Effectiveness and Safety of Polygeline in Patients with Hypovolemia due to Trauma

Ajai Singh, Sabir Ali, Rohita Shetty

Department of Orthopedic Surgery, King George’s Medical University, Lucknow, Uttar Pradesh, 1Acute Care Division, Abbott Healthcare Pvt Ltd, Mumbai, Maharashtra, India

Abstract

Background: This retrospective study examined the effectiveness and safety of polygeline in adult patients with hypovolemia due to traumatic injury. Materials and Methods: Polygeline was administered after evaluating the amount of blood loss and estimating hematological and biochemical parameters. Changes in vital signs, serum electrolytes, arterial pH, and serum lactate were evaluated. The safety was evaluated by recording the adverse events if any. Results: Sixty patients with the mean age 37.5 ± 11.26 years were included in the study. All patients had blood loss <20%. The mean total polygeline administered was 1025.0 ± 464.18 ml. Blood transfusion was required in 3.33% of patients. Diastolic, systolic, and mean arterial blood pressure and pulse rate significantly increased after 1 h of polygeline administration (P < 0.0001). There was a trend toward increase in urine output (P = 0.0715) after 1 h. The improvement in vital parameters was consistent at 6, 14, and 18 h after administration of polygeline. Arterial pH significantly increased from 7.2 ± 0.12 to 7.3 ± 0.11 after 1 h of administration (P < 0.0001) and was consistent till 24 h (P = 0.035). Blood lactate decreased after 1 h (P < 0.0001). Changes in laboratory parameters were not clinically significant. After mean duration hospital stay of 10.5 ± 4.63 days all patients were discharged without any clinically significant abnormality or adverse event. Conclusion: Polygeline improved hemodynamic stability in patients with hypovolemia due to traumatic injury. The improvement was seen within 1 h (golden hour) of polygeline administration and maintained consistently. Polygeline can be safely administered to patients with traumatic injury to improve hemodynamic parameters and achieve stability.

Keywords: Colloids, hemorrhage, trauma

Introduction

Severe traumatic injury is one of the major health problems resulting in deaths of more than 5 million people across the world with deaths due to uncontrolled bleeding in many cases.[1] Similarly in India, traumatic injury is a significant issue. According to the global status report on road safety 2013, annually more than 0.2 million people die in road traffic accidents in India.[2]

In an Indian study conducted in a major trauma center, the most common incidence of trauma in people was between 15 and 30 years of age.[3] The management of traumatic hemorrhagic shock mainly includes hemodynamic and coagulation management.[4] Hemodynamic management primarily consists of the fluid therapy and use of vasopressor agents, if needed. The use of intravenous fluids is one of the most common and universal interventions in hypovolemia due to traumatic injury. In clinical practice, colloids are often used along with crystalloids for fluid management. The overaggressive fluid administration should be avoided as it may lead to adverse consequences such as disruption of clot and further exacerbation of bleeding.[5] Colloids being high molecular weight substances mainly remain in the intravascular compartment and create oncotic pressure. Colloids have an advantage of better intravascular persistence when compared to crystalloids. Colloid preparations differ in their properties because of molecular weight, osmolality, oncotic pressure, and half-life variance across the group. Gelatins are one of the colloidal preparations available for fluid volume replacement. The early gelatins, because of high molecular weight, had limitations for clinical use. Modified gelatine preparations have

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Address for correspondence: Dr. Ajai Singh, Department of Orthopedic Surgery, King George’s Medical University, Lucknow, Uttar Pradesh, India. E-mail: as29762@gmail.com

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lower molecular weight compared to older ones. Polygeline, a modified gelatine preparation is available as Hemaccel. Hemaccel is a polymer of urea and polypeptides prepared from gelatin is available as a 3.5% solution. It also contains sodium, potassium, calcium, and chloride ions. Polygeline is readily excreted in the urine due to its short half-life. Data on efficacy and safety of polygeline in hypovolemia due to traumatic injuries are limited.

Objective
The objective of this study was to evaluate effectiveness and safety of polygeline in adult patients with hypovolemia due to accidental trauma.

