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The Efficacy of Albumin Dialysis in the Reversal of Refractory Vasoplegic Shock Due to Amlodipine Toxicity

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Objectives: Calcium channel blockers are highly protein-bound medications frequently used in the management of hypertension. Overdose results in severe hypotension and is the fourth most common cause of toxicity-related deaths in the United States. Management is mostly supportive, with currently no standard role for targeted drug removal. The protein-bound nature of these medications presents the option of utilizing albumin dialysis for their removal and for the reversal of associated shock.

Design and Subjects: We present two cases of life-threatening intentional amlodipine overdoses successfully treated with albumin dialysis. Both patients experienced profound distributive shock in the setting of preserved cardiac contractility that was refractory to maximal vasoactive agent support.

Interventions and Results: After initiation of albumin dialysis, the patients showed rapid hemodynamic improvement and were able to be weaned off vasopressor support.

Conclusions: These cases demonstrate the safety and efficacy of albumin dialysis in the management of near-fatal calcium channel blocker overdoses related to amlodipine and offer an additional therapeutic option apart from conventional supportive care. Importantly, these cases were not associated with impaired cardiac contractility, thereby making venoarterial extracorporeal membrane oxygenation a less preferable option. Furthermore, this therapeutic benefit of albumin dialysis can potentially be extended to the management of toxicity related to other highly protein-bound drugs and toxins.

Key Words: albumin dialysis; amlodipine; calcium channel blocker; continuous renal replacement therapy; toxicology; vasoplegia

According to the National Poison Data System, calcium channel blocker (CCB) toxicity was the fourth highest cause of toxicity-related deaths in 2016, accounting for over 5% of fatal exposures (1). Non-dihydropyridine CCB (e.g., verapamil, diltiazem) toxicity can cause negative inotropic and chronotropic effects, in particular, resulting in life-threatening cardiogenic shock. Typical therapies are supportive, aimed to temporize hemodynamic derangements until inherent elimination can occur. Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is an additional therapeutic option in this context. In contrast, dihydropyridine CCB (e.g., amlodipine) toxicity is predominantly associated with systemic vasodilation and less cardiac depression, thereby resulting in distributive shock; in this setting, VA-ECMO has not traditionally been used given preserved cardiac function.

Amlodipine is a long-acting dihydropyridine CCB that is 98% protein bound with a terminal elimination half-life of 40–50 hours (2). Given the highly protein-bound nature of amlodipine, extracorporeal removal using albumin dialysis is a mechanistically attractive option to reverse refractory vasoplegia due to its toxicity. We present two cases of refractory shock secondary to amlodipine overdose that were successfully treated with albumin dialysis using the Molecular Adsorbent Recirculating System (MARS) (Baxter Inc., Deerfield, IL).

CASE 1

A 47-year-old male status post liver transplant for autoimmune hepatitis few years before presented to the emergency department (ED) following an intentional overdose of 145 mg of amlodipine. He was hemodynamically stable on arrival to the ED, and laboratory values were unremarkable. Upon admission to the ICU, however, the patient developed sudden profound shock with an abrupt drop in systolic blood pressure from 140 to 50 mm Hg.

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Electrocardiography demonstrated sinus tachycardia at 120 beats/min. A transthoracic echo (TTE) demonstrated preserved cardiac contractility with an ejection fraction (EF) of 60%.

Vasopressors were rapidly uptitrated, including norepinephrine, epinephrine, and vasopressin, and he was intubated given his instability. Poison control was consulted, and the patient was given the following additional therapies: glucagon 10 mg followed by multiple 5-mg doses, four 250-mL doses of 20% fat emulsion, calcium gluconate infusion at 1.5 g/hr, hydrocortisone 100 mg followed by 50 mg every 6 hours, and uptitration of an insulin infusion to 1 U/kg/hr with concurrent dextrose infusion to maintain euglycemia (Fig. 1A). The patient was unable to tolerate higher doses of the insulin infusion due to persistent hypokalemia and hypoglycemia even with maximal glycemic support and potassium repletion efforts. Despite these interventions, the patient remained hemodynamically unstable with a mean arterial pressure (MAP) of less than 65 mm Hg.

