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Positive effect of intravenous iron-oxide administration on left ventricular remodelling in patients with acute ST-elevation myocardial infarction – A cardiovascular magnetic resonance (CMR) study

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ABSTRACT

Objectives: This study investigated the safety profile and potential "therapeutic" effect of intravenous ultrasmall superparamagnetic iron-oxide (USPIO)-based iron administration regarding infarct healing in patients with ST-elevation myocardial infarction (STEMI). USPIO-administration was recently shown to enable an improved characterization of myocardial infarct pathology in acute STEMI patients.

Materials and Methods: Seventeen study patients (IRON, 54 ± 9 yrs, 88% male) and 22 matched controls (CONTROL, 57 ± 9 yrs, 77% male) both with primary reperfused STEMI underwent multi-parametric CMR studies in the first week and three months after acute MI. Only IRON patients received a single intravenous bolus of 510 mg elemental iron as ferumoxytol (Feraheme™) within four days following acute MI.

Results: Three months later, all patients were alive and there were no adverse cardiac events. Significant improvement in left ventricular (LV) ejection fraction (IRON: 53 ± 10% to 59 ± 9%, p = 0.002; CONTROL: 54 ± 6% to 57 ± 10%, p = 0.005) as well as shrinkage of infarct size were seen in both groups at follow-up. There was a more pronounced decrease in infarct size in the IRON group (IRON: −10.3 ± 5.4% vs. CONTROL: −7.0 ± 8.4%, p =0.050) in addition to a significant decrease in both endocardial extent and prevalence of transmural infarctions in IRON but not in CONTROL patients. A significant decrease in LV end systolic volume was only seen in the IRON group (71 ± 25 mL to 59 ± 25 mL, p = 0.002).

Conclusions: Intravenous iron administration in acute STEMI patients seems to be associated with an improved infarct healing and a beneficial global left ventricular remodelling. These findings together with the good safety profile make USPIO-based iron administration a promising future candidate as a "diagnostic" and "therapeutic" adjunctive solution in acute MI management.

1. Introduction

Primary reperfusion by percutaneous coronary intervention (PCI) has become the standard treatment in ST-segment elevation myocardial infarction (STEMI). Successful PCI reduces infarct size, preserves left ventricular (LV) function and improves survival [1–3]. Nevertheless, despite early recanalization of obstructed coronaries, subsequent adverse LV remodelling with progressive LV dilation and decrease in LV function remains an important clinical and prognostic issue. Up to two thirds of STEMI patients treated with primary PCI present with LV dilation at four months and approximately one third of them continue to show progressive dilation at six months [3,4]. In such patients, infarct mass was the best predictor of adverse remodeling [3]. Therefore, intensive efforts are currently made in order to find new adjunctive therapies to PCI aiming at reducing infarct size and improving ventricular remodeling following acute MI [5].

In the last decades, the role of iron metabolism in cardiovascular disease has been extensively explored [6–11]. Treatment with intravenous iron in patients demonstrating iron deficiency and suffering from ischemic as well as non ischemic chronic heart failure did not only improve symptoms, but also functional capacity and quality of life — even in the absence of anemia [12]. On the other hand, in the acute setting of STEMI, changes in iron status — with a decline in circulating levels and

Abbreviations: BfArM, German Federal Institute for Drugs and Medical Devices; CAD, coronary artery disease; ceCMR, contrast-enhanced CMR; CMR, cardiovascular magnetic resonance imaging; LGE, late-gadolinium-enhancement; MI, myocardial infarction; MVO, microvascular obstruction; NIMINI-MMRI, **N**on-**i**nvasive **m**yocardial **in**flammation **i**maging based on new **m**olecular **m**agnetic **r**esonance **i**maging contrast agents and methods; PCI, percutaneous coronary intervention; SE, spin-echo; SPIO, superparamagnetic iron oxide nanoparticles; SSFP, steady-state free precession; STEMI, ST-elevation myocardial infarction; STIR, short tau inversion recovery; USPIO, ultrasmall superparamagnetic iron oxide nanoparticle.

