International Journal of Surgery 33 (2016) S119–S125

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Original research

Resection of hepatocellular carcinoma in elderly patients and the role of energy balance

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ARTICLE INFO

Article history:
Available online 21 June 2016

Keywords:
Statins
Coenzyme Q10
Liver failure
HCC
Elderly patients

ABSTRACT

Introduction: Progressive functional impairment with age has a significant impact on perioperative risk management. Chronic liver diseases induce a strong oxidative stress; in the elderly, in particular, impaired elimination of free radicals leads to insufficient DNA repair. The events associated with a weak response to growth factors after hepatectomy leads to a decline in liver regeneration. Hypercholesterolemia is highly prevalent in the elderly, which may alter the coenzyme Q10 (CoQ) levels and in turn the cellular energy balance. This condition is commonly treated with statins. The aim of this study is to investigate the role of preoperative cellular energy balance in predicting hepatocellular carcinoma (HCC) postresection outcomes.

Materials and methods: In a 5-year period (2009–2013), elderly patients with hypercholesterolemia, cardiovascular disease, and diabetes mellitus, undergoing HCC resection, were recruited and grouped by age (<75 and ≥ 75 years old). All patients were previously treated with statins. The risk factors associated with hospital morbidity/mortality and prolonged length of stay (LOS) were evaluated.

Results: Forty-five elderly patients were recruited and grouped according to their treatment: Group 1 (n = 23) was treated with statins alone (control group), whereas Group 2 (n = 22) was treated with statins and a CoQ analogue, 3 weeks from the surgery and at least a month later (experimental group). The majority of our patients were treated with atorvastatin [n = 28 (53.84%)] and the minority with simvastatin [n = 17 (32.69%)], 20 mg/day, for at least 3 years before the surgery. Perioperative mortality was observed in one patient of Group 1 (4.3%). Morbidities were noted in 13 patients of Group 1 (56.5%) and four patients of Group 2 (18.2%). The control group showed delayed functional recovery, muscle weakness, increased infection rate, and pleural effusion due to prolonged bed rest (hospital stay 13 days (7–19) vs. 8.5 days (5–12)), compared with the experimental group. The overall survival at 5 years was similar for both groups (n = 10 patients (43%) in Group 1 vs. n = 10 patients (45%) in Group 2).

Conclusion: In the elderly population, survival is closely linked to postoperative morbidity and mortality. In our study, prolonged LOS was found to be related to delayed bioenergetic recovery. When limited, risk factors such as infections, neutropenia, and red blood cell transfusions could lower LOS and mortality of

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http://dx.doi.org/10.1016/j.ijsu.2016.06.020

elderly patients with HCC. Higher age was associated with greater postoperative morbidity and successful hospital stay.

1. Introduction

Age is a multifactorial process resulting in changes at the molecular, cellular, and tissue level; it leads to physiological inefficiency, which may favor related pathological events [1]. Moreover, the state of senescence is accompanied by decreased or no expression of antioxidants, resulting in significant oxidative stress [2]. During liver surgery, hepatic ischemia triggers a metabolic change toward anaerobic activities, which gradually arrests adenosine triphosphate (ATP)-dependent cellular mechanisms. The ATP depletion, acceleration of glycolysis, increased lactate production, and imbalance in H^+, Na^+, and Ca^{2+} exert harmful effects on hepatocytes [3]. Coenzyme Q10 (CoQ) acts as an antioxidant and stabilizes the cellular membrane; it is a key player in mitochondrial respiration and energy production. Alterations in mitochondrial CoQ content are associated with severe dysfunctions [4].

Studies have shown that statins inhibit the conversion of 3-hydroxy-3-methyl-glutaryl (HMG)-CoA to mevalonate, a precursor of cholesterol and CoQ. The decrease in mitochondrial CoQ levels is associated with a moderately higher rate of cell death, possibly because of the increase in DNA oxidative damage and decrease in ATP synthesis. Several trials [5] have evaluated the impact of statins on hypercholesterolemia and cardiovascular events in adults, but only few have focused on an elderly population. Moreover, studies on the so-called “oldest old,” also known as “very elderly,” are lacking in this scientific field.

