Polygeline in hypovolemia due to traumatic injury: Results of an open label study in Indian population

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ABSTRACT

Objective: Evaluation of efficacy and safety of polygeline in adult patients with hypovolemia.

Materials and Methods: In an open label, non-comparative study intravenous infusion of polygeline was administered to adult patients with hypovolemia following traumatic injury. Efficacy was evaluated by noting changes in the signs and symptoms of hypovolemia while safety was evaluated by recording adverse events.

Results: Forty nine patients with mean age 33.67 ± 15.36 years having long bones fracture were enrolled. The mean and percentage of blood loss was 1291.30 ± 168.43 ml and 26.09 ± 3.13% respectively. Polygeline was given to all patients while other intravenous fluids were required in 44 patients. Baseline heart rate reduced from 100.09 ± 9.13 per minute to 98.45 ± 12.60 and 86 ± 10.10 at one hour (P < 0.05) and at two hours (P < 0.001) respectively. The reduction in heart rate was significant at other time points (<0.001) too. Systolic blood pressure (BP) increased from 79.06 ± 10.22 to 94.27 ± 9.18 mm Hg at one hour and 109.18 ± 6.80 mm Hg at two hours (both one and two hours; P < 0.001). Similarly diastolic BP also increased from 57.79 ± 10.59 to 62.89 ± 9.62 mm Hg at one hour and 69.41 ± 11.59 mm Hg at two hours (both one and two hours; P < 0.001). Rise in blood pressure was consistent till 24 hours. Overall improvement was seen in 97.92% patients. Improvement in pallor, dry tongue, and skin changes six and 24 hours was observed in 77.08%, 79.17%, 59.57% and 87.50%, 100% and 93.62% patients respectively (all parameters at six and 24 hours P < 0.0001). No patient reported adverse event.

Conclusion: Polygeline is safe and effective treatment for correcting hemodynamic instability in hypovolemia due to trauma. Use of polygeline resulted in early and significant improvement in hemodynamic parameters.

Key Words: Colloids, efficacy, hemorrhage, hypovolemia, polygeline, trauma

INTRODUCTION

Traumatic injury is a significant global health problem resulting in more than five million annual deaths because of severe injury worldwide. Post-traumatic bleeding, if uncontrolled can potentially lead to death.[1] Undoubtedly, intraperitoneal and intrathoracic bleeding are risk factors for hypovolemic shock in trauma; however, non-cavitary blood loss due to fracture of long bone can also lead to hypovolemic shock.[2] The principles of management of patients following traumatic injury include diagnosis and management of blood loss in order to restore tissue perfusion and hemodynamic stability.[3] Appropriate fluid resuscitation is essential for maintaining tissue perfusion.[3] In fact, the first therapeutic intervention is fluid resuscitation...
in patients with bleeding due to trauma.\textsuperscript{[4]} Hence, fluid therapy is strongly recommended in the patients with bleeding due to trauma.\textsuperscript{[1]} Crystalloid and colloids are often used in the management of such patients. Colloidal preparations can achieve fluid resuscitation goals quickly due to rapid plasma expansion\textsuperscript{[4]} and are commonly used fluid therapies in patients with hypovolemic shock.\textsuperscript{[3]} Polygeline, a cross linked polymer of urea and polypeptides prepared from degraded gelatin\textsuperscript{[6,7]} is one such preparation available in India and routinely used in patients with hypovolemia due to trauma. Polygeline has half life of 2-6 hours which is increased in patients with renal impairment.\textsuperscript{[5]} The published literature regarding use of polygeline in the management of hypovolemia following fracture of long bone is limited.

**Objective**
The objective of the study was to evaluate the efficacy and safety of polygeline in the treatment of hypovolemia due to traumatic injury resulting in fracture of long bones.

**MATERIALS AND METHODS**

In an open label, non-comparative, single centre study adult patients with >18 years of age with clinical diagnosis of hypovolemia following fracture of long bones were enrolled after their informed consent. Patients with hypersensitivity to polygeline or any other constituent were excluded from the study. Pregnant and breast feeding women, patients with concomitant asthma and unconscious patients were not included in the study. Serum electrolytes, biochemical tests and haematological tests including prothrombin time were done at baseline. Polygeline available in flexible plastic infusion bottles containing 500 mL of a 3.5% colloidal solution of polygeline was infused intravenously. The speed and duration of the infusion was adjusted according to the blood pressure readings. Patients with less than 20% blood loss were given only polygeline while those with >20% blood loss were treated with polygeline and other fluid therapy like blood transfusion or crystalloid solution as per the clinical judgement of the investigator. Clinical assessment was done at baseline and repeated every hour till six hours and then at ten, 14, 18 and 24 hours. Vital parameters (pulse rate, blood pressure, respiratory rate, body temperature), fluid input and urine output were be monitored every hour for six hours followed by every four hours till 24 hours or as deemed appropriate by the investigator. The efficacy was assessed based on the signs and symptoms of hypovolemia i.e., pallor, condition of skin (cold, clammy) and vital signs i.e., temperature, pulse rate, blood pressure and respiratory rate monitoring. Fluid input and urine output was recorded throughout the study. Clinical improvement was defined as correction of hypovolemia while clinical failure was defined as no significant clinical response to therapy. Safety of the study medication was evaluated by recording adverse events and any clinically significant abnormality. The study was started after receiving an approval from institutional ethics committee.

