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Hemoperfusion for Clinically Suspected Organophosphate and Carbamate Poisoning in Critically Ill Patients: A Randomized Trial

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Keywords
Hemadsorption · Hemoperfusion · Toxicology · Critically ill · Organophosphate · Continuous veno-venous hemofiltration

Abstract
Introduction: Organophosphate poisoning occurs frequently, and despite treatment, increased severity and intensive care unit (ICU) admissions have been observed. We hypothesized that early hemoperfusion/hemadsorption (HA) therapy would change the clinical course of the disease. ***Methods:*** We performed a prospective, open, randomized controlled study at an academic ICU. Adult patients referred for an acute cholinergic toxidrome were screened. Patients meeting inclusion and exclusion criteria were randomized to standard of care (SoC) or HA therapy plus SoC, which included 2 6-h cycles of HA 12 h apart beginning within the first 24 h of ICU admission. The primary outcome was a comparison of ICU length of stay (LOS). ***Results:*** There were no significant baseline differences between the groups. The median ICU LOS was 6.5 days (IQR 4.5–10) in the HA group compared to 8 days (IQR 3.5–17) for the control group, $p = 0.58$. Among patients with an excess ICU LOS ≥7 days, the median ICU LOS was significantly shorter for the HA group, 10 days (IQR 8–12) compared to 17 days (IQR 14–22) for the control group, $p = 0.001$, resulting in a cost saving of EUR 7308 per patient. Duration (8 days vs. 13.5 days) and cumulative dosage (316 mg vs. 887 mg) of atropine among patients with excess ICU LOS were significantly lower in the HA group compared to the SoC group, respectively. A similar reduction in the duration of mechanical ventilation (HA = 6 days vs. SoC = 15 days, $p = 0.001$) was found. The combination of day 28 mortality and severe complications was lower in the HA group (10%, $n = 2/20$) compared to the SoC group (42%, 14/33) $p = 0.01$. ***Conclusion:*** HA therapy resulted in significant cost savings driven by a reduced LOS among patients with excess ICU LOS ≥7 days. This therapy was also associated with a significant reduction in the combination of day 28 mortality and severe complications including cardiac arrest, organ dysfunction, reintubation, and tracheostomy.

Introduction

Self-poisoning with organophosphate poisoning (OPP) is thought to kill at least 100,000 people worldwide annually.[1] Intentional pesticide ingestion is one the most prevalent means of attempted suicide and is esti-

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mated to account for a third of all suicides internationally. This burden is of particular concern in Asia, Africa, Central and South America, and on Pacific islands. Restriction of access to these toxins has been an important prevention strategy [2, 3].

Organophosphates are well absorbed through the lungs, gut, and skin inhibiting acetylcholinesterase resulting in the cholinergic toxidrome. Atropine is a competitive inhibitor of the muscarinic acetylcholine receptor, while oximes are acetylcholinesterase reactivators. Atropine is widely accepted as the supportive management for OPP, but oxime use has conflicting data [1, 4, 5].

South Africa's burden from OPP is comparable with other developing countries, and active, urgent surveillance to limit exposures and poisonings, particularly from illegal and unlabeled street pesticides, has been previously highlighted [6]. Locally, there has been an increase in intensive care unit (ICU) referral with greater severity and longer length of stay (LOS) documented [7]. This burden must be seen in the context of an under-resourced critical care environment that cannot accommodate large proportions of referred patients [8].

Restriction of access to toxins has had a paradoxical effect in South Africa. The withdrawal of a commercially available carbamate from the formal market by the company Bayer quickly resulted in the informal and unregulated market filling this "gap" with a variety of unlabeled organophosphates [9]. The subsequent increased need for ICU beds and more protracted and complicated ICU admissions is unsurprising [7].

In our setting, the application of novel treatment strategies such as hemoperfusion/hemadsorption (HA) therapy may be useful [10, 11]. Organophosphates are predominantly lipid-soluble and protein-bound molecules and may be removed by HA [11, 12]. Randomized trials evaluating HA in this setting are lacking. We hypothesized that early hemoperfusion/HA therapy would reduce the toxin load and change the clinical course of the disease in the ICU.