Hypercholesterolemia is highly prevalent in the elderly; statins are known to reduce cardiovascular events in patients with coronary artery disease and high levels of low-density lipoprotein cholesterol (LDLC). Statins exert lipid-lowering effects, confirming the correlation between mortality and a decrease in low-density lipoprotein (LDL) levels [5]. Recent research has focused on the antioxidant effects of statins in different cellular compartments and plasma lipoproteins [6].

For the first time, Folkers described the decreased CoQ10 levels in the plasma of cardiopathic patients after lovastatin treatment and of the rat liver [7,8]. Moreover, alterations in the mitochondrial Q10 content has been linked to further severe dysfunctions [9]. Several recent studies on humans have shown that different types of statins can lead to a parallel decrease in the levels of both coenzyme Q10 and cholesterol in plasma [5]. Many trials have evaluated the impact of statins on hypercholesterolemia and cardiovascular events in adults. However, only few have focused on elderly subjects [5], and studies on the so-called “oldest old” are lacking entirely.

Hepatocellular carcinoma (HCC) is the most common cancer in the elderly [10,11]: in the past decades, particularly in Western countries, the number of geriatric patients undergoing liver surgery has increased significantly [12,13]. Furthermore, in the elderly, impaired elimination of free radicals implies insufficient DNA repair. The aforementioned events associated with a diminished response to growth factors after hepatectomy lead to a decline in liver regeneration [14].

In elderly patients undergoing major surgery with a high risk of bleeding, the limited functional reserve may damage their vital organs due to inadequate perfusion; further, the most relevant side effect due to temporary vascular occlusion of the hepatic pedicle clamping is liver ischemia. The reperfusion process exacerbates the liver injury that occurs during the ischemia. This ischemia–reperfusion injury involves inflammation mediated by Kupffer cells (KCs)/neutrophil activation, and release of cytokines and reactive oxygen species (ROS), which accelerate the lysis of hepatocyte and sinusoidal endothelial cells (SECs) [15].

A decrease in liver weight, blood flow, and regenerative response to advanced age [16,17] may predispose elderly patients to a higher risk of postoperative liver failure (PLF) after a major hepatectomy, particularly in the presence of a concomitant cirrhosis. In fact, in a recent study, poorer functional hepatic regeneration was observed in elderly patients after major hepatectomy. The authors concluded that surgery should not be recommended as a treatment option in this age group [18].

The aim of our study is to investigate the impact of preoperative cellular energy balance on postoperative outcomes in elderly patients undergoing HCC resection.

2. Material and methods

Between January 2009 and October 2013, we performed an open-label, prospective, and parallel-group study approved by the Annunziata Hospital Ethics Committee, in accordance with the Declaration of Helsinki and the Guideline for Good Clinical Practice. Surgeons of the Department of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, University of Bologna; Department of Surgery, Annunziata Hospital of Cosenza; and Department of Medical and Surgical Sciences of University “*Magna Graecia*” of Catanzaro participated in the study.

Before the study commenced, all participants provided written informed consent.

The inclusion criteria were elderly patients (>65 years old); body mass index of 25–30; presence of cardiovascular diseases, hypertension, diabetes mellitus, and dyslipidemia; treatment with statins (for at least 3 years from the time of surgery), and candidates for HCC liver resections.

The exclusion criteria were a body mass index >30, no statin treatments, and no ischemic cardiovascular diseases.

All patients were stratified as follows: preoperative data of viral serological test, laboratory test, evaluation of the severity of liver dysfunction (Child–Pugh and Model for End-Stage Liver Disease (MELD) scores) [19–21], evaluation of comorbidities according to the Charlson comorbidity score, transabdominal ultrasound, and computed tomography (CT) or magnetic resonance imaging (MRI). Patients with normal liver function were excluded as well.

For each patients, the following data were collected: history of smoking, hypertension, diabetes mellitus, dyslipidemia, liver disease with portal hypertension and obesity, hepatitis, blood biochemical findings, serum levels of α-fetoprotein (AFP), and preoperative liver function (assessment with the Child–Pugh and MELD scores).

We defined the anatomical liver resections based on the Couinaud classification [21–23]. Major hepatectomy was defined as a resection of >3 segments, whereas minor hepatectomy was defined as a resection of <3 segments [23,24]. The intraoperative ultrasound (IOUS) evaluation was routinely performed to confirm the characteristics of HCC, determine the association between vascular