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Perioperative myocardial infarction in elderly patients with hip fracture. Is there a role for early coronary angiography?☆

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ABSTRACT

Objectives: To evaluate the effects of perioperative myocardial infarction in patients with hip fracture referred to multidisciplinary unit at a tertiary teaching hospital.
Methods: 1030 patients with hip fracture underwent troponin measurement, electrocardiogram and echocardiogram at admission, 24 and 48 h after surgery. Exclusion criteria were age < 70 years, severe aortic stenosis, myocardial infarction <30 days, stress cardiomyopathy, renal failure, sepsis, active neoplastic disease. Endpoints were 30-day and 1 year mortality.
Results: Troponin I levels ≥0.5 μg/l were found in 129/1030. 37 of them were excluded according to reported criteria. In the 92 patients included in the study in hospital and 1 year mortality were significantly higher than in controls (12.5% vs 3.5%, p .0012 and respectively 44% vs 16.1% at 12 months, p < .001). 18 patients underwent coronary angiography within 1 week from hip surgery. All had multivessel coronary artery disease. One patient died after angiography. At multivariate logistic analysis age (OR 1.09, 95% CI = 1.01 to 1.19, p = .044) and creatinine values (OR = 7. 55, 95% CI = 1.26 to 45.3, p = .02) were independent predictive factors of 1 year mortality whereas coronary revascularization (OR = 0.15, 95% CI = 0.03 to 0.78, p = .024) was an independent factor associated with improved survival.
Conclusions: Perioperative TnI elevation is associated with a significantly increase in 30-day and 1-year mortality. Severe coronary disease may be suspected in patients with perioperative myocardial infarction after hip fracture surgery. Our study is one of the first providing data on the safety and feasibility of early (inhospital) coronary angiograpy and PCI after hip surgery. Further studies are needed to establish indication of coronary angiography in these patients.

1. Introduction

The incidence of perioperative acute myocardial infarction (MI) in hip fracture has been reported between 6 and 33% [1–2]. Most patients are asymptomatic and diagnosis is made on the basis of ECG changes and/or troponin increase [3–5]. About 70% of perioperative myocardial infarctions occur after surgery while in the remaining 30% diagnosis is made already at hospital admission. This latter group has more frequently a history of previous coronary artery disease [6]. Although criteria suggested by the third universal diagnosis of myocardial infarction should be used [7], with few exceptions [8] diagnosis has been made essentially on the basis of increased troponin values [3–5,9]. Even small troponin increases, above upper 99th percentile of a normal reference population, has been associated with prolonged hospitalization and, more relevant, with increased in-hospital and long-term mortality [3,7]. Several clinical conditions associated with a poor prognosis such sepsis, pulmonary embolism, renal failure and acute respiratory failure may cause isolated troponin increase. This may be a confounding factor in the pathophysiological interpretation of perioperative biomarker increase [10–11]. Troponin I measurements >0.5 μg/l have been considered markers of definite myocardial damage [2] and a relationship between higher values and poor prognosis has been clearly reported [2,12]. ST elevation myocardial infarction occurs in <3% of patients and the most of perioperative myocardial infarctions are referred as type 2 myocardial infarction. Nevertheless at present none of the published

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studies provided information about coronary anatomy in these patients. Intervention in patients with troponin elevation after emergency orthopedic surgery has been essentially limited to intensive post-operative monitoring [13]. Recently the in MANAGE trial [14] patients with postoperative troponin elevation after noncardiac surgery were treated using 110 mg of dabigatran twice daily. A 28% reduction in vascular events was demonstrated at 16 months without an increase in major bleeding. A multidisciplinary team for patients with hip fracture exists in University Hospital Careggi Florence since January 2102. The goal of this group was to stratify the risk before surgery, guide the anesthesiology strategy, prevent and treat early complications of surgery, decrease perioperative mortality and improve life expectancy and quality of life [15]. Aim of this study was to evaluate incidence, clinical characteristics, post surgical management strategy, including early coronary angiography, in patients with significant troponin increase (>0,5 μg/l) after hip fracture. In-hospital and 1-year survival are also reported.

