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CASE REPORT

Beyond vasopressor support: VA-ECMO for refractory calcium channel blocker overdose

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Calcium channel blocker (CCB) overdose is a life-threatening toxicological emergency associated with vasoplegia and multiorgan failure. We report a case of a 15-year-old male who presented with polypharmacy ingestion and refractory shock despite high-dose insulin euglycemic therapy, calcium supplementation and vasopressor support. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) was initiated 48 hours after ingestion and 40 hours after intensive care unit (ICU) admission. The patient was decannulated after 72 hours on ECMO, and discharged home on day 7 of ICU admission. This case highlights the role of VA-ECMO as a rescue intervention in severe CCB toxicity where conventional therapies fail.

Keywords: calcium channel blocker overdose, high-dose insulin euglycaemic therapy, veno-arterial extracorporeal membrane oxygenation, vasoplegic shock, resource-limited setting

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Calcium channel blockers (CCBs) are widely available in South Africa (SA).[1] CCB overdose is a frequent toxicological emergency, often leading to profound vasoplegia and multiorgan failure, with a mortality rate as high as 35%.[2] The mainstay of treatment includes high-dose insulin euglycaemia therapy (HIET), exogenous calcium supplementation and vasopressors to achieve adequate blood pressure.

We report a severe dihydropyridine CCB overdose with refractory vasoplegic shock, successfully supported with veno-arterial extracorporeal membrane oxygenation (VA-ECMO) in an SA public hospital.

Although evidence supports the utility of VA-ECMO in such patients, the optimal timing is unclear.[3] Our case demonstrates the successful use of VA-ECMO as a rescue supportive therapy in a resource-limited environment for a patient presenting to a district-level hospital and referred to a state sector ICU with an ECMO service.

Case report

A 15-year-old male presented to a district-level emergency centre at 16h20 after ingesting approximately amlodipine 240 mg, simvastatin 240 mg and enalapril 240 mg, based on pill counts and collateral history. On arrival, he was profoundly hypotensive with a blood pressure (BP) of 66/22 mmHg, but initially presented with no clinical signs of end-organ dysfunction. He received 10 mL of calcium gluconate, 2 L of crystalloid and 2 IU/kg/h of HIET with 0.01 µg/kg/min of adrenaline titrated to a mean arterial pressure of 65. Activated charcoal was not given.

On presentation, his biochemistry indicated stage 3 acute kidney injury (AKI) according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, with a creatinine level of 303 µmol/L and urea of 10.6 mmol/L. He was transferred to the tertiary centre ICU by 23h45, where he remained in vasoplegic shock despite escalating support overnight. On arrival, he had a sequential organ failure assessment score (SOFA) of 7, with PaO_2/FiO2 ratio of 430, and was neurologically intact. Within 8 hours in ICU, his oxygenation had worsened, with a PaO_2/FiO2 ratio of 230, prompting high-flow nasal cannula support. Adrenaline was escalated despite 6 IU/kg/hr HIET, with progression to oligo-anuria.

Within 24 hours, he had progressive respiratory failure, requiring intubation and mechanical ventilation. His vasopressor requirements escalated to 1 µg/kg/min of adrenaline and 0.03 units/min of vasopressin. He had a generalised tonic-clonic seizure secondary to hypoglycaemia. He was started on continuous veno-venous haemodiafiltration (CVVHDF) due to persistent anuria and profound pulmonary oedema, with a PaO_2/FiO2 ratio of 84 on the ventilator.

Transthoracic echocardiography and cardiac output monitoring confirmed profound vasoplegic shock, with decreased systemic vascular resistance 326 dynes.sec.cm^{-5} and increased cardiac output at 10 L/min. Given his refractory vasoplegic shock and multiorgan failure, the multidisciplinary ECMO governance team approved VA-ECMO as the most appropriate intervention for ongoing support. His SOFA score prior to ECMO initiation was 15.

VA-ECMO was initiated via percutaneous right femoral cannulation in theatre. A 24 Fr venous cannula was placed via the femoral vein into the right atrium under transoesophageal echocardiography guidance. An 18 Fr arterial cannula was inserted retrograde into the femoral artery with an 8 Fr distal perfusion catheter in the right femoral artery. The blood flow rate was 4.5 L/min, the sweep gas flow rate 5 L/min and the fraction of delivered oxygen 1.0.

