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Original Research Article

Polygeline in patients with hypovolemia caused by accidental trauma: a prospective, multicentric, safety study

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ABSTRACT

Background: Objective of present study was to evaluate the safety of polygeline (Haemaccel®) and its effect on vital sign parameters in patients with hypovolemia caused by accidental trauma.
Methods: Adverse drug reactions (ADRs) of polygeline within 6 hours after administration, and the effect of polygeline infusion on vital sign parameters, in trauma patients hospitalized at the emergency department, were evaluated in this prospective, multicentric, post-marketing observational study.
Results: One hundred forty patients (men: 81.4%; women: 18.6%), with a mean (±standard deviation) age of 33.7±10.6 years, were enrolled. At the time of admission, mean blood volume loss was 1400.1±558.8ml, with 86.4% patients reporting blood volume loss of >15%; 49.3% patients presented with class-II hypovolemia. No ADRs or any unusual clinically significant changes were reported within 6 hours of polygeline administration. All vital parameters (blood pressure and pulse rate) significantly improved at 1 hour of polygeline administration; this trend was sustained until 6 hours ($p<0.001$). Reduction in respiratory rate was significant at 1 and 6 hours versus baseline ($p<0.001$). Urine output and central venous oxygen saturation also showed significant improvement at 1 and 6 hours after treatment initiation ($p<0.001$). Arterial pH and mean blood lactate levels also showed a significant change from the baseline ($p<0.05$) at both 1 and 6 hours.
Conclusions: Polygeline was found to be safe and effective in improving hemodynamic stability in patients with hypovolemia due to accidental trauma.

Keywords: Colloids, Hemorrhage, Hypovolemia, Polygeline, Trauma

INTRODUCTION

India has one of the highest numbers of fatalities due to road accidents. As per the report by the Ministry of Road Transport, Government of India, nearly 0.15 million people died in road traffic accidents in India in 2016.[1] Hypovolemic shock resulting in reduced intravascular volume and impaired tissue perfusion is a major cause of mortality after accidental trauma.

Fluid resuscitation with colloids or crystalloids is considered the mainstay of emergency therapeutic intervention in these patients with traumatic hypovolemic shock. In a prospective review of 111 consecutive patients who died after admission for treatment of injuries, the most common shortcomings in patient management were related to inadequate fluid resuscitation.[2]

Although crystalloids form the first line of management, colloid solutions are considered to be more efficient than crystalloids in terms of the amount of fluid that remains in the intravascular space; a smaller amount of fluid is required when using colloids compared to crystalloids in achieving similar hemodynamic goals.[3-6] Further, colloidal preparations may achieve fluid resuscitation goals quickly because of rapid plasma expansion and hence are commonly used in fluid therapies in patients with hypovolemic shock.[6-8]

However, concerns have been raised about the safety of colloids amidst their side effects such as coagulopathy, renal failure, and tissue storage, which in turn may result in conditions such as pruritus or extensive organ depositions.[9] Additionally, colloids cause alterations in the immune response to critical illness and account for 2.5% of all anaphylactic reactions intraoperatively.[10] Compared with the natural colloid albumin, gelatins are also found to be associated with higher incidences of anaphylactic reactions.[11]

Polygeline (Haemaccel®) 3.5% is a gelatin-based (urea-cross-linked gelatin) colloidal intravenous solution with electrolytes. It is an effective volume expander, widely used in the resuscitation of trauma patients.[8] In view of the reported cases of anaphylactic reactions to colloids, it is imperative to understand the safety aspects of polygeline in a real-world healthcare emergency setting. Moreover, the safety of polygeline, especially immediate hypersensitivity reactions or cross-sensitivity with other agents, in a real-world setting, has not been studied so far.

Furthermore, as immediate resuscitation is of utmost importance in emergency departments, serious adverse drug reactions (ADRs) due to polygeline may be under-reported. Hence, the objective of this study was to assess the safety of polygeline within 6 hours of its administration to patients with hypovolemia after accidental trauma being treated in the emergency department. The volume of blood transfusion required with polygeline for the management of hypovolemia, due to accidental trauma, was also assessed.