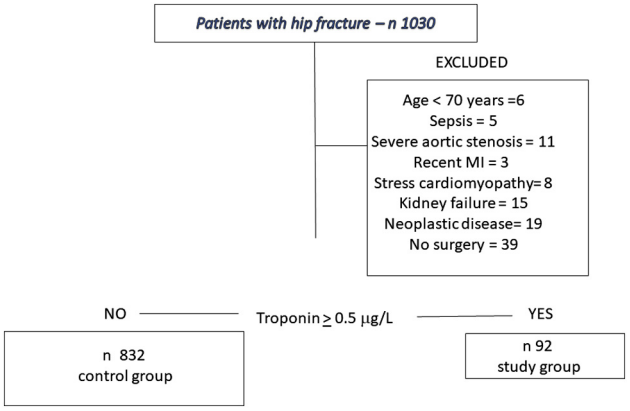

Fig. 1. Flowchart of patients enrolled in the study.

2. Methods

An observational prospective study was conducted at the University Hospital Careggi in Florence, Italy. The study is part of a project of Italian Health Ministry and Regione Toscana - RF-2010-2316600 - and was approved by the Ethical Committee of Regione Toscana. At admission all patients gave signed informed consent to collect and analyze clinical data for research purposes. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

For the preparation of the manuscript the STROBE guidelines were followed. Recruitment occurred between January 2013 and December 2015 and included all consecutive patients admitted to our hospital with diagnosis of hip fracture. At hospital admission, all patients with hip fracture underwent orthopedic examination and radiological investigation, venous line positioning, ECG, laboratory examinations including troponin I assay, and chest X-ray. Troponin and ECG were repeated at the end of surgery and thereafter at 12, 24 and 48 h. Echocardiography was performed in all patients before surgery and repeated within 48 h in all patients with troponin changes. In the study were included patients with perioperative troponin increase and a cut off value ≥0.5 μg/l was used to assess definite myocardial damage in order to increase specificity and limit the risk to include troponin increase due to conditions not related to ischemic injury [2,12]. The highest value was reported for statistical analysis. ECG abnormalities suggesting myocardial ischemia such as ST elevation or depression and finally typical T wave changes were considered. Newly recorded left wall motion abnormalities or abnormalities consistent with ECG changes in absence of prior examinations were considered suggestive of ischemic myocardial damage. Exclusion criteria were age < 70 years, severe aortic stenosis (aortic valve area < 1.0 cm^2), recent myocardial infarction (<30 days), acute stress cardiomyopathy diagnosed according to Mayo clinic criteria [15], renal failure (creatinine clearance <20 ml/min), sepsis, active neoplastic disease and conservative treatment (Fig. 1). Coronary angiography was proposed to patients who had a chance of recovery, on the basis of preoperative functional and cognitive conditions, and in whom a decreased life expectancy other than impaired quality of life was expected due to coronary artery disease. The degree of cognitive impairment was assessed using the The Short Portable Mental Status Questionnaire (SPMSQ) [16] Functional capacity before trauma was evaluated using Barthel scale [17]. End point of the study were 30-day and 1-year mortality.

All patients included in the study were treated with aspirin 100 mg/day. Dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 md daily) was prescribed in patients underwent percutaneous coronary revascularization. Patients in atrial fibrillation resumed ongoing anticoagulant treatment 4–5 days after hip surgery, low molecular weight heparin was administered as full bridge therapy or at DVT prophylactic dose according to the risk profile in patients with AF. Three patients underwent coronary revascularization resumed warfarin with ongoing dual antiplatelet therapy. LMWH at DVT prophylactic dose was prosecuted for at least 35 days in patients in sinus rhythm. After percutaneous revascularization major bleeding was evaluated according to criteria proposed by the International Society of Thrombosis and Haemostasis [18].

