ORIGINAL ARTICLE

Efficacy of Polymyxin B Hemoperfusion for Treatment of Sepsis

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Abstract

Objectives: To study the efficacy of polymyxin B hemoperfusion in addition to standard care for sepsis treatment.

Materials and methods: Fifty sepsis patients (mean age 54.26 ± 14.64 years; 68% males) were randomized to either the case group ($n = 25$; receiving Polymyxin B hemoperfusion in addition to standard ICU care) or the control group ($n = 25$; receiving standard ICU care only). The patients were followed up at frequent intervals of 6, 12, 24, 48, and 72 hours. A last follow-up on day 7 was done. The duration of the ICU stay and survival until day 7 were recorded. Changes in clinical and biochemical parameters were also noted and compared.

Results: Mean sequential organ failure assessment (SOFA) scores at admission were 3.44 ± 1.00 and 2.80 ± 0.82, respectively, in cases and controls. Cases as compared to controls showed faster, and sustainable improvement. No significant difference between the two groups was seen for mortality at day 7.

Conclusion: Polymyxin B hemoperfusion tends to show a faster recovery and a non-significant trend towards reduced mortality in ICU-admitted sepsis patients.

Keywords: Intensive care unit, Mortality, Polymyxin B, Sepsis, Sequential organ failure assessment.

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Highlight

Polymyxin B hemoperfusion has a role to play in recovery benefit in treatment of Sepsis.

Introduction

Sepsis is defined as a response of the body to an infective focus. Sepsis is marked by a struggle between foreign microbial agents and the body's homeostatic mechanisms to settle their relative supremacy. There is a strong interplay of a number of pro- and anti-inflammatory pathways which get activated in sepsis. The control and regulation of these pathways is a complex process targeted at maintaining equilibrium. However, this equilibrium is disturbed in some circumstances, resulting in an excessive proinflammatory response, which is reflected clinically as "the systemic inflammatory response syndrome (SIRS), multisystem organ dysfunction and ultimately death".[1]

Despite advancements in therapeutic strategies and treatment options, sepsis still remains to be a cause of significant morbidity and mortality.[2] Clinical trials evaluating the role of different intervening agents that could affect the targeted points of inflammatory pathways have failed to yield an effective response. "The pathophysiological basis of sepsis is the dysregulated, overwhelming production of cytokines in both ends of the spectra, leading to an uncontrolled pro- and anti-inflammatory response".[3,4] Collection of such inflammatory mediators and bacterial toxins in the circulation triggers various physiological reactions that result in further deterioration of the affected patient. To overcome this, in recent years, the practice of performing extracorporeal blood purification is gaining popularity. It is postulated that such extracorporeal blood purification will help in getting rid of inflammatory mediators as well as bacterial toxins from the blood that would be helpful in modulating the host inflammatory response in a favorable manner.[5]

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Purification of blood from inflammatory mediators and cytokines can be done by high-volume hemofiltration (HVHF), CytoSorb hemoadsorption cartridge, and coupled plasma filtration adsorption (CPFA) among others.[6] Polymyxin B hemoperfusion is another popular technique for endotoxin removal in sepsis. During hemoperfusion blood comes into direct contact with adsorbents. These adsorbents employ a number of physicochemical principles, like hydrogen bonding, hydrophobic interaction, van der Waals forces, and ionic bonding, in order to pull the solute or endotoxins in the blood.[5]

Polymyxin B was primarily developed as an antibiotic and acts by disrupting the cell-membrane permeability of *Gram-negative bacteria*. However, it could not be systemically used owing to the issues the severe renal toxicity associated with it. However, subsequently, polymyxin B-immobilized polystyrene-derived fibers

were developed for use in extracorporeal therapy as a means to remove endotoxin from the blood.[5]

Contemporary evidence with respect to the use of Polymyxin B in sepsis shows conflicting results, with few of the studies demonstrating mortality benefits and improvements in organ dysfunction while others have not reported any mortality benefit.[7–10] Unfortunately, most of the existing evidence is in the preliminary phase and does not have the sound backing of a well-planned methodological study like randomized-controlled trials, hence, the present study was planned to evaluate the safety and efficacy of Polymyxin B hemoperfusion in treatment of sepsis at a tertiary care teaching hospital in north India.