Materials and Methods

Study Design

We performed a prospective, open randomized controlled study at an academic ICU. Our study protocol was approved by the university Ethical Review Board, and written informed consent from each patient or their legal surrogate was obtained before randomization.

Participants' Eligibility

Inclusion Criteria

Participants, 18 years or older with a history of acute poisoning and clinical features of a cholinergic toxidrome (salivation, lacrimation, urinary incontinence, diarrhea, emesis, etc.), were considered for recruitment within the first 24 h of ICU admission. Due to the recruitment timeline, it was not possible to identify the exact toxin prior to inclusion.

Exclusion Criteria

Patients suspicious for significant polypharmacy overdose or a known contra-indication to anticoagulation were excluded. COVID-19-positive patients were also excluded.

Data Collection

Study data were recorded into the electronic study record. Informed consent was filed as a paper record.

Interventions

Standard of Care/Control Group

The standard of care (SoC) practiced routinely included supportive and antidote therapy. The latter included atropine or glycopyrrolate administered via continuous intravenous infusion and titrated by the clinician to control muscarinic symptoms. The main muscarinic symptoms routinely used to titrate therapy were bronchorrhea and oral secretions. Atropine was used as the primary antidote with glycopyrrolate used as an alternative based on clinical discretion. Prophylactic doses of low molecular weight heparin (enoxaparin 40 mg) were administered subcutaneously daily.

Hemoperfusion/HA Therapy

This consisted of SoC plus two cycles of HA, each of 6-h duration, the first cycle on ICU admission day (day 1) and the second on day 2 separated by at least 12 h. The HA filter (HA-230, Jafron, Zhuhai City, China) was connected in series with a renal replacement therapy (RRT) circuit. We used a bicarbonate-based predilution at 500 mL/h with no post-dilution or dialysis. The blood pump was set at 150–200 mL/min. Heparin was administered into the RRT circuit using a bolus dose of 10–20 units/kg actual body weight followed by an infusion at 5–15 units/kg for each HA cycle. Prophylactic doses of low molecular weight heparin (enoxaparin 40 mg) were administered daily.

Outcomes

The primary outcome was to determine if HA therapy reduced the length of ICU stay (ICU LOS). Secondary outcomes included a post hoc comparison among patients with excess ICU LOS ≥7 days, a comparison of cost of ICU stay, duration and cumulative dose of antidote therapy, duration of mechanical ventilation (MV), and both ICU complications (frequency and severity) and day 28 mortality between the two groups. Vasopressor comparison was omitted due to limited use (3 patients).

Study Definitions

Excess ICU LOS

For comparison of continuous variables of the secondary outcomes, we used 7 days or more (≥7) to define excess ICU LOS. This was based on the impact that intermediate syndrome (IMS) has on need for prolonged ICU support (7–21 ICU days) [13–16]. A pre-