2.1. Statistical analysis

Categorical variables are reported as frequency and percentage. Values for continuous variables were given as the mean (±SD). Categorical variables were compared using the χ^2 test or the Fisher exact test. Thirty six patients comparable for age, sex, left ventricular ejection fraction and without cognitive impairment were matched in a 2:1 ratio with the 18 patients underwent coronary angiography. Two-tailed Kaplan-Meier curves were used for the survival analysis. Differences between groups were compared using Log-Rank test. After the univariate analyses, a logistic multivariable regression analysis was performed to identify independent predictors for mortality. Because of multiple testing, only variable with a two-sided $p < .05$ in the univariate analysis were accepted for the model. Statistical analysis was performed with the use of the SPSS statistical software program (SPSS Inc., Chicago, IL, USA). A probability value of <.05 was considered to be statistically significant.

3. Results

1030 consecutive patients with hip fracture were referred to the Trauma Centre of the University Hospital Careggi Florence between January 1st 2013 and December 31st 2015. Following the criteria reported in the Methods section, 105 patients were excluded from the study (37 had increased troponin levels). The study group was composed by 92 patients (63 women and 29 men, mean age 86.7 ± 7.8 years) who had at least one perioperative troponin level ≥ 0.5 μg/l suggesting definite myocardial damage. One third of them had a TnI increase already at hospital admission. The remaining 832 patients became the control group. Among these 134 patients recalled retrospectively from electronic medical records had minor TnI increase (0.10–0.49 μg/l). In these patients in hospital mortality was 4.9% not significantly higher than in patients without troponin increase.

Clinical characteristics of patients are reported in Table 1. History of coronary artery disease, diabetes mellitus, peripheral artery disease was significantly more frequent in patients with perioperative myocardial infarction than in controls. Hip surgery was performed within 48 h from hospital admission in 54/92 (59.3%) of patients in study group in comparison to 594/832 (66%) of control group. Blood losses were not different in the two groups.

In our study 18 out of 92 patients underwent early coronary angiography. The procedure was performed during hospitalization, on average within 4 days after hip surgery. All patients were found to have severe coronary disease (stenosis ≥70% of two or three major epicardial vessels, proximal LAD was involved in 18/18 patients). Patients referred for coronary angiography were younger (81.9 vs 87.5 years, $p = .02$) and had no significant cognitive impairment (SPMSQ with <5 errors: 0/18 vs 29/74, $p = .05$). The two groups did not differ with regard to gender, history of ischemic heart disease, hypertension, peripheral vascular disease or diabetes mellitus, LVEF and finally pulmonary artery pressure. Electrocardiographic and/or echocardiographic abnormalities were not significantly more frequent in patients referred for angiography (15/18–82% vs 594/832–66%). Creatinine values were significantly lower in patients underwent angiography. One patient with 90% ostial left main stenosis died of refractory asystole during the procedure. No other complications were observed, in particular we did not find any significant bleeding from the orthopedic surgical site neither major bleeding according to the International Society of Thrombosis and Haemostasis criteria [18]. Percutaneous revascularization was performed at the end of diagnostic procedure in 15 patients while 2 underwent surgical revascularization within two weeks.

11 of the 92 patients (12.5%) died during hospitalization in comparison to 30/832 (3.5%) in control group ($p = .003$). They were older (89.4 vs 86.4 years), however the difference was not statistically significant. Similarly a higher mortality trend was found in males (50% vs 32%). Cognitive impairment was related to a significantly higher mortality

Table 1
Clinical characteristics of patients included in the study.

	AMI n = 92	Controls n = 832	p
Male/female (%)	31	29	ns
Mean age (SD)	86.7 (8.8)	84.0 (8,0)	.0017
Time to surgery < 48 h (%)	59.9	66	ns
Preoperative Hb (g/dl)	11.8 ± 1.5	11.6 ± 1.8	ns
Post-operative Hb (g/dl)	9.3 ± 1.4	9.4 ± 1.5	ns
Length of hospitalization (days) mean (SD)	14.4 (6)	13.1 (3.4)	.0012
CAD (%)	34	15.7	<.0001
Heart failure (%)	13	7	ns
Diabetes (%)	38	8	<.0001
Hypertension (%)	72	63	ns
Dementia (SPMSQ > 5 errors) (%)	34	32	ns
Atrial fibrillation (%)	15	8	.021
Peripheral vascular disease (%)	30	4	<.0001