**Statistical analysis**
Continuous variables such as heart rate, blood pressure, respiratory rate and temperature are expressed as mean ± SD while categorical variables are expressed as frequency and percentages. The changes in continuous variables were compared with paired “t” test while Chi square test was applied to assess improvement in categorical variables. \( P \) value of < 0.05 was considered statistically significant.

**RESULTS**
A total of 49 patients (male-77.6%; female-22.4%) with mean age of 33.67 ± 15.36 years having fracture of long bones were enrolled in the study. The mean and percentage blood loss was 1291.30 ± 168.43 ml and 26.09 ± 3.13% respectively. Blood loss of more than 20% was present in 97.96% patients while only one patient had blood loss of less than 20%. The baseline biochemistry parameters are shown in Table 1.

Polygeline infusion was given to all patients. A total of 89.80% patients received polygeline infusion <1000 ml in 24 hours while 10.20% patients required more than 1000 ml polygeline infusion in 24 hours. Other intravenous fluids were required in 44 patients in 24 hours. Blood and crystalloid infusion was given in 22 patients each.

Baseline systolic blood pressure of 79.06 ± 10.22 mm Hg increased to 94.27 ± 9.18 mm Hg at the end of one hour and to 109.18 ± 6.80 mm Hg at the end of two hours. The rise in systolic blood pressure was 19.24% and 38.09% at the end of one and two hours respectively (\( P < 0.001 \)). The mean blood pressure after 24 hours of administration of polygeline was 112.07 ± 9.36 mm Hg. The improvement in systolic blood pressure was significant at all time points [\( P < 0.001 \); Figure 1].

Baseline diastolic blood pressure improved from 57.79 ± 10.59 to 62.89 ± 9.62 mm Hg at the end of one hour and to 69.41 ± 11.59 mm Hg at the end of two hours. The rise in diastolic blood pressure at the end of one and two hours was 8.84% and 20.11% respectively (\( P < 0.001 \)). The diastolic blood pressure was maintained

**Table 1: Baseline biochemistry parameters**

| Serum Electrolyte | Mean (±SD) | Range |
|-------------------|------------|-------|
| Sodium (mEq/L) \( (n=49) \) | 137.94 (±4.90) | 125-145 |
| Potassium (mEq/L) \( (n=49) \) | 4.28 (±0.41) | 3.5-6.8 |
| Calcium \( (n=48) \) | 4.08 (±0.35) | 3-5 |

SD: Standard deviation.
above 70 mm Hg over 24 hours. The improvement in diastolic blood pressure was significant at all measured time points ($P < 0.001$) [Figure 1, Table 2].

Changes in other vital parameters compared to baseline are shown in Table 2. Baseline heart rate of 100.09 ± 8.13 reduced to 98.45 ± 12.65 per minute at the end of one hour ($P < 0.05$) and to 86.00 ± 10.10 per minute at the end of two hours ($P < 0.001$). The improvement was significant at other time points ($P < 0.001$) too. The change in respiratory rate and body temperature was not significant ($P > 0.05$ at all measured time points). Overall improvement was seen in 97.92% patients while only one patient did not show an improvement.

Improvement in pallor was seen in 77.08% and 87.50% patients at six hours and 24 hours respectively (both six and 24 hours; $P < 0.0001$). Similarly, improvement in dry tongue was seen in 79.17% and 100% patients at six and 24 hours respectively (both six and 24 hours; $P < 0.0001$). Improvement in skin changes was observed in 59.57% patients at six hours ($P < 0.0001$) and 93.62% patients at 24 hours ($P < 0.0001$)[Figure 2]. Urine output improved from 507.95 ± 72.29 ml at baseline to 631.11 ± 43.02 ml after two hours ($P < 0.001$). The improvement in urine output was consistent up to 24 hours.

The study medication was very well tolerated by study participants. No adverse events including allergic manifestations were reported by the patients during study period. Similarly, no clinically significant abnormal changes were observed during entire study period.