Materials and Methods
In this nonrandomized, noncomparative, retrospective study, patients with hypovolemia due to an accidental traumatic injury received intravenous polygeline after estimating the amount of blood loss and laboratory parameters. Hematological and coagulation parameters including hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, packed cell volume, prothrombin time and partial thromboplastin time, and biochemical parameters (blood urea and serum creatinine) were checked before giving polygeline. On the basis of blood loss, the patients were classified into different classes of hemorrhagic shock. Total amount of polygeline administered during treatment was measured. The number of patients requiring transfusion of blood/blood components was noted. Changes in vital signs (pulse rate, blood pressure, and respiratory rate), urine output, time taken to achieve hemodynamic stabilization, change in arterial pH and lactate (from baseline), and duration of hospital stay (total number of days from the date of admission to discharge/referral/death) were measured. Hemodynamic stabilization was defined as mean arterial pressure (MAP) ≥65 mmHg and any one of the following maintained for 4 h: central venous pressure between 8 and 12 mmHg or urine output >1 ml/kg/h or central venous oxygen saturation (ScvO₂) ≥70% or lactate ≤4 mmol/L. Time to achieve hemodynamic stabilization was calculated as the time taken for each of the parameters to reach the level. Clinical outcome, survival rate, and mortality rates were recorded. Safety was evaluated on the basis of incidence of adverse events if any.

Statistical analysis
Continuous data are summarized with descriptive statistics such as mean (± standard deviation), and categorical data are summarized using frequencies and percentages. The statistical and safety analyses were performed using SAS® version 9.3 (SAS Institute Inc., USA). Paired t-test was used to analyze the difference in vital parameters and laboratory values after treatment compared to baseline. All statistical testing were compared with two-sided significance level α = 0.05. The value of P < 0.05 was considered statistically significant.

Results
A total of sixty patients with mean age of 37.5 ± 11.26 years were included in this study. Sixty percent patients in the study were <40 years of age (Table 1).

The majority of patients had blood loss of Class I (80%), whereas 20% had Class II. A total of 62% patients had about 500 ml blood loss, whereas 200, 250, 300, 400, 700, 750, 800, and 1000 ml blood loss was seen in 3%, 5%, 7%, 2%, 2%, 12%, 2%, and 7% of patients, respectively. A total of 55% and 25% of patients were anxious and confused, respectively whereas 20% did not have any central nervous system (CNS) related symptom. The American College of Surgeons Advanced Trauma Life Support (ATLS) classification of patients in the study based on clinical presentation is shown in Figure 1.

Hematological and biochemical parameters before administration of polygeline are given in Table 2.

The mean total polygeline administered was 1025.0 ± 464.18 ml. The percentage of patients administered 500, 1000, 1500, and 2000 ml polygeline were 28%, 48% 15%, and 7%, respectively.
Only 2% of patients required 2500 ml polygeline. Blood transfusion was required in 2 (3.33%) patients. Mean volume of blood administered was 350 ml.

All the vital parameters (diastolic blood pressure, systolic blood pressure, and pulse rate) and mean arterial blood pressure significantly increased after 1 h of polygeline administration ($P<0.0001$). The reduction in respiratory rate was also significant after 1 h. The improvement observed in all vital parameters was significant and consistent at 6, 14, and 18 h after administration of polygeline. The increase in blood pressure and pulse rate was significant at 24 h also [Table 3].

Urine output showed nonsignificant improvement after 1 h ($P = 0.0715$). Similarly, trend of improvement was observed in respiratory rate ($P = 0.0773$) at 24 h, whereas the increase in urine output was not significant after 24 h [Table 3].

Administration of polygeline resulted in significant increase in serum sodium and chloride level ($P<0.0001$) whereas the change in serum calcium was not significant ($P = 0.1755$) [Table 4].

The baseline arterial pH of 7.2 ± 0.12 increased significantly after 1 h of administration ($P < 0.0001$) was consistent till 24 h ($P = 0.035$) corresponding blood lactate decreased significantly after 1 h ($P < 0.0001$) and was consistent till 18 h ($P = 0.0004$). The difference in lactate blood at 24 h was not significant [Table 5].

All sixty patients achieved hemodynamic stabilization (MAP ≥65 mmHg and lactate <4 mmol/L) with median time of 14 h. Fifty-six patients required the median time of 14 h for achieving urine output ≥2 ml/kg. Similarly, 57 patients needed median time of 14 h to reach ScvO$_2$ >70%.

Changes in hemoglobin, RBC count, blood urea and serum creatinine were not significant [Table 6]. There was increase in WBC count, but not clinically significant.

The mean duration of hospital stay was 10.5 ± 4.63 days. All patients were discharged without any clinically significant abnormality resulting in 100% survival rate. No patients in the study reported any adverse events.