Hepatology and nephrology services were consulted, and MARS with continuous renal replacement therapy (CRRT) were started within 6 hours of admission. Two hours after initiation, the MARS circuit clotted; however, once flow in the circuit was restored, the patient's hemodynamics improved rapidly, and vasopressors were able to be weaned off within 20 hours of initiation. The patient was ultimately extubated and transferred out of the ICU on day 3 of hospitalization and suffered no lasting organ dysfunction.

CASE 2

A 39-year-old woman with a medical history of hypertension and prior stroke with residual right-sided deficits presented to an outside ED hemodynamically stable following an intentional overdose of 600 mg of amlodipine and 400 mg of lisinopril. Poison control was contacted, and she was given activated charcoal, glucagon, and IV fluids, and was admitted to the ICU for monitoring.

Upon arrival to the ICU at the outside hospital, the patient became acutely hypotensive and was intubated given her instability. Cardiac workup revealed sinus tachycardia on electrocardiography and preserved EF on TTE. Vasopressors were quickly uptitrated, including norepinephrine, epinephrine, vasopressin, and angiotensin II. She was given a total of 16 g of calcium gluconate divided over multiple doses, two 150-mg doses of methylene blue, three 50-mg doses of hydrocortisone, and a total of 770 mL of 20% fat emulsion divided over three doses. An insulin infusion was also started and rapidly uptitrated to 6 U/kg/hr with concurrent dextrose infusion to maintain euglycemia (Fig. 1B). She had a metabolic acidosis that continued to worsen and was started on a bicarbonate drip and CRRT with nephrology consultation.

Despite these interventions, the patient continued to be profoundly hypotensive with MAPs in the 40s with a worsening acidosis and rising lactate. She was then transferred to our ICU for MARS therapy on hospital day 2. After beginning MARS, vasopressors and adjunctive therapies were weaned within hours, and the patient was ultimately stabilized. She was discharged on hospital day 12 without any lasting organ dysfunction.

DISCUSSION

The MARS is the most common form of albumin dialysis and has typically been used to remove endogenous hepatic toxins as a treatment for hepatic encephalopathy, or as a bridge to recovery or liver transplant in acute or acute on chronic liver failure. MARS involves an initial dialysate of 600 mL of 16% albumin solution that recirculates through a MARS dialysis membrane, a CRRT membrane, charcoal filter, and anion exchanger (Fig. 2A). This albumin-enriched dialysate combined with a larger membrane pore size permits the removal of larger molecules up to 50 kDa that cannot be cleared by conventional hemodialysis, allowing removal of both water soluble substances such as ammonia, and larger albumin-bound toxins such as endogenous benzodiazepines, nitric oxide, and bilirubin from the patient's blood (Fig. 2B). The albumin effluent derived from the MARS dialysis membrane then gets sequentially dialyzed across a conventional CRRT membrane that removes water soluble toxins, and then passes through a activated charcoal filter and anion exchange column that remove protein-bound toxins.

Also, in a nonhepatic context, MARS has been used efficaciously in cases of overdose of highly protein-bound CCBs such as amlodipine, verapamil, and diltiazem, with noted decrease in vasopressor requirements within several hours of initiation (3–6). Such cases have noted a decrease in the half-life elimination and a drop in serum levels of these medications with the use of MARS, indicating enhanced elimination through albumin dialysis (3, 5). However, one study by Gerard et al (4) did not demonstrate a significant amount of amlodipine in the dialysate, instead suggesting direct enhanced elimination may not be the only mechanism leading to hemodynamic improvements in these patients.