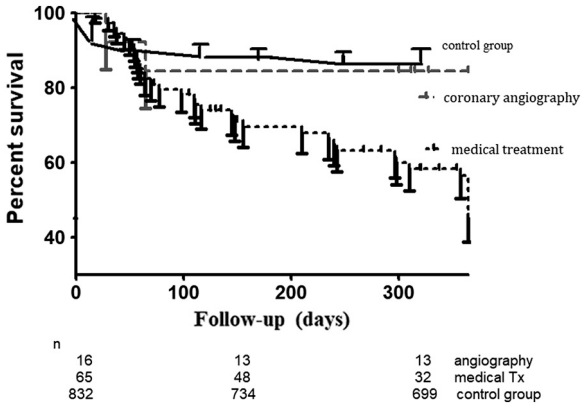

Fig. 2. Survival in control group, patients undergone coronary revascularization patients treated with medical therapy and overall survival after perioperative AMI.

(p = .003). Finally serum creatinine concentrations were higher in patients who died during hospitalization.

Thirty-five out of 81 patients (44%) with perioperative myocardial infarction that were discharged alive from hospital died at one-year in comparison to 133/832 (16.1%) of control group (p < .0001). Death in study group was cardiac in 32 patients, non-cardiac in 9 (3 related to late septic complications, 3 to stroke, 3 to other causes). We did not find significant differences in long-term survival between patients with or without ECG and/or echocardiographic ischemic changes. None of patients discharged alive from hospital underwent invasive evaluation during follow-up period. 13/16 patients (81%) that underwent coronary angiography and revascularization in the early postoperative period after hip fracture were alive at one year follow-up in comparison to 31/65 (42%) treated with medical therapy alone (Fig. 2). Multivariate logistic analysis showed that both in the whole population and in patients discharged alive after surgery age (OR = 1.09, 95% CI = 1.01 to 1.19, p = .044 and respectively OR = 1.11, 95% CI = 1.01 to 1.22, p = .041) and creatinine values (OR = 7.55, 95% CI = 1.26 to 45.3, p = .02 and respectively OR = 4.88, 95% CI = 1.04 to 22.94, p = .04) were independent predictive factors of 1 year mortality whereas coronary revascularization (OR = 0.15, 95% CI = 0.03 to 0.78, p = .024 and respectively OR = 0.06, 95% CI = 0.02 to 0.72, p = .026) was an independent factor associated with improved survival. Only in patients discharged alive from hospital a preserved cognitive function was associated with a better outcome (OR = 0.21, 95% CI = 0.05 to 0.89, p = .034).

A case–control matching was made to better understand the effects of coronary revascularization. Thirty six patients comparable for age, sex, left ventricular ejection fraction and without cognitive impairment were matched in a 2:1 ratio with the 18 patients underwent coronary revascularization. At 1 year survival were respectively 73% in patients underwent coronary revascularization and 44% in those who did not. No significant differences were found between the two groups regarding other parameters considered (Table 2).

4. Discussion

Troponin increase, even after adjustment for confounding factors, has been demonstrated to be an independent risk factor for early and long term mortality as well as for longer hospital stay and higher need for institutionalization [12,19–21]. The relationship between troponin increase and myocardial damage however has been questioned by some authors [8,12,21].

According to different diagnostic criteria the incidence of perioperative acute myocardial infarction in patients hospitalized for hip fracture varies from 6 to 35% [1,12,21]. The diagnosis of perioperative myocardial infarction is often underestimated since most patients are asymptomatic and diagnosis is made on the basis of ECG changes and/or troponin assay [2,19–23]. Moreover, in these patients perioperative myocardial infarction was often the first clinical manifestation of coronary heart disease.

In a retrospective study from Olmsted County, Minnesota [3] incidence of perioperative myocardial infarction was 13.8% among 1212 consecutive patients admitted for hip fracture, Most events occurred in the first 48 h after surgery. In-hospital mortality was 14.4% while 1-year survival was 60.5%. The majority of patients did not experience ischemic symptoms and cardiac biomarkers were required for the diagnosis.

