CAGS AND ACS EVIDENCE BASED REVIEWS IN SURGERY. 50

Is early transfusion of plasma and platelets in higher ratios associated with decreased in-hospital mortality in bleeding patients?

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The term "evidence-based medicine" was first coined by Sackett and colleagues as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients."1 The key to practising evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding. For clinicians to practise evidence-based medicine, they must have the skills to read and interpret the medical literature so that they can determine the validity, reliability, credibility and utility of individual articles. These skills are known as critical appraisal skills, and they require some knowledge of biostatistics, clinical epidemiology, decision analysis and economics, and clinical knowledge.

Evidence Based Reviews in Surgery (EBRS) is a program jointly sponsored by the Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS). The primary objective of EBRS is to help practising surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected for their clinical relevance to general surgeons and because they cover a spectrum of issues important to surgeons, including causation or risk factors for disease, natural history or prognosis of disease, how to quantify disease, diagnostic tests, early diagnosis and the effectiveness of treatment. A methodological article guides the reader in critical appraisal of the clinical article. Methodological and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS website, where they are archived indefinitely. In addition, a listserv allows participants to discuss the monthly article. Surgeons who participate in the monthly packages can obtain Royal College of Physicians and Surgeons of Canada Maintenance of Certification credits and/or continuing medical education credits for the current article only by reading the monthly articles, participating in the listserv discussion, reading the methodological and clinical reviews and completing the monthly online evaluation and multiple choice questions.

We hope readers will find EBRS useful in improving their critical appraisal skills and in keeping abreast of new developments in general surgery. Four reviews are published in condensed versions in the *Canadian Journal of Surgery* and 4 are published in the *Journal of the American College of Surgeons*. For further information about EBRS, please refer to the CAGS or ACS websites. Questions and comments can be directed to the program administrator, Marg McKenzie, at mmckenzie@mtsinai.on.ca.

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1. Evidence-Based Medicine Working Group. Evidence-based medicine. *JAMA* 1992;268:2420-5.

SELECTED ARTICLE

Holcomb JB, del Junco DJ, Fox EE, et al.; the PROMMTT Study Group. The Prospective, Observational Multicentre Major Trauma Transfusion (PROMMTT) Study. *Arch Surg* 2012 15:1-10.

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KEY POINTS ABOUT THE ARTICLE

Question: Is early transfusion of plasma:red blood cell (RBC) and platelet:RBC in higher ratios associated with decreased in-hospital mortality in bleeding patients? **Design:** Prospective cohort study. **Setting:** Ten level 1 U.S. trauma centres. **Patients:** Adult trauma patients surviving for 30 minutes after admission who received a transfusion of at least 1 unit of RBCs within 6 hours of admission and at least 3 total units of RBCs, plasma or platelets within 24 hours. **Main outcome:** In-hospital mortality. **Results:** Of a total of 34 632 patients, 905 (2.6%) met the inclusion criteria. Plasma:RBC and platelet:RBC ratios were not constant during the first 24 hours (both $p < 0.001$). In a multivariable time-dependent Cox model, increased plasma:RBC ratios (adjusted hazard ratio [HR] 0.31, 95% confidence interval [CI] 0.16–0.58) and platelet:RBC ratios (adjusted HR 0.55, 95% CI 0.31–0.98) were independently associated with decreased 6-hour mortality when hemorrhagic death predominated. In the first 6 hours, patients with ratios less than 1:2 were 3 to 4 times more likely to die than patients with ratios of 1:1 or higher. After 24 hours, plasma and platelet ratios were not associated with mortality. **Conclusion:** Higher plasma:RBC and platelet:RBC ratios early in resuscitation were associated with decreased mortality in patients who received transfusions of at least 3 units of blood products during the first 24 hours after admission. Further assessment with a randomized controlled trial is required.

COMMENTARY

The term damage control resuscitation (DCR) describes a therapeutic approach to critically injured patients with ongoing hemorrhage.[1] It involves simultaneous therapies to arrest persistent bleeding (prehospital, surgical and/or percutaneous techniques) and resuscitate with a more rapid, balanced and aggressive transfusion of blood components that theoretically approximate whole blood (plasma, platelets, RBCs). In an ideal setting, DCR approaches at least a 1:2 ratio of plasma:RBC and often a 1:1:1 ratio of plasma:platelet:RBC.[2] This technique also possesses the added benefit of minimizing crystalloid administration and, therefore, seems to reduce coagulopathy, acidosis, hypothermia, endothelial permeability and the total time to definitive closure of the patient's abdominal wall.