Published case reports of MARS in the context of liver failure may provide insight into potential other mechanisms of hemodynamic improvement apart from drug elimination. These reports in patients with hepatic failure have demonstrated increases in MAP and systemic vascular resistance following a single MARS session (7–9). This improvement in systemic hemodynamics is postulated to be due to MARS' ability to act as a scavenger for endogenous vasoactive substances, such as nitric oxide. MARS removes plasma nitric oxide that is bound to albumin as S-nitrosothiol, with studies documenting a 50% decrease in nitric oxide levels in a single session (9, 10). MARS has also been shown to decrease free radical production, reduce oxidative stress, and eliminate pro-inflammatory cytokines such as tumor necrosis factor- α , interleukin-6, and interleukin-8 (9, 11).

In our cases, amlodipine levels in the serum or dialysate were not measured; the absence of these data raises the question whether our observed hemodynamic improvements were primarily due to exogenous clearance of amlodipine or elimination of endogenous vasoactive substances. Nevertheless, in our extensive experience with the use of MARS in liver failure patients, we have not observed a demonstrable hemodynamic benefit related to the potential elimination of endogenous vasoactive substances, and therefore, we would postulate that MARS in the context of our cases is working predominantly by removing drug. In future studies, analyzing both serum and dialysate levels of toxins may be beneficial as we continue exploring the potential use of MARS in managing critical toxicologic overdoses.