Materials and Methods

This prospective study was carried out at Department of General medicine, Command Hospital (CH), Central Command (CC), Lucknow, Uttar Pradesh, India after getting approval from Institutional Ethics Committee and after obtaining informed consent from the patients/caregivers to patients. A total of 50 consecutive ICU admitted sepsis patients aged between 16 and 70 years, requiring vasopressor to maintain MAP >65 mm Hg despite adequate volume resuscitation, having at least one of the following criteria for new onset organ dysfunction, viz. (1) Positive pressure ventilation (2) Thrombocytopenia with a platelet count <150,000 µ/L or 50% fall in the platelet count, (3) Fall in urine output < 0.5 mL/kg/hr for about 6 hours in spite of adequate fluid resuscitation were enrolled in the study. Patients not maintaining a minimum mean arterial pressure (MAP) of ≥65 mm Hg in spite of fluid resuscitation and optimal vasopressor support, having end stage kidney disease, patients having severe congestive heart failure with NYHA Class IV symptoms, post CPR patients without immediate return to communicative state, acute myocardial infarction in last 28 days, pregnant women, patients having uncontrolled hemorrhage, major trauma within the last 36 hours, those having severe leucopenia (<1,000 cells/mm^3) or severe thrombocytopenia (<30,000 cells/mm^3), HIV patients, extensive third-degree burn patients, body weight <35 kg, patients showing hypersensitivity to polymyxin B, patients with known sensitivity or allergy to heparin or has a history of heparin associated thrombocytopenia and those having any other chronic illness with poor chance of survival to hospital discharge.

The patients were then randomized using sealed and opaque envelopes into one of two study groups as follows:

Cases (n = 25): In these patients, polymyxin B hemoperfusion cartridge filter was used in addition to the standard ICU protocol used for the management of sepsis patients at our facility. A total of 2 sessions spanning 2 hours, 24 hours apart, were carried out.

Controls (n = 25): In these patients underwent, standard ICU protocol for the management of sepsis patients was used.

Heparin was used as the anticoagulant as and where necessary and feasible. The recommended heparin doses for PMX were as follows: Priming (circuit) 4 Units (U)/mL; Bolus 2,500 U, Maintenance (per hemoperfusion line) 10 U/kg/hr. to a maximum of 1,000 U/hr.

All the patients were followed up at 6, 12, 24, 48, 72 hours and day 7 after admission. At each follow-up following parameters were noted:

- Blood pressure
- Urinary output
- Serum lactate
- Platelet count
- Glasgow coma score (GCS)
- Sequential Organ Failure Assessment (SOFA)
- Duration of ICU stay upto day 7
- Death

Improvement in SOFA scores at 72 hours was the primary outcome of concern. Secondary outcomes were change in blood pressure, urine output, Urea, Serum Creatinine, electrolytes at 72 hours.

Final outcome was assessed at day 7.

Statistical Analysis

Data analysis was done using IBM Stats 21.0 version (SPSS 21.0). Chi-square, Independent samples '*t*'-test, and paired '*t*'-tests were used to compare the data.

Results

The mean age of cases and controls was 53.04 ± 15.50 and 55.48 ± 13.92 years, respectively ($p = 0.561$). Majority of cases (56%) as well as controls (80%) were males ($p = 0.069$). The mean body weight of cases was 60.48 ± 7.38 kg, which was comparable to that of controls (60.80 ± 10.50 years) ($p = 0.901$). Statistically, there was no significant difference between the two groups for age, sex, systolic blood pressure, urinary output, serum lactate, platelet count, interleukin-6 and procalcitonin levels. Mean SOFA, Vasopressor dependency index and D-Dimer were significantly higher in cases as compared to controls ($p < 0.05$). Culture positivity rate was 20% in cases as compared to 15% in controls, but this difference was not significant statistically ($p = 0.440$) (Table 1).