Hietala et al. [4] observed an increase of TnT in 35.5% of patients with hip fracture. Nearly half of these patients showed troponin increase before surgery. A troponin T increase >0.15 μg/l was also predictive of 30-day mortality (24% v 17% in patients with smaller troponin increases). In this study increase of troponin was the only independent predictor of 30-day mortality. Fisher et al. [12] showed that a perioperative increase of troponin I > 0.06 μg/l was an independent determinant of length of hospital stay and need for long term residential care facilities. A troponin I > 1 μg/l was predictor of all-cause mortality with 98% specificity and 89% negative predictive value. Recently Vallet et al. [8] reported that patients with acute coronary syndrome, diagnosed on the basis of ECG changes associated with troponin increase, but not those with isolated troponin rise had poor long term prognosis after hip fracture surgery. A six month combined end-point of death and/or re-hospitalization was found in 44% of acute coronary syndrome patients in comparison to 29% in patients

Table 2
Case – control comparison between patients underwent or not to coronary angiography.

	Case (n = 18)	Controls (n = 36)	p
M/F (%)	70	69	.92
Age mean (SD)	85 + 8	86 + 5	.71
Peak preoperative TnI (mg/dl) median	0.74	0.50	.86
Peakpostoperative TnI (mg/dl) median	1.530	1.395	.55
Preoperative Hb (g/dl)	11.8 ± 0.9	11.9 ± 1.6	.80
Post-operative Hb (g/dl)	9.6 ± 1.3	9.5 ± 1.6	.81
RBC transfusion (%)	61	56	.77
LVEF	50 ± 6	51 ± 8	.64
Pulmonary artery pressure (mm Hg)	38 ± 13	35 ± 11	.37
Creatinine (mg/dl)	0.9 ± 0.3	1.0 ± 0.3	.25
B-blockers, (%)	88	91	.76
Aspirin, (%)	100	94	.68
AT1/ACE inhibitors, (%)	72	26	.23
Statins, (%)	88	72	.60
Oral anticoagulants, (%)	16	25	.74
CAD, (%)	38	30	.73
Diabetes, (%)	38	36	.50
Hypertension, (%)	70	63	.36
Peripheral artery disease, (%)	36	32	.75
Atrial fibrillation, (%)	16	22	.66
1 year mortality (%)	27	56	.041

AT1 = angiotensin 1 receptor blockers, ACE = angiotensin converting enzyme inhibitors, CAD = coronary artery disease, LVEF = left ventricle ejection fraction.

with isolated troponin increase and 26% in the control group. In their study, only 1 patient with acute coronary syndrome underwent coronary angiography. Few investigation evaluated the effects of cardiology intervention, essentially limited to intensive post-operative monitoring. Chong et al. [13] did not find any significant difference in 1 year mortality between patients were randomized to cardiology care versus standard ward management. Multivariate predictors of 1 year mortality were post-operative troponin elevation OR 4.3 (95% CI, 1.1–16.4, p = .035), age OR 1.1 (95% CI, 1.02–1.2, p = .016) and number of comorbidities OR 2.1 (95% CI, 1.3–3.5, p = .004). Recently MANAGE trial [14] randomized 1754 patients with postoperative troponin elevation after non-cardiac surgery to dabigatran 110 mg twice daily or placebo. At a follow-up of 16 months, dabigatran induced a significant reduction of a composite end-point (occurrence of a major vascular complication, a composite of vascular mortality and non-fatal myocardial infarction, non-hemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism). Mean age was 45 years, 33% had orthopedic surgery finally an history of coronary disease was present in 14% at enrollment. Only 14 patients (<1%) underwent coronary angiography.

Surgical treatment of hip fracture within 48 h from trauma has been reported to be associated with lower mortality, higher probability of functional recovery and decrease of complication rate associated with prolonged immobilization [23–25].