**Discussion**

Traumatic injury is a common problem in day to day life. Severe traumatic injury leading to hypovolemia requires immediate medical intervention. Fluid therapy plays a critical role in the management of hypovolemia. In this retrospective study, we evaluated the effectiveness and safety of Hemaccel, a polygeline colloidal preparation in sixty patients with hypovolemia due to traumatic injury. As per the ATLS classification system,[8] based on blood loss, vital signs, urine output, and mental status we classified the study participants into four classes. Considering blood loss, majority of our patients were into Class I type of blood loss, that is, blood loss of up to 750 ml or up to 15% blood loss.

Colloids have been used for volume replacement in patients admitted in Intensive Care Unit.[9] Similarly, its use has also been used in surgical cases,[10] and following coronary artery bypass surgery.[11] A Cochrane systematic review on colloids for fluid resuscitation concluded that there is no evidence to suggest one colloid solution is more effective or safe than the other but, polygeline has been reported to be effective and safe for correction of hypovolemia.[12] The mean total polygeline administered was 1025.0 ± 464.18 ml. With the advances in the management of resuscitation, a concept of “permissive hypotension” is being practiced in many centers. During the phase of active bleeding elevated MAP further, increases the risk of hemorrhage. Permissive hypotension (also known as hypotensive resuscitation) is a concept of less aggressive fluid administration. Centers following this practice, keep MAP lower than normal for lesser blood loss. Permissive hypotension may have a survival benefit.[13] In our study, the volume of polygeline was administered based on the patient’s condition and was well tolerated by all patients without increased bleeding.

The mean hospital stay duration for all patients was 10.5 days. 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. There was rapid onset of improvement in blood pressure and respiratory rate seen after 1 h of administration and was consistent over 24 h. Urine output also started improving after 1 h of administration.

### Table 3: Changes in clinical parameters after administration of polygeline

| Parameter                     | Baseline | 1 h ($P$) | 6 h ($P$) | 14 h ($P$) | 18 h ($P$) | 24 h ($P$) |
|-------------------------------|----------|-----------|-----------|-----------|-----------|-----------|
| Diastolic blood pressure (mmHg) | 59.0±9.24 | 64.5±11.05 ($<0.0001$) | 73.4±11.43 ($<0.0001$) | 78.0±7.94 ($<0.0001$) | 80.6±3.91 ($<0.0001$) | 80.0±0.00 (0.0577) |
| Mean arterial pressure (mmHg)  | 66.0±10.24 | 71.5±12.52 ($<0.0001$) | 81.7±12.87 ($<0.0001$) | 88.1±9.68 ($<0.0001$) | 91.6±4.31 ($<0.0001$) | 90.5±5.51 (0.0402) |
| Systolic blood pressure (mmHg) | 79.8±13.55 | 86.0±16.10 ($<0.0001$) | 97.8±17.9 ($<0.0001$) | 109.2±14.02 ($<0.0001$) | 114.4±8.27 ($<0.0001$) | 113.8±14.93 (0.0354) |
| Pulse rate (/min)              | 112.9±12.14 | 107.2±12.42 ($<0.0001$) | 94.7±13.22 ($<0.0001$) | 85.9±13.07 ($<0.0001$) | 80.1±6.36 ($<0.0001$) | 92.5±5.00 (0.0273) |
| Respiratory rate (/min)        | 21.0±5.84 | 18.5±5.10 ($<0.0001$) | 14.9±4.27 ($<0.0001$) | 13.5±2.73 ($<0.0001$) | 12.2±0.73 ($<0.0001$) | 12.8±1.50 (0.0773) |
| Urine output (ml/min)          | 0.2±0.12 | 0.2±0.17 ($<0.0001$) | 0.2±0.11 ($<0.0001$) | 0.3±0.08 ($<0.0001$) | 0.3±0.08 ($<0.0001$) | 0.3±0.14 (0.3189) |

**SD**: Standard deviation
intravenous polygeline administration. Survival rate was 100%. Laboratory investigation reports of blood urea, serum creatinine, hemoglobin, RBC count, and serum calcium, showed no abnormality at the time of discharge. Records showed an increase in baseline arterial pH after 1 h which was consistently maintained till 24 h with corresponding reduction in blood lactate.