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rise in iron stores as expressed by serum Ferritin — are documented but their exact role and clinical significance is still to be elucidated [7,11]. So far, there are no data available regarding the safety and potential therapeutic or detrimental effect of iron administration in patients with acute MI.

Recently, ferumoxytol (Feraheme™), an ultrasmall superparamagnetic iron oxide (USPIO) with a particle diameter of ~30 nm, was approved for iron-replacement therapy in patients with anemia due to chronic renal failure by the FDA. As described previously, iron-oxide nanoparticles accumulate in lysosomes (following cellular internalization), in which the low pH breaks the iron oxide core down into iron ions. These ions are then incorporated back into the hemoglobin pool [13]. Interestingly, ferumoxytol is also attractive as a magnetic resonance imaging (MRI) contrast agent because of its magnetic relaxivity properties and because it can be given as a bolus. Moreover, in contrast to gadolinium-based contrast agents, there is no renal elimination of ferumoxytol. Recently, ferumoxytol was investigated as MRI contrast agent to detect cellular inflammation [14,15]. Preliminary results suggest that ferumoxytol enables a detailed characterization of acute MI pathology by detecting infiltrating macrophages and altered perfusion kinetic [6,16].

The present study (Non-invasive myocardial inflammation imaging based on new molecular magnetic resonance imaging contrast agents and methods, NIMINI-3) was performed in order to investigate a) the safety profile and b) the potential "therapeutic" effect of intravenous USPIO-based iron administration regarding infarct healing and short-term ventricular remodeling in patients with STEMI.

2. Methods

2.1. Study population

The present NIMINI-3 study was based on the follow-up of those patients that participated in the previous NIMINI-2 study [17]. NIMINI-2 was a prospective, non-randomized, non-blinded, single agent phase III clinical trial that investigated whether CMR using ferumoxytol allows improved characterization of infarct pathology compared to conventional gadolinium-based necrosis/fibrosis imaging in patients with acute MI [16,17]. Seventeen patients who had experienced recent acute STEMI were included into the NIMINI-2 study between June 2010 and December 2011 and represented the study group (IRON) of the present NIMINI-3 study. The control group (CONTROL) consisted of 22 age-, gender- and cardiovascular risk factor matched STEMI patients that were enrolled between April 2010 and July 2012. Patients were diagnosed according to the universal definition of myocardial infarction and all underwent successful primary PCI with stent placement (within 12 hours of symptom onset) [18]. Exclusion criteria were: prior documented MI, cardiovascular compromise (Killip class ≥ III), severe kidney or liver failure, contraindications to CMR and, for the IRON group, known allergy to iron-containing compounds. The German Federal Institute for Drugs and Medical Devices (BfArM) and the ethics committee of the University of Tübingen approved the study protocol, and all participating patients provided written informed consent.

2.2. CMR data acquisition

ECG-gated CMR studies were performed in the first week after reperfusion (baseline) and at three months after the acute event (follow-up) on a 1.5-T Aera (Siemens Medical Solutions, Erlangen, Germany) using commercially available cardiac software, electrocardiographic triggering, and cardiac-dedicated surface coils. CMR included steady state free precession cine imaging, T2-weighted STIR "edema" imaging and T1-weighted late gadolinium enhancement (LGE) imaging after intravenous contrast administration (0.15 mmol/kg Magnevist®) as previously described in detail [16,17].

2.3. Iron administration

Within 24 hours following the baseline CMR scan, IRON patients received a single intravenous bolus (as recommended by the manufacturer) of 17 mL ferumoxytol (Feraheme™) containing 510 mg elemental iron. Throughout iron infusion, all patients were clinically and electrocardiographically monitored. All IRON patients underwent a multi-parametric CMR study 48 h after intravenous administration of ferumoxytol as part of the NIMINI-2 study protocol as described elsewhere [16,17].

