes, 72 hours apart, the comparator (10% glucose) first, followed by FCM and IS:



STUDY PARAMETERS:

a) Markers of kidney damage: urinary excretions of beta-2 microglobulin (bMG), protein (P) and albumin (A), expressed as ratios to urinary creatinine (Cr), were measured by routine biochemistry before, 30 minutes and 24 hours after each infusion:

b) Endothelial function – flow mediated dilatation (FMD), measured by ultrasound on the brachial artery from the contralateral arm, was performed 15 minutes before and after each infusion.

c) Estimated GFR (calculated from serum creatinine by MDRD4) was assessed before and 24 hours after each infusion.

STATISTICAL ANALYSIS:

Data were presented as median with [1st and 3rd quartile].

The post-/pre-infusion differences (Δ) for each parameter were compared by Wilcoxon paired test. A *p* value <0.05 indicated statistical significance.

SUBJECTS

Thirty-one iron-näive subjects with CKD stages 3 to 5 not on renal replacement therapy, in stable clinical condition, 61 [48-73] years, 20% males, 23% diabetes mellitus, eGFR 22 [17-38] mL/min, who required IV iron as part of their routine medical care were enrolled. Absolute iron deficiency (serum ferritin <100ng/ml) was seen in 55%, while an additional 35% had transferrin saturation (TSAT) <20% with ferritin 100-309ng/mL. Only two subjects received erythropoiesis-stimulating agents (beta-epoietinum s.c.).

Signs of iron overload, hemolytic anemias, acute infections, recent exposure to nephrotoxic drugs or iodine contrast agents, nephrotic syndrome, and severe systemic atherosclerosis were exclusion criteria.

SUBJECTS' CHARACTERISTICS (N=31)

CKD stage:	
Stage 3	41%
Stage 4	39%
Stage 5 non-dialysis	20%
Primary kidney disease:	
Glomerular nephropathies	38%
Vascular nephropaties	29%
Tubulo-interstitial nephropathies	16%
Hereditary nephropaties	10%
Unknown	7%
CKD vintage (years)	3 [1-6.5]
Serum hemoglobin (g/dL)	10.8 [10.3-11.4]
Serum ferritin (ng/mL)	79 [36-146]
Transferrin saturation (%)	14 [11-21]
C-reactive protein (mg/L)	3 [2-5]

RESULTS

No differences in baseline parameters before study interventions existed:

Parameter *	*Before G 10%*	*Before IS*	*Before FCM*
Urinary bMG/Cr ratio (mg/g)	4.0 [0.9 – 21.1]	4.4 [0.7 – 16.0]	3.9 [0.4 – 23.0]
Urinary P/Cr ratio (g/g)	0.1 [0.0 – 1.3]	0.0 [0.0 – 1.3]	0.0 [0.0 – 1.0]
Urinary A/Cr ratio (mg/g)	143 [25 – 692]	110 [24 – 795]	153 [19 – 505]
eGFR (mL/min)	22 [17 – 38]	23 [17 – 37]	24 [13 – 36]
Flow mediated dilatation (%)	15.0 [11.1 – 19.2]	16.0 [9.3 – 21.9]	15.4 [11.4 – 20.5]

* Median [1st and 3rd quartile]; bMG: beta-2 microglobulin; P: protein; A: albumin.