Hemodynamic parameters and overall status of all patients was improved at the time of discharge as per records. Colloidal preparations interfere with hemostasis mechanisms due to hemodilution or other specific effects on platelet function or coagulation parameters. Gelatin has been shown to impair platelet adhesion during heart surgery. The risk of gelatins causing dilutional coagulopathy is less compared to dextrans and starches. To rule out existing coagulopathy, we measured partial thromboplastin time and prothrombin time before administering polygeline which were 27 ± 3.09 and 10.1 ± 1.73, respectively.

Hemacel contains polygeline with electrolytes sodium, potassium, calcium, and chloride ions. In this study, there was an increase in serum sodium and chloride level compared to baseline. Gelatins produce 70%–80% volume expansion and therefore holds a promising place in patients with hypovolemia. The half-life of gelatins is 4–6 h. In our study, blood transfusion was required in only two patients.

Table 4: Changes in serum electrolytes after administration of polygeline

| Parameter (unit) | On admission (baseline) | At the time of discharge | Change from baseline (P) |
|------------------|-------------------------|--------------------------|-------------------------|
| Serum sodium (mmol/L) | 128.5±6.01 | 141.1±2.28 | <0.0001 |
| Serum chloride (mmol/L) | 90.8±7.37 | 103.3±2.45 | <0.0001 |
| Serum calcium (mg/dL) | 9.2±0.88 | 9.8±0.85 | 0.1755 |

Hypovolemia resulted in anxiety or confusion (CNS symptoms) in 80% of study patients. Intravenous polygeline treatment was well tolerated by study participants. The mean molecular weight of the polygeline is 30,000. After infusion, gelatins are rapidly eliminated by the kidney with about 71% elimination in urine by 24 h and very less amount is metabolized. Older generation hydroxyethyl starches with high molar substitution can accumulate in the plasma while gelatins are readily excreted without effect of renal impairment.

The newer hydroxyethyl starch preparations having low molecular weight and lower molecular substitution are associated with lesser adverse events. Such preparations tend to have better safety profile in terms of hemostasis and renal function. An in vitro study showed hydroxyethyl starch preparation 130/0.4 to have lesser negative impact on platelet function compared to hydroxyethyl starch preparations having greater molecular weight and degree of substitution.

To evaluate the effect on renal functions, we repeated serum creatinine and blood urea. No significant effect of polygeline was seen on these parameters. These observations demonstrate the renal safety of polygeline in traumatic patients with hypovolemia.

Allergic reactions such as fever, chills, rash, gastrointestinal disturbances, or hypotension could be possible due to histamine release induced by colloids such as albumin, hetastarch, and polygeline. In our study, no patient reported allergic or anaphylactic reaction with polygeline. Similarly, no other adverse event was reported throughout the study.

Overall results of this retrospective study show that polygeline is effective in traumatic patients with hypovolemia. Similarly, the absence of adverse events or clinically significant abnormality demonstrated well-tolerated safety profile of polygeline.

The study has some limitations. We included a majority of patients with <20% blood loss (80% patients with ATLS Class I

Table 5: Changes in other laboratory parameters after administration of polygeline

| Parameter | Mean±SD |
|-----------|---------|
| Arterial pH | 7.2±0.12 (0.0001) |
| Blood lactate (mmol/L) | 5.2±1.19 (0.0001) |
| Central venous oxygen saturation (%) | 67.6±11.72 (0.0001) |

SD: Standard deviation

Table 6: Laboratory values

| Parameter (unit) | On admission (baseline) | At the time of discharge | Change from baseline (P) |
|------------------|-------------------------|--------------------------|-------------------------|
| Hemoglobin (g/dL) | 11.4±1.12 | 11.3±1.03 | 0.9374 |
| RBC count (×10⁶/µL) | 4.3±0.50 | 4.1±0.76 | 0.7608 |
| WBC - total (×10⁹/µL) | 7.348±1737.67 | 9192±1182.13 | 0.0360 |
| Blood urea (mg/dL) | 26.3±5.18 | 23.3±1.15 | 0.3828 |
| Serum creatinine (mg/dL) | 1.3±1.81 | 0.8±0.21 | 0.5000 |

RBC: Red blood cell, WBC: White blood cell
and 20% Class II). The small sample size and convenience sampling are the other limitations of this study. Randomized studies with large sample size are required to confirm the observations of our study.

**Conclusion**

Intravenous administration of polygeline significantly contributed to the improvement of clinical outcomes of hypovolemia due to trauma. The survival rate was 100%. Polygeline did not adversely affect renal functions or cause significant clinical adverse events. 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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**Conflicts of interest**

There are no conflicts of interest.

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