

RESEARCH ARTICLE



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Establishing low-density lipoprotein apheresis tolerability in patients with prior anaphylactoid reactions to lipoprotein apheresis using magnesium sulfate

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Abstract

Background: Lipoprotein apheresis (LA) tolerability is a key factor for the utilization of this therapy. Common reactions to LA are hypotension and nausea. Serious reactions include severe hypotension and anaphylactoid reactions (0.13%-1.3% and 0.2%-0.4%, respectively). The bradykinin response drives these reactions and can worsen with the use of angiotensin-converting-enzyme inhibitors. Efforts to mitigate these reactions are necessary for the tolerability of LA with a dextran sulfate-adsorption (DSA) system.

Materials and Methods: In an effort to increase apheresis tolerability, seven patients at The University of Kansas, Department of Clinical Pharmacology, who had prior anaphylactoid reactions (defined as general cutaneous flushing, nausea/vomiting, tongue swelling, lightheadedness, and hypotension) to the DSA despite pharmacologic intervention, were treated with pre-LA intravenous magnesium adapted from a protocol developed by co-author Eliaz. This protocol consists of 1.5 g of magnesium sulfate administered over 45 minutes. All seven patients were treated with intravenous magnesium sulfate immediately before LA.

Results: No episodes of anaphylactoid reactions during LA have been reported to date.

Conclusions: Magnesium infusion before DSA can be utilized to establish tolerability in patients with prior anaphylactoid reactions to LA. Proposed mechanisms include temporary stabilization of the negative-positive interactions of the dextran sulfate filter leading to a reduction of circulating bradykinin, reduction of nitric oxide, and reduction of the sympathetic response to LA.

KEYWORDS

bradykinin, dextran sulfate, familial hypercholesterolemia, lipoprotein apheresis, lipoprotein(a)-hyperlipoproteinemia

1 | INTRODUCTION

Lipoprotein apheresis (LA) is indicated as a lipid-lowering therapy in patients with homozygous familial

hypercholesterolemia (HoFH), heterozygous FH (HeFH), lipoprotein (a) [Lp(a)] hyperlipoproteinemia, and focal segmental glomerulosclerosis (FSGS).¹⁻³ The estimated incidence is 1 in 200 to 500 for heterozygotes and 1 in

160 000 to 1 000 000 for homozygotes, 1 in 5 for elevated Lp(a) and the research surrounding these populations for screening and intervention continues to expand.⁴ Tolerability is a critical factor for the utilization of LA. The most common anaphylactoid reactions to LA are hypotension, nausea, and vomiting.⁵ More serious adverse effects, including severe hypotension and allergic/anaphylactoid reactions, occur more rarely (0.13%-1.3% and 0.2%-0.4%, respectively).⁵ Proposed mechanisms of anaphylactoid reactions to LA have been described in regard to the generation of bradykinin and subsequent activation of the pro-inflammatory cascade. This reaction occurs through contact activation of plasma kallikrein (depicted nicely by Naudin et al,⁶ in Figure 1) and is the reason for contraindication of angiotensin convertase enzyme (ACE) inhibitors during LA.^{7,8} Even without ACE inhibitors, patients can still experience anaphylactoid reactions to LA. Tolerability of LA and continuation of therapy depend on the successful mitigation of these reactions.

This is especially important as the US market now has a single manufacturer of apheresis devices, the Liposorber System LA device made by Kaneka Medical Products, which uses dextran sulfate adsorption (DSA) as the