**DISCUSSION**

Non-cavitary blood loss due to long bone fractures can be responsible for shock in many patients.\[^2\] Significance of fluid therapy in patients undergoing repair of fracture of long bones such as proximal femoral fracture has been documented by Sinclair and colleagues.\[^8\]

We evaluated efficacy and safety of intravenous polygeline in adult patients hypovolemia associated with long bone fractures. Mean age of 33.67 years with predominantly male population in our study indicate common occurrence of long bone fractures in the males with active age group. In our study, patients with hypovolemia due to long bone fracture responded very well to intravenously administered polygeline. Overall, polygeline administration was associated with significant improvement in pallor, dry tongue, and skin changes. The improvement observed in pallor at six and 24 hours could be attributed to blood transfusion in 22 patients. Significant improvement in heart rate and blood pressure was associated with improvement in signs of dehydration such as dry tongue and skin changes indicating improvement in hemodynamic stability with

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**Table 2: Improvement in vital parameters**

| Time point | Heart rate (Beats/min) | Blood pressure (mm Hg) | Respiratory rate (per minute) | Body temperature ($^\circ$F) |
|------------|------------------------|------------------------|-------------------------------|-----------------------------|
|            | $N = 49$               | $N = 49$               | $N = 49$                      | $N = 49$                    |
|            | Mean (± SD)            | Systolic               | Diastolic                     | Mean (± SD)                 | Mean (± SD)                 |
| Baseline   | 100.09 (±8.13)         | 79.06 (±10.22)         | 57.79 (±10.59)                | 28.36 (±3.55)               | 97.40 (±0.78)               |
| One hour   | 98.45 (±12.65)         | 94.27 (±9.18)          | 62.89 (±9.62)                 | 25.57 (±2.64)               | 97.61 (±0.74)               |
| Two hours  | 86.00 (±10.10)         | 109.18 (±6.80)         | 69.41 (±11.59)                | 24.16 (±1.45)               | 97.69 (±0.76)               |
| Three hours| 85.68 (±11.04)         | 108.86 (±7.74)         | 74.56 (±10.48)                | 23.84 (±2.39)               | 97.89 (±0.75)               |
| Four hours | 77.16 (±5.79)          | 110.38 (±7.74)         | 75.86 (±14.45)                | 23.56 (±2.39)               | 98.10 (±0.71)               |
| Five hours | 78.36 (±6.73)          | 111.58 (±6.68)         | 77.06 (±15.39)                | 25.56 (±3.33)               | 98.18 (±0.73)               |
| Six hours  | 79.56 (±7.67)          | 112.81 (±9.62)         | 78.29 (±16.33)                | 27.79 (±4.27)               | 98.38 (±0.72)               |
| Ten hours  | 80.79 (±8.61)          | 113.01 (±9.72)         | 78.49 (±16.43)                | 27.99 (±4.37)               | 98.17 (±0.76)               |
| 14 hours   | 80.99 (±8.71)          | 112.69 (±9.48)         | 78.17 (±16.19)                | 27.67 (±4.13)               | 98.25 (±0.78)               |
| 18 hours   | 80.67 (±8.47)          | 112.39 (±9.60)         | 77.87 (±16.31)                | 27.37 (±4.25)               | 98.15 (±0.77)               |
| 24 hours   | 80.37 (±8.59)          | 112.07 (±9.36)         | 77.55 (±16.07)                | 27.05 (±4.01)               | 98.23 (±0.79)               |

SD: Standard deviation
Correction of hypovolemia. The improvement in heart rate and blood pressure was significant as early as after one hour. Close to 90% patients also received other intravenous fluids. The possibility of confounding effects of this treatment should be considered.

Colloids are broadly divided into natural and synthetic preparations. Modified gelatins, known as new generation gelatins are available for clinical use. The clinical advantages for use of gelatins include less renal impairment due to small molecular size.\(^6\) In our study, fluid resuscitation with polygeline resulted in significant improvement in urine output. We did not specifically measure the laboratory indicators of renal functions such serum creatinine or glomerular filtration rate.

Though functionally similar, colloids differ in their safety aspects.\(^9\) Colloids can cause dose-dependent dilutional coagulopathy\(^10\) and impair blood coagulation.\(^11\) The potential of dilutional coagulopathy differs between different colloids, highest with dextran followed by starch, gelatins and albumin.\(^10\) Intravenous administration of polygeline was very well tolerated by the patients in our study without any adverse event. We did not monitor blood coagulation parameters, which was one of the limitations of our study.

Colloids are useful in the fluid resuscitation strategies in non-surgical conditions such as cirrhotic ascites and stage I-II of dengue hemorrhagic fever\(^12,13\) as well as surgical\(^9\) patients. Our results show their usefulness in hypovolemia due to long bone fractures. We observed that polygeline is clinically safe and effective in correcting hemodynamic instability due to hypovolemia following injury due to trauma.

In the absence many large scale clinical studies either in favor or against the use of non-blood component fluid resuscitation,\(^14\) our study provides insights into the effect of colloid therapy in the management of hypovolemia due to traumatic injury.

Observational, open label study design, small sample size and subjects parameters of evaluation are the limitations of this study. Randomized controlled clinical study in a larger number of patients is required to confirm the observations of this study.

**CONCLUSION**

Treatment with polygeline results in early and consistent improvement in blood pressure and heart rate in patients with hemodynamic instability due to hypovolemia. The improvement in hemodynamic parameters is also associated with improvement of clinical features; hence polygeline can be safely used in patients with hypovolemia due to trauma.

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**Conflicts of interest**
There are no conflicts of interest.

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