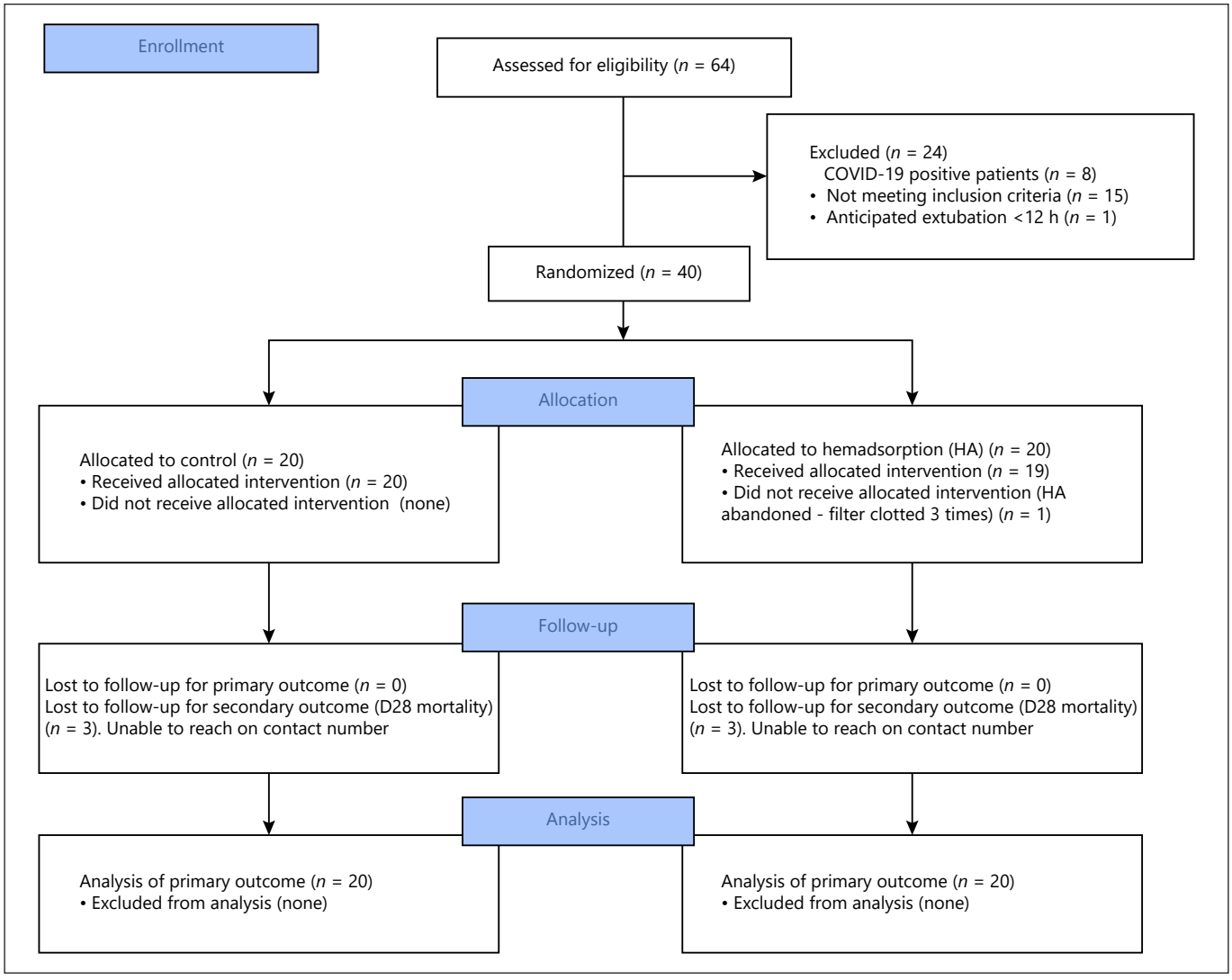

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Fig. 1. Screening, randomization, and follow-up.

vious study in our ICU also had a median ICU LOS of 7 days [7]. This allowed us to make a meaningful comparison of equal numbers of both the SoC and HA groups, $n = 10$ in each. We opted to use this prolonged stay rather than proposed definitions for IMS as these may be vague in terms of their ability to exclude delayed neuropathy [14, 17]. The analysis of cost and the combination of day 28 mortality and complication frequency was performed on the entire study population.

ICU Costs

These were estimated from published ICU costs in a tertiary academic hospital in South Africa adjusted for 5% inflation per annum to determine 2021 costs in South African rands (ZAR) [18]. RRT and the HA consumables were priced at 2021 tariffs for our hospital. The EUR/ZAR rate of 15.8 on April 22, 2022, was used for cost estimations in Euros.

Sample Size

We used the primary outcome for sample size determination. The number of participants n was based on the expected proportion of patients with a prolonged stay decreasing from 45% to 10% with HA. Using a power of 80% and a 5% significance level, we required 16 patients per group.

Randomization

After informed consent was obtained, equal numbers of patients were randomized to each group using a computer-generated random number list. Allocation by another (enrolling) investigator was concealed with the use of sealed brown paper envelopes. Treating clinicians could not be blinded to the study intervention (HA).