He was monitored with near-infrared spectroscopy (NIRS) with sampling from a right radial arterial line to monitor for Harlequin syndrome. We used 4-channel NIRS, with sensors connected bilaterally over the cerebral hemispheres and lower limbs. Initially, a degree of Harlequin syndrome was evident, with an initial right radial arterial PO_2 of 10 kPa (75 mmHg), considered adequate in this context, but markedly lower than the left femoral arterial PO_2 of 45 kPa (338 mmHg). During this time, cerebral oximetry reflected values >65%. After VA-ECMO, the urine output improved to 2

500 mL/12hr, with improved lung compliance. Heparin was initiated, targeting an activated clotting time of 200 - 220 seconds.

His vasopressor and inotrope requirements progressively decreased – reduced by one-third on day 1, halved by day 2 and completely weaned off by day 3. CVVHDF was discontinued 48 hours after ECMO initiation. He was decannulated from ECMO in theatre after 3 days with arterial repair, and remained haemodynamically stable. He was extubated on day 5 of admission without requiring supplemental oxygen. No ECMO-related complications were observed during this admission. Routine compression ultrasound of the femoral vein was performed to exclude thrombus post decannulation.

On day 6, he was transferred to the psychiatric unit, fully mobile and without organ dysfunction. He was discharged home after 24-hour observation, with psychiatric outpatient follow-up the next week.

The timeline of clinical events is shown in Fig. 1.

Discussion

Local data on the prevalence or mortality of CCB overdose are lacking. However, according to the 2023 American Poison Control report, antihypertensives were the fifth most common cause of overdose,[4] with CCB overdose associated with a mortality rate as high as 35%.[2]

CCBs are categorised into two classes – dihydropyridines and nondihydropyridines. Dihydropyridines, such as amlodipine, affect vascular smooth myocytes with little effect on the myocardium or conduction system. However, at toxic doses, they can cause severe vasoplegia, causing tissue hypoperfusion. The concomitant ingestion of angiotensin-converting enzyme inhibitors may have exacerbated refractory shock by further impairing the vasoconstrictive response in this patient. A study examining patients with dihydropyridine CCB poisoning found that concomitant ingestion of angiotensin axis antagonists was associated with more significant hypotension, and increased requirement for haemodynamic support.[5]

The current medical treatment of CCB overdose is limited to case reports, retrospective studies and expert opinion.[6] The mainstay treatment includes: high-dose insulin therapy, vasopressors, exogenous calcium supplementation and supportive care.[7] Haemodialysis is ineffective in clearing CCBs due to their high protein binding and lipophilicity. In contrast, certain angiotensin-converting enzyme inhibitors, such as enalapril, are partially dialysable as their active metabolite, enalaprilat, has a low protein binding capacity and a high free serum fraction.[8]

HIET is widely used in CCB overdose, and purportedly improves inotropy, as CCBs inhibit calcium influx through L-type calcium channels. High-dose insulin enhances myocardial contractility by promoting glucose uptake and utilisation, which is considered a more efficient substrate for energy production.[9] Despite comprehensive medical management, including 6 IU/kg/hr HIET, high-dose vasopressor, open lung ventilation and CVVHDF, our patient remained in refractory shock, necessitating further escalation.

A common theme in managing CCB overdose is that vasoplegia is frequently accompanied by AKI due to profound hypotension. Large volumes of intravenous fluids are often required to administer HIET and vasopressors, as HIET necessitates both insulin and high-dose glucose infusions. This can contribute to pulmonary oedema and respiratory failure, creating a cycle of multiorgan failure requiring high-dose vasopressors, mechanical ventilation and renal replacement therapy.

