Investigating the Effect of a Single Infusion of Reconstituted High-Density Lipoprotein in Patients with Symptomatic Carotid Plaques

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Background: Elevation of plasma high-density lipoprotein (HDL) cholesterol concentration reduces cardiovascular mortality and morbidity. HDLs have been shown to possess acute anti-inflammatory, antioxidant, and antithrombotic properties. We hypothesize that HDL therapy can acutely alter local and systemic manifestations of plaque instability.

Methods: Forty patients with early symptomatic carotid disease were randomized to either receive reconstituted HDL (rHDL) 40 mg/kg ($n = 20$) or placebo ($n = 20$). Carotid endarterectomies were performed 24 hr later. Plaques were obtained intraoperatively and used for measurement of thrombomodulatory genes expression. Plasma samples were collected before the infusion, 24 and 48 hr later to measure changes in systemic markers of plaque instability.

Results: No significant differences were noted in thrombomodulatory genes expression between the 2 groups. Systemic levels of tissue factor, matrix metalloproteinase 9 (MMP-9), and monocyte chemotactic factor-1 (MCP-1) were significantly reduced in the rHDL group. However, the effects on MMP-9 and MCP-1 were abolished in the immediate postoperative period. Although rHDL did not affect plasma interleukin-6 levels 24 hr following the infusion, it prevented the significant postoperative elevation seen in the placebo group.

Conclusions: A single infusion of rHDL can acutely alter plasma biomarkers associated with plaque instability and cardiovascular morbidity.

INTRODUCTION

Carotid plaque instability is at least partly responsible for the high stroke recurrence rate following an ischemic cerebrovascular event. Interestingly, the risk falls rapidly with time as the plaque heals. Therefore, early intervention is vital to prevent further neurological complications. Although good long-term results have been shown with pharmacological therapy with regard to plaque stabilization and event recurrence, the acute effects remain questionable. Therefore, surgical removal of the plaque by means of a carotid endarterectomy (CEA) remains the best option for acute protection against further embolization or vessel occlusion. Despite the significant benefit gained from early CEA in terms of prevention of event recurrence, surgical endarterectomy has been associated with relatively higher mortality and morbidity rates

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when compared with delayed (6–8 weeks post event) CEA and that for asymptomatic carotid disease.[1] This is thought to be related to plaque instability and the acute activation of inflammatory mediators.[2] It is therefore important to identify pharmacotherapeutic agents that could acutely stabilize plaques and/or modify their activity. This could result in improving surgical outcomes and reducing the rate of event recurrence while patients are awaiting surgery.

High-density lipoproteins (HDLs) and their reconstituted particles have several acute antiatherogenic properties that would make them potential therapeutic candidates. HDLs' ability to induce reverse cholesterol transport (RCT) was one of the earliest recognized properties, and many of the antiatherogenic functions were attributed to this process. More recent work showed that HDLs and their reconstituted particles have other antiatherogenic effects independent of RCT.[3] These include antioxidant effects, anti-inflammatory effects, antithrombotic effects, and modification of endothelial function.[4–7]

Many strategies have been used to raise plasma HDL concentration including intravenous administration of reconstituted HDL (rHDL).[8] This treatment modality has been shown to be safe and effective in raising plasma HDL levels.[9,10] rHDL has been shown to effectively induce cholesterol reflux and inhibit proinflammatory changes and platelet aggregation.[11–13] In the ERASE (Effect of Reconstituted HDL on Atherosclerosis and Efficacy) trial, it was shown that short-term rHDL infusions can induce plaque regression within 4 weeks of treatment in acute coronary syndrome patients.[10] Additionally, rHDL therapy was associated with significant improvement in plaque characterization indices. More recently, Shaw et al.[9] tested the effects of a single high-dose rHDL (80 mg/kg) infusion on plaques from claudicants undergoing superficial femoral artery atherectomy. They have demonstrated that rHDL infusion could lead to acute reduction in plaque lipid content and both local and systemic measures of inflammation. Theoretically, this suggests that rHDL may represent a useful agent for patients with acute ischemic cardiovascular (CV) events, but more work is needed to evaluate the acute effects on other parameters and markers of disease activity.

Our study aimed to examine the acute effects of a low-dose (40 mg/kg) infusion of rHDL, the recommended tolerable dose in humans, to modulate carotid plaque characteristics 24 hr after infusion, and systemic biomarkers of inflammation 24 and 48 hr after infusion.

METHODS

Study Design and Patient Cohort

Patients were recruited from the stroke unit or the open access transient ischemic attack clinic at St George's Hospital NHS Trust, London, UK. All patients with symptomatic carotid artery stenosis that would benefit from urgent intervention (carotid stenosis >50%) were included in the trial. All patients had a carotid territory neurological event less than 1 month before CEA and trial participation. Patients' symptoms were determined by a consultant neurologist following a brain computed tomography and magnetic resonance imaging.

All patients underwent a preoperative duplex ultrasound (7.5-MHz linear transducer, SONOS 2000; Hewlett-Packard, Andover, MA) assessment by an experienced vascular technologist for plaque classification (Gray-Weale system) and quantification of degree of stenosis.

Forty patients with early symptomatic (within 1 month) carotid artery disease undergoing CEA were recruited and randomly allocated to one of the 2 groups. The first group received a preoperative infusion of rHDL at a concentration of 40 mg/kg. The second group received an equivalent volume of phosphate buffered saline (PBS). CEA was performed 24 hr later. Plaques were retrieved intraoperatively and preserved in RNAlater (Ambion, Paisley, UK). Plasma samples were collected before the infusion (P1), then 24 (P2) and 48 (P3) hours after the infusion (Fig. 1).

This trial has conformed to the principles outlined in the Declaration of Helsinki. Before consenting to enroll in the trial, all patients were provided with an invitation to participate. This invitation detailed the purpose of the study and the content of the infusion they would receive, detailing that rHDL is considered a plasma product with an equivalent safety profile to other blood products. All patients were given the right to withdraw their consent at any time during or after the trial. None of the volunteer patients refused to join the trial or withdrew consent after agreeing to participate.

The study design was approved by the Local Research Ethics Committee and registered with Clinicaltrials.org (Unique Identifier: NCT00822302).

Inclusion Criteria

All symptomatic patients (symptoms <1 month) with confirmed internal carotid artery stenosis >50%, who are listed for urgent CEA.