Overall one third of patients had a significant increase of troponin already at hospital admission [4]. Although ESC and AHA/ACC guidelines on cardiovascular assessment and treatment in non-cardiac surgery suggest that urgent treatment should not be deferred in patients with acute coronary syndromes [24–26] there are no data regarding the need for clinical stabilization in high risk patients with hip fracture and preoperative troponin increase.

Results from the present study from a multidisciplinary hip fracture team showed a 9.6% incidence of perioperative myocardial infarction. A cut-off value of troponin I (≥0.5 μg/l), suggestive of definite myocardial damage [2,12], was used to increase sensitivity and specificity of the diagnosis. This may account for the lower incidence of perioperative myocardial in comparison to other studies [22–24]. In hospital and 1 year mortality were significantly higher in patients with troponin increase than in controls (12.5% vs 3.5%, p = .0012 and 44% vs 16.1%, p < .0001, respectively). We did not find long-term survival differences between patients with or without ECG and/or echocardiographic ischemic changes and our data confirm that myocardial damage assessed by increased biomarker levels is an independent poor prognostic factor in patient undergoing hip fracture surgery.

At present ESC or AHA/ACC guidelines do not provide any suggestion about early invasive evaluation in patients with perioperative myocardial infarction after non-cardiac surgery [27–28]. Despite the demonstration of a clear relation between decreased long term survival and troponin increase after hip fracture surgery and other non cardiac surgical procedure, it is still debated the pathophysiological mechanism related to troponin increase (ischemic or non-ischemic cause). None of these studies however evaluated coronary anatomy. Several mechanisms may favor cardiac damage in the perioperative period [29–30], but the demonstration of critical lesions in all patients undergoing coronary angiography in our study may suggest that myocardial necrosis is mainly associated with severe multivessel coronary artery disease thus justifying the poor long-term outcome. In patients discharged alive after revascularization mortality at 1 year was lower than 20%, however our investigation was not addressed to demonstrate the absolute benefits of coronary revascularization after perioperative myocardial infarction, since the study did not have numerical power. The main purpose of present paper was to evaluated the feasibility and safety of early coronary angiography in patients with perioperative myocardial infarction after hip fracture surgery in order to clear still debated pathophysiologic mechanisms. We acknowledge that a selection bias is likely since coronary angiography was avoided in frail patients, defined as subjects with moderate to severe functional and cognitive impairment, patients with a poor prognosis irrespective of the presence and treatment of coronary artery disease. However a case control matching, in which patients with cognitive impairment were excluded from analysis, confirmed the different survival rates between the two groups. Therefore results from present investigation may be useful to open a discussion about the proper management of perioperative myocardial infarction in non-cardiac surgery.

5. Limitations of the study

The main limit of present study is the small number of enrolled patients. In particular only 20% underwent early coronary angiography. Therefore results do not allow to draw strong conclusions. On the other hand the finding that all patients undergoing coronary angiography had multivessel coronary artery disease, a data never reported before, may give useful pathophysiological information and offer indications to design further studies. Although the population included in the study is a high risk elderly group, >25% may be successfully revascularized with improvement in quality of life and life expectancy. The effects of coronary revascularization on survival are effectively weakened by a selection bias and need confirmation by large multicenter registries. More information are required also on the safety of the procedure. Further studies, including randomized studies, may allow to identify clinical criteria for an early invasive strategy in patients with perioperative myocardial infarction after hip surgery. Another point to be outlined is that although even small troponin increases have been related with increased in-hospital and long-term mortality, in our prospective study an arbitrary cut off value ≥0.5 μg/l was used in order to limit the risk to include troponin increase due to conditions not related to ischemic injury [2,12].

6. Conclusions

Perioperative myocardial infarction ascertained by significant troponin increase is associated with a poor in hospital and long term prognosis in patients undergoing surgery for hip fracture. When coronary angiography was performed severe multivessel disease was consistently present. Early invasive treatment with percutaneous revascularization might significantly improve long term survival in selected patients. Further studies are needed to assess the indications to an early invasive strategy in patients with perioperative MI after surgery for hip fracture.

Declarations of interest

None.

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