At 72 hours, the survival rate was 44% in cases as compared to 48% in controls, thus showing no statistically significant difference between the two groups ($p = 0.776$). Among survivors, as compared to baseline, cases showed a significant decline in VDI, S. lactate, SOFA, interleukin-6, CRP, procalcitonin and D-dimer levels and a significant increase in urinary output. Among controls too, a significant decline in S. lactate, SOFA, interleukin-6, CRP, procalcitonin and D-dimer levels was seen. Controls did not show a significant decline in VDI as compared to baseline but showed a significant decline in platelet count ($p < 0.05$) (Table 2).

At day 7, the survival rate was 44% in cases as compared to 40% in controls, but this difference was not significant statistically ($p = 0.774$). Among survivors, as compared to baseline cases, there was a significant decline in VDI, S. lactate, SOFA, interleukin-6, CRP, procalcitonin and D-dimer levels and a significant increase in urinary output. However, among controls, a significant decline from baseline was seen in S. lactate, interleukin-6, CRP, procalcitonin and D-dimer levels. As compared to baseline, controls did not show a significant change in urinary output, VDI and SOFA scores but showed a significant decline in platelet count (Table 3).

Discussion

The present study showed a faster, and more sustainable recovery path in sepsis cases treated with use of polymyxin B in addition to the standard treatment protocol as compared to those placed on the standard treatment protocol alone, though no significant impact of additional use of polymyxin B could be seen on mortality.

Table 1: Baseline characteristics of the patients in two study groups ($n = 30$)

		Cases (n = 25)		*Controls (n = 25)*		*Statistical significance*	
S. No.	*Variable/Parameter*	*Mean*	*SD*	*Mean*	*SD*	*t*	*p*
1.	Age (years)	53.04	15.50	55.48	13.92	–0.585	0.561
2.	Male:Female	14 (56%): 11 (44%)		20 (80%): 5 (20%)		$\chi^2 = 3.309$; $p = 0.069$	
3.	Body weight (kg)	60.48	7.38	60.80	10.50	–0.125	0.901
4.	SBP (mm Hg)	118.6	19.22	128.9	22.42	–1.734	0.089
5.	Urinary output (mL/24 hr)	164.6	305.3	272.6	305.6	–1.250	0.217
6.	S. lactate (mmol/L)	4.14	0.79	4.09	0.88	0.216	0.830
7.	Platelet count (L/cumm)	1.57	0.97	2.00	1.29	–1.337	0.188
8.	SOFA	3.44	1.00	2.80	0.82	2.474	0.017
9.	Interleukin-6	33.18	6.06	37.01	12.18	–1.411	0.165
10.	CRP	27.11	7.21	28.20	7.57	–0.521	0.605
11.	Procalcitonin	20.40	4.38	19.81	5.98	0.402	0.690
12.	D-dimer	1043	521	706.2	216.6	2.892	0.004
13.	Vasopressor dependency index (VDI)	25.57	18.32	8.50	7.48	4.312	<0.001
14.	Culture positivity	5 (20%)		3 (15%)		$\chi^2 = 0.595$; $p = 0.440$	

Table 2: Comparison of change in different study parameters in two study groups at 72 hours

		Cases (n = 25)		*Controls (n = 25)*	
S. No.	*Variable/Parameter*	*Mean*	*SD*	*Mean*	*SD*
		11/25 (44%)		12/25 (48%)	
		$\chi^2 = 0.081$; $p = 0.776$			
No. of survivors at 72 hours		*(n = 11)*		*(n = 12)*	
1.	SBP (mm Hg)	–9.46	23.98	–6.92	35.79
2.	VDI	–11.31	7.06*	3.90	14.89
3.	Urinary output (mL/24 hr)	531.36	765.96*	21.92	363.62
4.	S. lactate (mmol/L)	–3.09	0.47*	–1.62	1.25*
5.	Platelet count (L/cumm)	0.00	0.93	–0.62	0.92*
6.	SOFA	–2.46	0.69*	–0.50	1.38
7.	Interleukin-6	–25.49	5.92*	–15.36	7.92*
8.	CRP	–16.42	8.21*	–13.93	9.15*
9.	Procalcitonin	–19.99	3.82	–11.59	5.10*
10.	D-dimer	–549.0	399.0*	–321.9	219.6*

*Significant at $p < 0.05$ as compared to corresponding baseline value in the group

One of the most important impacts of the polymyxin B use was a swift reduction in vasopressor dependency and a significant improvement in urinary output. Polymyxin B use also seemed to have a protective effect against a fall in platelet count in the patients. The extent of improvement in SOFA scores was also higher in Polymyxin added group as compared to controls.