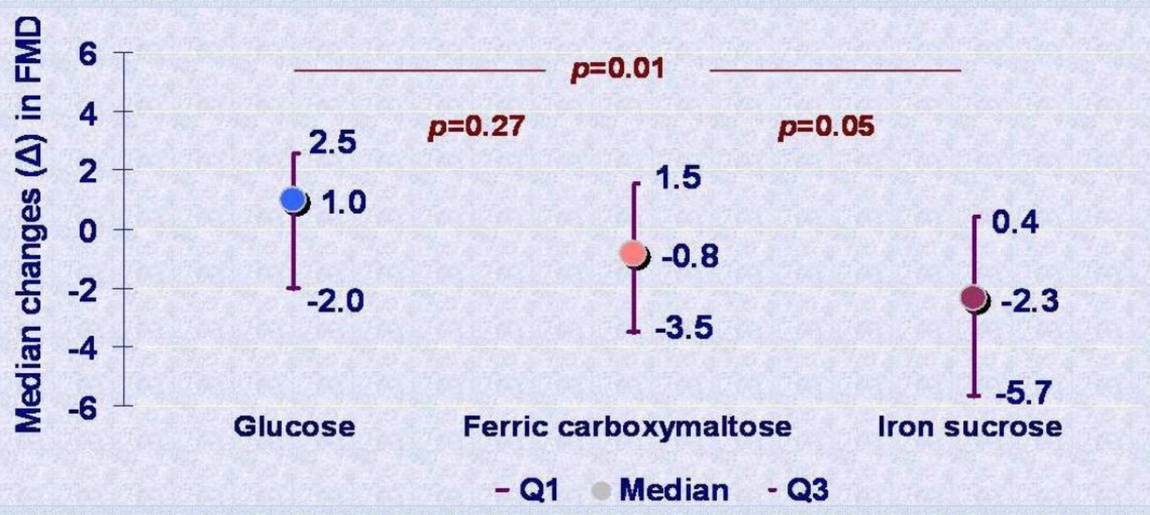
ENDOTHELIAL FUNCTION AFTER A SINGLE DOSE OF IV IRON

FMD decreased in more patients only after IS than after glucose (74% vs. 45%, *p*=0.02, and 61% vs. 45%, *p*=0.20, respectively).

Also, the median change in FMD showed an augmented decline when IS but not FCM was infused, as compared to glucose (*Figure 1*).

In addition to the trend towards higher decrease in ΔFMD (*p*=0.05) observed between the two iron formulations, the median FMD at the end of IS infusion was lower than after FCM (12.3 [9.5 to 17.1] vs. 17.0 [10.1 to 19.2], *p*=0.04).

Figure 1. CHANGES IN FLOW MEDIATED DILATATION (FMD)

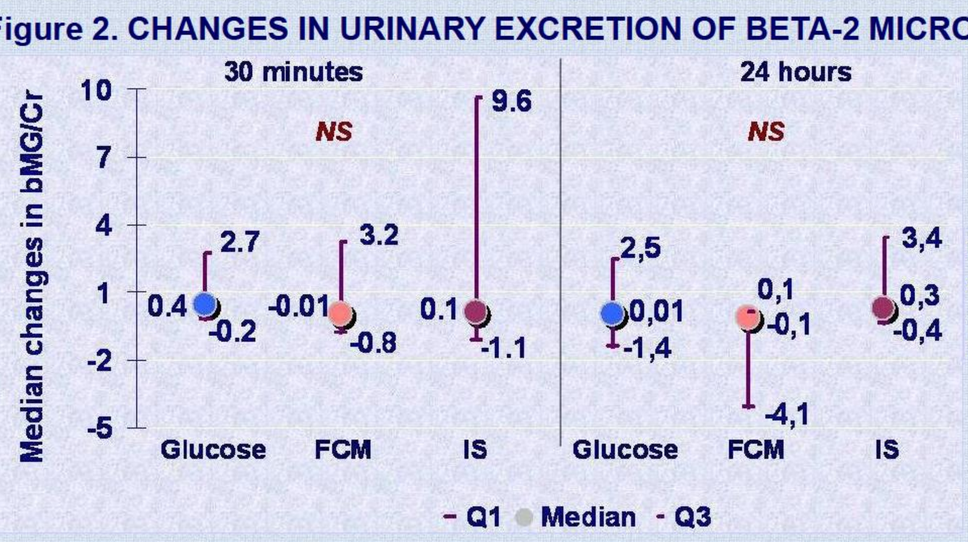


KIDNEY DAMAGE MARKERS AFTER A SINGLE DOSE OF IV IRON

Proteinuria, albuminuria, and estimated GFR had only minor variations. Both early and late changes in urinary bMG (expressed as ΔbMG/Cr) after IV iron infusions were comparable to those noticed after glucose, as well (*Figure 2*).

Urinary excretion of bMG were similar at both studied moments after either iron formulation and the comparator: 3.0 [0.6 to 27.7], 8.9 [0.5 to 18.3], and 3.5 [0.8 to 20.9] mg/g at 30 minutes, *p* >0.8, and 3.2 [1.1 to 21.2], 4.4 [0.5 to 15.1], and 4.3 [0.3 to 19.7] mg/g at 24 hours, *p* >0.8, after IS, FCM, and glucose, respectively.

Figure 2. CHANGES IN URINARY EXCRETION OF BETA-2 MICROGLOBULIN



FCM: ferric carboxymaltose

IS: iron sucrose

Taken together these data suggest iron sucrose-related decrease in arterial reactivity and argue against acute tubular toxicity induced by either iron formulation.

CONCLUSIONS

Endothelial dysfunction seems to be acutely induced by a single common-used, dose of IV iron sucrose, but not by ferric carboxymaltose, in non-dialysis CKD patients. Neither IV iron formulations seem to exert any acute tubular toxicity. These preliminary results could hint in favor of ferric carboxymaltose over iron sucrose, at least with respect to endothelial function, in aged patients with moderate to severe GFR decrease and mild anemia.

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