VA-ECMO may improve outcomes in refractory CCB overdose.[3,10,11] Our use of VA-ECMO was prompted by refractory vasoplegic shock and severe hypoxaemia. Right femoral access was chosen for its technical ease and to avoid graft placement or sternotomy. However, femoral access carries a higher risk of Harlequin syndrome, as oxygenated blood is delivered distal to the left ventricular outflow tract. To prevent limb ischaemia, a distal perfusion catheter was used, and NIRS monitoring was utilised to detect Harlequin syndrome. NIRS monitoring showed an initial regional oxygen saturation of 36% on the cannulated limb, which spontaneously improved to 60% within 4 hours post cannulation.

Given the reversible nature of vasoplegic shock, renal failure and hypoxaemia, the goal was to provide respiratory and haemodynamic support until the amlodipine was metabolised.

A systematic review of 26 cases highlights the current clinical practice of early ECMO initiation for refractory CCB overdose. The most common therapies commenced in these patients prior to ECMO treatment were: HIET (76.9%), calcium (73.1%), vasopressor (65%), intralipid (53.9%), glucagon (38.5%), and methylene blue (30.8%).[3] Of these patients, 70.6% were on ≥3 vasopressors, and 41.2% were on ≥4 before ECMO initiation.[3] The median hospital day of cannulation was day 1, and the median ECMO duration was 4 days. ECMO -specific complication rates were reported in 11.4% of the cannulated cases.[3] Among these, one patient required an above-knee amputation, while another underwent lower extremity fasciotomy.

In our patient, ECMO was initiated on day 2 of ICU admission, after he had developed multiorgan failure and cardiovascular collapse despite high-dose adrenaline and vasopressin. Unlike in other reported cases, we did not utilise methylene blue, glucagon, or intralipid. While glucagon may provide modest chronotropic and inotropic effects,[12] obtaining sufficient quantities for therapeutic use is often challenging in our setting, and robust evidence supporting its effectiveness remains limited. Methylene blue is a nitric oxide synthase inhibitor that is used in refractory shock.[10] However, its effect on CCB overdose is mixed, and the overall evidence remains anecdotal.[10] Intralipid therapy is currently not recommended, as a large retrospective study did not find any benefit in CCB overdose.[13] Additionally, some data suggest that it may enhance the gastrointestinal absorption of lipophilic drugs.[14]

The 2023 American Heart Association classifies glucagon and methylene blue as class 2b recommendations, and intralipid as class 3.[10] Given this, the decision to not utilise these therapies aligns with current evidence and clinical prudence.

Although the delay allowed for a full trial of conventional supportive therapy, it raises the possibility that earlier ECMO initiation could have mitigated the progression to multiorgan failure. The current literature reflects early ECMO (within 24 hours of admission) in refractory CCB overdose;[15] however, the inherent risks that ECMO carries warrants careful patient selection. In our case, the delay allowed for an adequate trial of vasopressor therapy prior to ECMO. The resultant multiorgan failure may suggest a missed window for earlier intervention. Future considerations should weigh the benefits of early ECMO initiation against the risks of premature escalation.

Haemoadsorption has been described as adjunctive therapy in CCB overdose.[16] Haemoadsorption using a styrene resin may aid in the clearance of CCB. In one reported case, the use of this technique was associated with shock resolution within 38 hours. Haemoadsorption can be instituted with less complexity than VA-ECMO through a standard renal dialysis catheter and low blood-flow rates. Further study is warranted to clarify patient selection prior to multiorgan failure or recovery on standard therapy.