METHODS

Study design

This was a prospective, open-label, non-comparative, observational, post-marketing study (ELEC5001) evaluating the safety of polygeline up to 6 hours after administration in patients presented with hypovolemia due to accidental trauma, hospitalized in the emergency department of three hospitals across three cities in India. The study was conducted from November 2016 to July 2017. All patients were administered polygeline intravenously as per prescribing information and treating physician's discretion and were followed up to 6 hours after administration.

The study was conducted in accordance with the principles of Declaration of Helsinki and in compliance with Good Clinical Practice guidelines. The study protocol and the informed consent form were reviewed and approved by respective Institutional Review Boards before study initiation. Since the study was conducted in accidental trauma patients, being treated on priority basis, informed consent for collecting patient data was primarily obtained from patient's Legally Acceptable Representative (LAR) or patient themselves when they could give consent.

Study population

Patients, aged 18 to 55 years, with any class of hypovolemia caused by accidental trauma (per Advanced Trauma Life Support criteria of acute hemorrhage), treated with polygeline within 3 hours of admission were included in this study. Patients in whom polygeline was administrated for other indications such as surgical trauma, cardiac surgery, during labor and those with impaired renal or hepatic function were excluded from the study.

Endpoints

The primary endpoint of the study was to evaluate the number and nature of ADRs observed within 6 hours of polygeline administration in patients with hypovolemia due to accidental trauma. The secondary endpoint was to evaluate the percentage of patients transfused with whole blood and the average volume of blood transfused while on polygeline treatment.

Assessments

Vitals and physical examination findings such as systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), arterial pH, pulse rate (PR), respiratory rate (RR), urine output, central venous oxygen saturation, and blood lactate were recorded on admission and at 1 and 6 hours after polygeline administration.

Statistical analysis

Baseline values are presented in terms of mean and standard deviation (SD) for continuous variables, and categorical data are summarized through numbers and percentages. Effect of polygeline on vital and physical examination parameters was assessed by comparing baseline values with follow-up values recorded at 1 and 6 hours after administration using a paired t-test. All statistical tests were two-sided and $p<0.05$ was considered statistically significant.

RESULTS

A total of 140 patients out of 114 men (81.4%) and 26 women (18.6%), with a mean (±SD) age of 33.7±10.6

years, were enrolled. The mean blood volume loss was 1400.1mL, with 19 (13.6%) patients reporting blood volume loss of ≤15% and 121 (86.4%) patients reporting blood volume loss of >15%.

Table 1: Demographic and clinical characteristics.

Demographic and clinical characteristics (n=140)	
Age (years) (Mean±SD)	33.7±10.6
Sex (male, female) n (%)	114 (81.4%), 26 (18.6%)
Weight (kg) (Mean±SD)	62.8±9.6
Blood volume loss (ml) (Mean±SD)	1400.1±558.8
Type of trauma, n (%)	
Accidental trauma	140 (100%)
Degree of hypovolemia, n (%)	
Loss of blood ≤15%	19 (13.6%)
Loss of blood >15%	121 (86.4%)
Grade of hypovolemia, n (%)	
Class I	19 (13.6%)
Class II	69 (49.3%)
Class III	44 (31.4%)
Class IV	8 (5.7%)
Clinical signs and symptoms of hypovolemia, n (%)	
Anxiety	104 (74.3%)
Tachycardia (>100 beats/min)	85 (60.7%)
Hypotension (systolic blood pressure <90mmHg)	64 (45.7%)
Dizziness	54 (38.6%)
Confusion	46 (32.9%)
Loss of consciousness	36 (25.7%)
Profuse sweating	34 (24.3%)
Decreased or no urine output (<1mL/kg/hr)	33 (23.6%)
Tachypnea (>30 breaths/min)	32 (22.9%)
Chest pain	21 (15.0%)
Cyanosis	9 (6.4%)
Bradypnea (<10 breaths/min)	1 (0.7%)
Vital sign parameters (Mean±SD)	
Systolic blood pressure (mmHg) (n=140)	94.19±20.13
Diastolic blood pressure (mmHg) (n=140)	62.76±12.66
Mean arterial pressure (mmHg) (n=137)	71.41±13.72
Arterial pH (n=105)	7.19±0.19
Pulse rate (beats/min) (n=140)	103.57±14.85
Respiratory rate (breaths/min) (n=140)	23.68±5.02
Urine output (mL/hr) (n=113)	28.59±19.15
Central venous oxygen saturation (%) (n=133)	94.93±5.44
Blood lactate (mmol/L) (n=52)	3.00±1.24