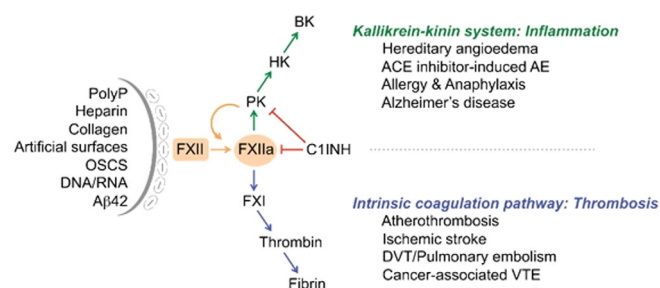


FIGURE 1 Factor XII contact activation and contact system-mediated thrombotic and inflammatory disorders. FXII binding to negatively charged surfaces leads to the active protease FXIIa. Activators that initiate FXIIa formation in vivo include polyphosphate (polyP), heparin, collagen, nucleic acids (DNA and RNA), oversulfated chondroitin sulfate (OSCS), amyloid β peptide 1-42 ($A\beta_{42}$), and artificial surfaces (eg, glass or some polymers). FXIIa activates the intrinsic coagulation pathway through FXI, leading to thrombin and fibrin formation. Alternatively, FXIIa activates the kallikrein-kinin system via plasma kallikrein (PK), which releases the proinflammatory mediator bradykinin (BK) from high-molecular-weight kininogen (HK). PK reciprocally activates FXII in a positive feedback loop. The main inhibitor of contact system proteases FXIIa and PK is C1 esterase inhibitor (C1INH). The contact system contributes to an array of proinflammatory and procoagulant disorders. ACE, angiotensin-converting enzyme; AE, angioedema; DVT, deep vein thrombosis; VTE, venous thromboembolism. This figure is reproduced with licensing permission by publisher Georg Thieme Verlag KG through Copyright Clearance Center (<http://www.copyright.com/>) from Naudin et al⁶

mechanism of LA. The molecular mechanism of LA with DSA involves negatively charged cellulose bound dextran sulfate binding to and eliminating positively charged lipoproteins containing apolipoprotein B-100, which includes low-density lipoprotein (LDL), intermediate-density lipoprotein (IDL), very low-density lipoprotein (VLDL), Lp(a) and a host of inflammatory markers (C-RP, galactin-3, Interleukin-6...).⁹⁻¹¹ The negatively charged cellulose bound dextran sulfate is the nidus for contact activation. A standardized approach to pre-treatment before an LA session can help establish the tolerability of this therapy. One such method, developed by Dr Isaac Eliaz at his medical center in Santa Rosa, CA, adapted and described here, was applied in a case series of patients undergoing LA. Specifically, seven of these patients, the patients being treated at The University of Kansas, experienced prior anaphylactoid reactions to the DSA system and now tolerate full LA sessions after utilizing pre-LA infusion of magnesium.

2 | METHODS

The seven patients with prior anaphylactoid reactions (defined as general cutaneous flushing, nausea/vomiting, tongue swelling, lightheadedness, and hypotension) were initially started on LA with the Kanaka's DSA device but had to switch to the B. Braun Medical's heparin-induced extracorporeal LDL precipitation (HELP) system due to anaphylactoid reactions. The HELP device is no longer available after being pulled from the US market. These patients were transitioned back to the DSA system out of necessity.

The mean age of the seven patients that experienced an anaphylactoid reaction was 66 years of age. Of these 7 patients, 6 are female and 1 male. The seven who had the anaphylactoid reaction were being treated for atherosclerotic vascular disease, and indications for apheresis include FH (1), FH with elevated Lp(a) (2), elevated Lp(a) (2), coronary artery disease with statin intolerance (1), and severe statin intolerance (1). Further patient history is outlined in Table 1. All seven patients previously tolerated LA with the HELP system. No mitigating interventions to establish tolerability were undertaken prior to the initial transfer to the HELP system. Prior anaphylactoid reactions to the DSA system included general cutaneous flushing, nausea/vomiting, tongue swelling, lightheadedness, and hypotension. In preparation to transition back to the DSA system, discussions were held with each patient regarding strategies to mitigate any potential anaphylactoid reaction. Potential mitigating interventions included the patients taking anti-histaminergic medication the night before an LA session. The specific anti-histaminergic medication used, and the specific dosages were not the same across the

TABLE 1 Baseline characteristics of patients using magnesium sulfate for LDL-C apheresis anaphylactoid reaction mitigation

