DEM Journal Club

Article Appraisal

Article: Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs. a 1:1:2 Ratio and Mortality in Patients with Severe Trauma. The PROPPR Randomized Clinical Trial

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Background and Study Objective(s):

Injury is the leading cause of death among individuals between the ages of 1 and 44. Between 20% and 40% of trauma deaths occurring after hospital admission involve massive haemorrhage, and are thus potentially preventable with improved haemorrhage control and resuscitation techniques. To date, there has been no large, multicentre randomized control trial studying survival benefit that supports trauma resuscitation with a specific blood products regimen. The previous PROMTT study showed that clinicians were generally transfusing patients with either a 1:1:2 or 1:1:1 blood product ratio of plasma:platelets:RBCs, and that early transfusion of plasma was associated with improved survival. The study reviewed at Journal Club, widely known as the PROPPR Trial, was designed to determine the effectiveness and safety of a 1:1:1 transfusion ratio as compared to a 1:1:2 ratio in patients with severe trauma.

Study Design:

This was a pragmatic, multicentre, randomized control trial of 680 consecutively enrolled patients with severe trauma predicted to require a massive transfusion who arrived directly from the scene to 1 of 12 Level 1 Trauma Centres in North America between August 2012 and December 2013. Subjects were randomized within each site to receive either a 1:1:1 or a 1:1:2 transfusion ratio of plasma, platelets, and RBCs. The 1:1:1 group were transfused in a specified order: 6U platelets followed by single alternating units of RBCs and plasma to a total of 3U each. The 1:1:2 group were transfused with 2U of RBCs and 1U plasma to a total of 6U and 3U respectively, followed by 6U platelets. Transfusion of all study products was stopped once clinically indicated. Once a subject was randomized and enrolled, treating physicians were unblinded to the transfusion ratio assignment. Primary outcomes were 24-hour and 30-day all cause mortality. Secondary outcomes included time to hemostasis, blood product volumes transfused, incidence of 23-prespecified complications, incidence of surgical procedures, hospital /ventilator / ICU-free days, and functional status at time of discharge. The study was powered to detect an absolute difference in mortality of 10% and 12% at 24-hours and 30-days respectively, based on a prior though methodologically limited study that suggested a benefit of this magnitude may exist.

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Results:

680 patients were randomized: 338 received a 1:1:1 transfusion ratio and 342 received a 1:1:2 ratio. Most subjects were males, and baseline characteristics including severity of injury were similar between the two groups. There was no statistically significant difference found in mortality at 24 hours in the two groups (12.7% in the 1:1:1 group vs. 17% in the 1:1:2 group [95% CI: -9.6% to 1.1%]) or at 30-days (22.4% vs. 26.1% respectively [95% CI: -10.2% to 2.7%]). Exsanguination was the predominant cause of death in the first 24-hours, and was significantly decreased in the 1:1:1 group compared to the 1:1:2 group (9.2% vs. 14.6% respectively [95%CI: -10.4% to -0.5%, p=0.03]), however the lack of overall morality difference suggests patients who avoided death from hemorrage ultimately died from other causes. Although the 1:1:1 group received more plasma and platelets than the 1:1:2 group from admission until 24 hours (7U vs. 5U and 12U vs. 6U respectively), no significant differences were seen between the two groups in the rate of complications or other secondary outcomes.

Validity of Results:

The general sentiment amongst Journal Club attendees was this complex study was impressively carried out. The pragmatic nature of the study was noted to be more clinically relevant, however it was also noted that makes it difficult to know the effect, if any, of other interventions such as transexamic acid. It was noted that the study proved to be significantly underpowered, and beyond this the difference it was originally powered to detect was far higher than most would deem the “minimum” clinically significant difference, and some of the reasons for this were discussed at Journal Club. As a result, significant discussion occurred on whether or not this was truly a “negative” study from a “Bayesian” perspective, irrespective of the lack of significant p-value for the primary outcome and the 12% chance this difference arose by chance. A limitation to this study that was discussed in detail was the prespecified order in which blood products were transfused. Although both groups received blood products in a prespecified ratio, the 1:1:1 group were given 6U platelets initially, while the 1:1:2 group received platelets only after 9U of blood products had been transfused. The impact that this had on all cause mortality and death from exsanguination is unclear, but it was pointed out that the result was some or all of the differences found could simply be due to earlier and up front platelet administration, rather than the specifics of the ratio used.

Generalizability of Results:

It was felt that these results are likely generalizable to Canadian Emergency Departments: both trauma centres and community locations. It was noted, however, that the availability of rapid administration of plasma and platelets is more challenging at smaller centres in comparison to Level 1 Trauma Centres, which may make this more difficult to apply during the early stages of resuscitation at these facilities. As a side note, there was also some discussion about what constitutes a “standard” platelet transfusion, and whether or not this varies by site or between the US and Canada and thus may impact the generalizability of the results. Further information is being sought on this and will be added as an addendum to this appraisal.

The Bottom Line:

Although study found no statistically significant difference in all-cause mortality at 24-hours and 30-days in those transfused with plasma, platelets, and RBCs in a 1:1:1 ratio compared with a 1:1:2, the point estimate difference in morality of 4.2% along with the “tilt” of the 95% confidence interval suggests it is more likely than not that an actual difference exists that would be deemed clinically relevant. Moreover, the secondary results of this study suggest a significant reduction in deaths from exsanguination at 24 hours with a 1:1:1 approach, without a difference in complications. As a result, most Journal Club attendees felt the best approach based on current evidence is to target a 1:1:1 transfusion ratio early during resuscitation efforts. Finally, it should be kept in mind that the ideal order in which to transfuse platelets, plasma, and RBCs remains unclear at this time, and could also be important from the perspective of patient oriented outcomes.