Table 1. Baseline patient characteristics

Variable	All patients ($n = 40$)	SoC ($n = 20$)	HA ($n = 20$)	p value[#]
Age, years	29 (25–36.5)	33.5 (26–47)	26.5 (24.5–32)	0.05
Male, *n* (%)	27 (68)	13 (65)	14 (70)	0.74*
Height, cm	1.68 (0.07)	1.68 (0.07)	1.69 (0.08)	0.91
Weight, kg	68 (58–75) $n = 38$	70 (60–75) $n = 19$	65.7 (58–75)	0.86
BMI	23.3 (20.8–26.1) $n = 38$	23.3 (20.3–26.4) $n = 19$	23.7 (20.9–25.7)	0.99
GCS (10)	9 (5.5–10)	9.5 (7.5–10)	8.5 (5–10)	0.41
SAPS II score	30.6 (12.9)	31.8 (11.9)	29.5 (14)	0.5
D0 sCh, u/L	200 (200–219) $n = 38$	200 (200-200) $n = 19$	200 (200–337)	0.19
D0 platelet, $\times 10^9$/L	248 (79) $n = 39$	247 (85) $n = 19$	249 (74)	0.56

Mean (standard deviation) or median (IQR). HA, hemadsorption; D0, day 0; sCh, serum cholinesterase. [#] p value; Mann-Whitney U test. * χ^2 test.

Table 2. Outcomes for the entire study population

Variable	Valid *N*	Median	IQR	Sum
ICU antidote days	40	6.5	4–12	327
MV days	40	4.5	3–9.5	287
Days in ICU	40	6.5	4–12.5	359

Statistical Methods

Descriptive statistics were conducted on baseline characteristics. Mean (standard deviation) and median (interquartile range [IQR]) were determined for continuous measures, whereas proportions/percentages were determined for binary measures and were described with 95% confidence interval (CI). We used the Student *t* test or the Mann-Whitney U test to compare continuous data and the χ^2 test for percentages/proportions. Analysis was conducted using Statistica version 13.3 (StatSoft, USA).

Results

We enrolled 40 patients between March 10, 2020, and August 6, 2021. Figure 1 describes the participant flow. All patients received SoC therapy, while one of the 20 HA patients received less than 1 h of HA therapy due to repeated circuit clotting. Patients that did not meet the inclusion criteria included 4 patients with significant polypharmacy, 9 patients who were below 18 years of age and 2 patients could not be randomized due to HA filters being immediately unavailable. Baseline characteristics show no significant differences between the groups (Table 1).

Comorbidities

There were no patients with known nonpsychiatric comorbidities except for human immunodeficiency virus. Eight (8) out of 40 patients were human immunodeficiency virus positive, two in the HA group, and six in the SoC group. None suffered from acquired immunodeficiency syndrome defining conditions.

Baseline Organ Support

All 40 patients required MV for respiratory muscle weakness, a low Glasgow Coma Scale (GCS), or both. Three patients required vasopressor support: two in the SoC group and one in the HA group. No other organ support was required at baseline.

Primary Outcome

The median ICU LOS was 6.5 days (IQR 4.5–10 days) in the HA group compared to 8 days (IQR 3.5–17 days) for the control group, $p = 0.58$.

Secondary Outcomes

Post hoc Comparison of ICU LOS among Patients with Excess ICU LOS ≥7 Days

The median ICU LOS was significantly shorter for the HA group, 10 days (IQR 8–12 days) compared to 17 days (IQR 14–22 days) for the control group, $p = 0.001$ (Table 2). The excess ICU LOS ≥7 days contributed 277 of the 359 ICU days (77%) (Tables 2 and 3).

Patients with ICU LOS <7 days contributed 82 of the 359 ICU study days, and there was no significant difference between the 2 study groups, $p = 0.12$, Mann-Whitney U test. The SoC group had a 77% excess ICU LOS (0.77, CI: 0.68–0.86) (Table 3). The associated costs with 95% CIs are given in Table 4.