The findings in the present study were in consonance with those reported by Kim et al.[11] who also found that the total SOFA score, renal SOFA and coagulation SOFA improved in the PMX group, which was significant in comparison to the control group. In an earlier study, Cutuli et al.[12] too observed a significant improvement in the cumulative SOFA score as well as in different organ-specific components of SOFA within 72 hours of the first cycle of PMX. It may be highlighted that the use of PMX has been shown to be instrumental in modulating human leukocyte antigen DR, vasopressor need and other clinical benefits associated with endotoxin removal.[12–14] The findings of the present study also show that PMX helps to reduce inflammatory activity and tends to reduce the severity of sepsis.

The present study is one of the few studies evaluating the impact of PMX use on the clinical course of sepsis, however, most of the earlier studies had focused on the mortality. In the present study, we found that ICU mortality was lower in cases (56%) as compared to that in controls (60%), but this difference was not significant statistically.

As far as the impact of hemoperfusion by PMX on mortality is concerned, the current evidence is divided. There are many studies that similar to the present study do not find it to be significant however, there are some studies that find it to be useful in reducing the mortality.[7,12,13,15–19] There was one study that reported that PMX impact on mortality is dependent on the initial SOFA scores.[9] One of the reasons for absence of difference in mortality rate between the two groups could be owing to a small sample size and a high mortality rate.

Table 3: Comparison of Change in different study parameters in two study groups at day 7

S. No.	Variable/Parameter	Cases (n = 25) Mean	Cases (n = 25) SD	Controls (n = 25) Mean	Controls (n = 25) SD
		11/25 (44%)		10/25 (40%)	
		$\chi^2 = 0.082$; $p = 0.774$			
No. of survivors at day 7		*(n = 11)*		*(n = 12)*	
1.	SBP (mm Hg)	2.36	25.73	1.60	16.91
2.	VDI	–14.32	7.25*	–0.69	10.24
3.	Urinary output (mL/24 hr)	580.91	819.2*	19.00	523.1
4.	S. lactate (mmol/L)	–3.10	0.47*	–1.62	1.25*
5.	Platelet count (L/cumm)	0.19	0.98	–0.39	0.95
6.	SOFA	–2.45	0.69*	–0.50	1.38
7.	Interleukin-6	–29.10	5.83*	–23.37	8.26*
8.	CRP	–18.84	7.77*	–19.71	8.94*
9.	Procalcitonin	–21.09	3.63*	–14.49	6.54*
10.	D-dimer	–736.5	405.8*	–441.7	204.8*

*Significant improvement ($p < 0.05$) at day 7 as compared to baseline amongst survivors in both cases and controls

Despite showing some promising results, the present study suffered from certain limitations, like a small sample size, owing to which even the baseline characteristics could not be matched completely between the two groups and could have some confounding impact on the outcome too. Moreover, our facility, being a base services hospital, gets referrals from various primary and secondary care services facilities, and most of the sepsis patients are very serious and have a poor chance of survival, resulting in a high ICU mortality rate. We also feel that the use of some other ICU severity scores, like APACHE II could have helped to study other dimensions of hemoperfusion through PMX intervention. Further studies on a larger sample size with the inclusion of other variables that indicate the clinical course and outcome are recommended. However, within limitations, the present study shows the usefulness of hemoperfusion by PMX that is sufficient for the recommendation of its routine use.

Conclusion

The findings of the study showed that addition of polymyxin B hemoperfusion helped to improve the clinical course, particularly restoration of organ function, and outcomes in ICU admitted sepsis patients. Further studies on a larger sample size and longer duration of follow-up are recommended.

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