

Is There a Role for a Rheologic Agent in Transfusion?

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Abstract

Background: Decreased microvascular blood flow and hemodynamic changes potentially compromising tissue oxygen delivery have recently been reported in some sickle cell anemia patients following transfusion^{1,2}. While transfusion increases blood oxygen carrying capacity, it also increases blood viscosity. The anticipated benefits of transfusion could be diminished or lost if the net effect of decreased blood flow more than offsets increased O₂ carrying capacity.

Red blood cell (RBC) aggregates impair blood flow in the microcirculation where the majority of oxygen and nutrient exchange occur. Since older RBC aggregate more than younger RBC, we hypothesized that increased RBC aggregation following transfusion of older or "storage lesioned" RBC may contribute to decreased blood flow.

MST-188 (purified poloxamer 188) is a rheologic agent currently under investigation in a phase 3 trial in pediatric sickle patients hospitalized with acute vaso-occlusive crisis. We hypothesize that this poloxamer may inhibit aggregation of older or storage-injured RBC and potentially have utility in transfusion.

Objective: To determine the relative effect of poloxamer 188 on the aggregation of "older" versus "younger" RBC.

Methods: RBC obtained from 4 healthy donors were age-separated via centrifugation into younger (least-dense 10%) and older (most-dense 10%) cells, then re-suspended in 3% dextran 70 containing poloxamer 188 at 1 or 5 mg/ml. The extent of RBC aggregation (Aggregation Index) was measured using a Myrenne aggregometer system.

Results: Older RBC exhibited a mean aggregation index (AI) approximately 140% greater than younger RBC. Addition of poloxamer 188 resulted in a concentration dependent reduction in AI for both older and younger RBC, with the effect more pronounced for older RBC. At 5 mg/ml there was a greater than a 2- fold reduction in mean AI compared to control for older RBC.

Conclusion: Poloxamer 188 inhibits aggregation of older and younger RBC and may have utility for treating and/or preventing transfusion-induced decreases in microvascular blood flow. Studies of MST-188 using storage lesioned RBC are planned.

Background

Decreased microvascular blood flow and hemodynamic changes potentially compromising tissue oxygen delivery have recently been reported in some sickle cell anemia patients following transfusion.^{1,2} While transfusion increases blood oxygen carrying capacity, it also increases blood viscosity. The anticipated benefits of transfusion could be diminished or lost if the net effect of decreased blood flow more than offsets increased O₂ carrying capacity.

Red blood cell (RBC) aggregates impair blood flow in the microcirculation where the majority of oxygen and nutrient exchange occur. Since older RBC aggregate more than younger RBC,³ we hypothesized that increased RBC aggregation following transfusion of older or "storage lesioned" RBC may contribute to decreased blood flow.

MST-188 (purified poloxamer 188) is a rheologic agent that blocks hydrophobic adhesive interactions in the circulation. It is currently under investigation in a phase 3 multi-center trial in pediatric sickle cell patients hospitalized with acute vaso-occlusive crisis (EPIC: Evaluation of Purified Poloxamer 188 In Children). We hypothesize that poloxamer 188 may inhibit aggregation of older or storage-injured RBC and potentially have utility to offset transfusion related decreases in perfusion.

Materials & Methods

Blood samples were obtained by venipuncture into EDTA anti-coagulated tubes from 4 healthy adult volunteers. RBCs were age-separated via high speed centrifugation into populations of younger (least-dense 10%) and older (most-dense 10%) cells.⁴ Following age separation RBCs were re-suspended in 3% dextran 70 containing poloxamer 188 at 1 or 5 mg/ml. The extent of RBC aggregation (Aggregation Index) was measured using a Myrenne aggregometer system.

Results

The results of the RBC aggregation studies are shown in Figure 1 as the mean \pm the SEM obtained from four donors. Consistent with previous reports³, greater aggregation was observed with older compared to younger RBCs. The mean aggregation index (AI) observed with older RBC was 44 ± 5 compared to an AI of 18 ± 4 for younger RBC (at the 0 mg/ml concentration). The addition of poloxamer 188 (at 1.0 mg/ml and 5.0 mg/ml) reduced the aggregation index of both younger and older RBC in a concentration dependent manner.

Figure 1. Dextran 70 (3%) Induced Aggregation of Age Separated RBCs

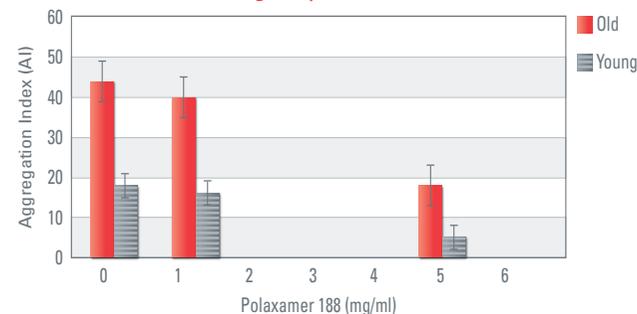
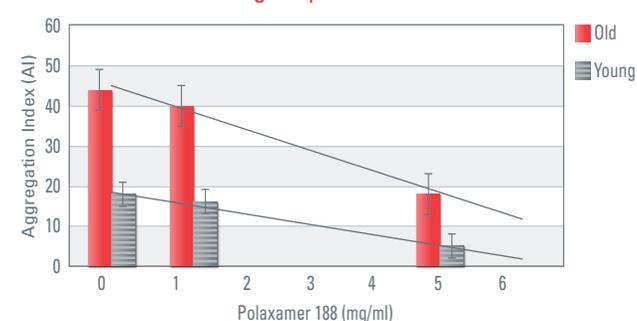


Figure 2 plots the slope of the inhibition of aggregation index achieved with poloxamer 188. In older RBCs the slope of the inhibition line was more than twice that for younger RBCs. This suggests that the potency of poloxamer 188 on RBC aggregation is proportionately greater in older versus younger cells.

Figure 2. Dextran 70 (3%) Induced Aggregation of Age Separated RBCs



Discussion

Red cell aggregation may be of relevance for identifying an impairment of aged or storage lesioned red blood cells with regard to their ability to flow within the microcirculation.

Poloxamer 188 is a polymeric agent composed of a central block of hydrophobic poly(oxypropylene) flanked on both sides with poly(oxyethylene). It is thought to improve blood flow in the low shear microcirculation by adhering to hydrophobic areas of cells and molecules and preventing hydrophobic adhesive interactions.

Results of this study suggest that poloxamer 188 inhibits the aggregation of both older and younger RBC. Interestingly, the potency of poloxamer 188 was greater on older RBC compared to younger cells. Although the mechanistic explanation of this observation is currently unknown, it may be that older cells have greater membrane damage with more adhesive hydrophobic domains amenable to repair by poloxamer 188.

If transfusion of older or storage lesioned RBC results in increased aggregation in the microcirculation (and a corresponding decrease in perfusion) MST-188 (purified poloxamer 188) may offer an option for increasing the efficacy of transfusion.

Additional studies investigating this hypothesis are planned.

References

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