N=total number of subjects in each treatment group; n=number of subjects with events; SD=standard deviation

Almost half of the patients (69 [49.3%]) presented with class II hypovolemia at the time of admission (class I: 13.60%; class III: 31.40%; class IV: 5.70%). A total of 104 (74.3%) patients had anxiety, 85 (60.7%) patients had tachycardia, and 64 (45.7%) patients had hypotension. About 111 (79.3) patients were on concomitant medications. Most commonly used concomitant medications were H_2-receptor antagonists (63 [45.0%]), Vitamin B complex (50 [35.7%]), calcium (32 [22.9%]), and serotonin ($5HT_3$) antagonists (28 [20.0%]). Demographic and clinical characteristics of the patients at baseline are provided in Table 1.

Mean volume of polygeline administered was 667±251.7mL. There were no treatment-emergent or other significant ADRs, including immediate allergic reactions, or events of death reported in this study. Overall, polygeline administration was found to be safe and well tolerated amongst accidental trauma patients with hypovolemia.

Sixty-nine (49.3%) patients required blood transfusion during the study, of which 26 (18.6%) received one cycle, 35 (25.0%) received two cycles, 5 (3.6%) received three cycles, and three (2.1%) received four cycles of blood transfusion. Mean volume of blood administered was 572.0±253.4mL.

The effects of polygeline intensive therapy on vital parameters are presented in Table 2. All the vital parameters (DBP, SBP, and PR) and MAP significantly improved at 1 hour of polygeline administration, which was sustained at 6 hours ($p<0.001$). The reduction in RR was significant at 1 and 6 hours ($p<0.001$).

Urine output also showed significant improvement at 1 and 6 hours ($p<0.001$) from baseline. The baseline arterial pH was 7.19, which increased significantly at 1 hour of polygeline administration ($p<0.05$) and was sustained until 6 hours ($p<0.05$).

Similar improvement was also noted in central venous oxygen saturation at 1 and 6 hours ($p<0.001$). Further, polygeline administration resulted in significant reduction in mean blood lactate levels ($p<0.001$) at 1 and 6 hours, compared with baseline.

DISCUSSION

Fluid resuscitation is the primary therapeutic intervention in patients with traumatic hemorrhagic shock, and plasma expanders play a key role in these hypovolemic patients in emergency settings.[7,12,13] Isotonic crystalloids and synthetic colloids remain the most widely used plasma expanders.

Colloidal preparations can achieve fluid resuscitation goals quickly because of rapid plasma expansion and are commonly used fluid therapies in patients with hypovolemic shock.[6,7] Colloids further have an advantage of better intravascular persistence when compared with crystalloids. The European guidelines for the management of bleeding after major trauma also recommend the addition of colloids to treat hemodynamically unstable bleeding trauma patients.[14] Though a Cochrane systematic review on colloids for fluid resuscitation concluded that no evidence exists to suggest one colloid solution is more effective or safe than the other; polygeline has been reported to be effective and safe for the correction of hypovolemia.[15]

Table 2: Mean change in vital parameters at 1 and 6 hours, compared with baseline (at admission).