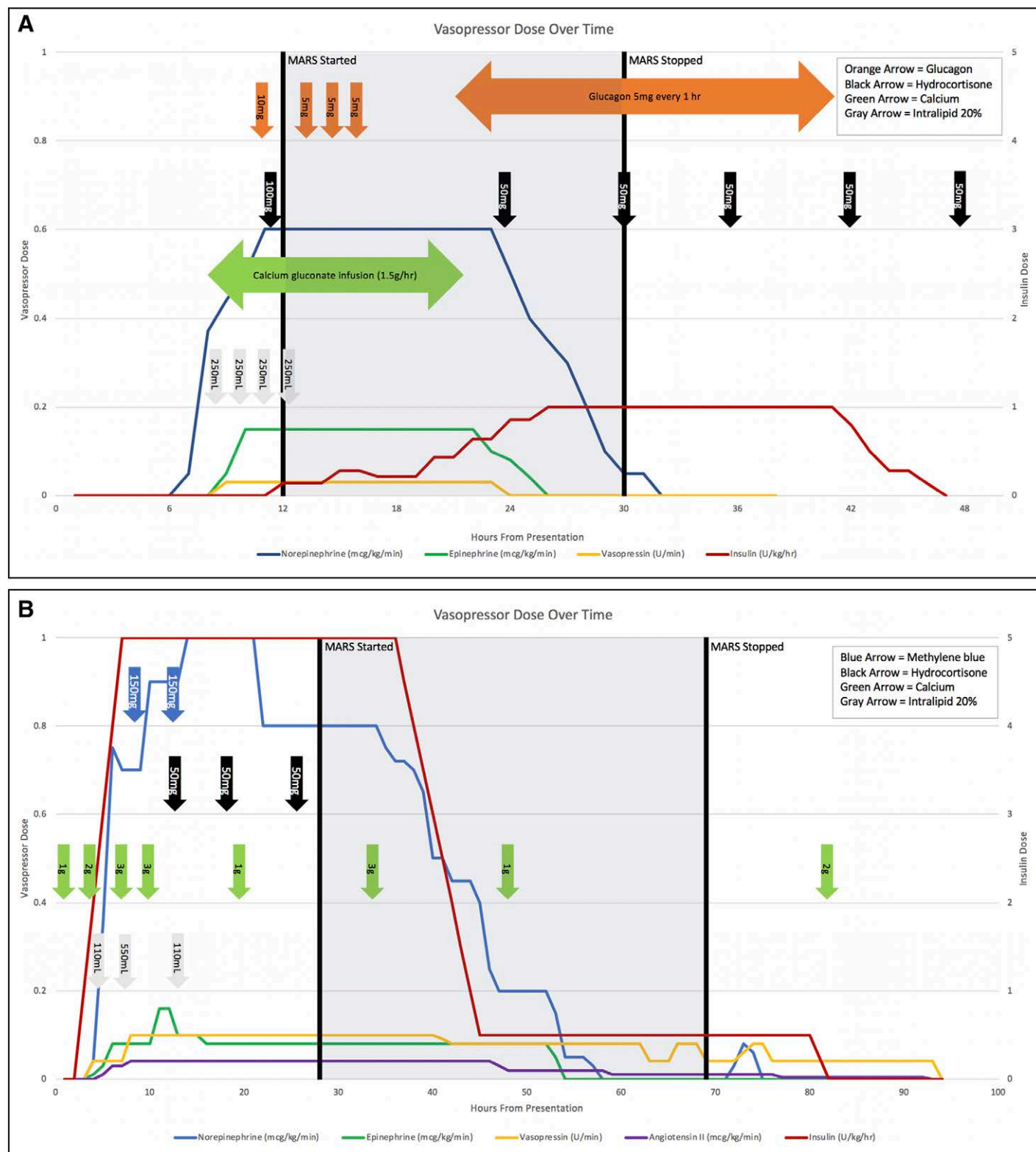


Figure 1. Graphs depicting vasopressor dosing in the two patients over time (hours), with the timing for initiation and termination of albumin dialysis noted. MARS = Molecular Adsorbent Recirculating System.

In the context of CCB toxicity, non-dihydropyridine CCBs typically act on calcium channels in the myocardium causing negative inotropy, and dihydropyridine CCBs act on the calcium channels in the vasculature causing vasoplegia. However,

in cases of massive overdose, these medications can spread overwhelmingly throughout serum and tissue, losing this difference in receptor affinity; as such, either type of CCB subclass could potentially result in cardiogenic and/or vasoplegic shock (12).