Patient level variables	Patients
No. of cases (N)	7
Mean age (in years)	66
50-64	3
65-79	4
Male	1
Female	6
Race	
White	7
Anaphylactoid reactions	
Cutaneous flushing	7
Nausea/vomiting	3
Lightheadedness	7
Tongue swelling	2
Hypotension	7
Severe hypotension	0
Comorbidities	
Elevated Lp(a)	4
Statin intolerance	5
History of rhabdomyolysis with statin use	1
Coronary artery disease	7
History of myocardial infarction	2
Cerebral vascular disease/stroke	1
Coronary artery stenting	4
History of coronary artery bypass grafting	2
Familial hypercholesterolemia	3
Hypertriglyceridemia	2
Diabetes	2
Hypertension	2
Obesity	2
Peripheral vascular disease	3
Angiotensin receptor blocker use	4
ACE-inhibitor use	0
PCSK-9 inhibitor use (1 former, 1 current)	2

Abbreviation: LDL, low-density lipoprotein.

patients. Also, 62.5 mg of methylprednisolone was administered intravenously to each patient before an LA session. Interestingly, the administration of systemic corticosteroids did not significantly change anaphylactoid reactions to LA. Subjective data was collected from each patient prior to transition to the DSA and individual subjective data to anaphylactoid reactions was reported with each apheresis session. Objective measures of blood pressure were recorded with each apheresis session to monitor for hypotension.

With persistent anaphylactoid reactions significantly affecting patients' tolerability of LA, we decided to adopt a part of the Kaneka tolerability protocol developed by Dr Eliaz during Amitabha Medical Center's transition from the HELP to the DSA system. This protocol uses magnesium sulfate infusion before LA session due to magnesium's impact on the vascular and the parasympathetic nervous systems.¹¹

On the day of an LA session, 1.5 g of magnesium sulfate (147.9 mg of elemental magnesium, 12.18 mEq of magnesium) was administered intravenously over 45 minutes. LA was initiated immediately following the completion of the magnesium infusion.

All patients completed signed statements for informed written consent to participate in the research aspect of the treatment.

3 | RESULTS

Apheresis tolerability persists to date, after the cessation of other medications. No adverse reactions, including nausea/vomiting, to magnesium administration have been observed in the patients with prior anaphylactoid reactions to DSA. In patients with prior anaphylactoid reactions, both antihistamine and systemic corticosteroid administration were stopped due to the resolution of symptoms with magnesium administration. Presently, no significant anaphylactoid reactions have been observed or reported by patients in any of the procedures using the magnesium protocol before the LA administration.

4 | DISCUSSION

LA plays a vital role in the treatment of homozygous and heterozygous FH, elevated Lp(a), FSGS, and atherosclerosis with statin intolerance. While LA is a safe and well-tolerated therapy, it is not without potential side effects. Nausea, vomiting, and hypotension comprise most adverse reactions to LA.⁵ Anaphylactoid reactions to LA can significantly impact a patient's experience with LA and could contribute to the cessation of necessary therapy due to intolerability. As demonstrated here, magnesium infusion prior to LA is an effective strategy to mitigate anaphylactoid reactions and establish LA tolerability.

Anaphylactoid reactions are driven through contact activation of the kallikrein system (Figure 1).⁶⁻⁸ Important to understanding the mechanism of anaphylactoid reactions during LA is the mechanism of action of bradykinin. Functionally, bradykinin interacts with primarily two different kinin receptors, namely B1 and B2 (Figure 2).¹² B1 receptor activation plays a role in chronic

inflammatory states through the generation of prostaglandin, nitric oxide, histamine, and other inflammatory cytokines.^{12,13} B2 receptor activation constitutes the majority of bradykinin side effects, again primarily through mediators such as prostaglandin, nitric oxide, histamine, and other cytokines. Clinical signs of bradykinin responses include pro-inflammatory and allergic states which can manifest as hypotension, cutaneous flushing, and other cardinal signs of inflammation.¹⁴ Interestingly, while the systemic signs of bradykinin-induced anaphylactoid reactions are well known, our patients did not benefit from traditional interventions for these types of reactions, namely anti-histamines and systemic corticosteroids. Newer research looking at bradykinin interaction with different neuronal tissues has expanded our understanding of how bradykinin works physiologically.