Variables	N=140	On Admission	1 Hour	Change (95% CI)	P value	N=140	6 Hours	Change (95% CI)	P value
	n	Mean±SD	Mean±SD			n	Mean±SD		
SBP (mmHg)	139	94.19±20.13	104.87±16.53	10.50[a] (8.34, 12.67)	0.001	136	111.95 ±12.06	18.12[a] (15.15, 21.09)	0.001
DBP (mmHg)	139	62.76±12.66	69.32±11.48	6.33[a] (4.71, 7.95)	0.001	136	73.57±10.60	10.65[a] (8.73, 12.57)	0.001
MAP (mmHg)	136	71.41±13.72	79.86±11.74	8.24[a] (6.41, 10.07)	0.001	132	85.88±9.98	14.05[a] (11.83, 16.26)	0.001
Arterial pH	95	7.19±0.19	7.21±0.19	0.01[b] (0.00, 0.01)	0.036	95	7.21±0.20	0.01[b] (0.00, 0.02)	0.021
PR (beats/min)	140	103.57±14.85	95.79±13.74	-7.78[a] (-9.27, -6.28)	0.001	137	89.79±13.91	-14.34[a] (-16.35, -12.34)	0.001
RR (breaths/min)	140	23.68±5.02	21.54±4.27	-2.14[a] (-2.57, -1.72)	0.001	137	20.16±3.73	-3.63[a] (-4.38, -2.88)	0.001
Urine output (mL/hr)	112	28.59±19.15	29.37±18.37	1.63[a] (1.04, 2.23)	0.001	111	29.66±18.02	3.70[a] (2.73, 4.67)	0.001
CVOS (%)	132	94.93±5.44	96.72±3.58	1.82[a] (1.08, 2.57)	0.001	129	97.72±2.58	2.86[a] (1.94, 3.77)	0.001
BL (mmol/L)	51	3.00±1.24	2.50±0.76	-0.39[a] (-0.54, -0.25)	0.001	51	1.83±0.55	-1.06[a] (-1.25, -0.86)	0.001

BL=blood lactate; CI=confidence interval; CVOS=central venous oxygen saturation; DBP=diastolic blood pressure; MAP=mean arterial pressure; PR=pulse rate; RR=respiratory rate; SBP=systolic blood pressure; SD=standard deviation; a: The mean difference is significant at the 0.001 level; b: The mean difference is significant at the 0.05 level

Many studies have reported about the anaphylactic reactions after polygeline infusion.[10,11] Other safety concerns reported with regard to polygeline use are coagulopathy and circulatory disturbances.[9-11,16] In one such study reported in Sweden between 1971 and 1977, 9 cases of anaphylactic reactions were observed. Symptoms occurred 0-30 min after polygeline infusion initiation. Symptoms like low BP, bronchospasm, shivering, fever and erticaria were reported.[17] The adverse reactions of polygeline could be attributed to the release of histamine from an excess of hexamethylene diisocyanate, the cross-linking agent used in the development of Haemaccel. The presence of excess traces of hexamethylene diisocyanate in the supernatant of this colloid is thought to have a direct effect on the mast cells, resulting in histamine release.[18] Nevertheless, certain reports have described a sudden decrease in blood pressure without any signs of histamine release.[19-21] In 1979, considering the increase in the adverse reactions reported, an improvisation in the manufacturing process of polygeline was undertaken to reduce the amount of hexamethylene diisocyanate.[22] Post this improvisation in the manufacturing process, there has been a decrease in the number of adverse reactions reported. Weis in 1983 in a multicentric trial noted 9 reactions in 1147 patients, of which eight were cutaneous in nature and one was a hypotensive effect; but no life-threatening events were reported.[23] These findings are consistent with the recent results reported by Singh and Ali and Singh et al, in patients with hypovolemia due to accidental trauma, where no ADRs were reported up to 24 hours after polygeline administration.[24,25]

In this study, the mean total volume of polygeline administered was 667±251.7mL, which was based on patients' condition. This dose was found to be well tolerated by all patients. In contrast to the concerns reported by reviews and meta-analyses regarding the safety of polygeline, no ADRs or any unusual clinically significant changes were reported within 6 hours of polygeline administration in this study.[9-11,16] Worsening of symptoms due to any underlying medical history was not reported for any patient.