Table 3. Outcomes among all patients and those with excess LOS (≥7 days)

	All patients		*p* value*	Excess LOS (≥7 days)		*p* value*	Sum (≥7 days)	
	SoC, n = 20	HA, *n* = 20		SoC, *n* = 10	HA, *n* = 10		SoC	HA
ICU days	8 (3.5–17)	6.5 (4.5–10)	0.58	17 (14–22)	10 (8–12)	0.001	177	100
ICU antidote days	7 (4–13.5)	6 (5–9.5)	0.44	13.5 (12–18)	8 (7–12)	0.009	142	92
MV days	7 (3–15)	6 (3–6)	0.22	15 (9–20)	6 (4–10)	0.001	155	67

Median values (IQR) provided. Sum, sum in days of the variable. * Mann-Whitney U test provided for excess LOS (≥7 days).

Table 4. Savings from the intervention (HA)

Group	Costs	Quantum
SoC	Excess ICU days (CI)	77 (68–86)
	*Cost per day	R 34,667
	Total ICU cost (CI)	R 2,669,359 (R 2,357,356 – R 2,981,362)
HA	Cost of the study intervention	
	CRRT × 2: R 8,000 per patient × 20	R 160,000
	HA filter: R 10,000/patient × 20	R 200,000
	Total intervention cost: HA group	R 360,000
HA	ICU savings from the intervention (CI)	R 2,309,359 (R1 997,356 – R2 621,362) *Estimated saving in EUR 146,162

EUR/ZAR rate of 15.8 on April 22, 2022, was used. CRRT, continuous renal replacement therapy. * Costs in ZAR at 2021 calculated rates [18].

Table 5. Antidote dose and platelet count

	All patients		*p* value*	Excess LOS (≥7 days)		*p* value*
	SoC, *n* = 20	HA, n = 20		SoC, *n* = 10	HA, *n* = 10	
Atropine, mg	431 (215–944)	315 (109–646)	0.26	887 (360–1,978)	316 (250–1,029)	0.04
Glycopyrrolate, mg	0 (0–104)	0 (0–0)	0.25	55(0–227)	0 (0–8.4)	0.21
Day 3 platelet	205 (148–247)	155 (125–201)	0.1	198 (71)	168 (52)	0.18

Median values (IQR) provided. Day 3 platelet, day 3 platelet count × 10^9/L. * Mann-Whitney U test for excess LOS (≥7 days).

Potential Savings

The potential savings if HA were applied to all patients in the SoC group are estimated to be R 115,468 (R 99,868 – R 131,068) per patient. This is equivalent to approximately EUR 7,308 per patient. In addition to these savings, 77 ICU bed days could potentially be gained.

Duration and Cumulative Dose of Antidote Therapy in the ICU

Antidote therapy included either atropine, glycopyrrolate, or both. Both the duration and cumulative dosage of antidote therapy (atropine) among patients with excess ICU LOS ≥7 days were significantly lower in the HA group compared to the SoC group (Tables 2 and 5).

Duration of MV

The HA group had a significantly shorter duration of MV among patients with excess ICU LOS ≥7 days when compared to SoC (Table 2).

Frequency of Complications and Day 28 Mortality

A total number of 53 complications occurred in the study population. We classified complications as severe if patients died (day 28 mortality), cardiac arrest occurred,