Brailoiu et al demonstrated that bradykinin acts on B2 receptors in the nucleus ambiguus to increase parasympathetic cardiac tone, ultimately leading to bradycardia.¹⁵ Indeed, increased parasympathetic tone, as manifested by bradycardia, could be felt clinically and could mimic anaphylactoid reactions.

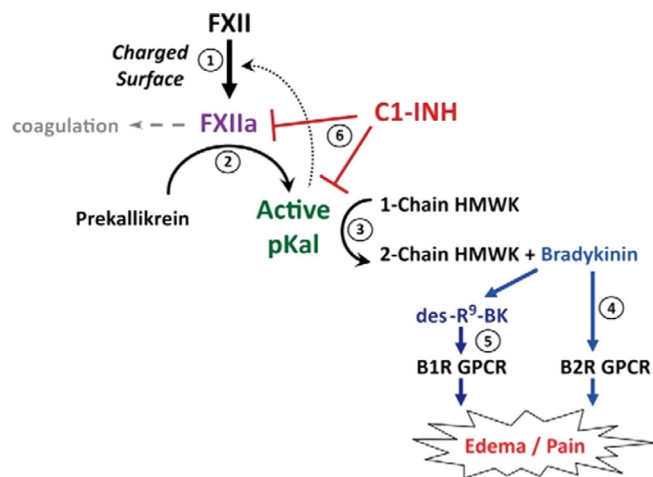


FIGURE 2 Activation cycle of the kallikrein-kinin enzymatic pathway. Autoactivation of the proenzyme form of factor XII to XIIa (step 1) initiates a proteolytic cascade that activates pKal (step 2), which in turn cleaves HMWK to release bradykinin (step 3) (in addition to the positive feedback activation of more FXII). Bradykinin subsequently binds and activates the bradykinin B₂ receptor (step 4), thereby initiating an intracellular signaling cascade that ultimately results in swelling and pain in the affected tissues. Exoprotease activity on bradykinin generates des-Arg⁹bradykinin, which signals through the bradykinin B₁ receptor (step 5). Individuals with HAE are deficient in C1-INH (step 6), the major inhibitor of active pKal and FXIIa, and subsequently exhibit unpredictable attacks of bradykinin-mediated pain and edema. This figure is reproduced with licensing permission from Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>) from Kenniston et al¹²

Understanding the contributions of bradykinin to anaphylactoid reactions serves as the foundation of intervention, and specifically in our case, to increase LA tolerability. Dr Eliaz originally developed the magnesium-based intervention in anticipation of transitioning his patients from the HELP to the DSA system, being aware of the bradykinin-driven allergic reaction with possible anaphylactoid reactions. The prophylactic protocol relies primarily on the intravenous administration of magnesium sulfate, 1.5 g minimum, over 30 to 45 minutes.

The complete Eliaz protocol also includes the administration pre-apheresis of oral cetirizine, 10 mg, and famotidine, 20 mg. Also, all patients use nasal cannula oxygen, 2 L/min, and if hypotensive at baseline, up to 4 L/min during the apheresis procedure. Starting in December of 2018, an additional 46 patients were treated by Dr Eliaz with the Kaneka Liposorber, using this protocol. Presently, over 200 total procedures have used this protocol, and to date, no significant adverse reactions have occurred. At the University of Kansas, Cetirizine, Famotidine, and nasal cannula oxygen were not used in conjunction with magnesium as patients had been treated with anti-histamines the night before LA without and significant improvement of anaphylactoid reactions. It was hypothesized that the magnesium was the most significant contributor to tolerability leading to this single agent being used at the University of Kansas.