Polygeline was found to be significantly effective ($p<0.05$) in improving vital signs (pulse rate and blood pressure), which are indicators of hemodynamic instability. Blood pressure, MAP, PR, and RR improved at 1 hour of administration and were consistent at 6 hours of treatment. Urine output and central venous oxygen saturation also showed improvement at 1 hour of intravenous polygeline administration. Furthermore, arterial pH increased from baseline after 1 hour, which was consistently maintained until 6 hours with corresponding reduction in blood lactate levels. The hemodynamic parameters and overall status of all patients were improved by 6 hours. This indicates that colloidal preparations such as polygeline are helpful in improving hemodynamic parameters in patients with hypovolemic shock.[26]

These outcomes are similar to the results reported by Singh et al, in a study of 69 patients with traumatic injury, where SBP and DBP increased significantly at 6 hours after treatment with polygeline.[25] Similar results were reported by Singh and Ali (2016) in patients with long bone fractures.[24] These reports were in line with the data published by Orgev in 1969 on the response to pre-operative resuscitation with polygeline in patients with severe and moderate degrees of shock.[27] In severe cases, the average SBP before resuscitation was 52mmHg, which increased to 115mmHg after resuscitation with Haemaccel. In moderate cases, the mean SBP improved from 88mmHg to 115mmHg after treatment.[27] This indicates that polygeline is useful in improving the blood pressure in patients with moderate and severe degrees of shock. The effectiveness of polygeline solution in preventing hypotension could be attributed to its longer stay in the intravascular compartment, as compared with crystalloids.[28] Renal dysfunction in trauma patients may develop for several reasons including insufficiently treated hypovolemia. However, gelatins have no considerable damaging effects on the kidneys.[29] New-generation gelatins are rapidly eliminated from the body mainly by glomerular filtration, with about 71% elimination in urine by 24 hours and a very less amount is metabolized.[30] This shows that polygeline does not accumulate in patients with renal failure. Hence, laboratory indicators of renal functions were not measured in this study.

Administration of blood and blood products is vital to the treatment of patients with severe hemorrhagic shock.[31] In this study, the mean blood volume loss was 1400.1mL. Only 69 (49.3%) of the patients treated with polygeline required blood transfusion. Out of these 69 patients, 67 (97.10%) reported blood volume loss of >15%, and most patients (30 [43.8%]) presented with class II hypovolemia. The mean volume of blood required was 572.0mL, with only 25% of patients receiving two or more transfusion cycles. This could be attributed to the fact that in such hypovolemic situations, polygeline was useful in maintaining plasma expansion because of its macromolecular structure, and, in more severe hemorrhage, could help in maintaining circulation until blood is available. New-generation gelatins such as polygeline do not impair hemostasis. They help in filling the lacunae that exist between crystalloids and blood products.[32]

The total volume and type of fluid infused during initial resuscitation has a strong influence on the outcome.[31] Even brief delays in blood replacement in patients with hemorrhagic shock may result in higher mortality rates and worsen cardiac responsiveness to hemorrhage.[33] The plasma expansion property of polygeline has a direct metabolic effect. The high expansion property of polygeline corrects blood volume more effectively, limiting the risks of tissue hypoperfusion responsible for lactic acidosis.

The compatibility of a plasma substitute with different drug products is of great importance for delivering safe, acceptable, and efficacious administration of two drugs simultaneously in severe and emergency conditions.[13] In our study, we found that polygeline could be safely co-administered with other drug products, such as antibacterials (e.g., cephalosporins), proton pump inhibitors, serotonin (5HT3) antagonists.

Limitations of this study include convenience sampling, lack of a comparator or control group, and short follow-up period. Nevertheless, the real-world clinical practice setting in which the study was conducted supplements for the genuineness of our findings. Long-term studies with a large sample size and a comparator group are warranted to substantiate our findings.

Polygeline was found to be safe and well-tolerated in this study. No ADRs or treatment-related adverse reactions were reported during the course of this study. Polygeline was also effective in improving hemodynamic parameters in patients with hypovolemia due to accidental trauma. The improvement was seen within 1 hour of polygeline administration and was maintained consistently until 6 hours. Thus, intravenous polygeline can be considered as a suitable resuscitative fluid along with the other modalities for the management of hemodynamic instability in patients with hypovolemia due to traumatic injury.

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