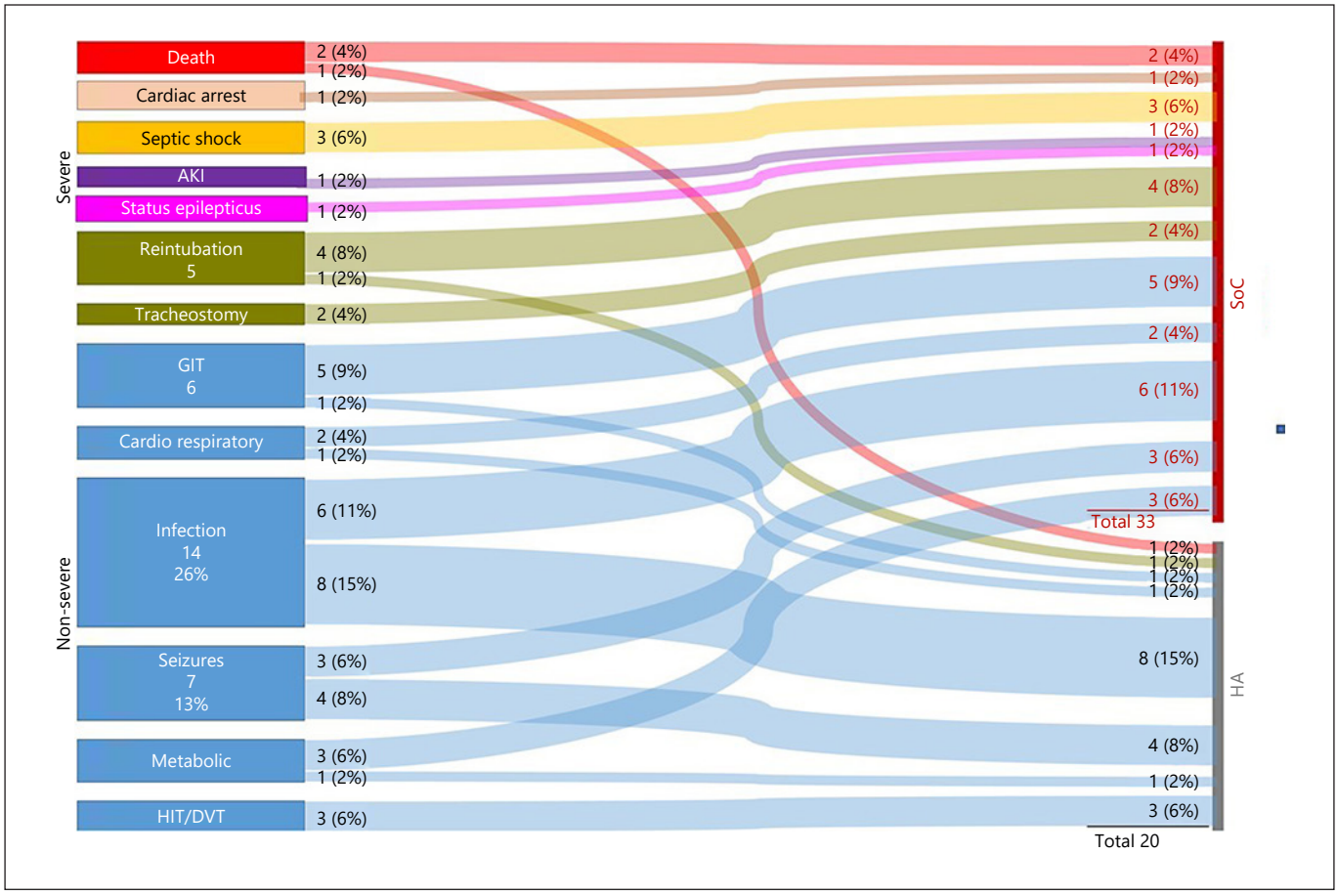

Fig. 2. Day 28 mortality and complication frequency. Severe complications (presented in multi-color) included death at 28 days, cardiac arrest, septic shock, acute kidney injury (AKI), status epilepticus, reintubation, and tracheostomy. Only 2 of the 20 complications that occurred in the HA group were severe, compared to 14 of the 33 complications in the SoC group, $p = 0.01$. The nonsevere complications (presented in blue) were equally distributed between the 2 groups, SoC (19) and HA (18).

organ dysfunction (septic shock, acute kidney injury, and status epilepticus) developed, and there was immediate necessity for ventilatory support after initial recovery (reintubation and tracheostomy). The HA group had a significantly lower proportion of severe complications (10%, $n = 2/20$) compared to 42% (14/33) in the SoC group, $p = 0.01$. This is a fourfold increase in severe complications in the SoC group compared to the HA group, RR = 4.2 (95% CI: 1.4–13.2) (Fig. 2). One patient died in the HA group (5%, 1/20) and two in the SoC group (10%, 2/20), $p = 0.54$, χ^2 test. Gastrointestinal complications included ileus and swallowing difficulties, cardiorespiratory complications included arrhythmias, nonspecific T-wave changes, and pneumothorax, while metabolic complications included hypoglycemia and hypernatremia not associated with neurological complications.