2.4. CMR data analysis

CMR analysis was performed off-line by two experienced readers blinded to the clinical data. Ventricular volumes, ejection fraction and left ventricular mass were derived by contouring endo- and epicardial borders on the short-axis cine images. On the short-axis LGE images, the number of left ventricular segments with positive LGE was first quantified using a standard left ventricular 17-segment model. Classification of myocardial segments with respect to the presence of myocardial damage was made dichotomously based on visual identification of LGE. In addition, the extent of LGE was planimetered on the short-axis contrast images with the use of ImageJ software (National Institutes of Health, Bethesda, Md, USA). Infarct transmurality was assessed on the LGE images using a model dividing each short–axis slice into 12 sectors and each sector into 3 equal circumferential segments (subendocardial, midmyocardial, subepicardial; in total 36 segments per slice). An infarct was considered transmural if all three segments were LGE positive in at least one sector. Endocardial extent of infarction was calculated by counting the number of endocardial segments with positive LGE for each short-axis slice, by summing them up and expressing this sum as percentage from the total number of endocardial segments (12 per slice). Microvascular obstruction (MVO) was defined as the dark area within the infarcted myocardium. In order to evaluate in-plane myocardial salvage after reperfusion, the area at risk (AAR) was determined on one T2-weighted STIR "edema" short-axis slice at the level of maximal edema using the same 36 segment per slice model. Corresponding in-plane baseline infarct size was obtained for the respective LGE short-axis slice. Salvage index was calculated as the difference between AAR and baseline infarct size normalized to AAR.

2.5. Statistical analysis

Continuous variables were expressed as mean ± SD. Skewed variables were expressed as median and interquartile range. Categorical variables were expressed as frequency with percentage. *t*-Student test was used for the between group comparison of patient characteristics and CMR parameters expressed as continuous variables, at the two time points. Paired samples *t*-Student test was used to assess timely changes in CMR parameters within patient groups. Levene's test was used for testing equality of variances. Non-parametric tests were used for not normally distributed variables (Mann–Whitney U test and Wilcoxon signed rank test for repeated measurements). Pearson correlation (r) was used to assess the relationship between different CMR parameters at different time points and their timely change (Δ values). The chi-square test with Yate's correction was used to compare non-continuous variables expressed as proportions. Statistical analysis was performed using SPSS software for Windows (version 18, SPSS, Chicago Illinois, US). A p-value ≤ 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Baseline demographic, clinical and infarct–related patient characteristics for the total study group as well as the IRON and CONTROL groups are presented in Table 1. There were no significant differences in demographic parameters and in the prevalence of cardiovascular risk factors between both groups. In addition, there were no significant differences regarding infarct-related characteristics and extent of myocardial necrosis as measured by the maximum plasma troponin T level between the IRON and CONTROL group. As for iron deficit laboratory tests, no patient demonstrated anemia (hemoglobin levels < 130 g/L) on admission and all patients had red cell mean corpuscular volumes within normal range (80–96 μ^3). Moreover, systemic inflammatory response quantified by maximum C-reactive protein levels did not differ significantly between groups. The ferumoxytol bolus was infused at 3 (IQR 2.5 – 4) days after admission and was well tolerated in all patients without any adverse events.

3.2. Baseline CMR findings

The baseline CMR scan was performed at a median of 3 (IQR 2–3) days from admission. Average LV ejection fraction was 53 ± 10% (IRON) and 54 ± 6% (CONTROL), respectively. As shown in Table 2, there were no significant differences in functional CMR parameters, i.e. baseline LV volumes, ejection fraction and myocardial mass between the IRON and CONTROL patients. On LGE images, all patients showed characteristic enhancement patterns for ischemic myocardial damage. Infarcted tissue comprised on average 27% of the total LV myocardium with 33% circumferential extent from total endocardial surface in both groups. All IRON patients and 77% of CONTROLs had transmural MI at baseline. No significant differences in infarct size, endocardial extent and prevalence of MVO or transmurality of MI were seen at baseline between both groups (Table 2). Moreover, the (in-plane) area-at-risk was similar in both groups (45 ± 14% in IRON and 44 ± 12% in CONTROL; p = NS).