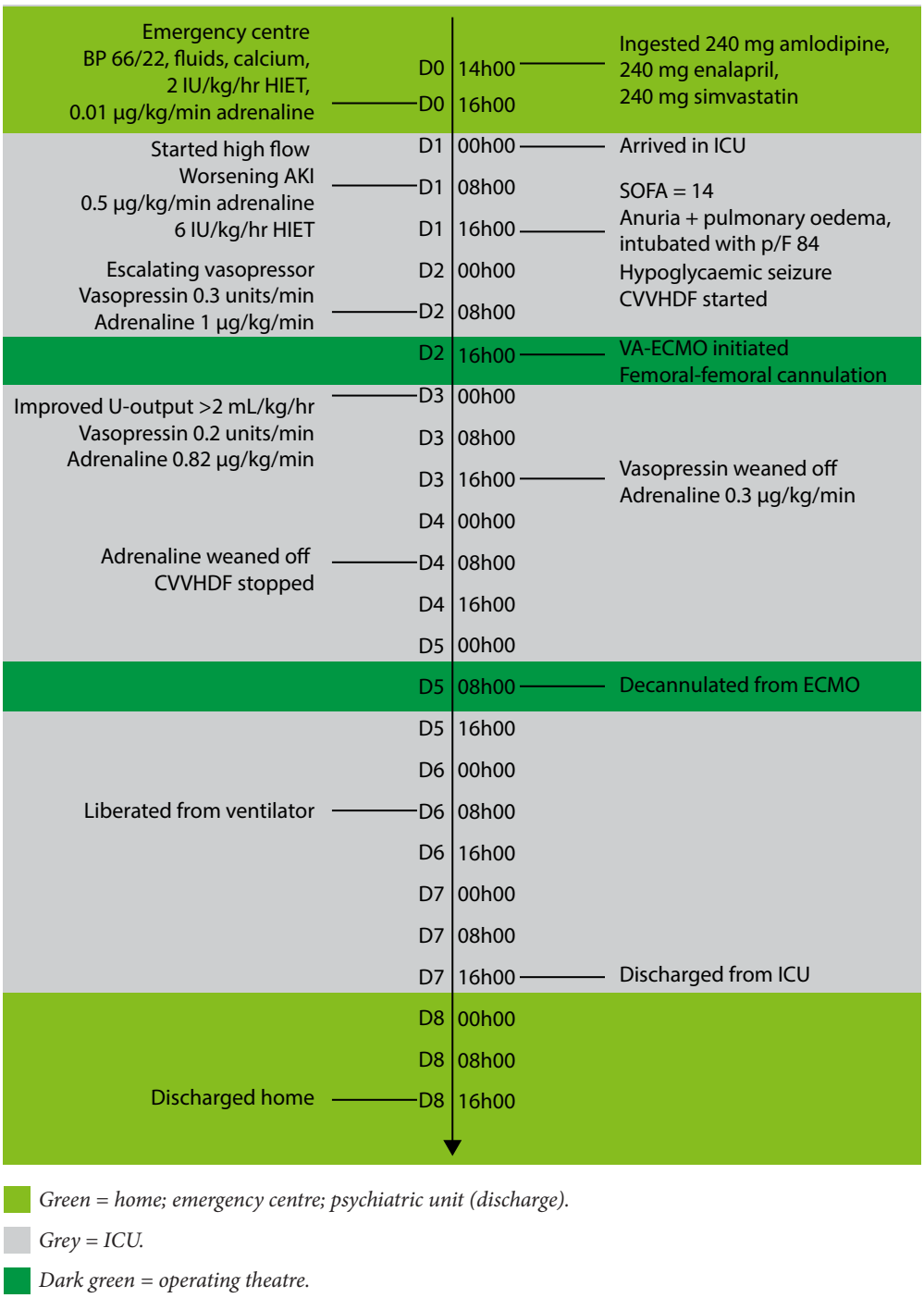

Fig. 1. Timeline of clinical events. (BP = blood pressure; HIET = high-dose insulin euglycaemia therapy; AKI = acute kidney injury; CVVHDF = continuous veno-venous haemodiafiltration; ICU = intensive care unit; SOFA = sequential organ failure assessment; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.)

Teaching points

- VA-ECMO may be considered as a rescue supportive modality for refractory CCB overdose in the SA public healthcare setting.
- Optimal timing of VA-ECMO initiation is early (within 24 hours), as reflected in the current literature.
- Other alternative therapies have limitations and less evidence base in refractory CCB overdose.

Conclusion

Access to VA-ECMO remains limited in SA. However, our case highlights its potential as a life-saving modality for refractory vasoplegic shock, demonstrated by the successful recovery of a 15-year-old male who initially presented to a district-level hospital and was subsequently transferred to a state-sector ICU. This case highlights the role of timely VA-ECMO initiation in achieving favourable outcomes in refractory CCB overdose.

Establishing referral pathways may enhance survival outcomes in refractory CCB overdose cases requiring VA-ECMO in SA.

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