Platelet Count

There were no significant differences in the mean platelet count between the SoC group and the HA group on admission and again on ICU day 3 (Tables 1 and 5). No study patients required red cell transfusion.

Discussion

This study is the first randomized controlled trial assessing the utility of hemoperfusion/HA therapy for acute OPP/carbamate poisoning requiring ICU admission. We found ten other observational or retrospective nonrandomized studies evaluating the role of hemoperfusion in a similar setting. See Table 6 for a summary of their findings.

Table 6. HA/hemoperfusion for OPP: published data

Reference	Study design	*n* (HA)	*n* (SoC)	Filter	Outcomes (HA vs. SoC)
Bo et al. [12]	Observational/ not stated	20, HA three cycles	16, HA one cycle	HA230	IMS 5% versus 25% Atropine 251 versus 622 mg
Peng et al. [17]	Controlled nonrandomized	67	41	Charcoal	ICU LOS days 4 versus 6 MV days 5 versus 8 Atropine mg 568 versus 1,228 Mortality 7.5% versus 34%
Martinez Cheucos et al. [19]	Observational	10	None	Charcoal	Clearance 0.1% Mortality 20%
Kang et al. [20]	Retrospective observational	40	28	Charcoal	Mortality 20% versus 18%
Hu et al. [21]	Observational/ not stated	28 (HA + CVH)	28 (HA + SLEDD)	HA 230	Mortality 7% versus 4.5%
Altintop et al. [22]	Retrospective	17	7	Charcoal	No comparisons. Severity associated with mortality
Guo et al. [23]	Observational/ retrospective	49	49	Unknown	Mortality 6% versus 29%
Liang et al. [24]	Controlled trial - no details	31	30	HA330	Mortality 19% versus 16% LOS days 7.5 versus 16.1 MV days 3.8 versus 6.8
Gil et al. [25]	Retrospective observational	67	No control	Charcoal	HA associations Excess mortality 44% Low platelets 31.1% Bleeding 3% Low calcium 69.1%
Dong et al. [26]	Prospective nonrandomized	34 (10 cycles with CRRT)	34	HA230	Mortality% 3 versus 17 LOS days 11 versus 18 MV days 2.3 versus 7.4 Atropine mg 119 versus 485

The main finding in our study was that the intervention (HA) resulted in a significant reduction in ICU LOS among patients with excess ICU LOS ≥7 days. We interpret this as a reduction in risk for or decreased severity of IMS. Bo et al. [12] used the same HA 230 filter as in our study. They compared three to four cycles of HA compared to one cycle in an observational study and found a shorter time to awakening and a lower incidence (5%) of IMS in the multicycle group compared to 25% for the single-cycle group.

Peng et al. [17] carried out a prospective nonrandomized trial using a charcoal filter with 1–3 2-h cycles. The incidence of IMS was not statistically different, 30% in the HA group versus 37% in the SoC group. The older charcoal filter used by Peng et al. [17] may explain the lack of clinical efficacy.

In a retrospective observational study, Guo et al. [23] showed that HA was associated with a shorter LOS and a lower rate of IMS. An observational study by Dong et al. [26] demonstrated a reduction in hospital LOS from 18 to 11 days using a combination of 10 cycles of HA therapy coupled with hemofiltration. This is in keeping with the reduction from 17 to 10 days in our study. A less evident but crucial consequence of prolonged ICU LOS is the effect on ICU bed turnaround time and overall reduced bed availability. This effect together with high ICU demand costs lives.

We did not find published data examining costs. Our data suggest a significant cost saving of approximately EUR 7300 per ICU patient driven by a shorter LOS among patients with excess ICU LOS ≥7 days. Unsurprisingly, we found HA therapy to be associated with a gain of 77

ICU bed days over the approximate study duration of 365 days. Given the scarce resources in lower and lower middle-income countries, a higher burden of unplanned ICU admissions and associated higher mortality, this benefit cannot be overstated [8, 27, 28].