Magnesium is the second most abundant intracellular cation and is involved in several important biochemical reactions. Magnesium has an antiarrhythmic effect and influences blood pressure levels by modulating vascular tone. Changes in extracellular magnesium content can modify the production and release of nitric oxide (NO), resulting in changes in arterial smooth muscle tone by affecting calcium concentrations. Increased levels of extracellular magnesium inhibit calcium influx. Oppositely, lower extracellular magnesium activates calcium influx via calcium channels. Increased intracellular magnesium results in decreased intracellular free calcium concentration promoting vasodilation. Magnesium also participates in glucose metabolism and insulin homeostasis. Magnesium deficiency is associated with oxidative stress, pro-inflammatory state, endothelial dysfunction, platelet aggregation, insulin resistance, and hyperglycemia.¹⁶

Magnesium sulfate has been used in anticonvulsant therapy in preeclampsia due to its neuroprotective action and a possible role in regulating vascular tone.¹⁷⁻¹⁹ The mechanism of action is thought to trigger cerebral vasodilation, thus reducing ischemia generated by cerebral vasospasm during an eclamptic event. It also competitively blocks the entry of calcium into synaptic endings, thereby altering neuromuscular transmission. Magnesium sulfate infusion is used as safe adjuvant therapy in acute asthma

exacerbation as a bronchodilator.²⁰ The exact mechanism of action is not known, but several have been proposed: again, its ability to inhibit the cellular uptake of calcium across smooth muscle membranes, which leads to bronchial smooth muscle relaxation.^{21,22} Magnesium helps to decrease the release of histamine by inhibiting the degranulation of mast cells; or that it decreases the amount of acetylcholine released at motor nerve terminals.²³

Previously, Vicković et al assessed the effects of magnesium sulfate on cardiovascular stability in patients undergoing various surgical procedures under general anesthesia, diagnosed with arterial hypertension grades 1 and 2. Immediately before induction of anesthesia with propofol, the treatment group received 30 mg/kg bolus dose and magnesium sulfate infusion at 10 mg/kg/h, while the control group received saline. A statistically significant difference was observed at 60 and 90 minutes of anesthesia for mean arterial pressure and heart rate, demonstrating magnesium sulfate as an effective adjuvant to anesthesia in patients with arterial hypertension.²⁴

The sympathetic nervous system (SNS) reacts to dangerous situations and is physiologically activated as a part of the “fight and flight” response. The SNS is not only active in extreme situations but is part of the constant regulation of non-stress physiologic bodily functions. The importance of bradykinin in regulating vasodilation, natriuresis, oxidative stress, fibrinolysis, inflammation, and apoptosis is established.²⁵ The SNS is downregulated by magnesium, which contributes to control of the fight or flight response the body may be experiencing. With the down-regulation of the SNS, magnesium allows for increased parasympathetic nervous system function to restore the body's normal non-stress functions.²⁶ Other forms of intravenous magnesium, such as magnesium chloride, may also work as well in similar elemental magnesium doses, as long as they are administered quickly enough to make a shift in the sympathetic response.

Last, with the infusion of magnesium, a positively charged molecule, there is a potential to interact with the negatively charged dextran sulfate on the filter. In theory, this could mimic competitive inhibition for the contact activation through the plasma, effectively decreasing the circulating bradykinin levels leading to less of or a complete resolution of anaphylactoid reactions. In effect, there is a potential that the magnesium infusion “stabilizes” the plasma against the mechanisms of contact activation to increase LA tolerability.

4.1 | Future directions

Efforts to increase LA tolerability in patients with anaphylactoid reactions is an essential task for continued use

of this therapy. Future directions include measuring pre-apheresis and post-apheresis magnesium concentrations to evaluate for potential shifting during therapy. To address the potential stabilization of the dextran sulfate filter through competitive inhibition of bradykinin generation, both pre- and post-apheresis bradykinin levels will be measured in conjunction with magnesium infusion.

5 | CONCLUSIONS

In conclusion, we present here an effective adjuvant protocol designed to address and potentially solve the bradykinin driven allergic reaction to DSA by using magnesium sulfate infusion before an LA session.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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