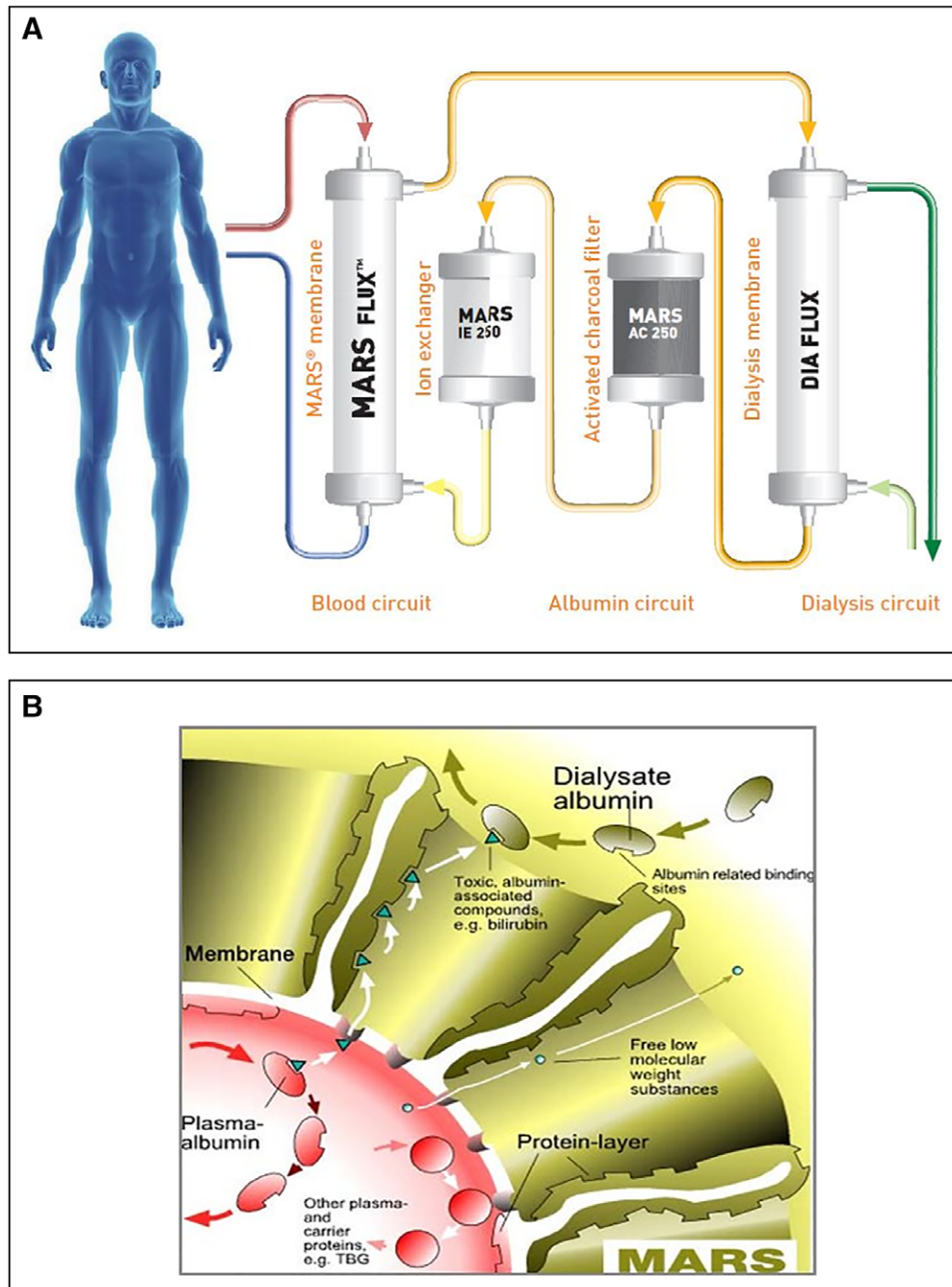


Figure 2. A. Details of the Molecular Adsorbent Recirculating System (MARS) circuit, which involves a dialysate of albumin solution that passes through a MARS dialysis membrane and then subsequently via a CRRT membrane, charcoal filter, and anion exchanger. **B.** Diagram of the MARS membrane, which illustrates the albumin dialysate, and the passage of both water soluble low molecular weight and larger albumin-bound toxins across the membrane. TBG = thyroxine-binding globulin. Reproduced with permission from Baxter.

Therefore, it is critical to perform echocardiographic assessment of cardiac function in all cases of CCB toxicity to consider VA-ECMO is the setting of refractory cardiogenic shock (13). In this case series, our patients had preserved cardiac function, thereby making VA-ECMO a less preferable option. VA-ECMO is expensive, labor intensive, and prone to complications, including hemorrhage, thrombosis, stroke, and limb ischemia (14). In cases of CCB toxicity resulting primarily in vasoplegic shock, MARS

provides a novel therapeutic strategy that can be life-saving in the setting of refractory shock.

MARS is generally considered a safe modality in critically ill patients. The blood flow rate is 180 mL/min, which should result in less hemodynamic instability than would be seen with conventional hemodialysis. Potential side effects include metabolic derangements if citrate is used as an anticoagulant, and unintentional medication elimination. If citrate is used as an anticoagulant, attention should be given to following calcium levels, and adjustments can be made to the citrate solution and/or dialysate flow rates. With respect to unintended medication elimination, MARS can remove protein-bound medications used in the critical care setting, including antibiotics (such as piperacillin/tazobactam, meropenem, moxifloxacin, and ceftriaxone), therapeutic antidotes such as *N*-acetylcysteine, and sedatives such as fentanyl and midazolam; these medications may require increased dosing or frequency to avoid subtherapeutic levels (15–19).

CCB toxicity is increasingly common and is a major cause of overdose-related deaths. The mainstay of treatment is typically supportive, with a consideration for VA-ECMO typically in cases of refractory cardiogenic shock due to CCB toxicity. Our cases demonstrate the remarkable efficacy of albumin dialysis with the MARS system in reversing refractory distributive shock in the setting of dihydropyridine toxicity by utilizing the protein-bound nature of the medication; therefore, this alternative therapeutic strategy should be considered in the management of this form of CCB toxicity. Furthermore, this case series highlights the potential application of albumin dialysis in the treatment of toxicologic emergencies related to other highly protein-bound drugs and toxins.

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