Our data demonstrated a lower antidote dose among patients with excess ICU LOS ≥7 days (316 mg vs. 887 mg) and duration (8 days vs. 13,5 days) in the HA group. Similar findings were demonstrated by Bo et al. and Dong et al. [12, 26] (Table 6). Overall, the lower atropine utilization associated with HA therapy is suggestive of enhanced toxin clearance.

A similar reduction in duration of MV was noted, 6 days for the HA group versus 15 days for SoC. Peng et al., Liang et al., and Dong et al. [16, 24, 26] have all shown similar reductions in the duration of MV (Table 6).

The combination of day 28 mortality and severe complications was significantly reduced in the HA group compared to the SoC group, 10% versus 42%, respectively. This is very relevant and implies that in addition to a reduction in ICU LOS, HA therapy impacted positively on clinical outcomes.

Gil et al. [25] described an association between HA therapy, low platelets (31%), and bleeding (3%). This was a retrospective noncomparative study and used charcoal as the adsorbent. Using new resin technology, we did not find significant thrombocytopenia or bleeding, requiring blood transfusion in this study. Our data provide evidence of the advantage of this new resin adsorber (HA 230), with respect to thrombocytopenia and bleeding risk compared to older charcoal filters.

There was 1 patient with a right lower limb deep venous thrombosis and 2 patients with clinically suspicious heparin-induced thrombosis. The timing was not consistent with heparin-induced thrombosis, and we did not have platelet factor 4 antibody assay investigations, but all 3 of these patients were found to be in HA group. These findings need to be further explored, and the use of citrate anticoagulation may be of value.

Limitations

This was a moderately sized trial at a single center, and caution is required when considering the generalizability of the findings. Despite these limitations, this is the first randomized controlled trial assessing the impact of HA therapy in significant detail. The ICU LOS advantage was shown among patients with excess LOS ≥7 days and not the entire group. However, the cost benefit, ICU bed days gained, and reduction of the combination of day 28 mortality and severe complications were found for the whole study population. This can be explained as IMS only affects up to 40% of patients, and these patients cannot be accurately predicted on admission.

Conclusion

HA therapy resulted in a significant cost saving driven by a reduced LOS among patients with excess ICU LOS ≥7 days. This therapy was also associated with a significant reduction of the combination of day 28 mortality and severe complications including cardiac arrest, organ dysfunction, reintubation, and tracheostomy.

Acknowledgment

We would like to acknowledge Rachel Mawelele for assisting with the co-ordination of activities during the study.

Statement of Ethics

This study protocol was reviewed and approved by the following ethical review board: Human Research Ethics Committee (Medical) [HREC] affiliated to the University of Witwatersrand, approval number [M190979]. The approval date was November 8, 2019. The trial is registered with a primary registry in the WHO registry network: the Pan African clinical trial registry (PACTR202009754904918). Written informed consent from each patient or their legal surrogate was obtained before randomization.

Conflict of Interest Statement

Shahed Omar received honoraria from Jafron Biomedical to the value of ZAR 26,000 (approximately USD 1,700) for Webinars during 2020 and 2021. All other authors have no conflicts of interest to declare.

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Jalo Enterprise Pty Ltd provided the hemadsorption filters for the study.

Author Contributions

Shahed Omar conceived the idea, designed the protocol, was involved in the analysis and interpretation of the work, created the first draft, approved the final version, and agreed to be accountable for all aspects of the work. Praveer Navin Sooka, Siyabonga Khoza, Martin Charles Van Rooyen, and Lushavhana Mashamba made a significant contribution to the acquisition of the data, revised the

draft critically, approved the final draft, and agreed to be accountable for all aspects of the work. S'fisosikayise Madi made a significant contribution to the analysis of the data, revised the draft critically, approved the final draft, and agreed to be accountable for all aspects of the work. Lufuno Rudo Mathivha made a significant contribution to the design of the work, revised the draft critically, approved the final draft, and agreed to be accountable for all aspects of the work. Jaya Anna George made a significant contribution to the conception of the work, revised the draft critically, approved the final draft, and agreed to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author. An electronic copy of de-identified data is available on request from the corresponding author.

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