The classical approach to massive hemorrhage management promulgated by older guidelines consisted of providing blood components as per laboratory-based triggers; for example, plasma transfusion was indicated to keep an international normalized ratio higher than 1.5 in a bleeding patient. In 2007, however, a report by Borgman and colleagues[3] challenged this approach by proposing early transfusion at higher plasma:RBC ratios. This retrospective work was supported by biologic plausibility and basic clinical science revealing that coagulopathy develops early in about 25% of injured patients and is associated with worse clinical outcomes. This approach seemed to be associated with remarkable clinical outcomes. Thus, the approach was quickly popularized and many more observational studies followed, many of which were criticized for poor methodological quality and survival bias.

The PROMMTT study,[4] therefore, constituted an important multicentre effort to address these questions in the most rigorous fashion short of a large multicentre randomized controlled trial. Many if not most of the previous studies were threatened by either survival bias (patients living long enough to receive the treatment appear to do better than those who die too early to receive it) or the competing mortality bias (causes of death other than hemorrhage begin to dominate trauma patient hospital course after the first 24 hours). However, the PROMMTT study carefully recorded the blood-component ratios at various times through the critical phases of care. Research assistants were available at all hours to screen and enroll patients and record the exact times of fluid infusion and blood-component transfusion as well as patient outcomes during direct observation. Direct bedside observation began at trauma team activation and continued until active resuscitation ended (defined as the time the centre transfusion protocol was discontinued, death occurred, or 2 hours elapsed since the last blood product transfusion, whichever came first). The study is unique in collecting these critical data with great precision. The investigators also avoided using the traditional definition of massive transfusion to determine eligibility, and the statistical analytic approaches attempted to minimize the effect of survival bias.

There were 34 362 trauma admissions in the 10 centres over an average of 58 weeks. Data collection was initiated for 12 560 (36.6%) patients, and of these 1245 (3.6%) met all PROMMTT study eligibility criteria. A total of 905 (2.6%) adult trauma patients who survived at least 30 minutes after admission and received at least 1 unit of RBCs within 6 hours of admission and at least 3 units of RBCs within 24 hours at 10 U.S. level 1 trauma centres were enrolled in the study. A distinct attribute of the study was the fact that the authors included patients who experienced major trauma rather than only those who were massively bleeding. In contrast, previous studies have included patients who required at least 10 units of RBCs in 24 hours.

Using a time-dependent model, researchers assessed the association of increased plasma and platelet ratios on in-hospital mortality. Within the first 6 hours, patients with ratios of less than 1:2 were found to be 3 to 4 times more likely to die than patients with ratios of 1:1. During the

first 6 hours, the majority of deaths were attributed to hemorrhage. No association between plasma:RBC or platelet:RBC ratios and mortality was observed after 24 hours of admission, when the majority of deaths were attributed to nonhemorrhagic causes.

The results of the PROMMTT study support the beliefs that in-hospital mortality remains high (21%) in patients who require any RBC transfusions within the first 6 hours, that earlier and higher ratios of plasma and platelets are associated with lower mortality within 6–24 hours after arrival and that this benefit is not observed among survivors beyond 24 hours. Because of its detailed, time-based analysis, the PROMMTT study provides the strongest evidence to date to support this treatment regimen. Despite the limitations, the study showed an apparent survival benefit with close resuscitation ratios of plasma:RBC and platelet:RBC in patients with severe hemorrhage. It is important to recognize some limitations of this prospective study. First, the vast majority of trauma patients had blunt trauma and not penetrating trauma. Second, only 35% had the abdominal cavity as a source of hemorrhage, with only 24% of the study group undergoing damage control surgery, whereas 26% had compressible limb injuries. Third, the mean quantity of RBC transfusion in the cohort analyzed was greater than 3 units over 24 hours, but it was evident that most of the patients analyzed did not receive more than 10 units of RBCs over 24 hours nor in the first 6 hours. In other words, how sick were these patients? Fourth, patients who died within the first 30 minutes were excluded from the analysis owing to predefined exclusion criteria. This last one raised the concern of survivor bias. Did this group receive any RBCs or plasma? If so, why were they excluded? Finally, no data on coagulation parameters, hemoglobin or platelet counts during resuscitation were provided. Therefore, it is not clear whether the strategy was effective in addressing hemostatic derangements. No information was provided on the use of tranexamic acid, an antifibrinolytic agent, which has been shown to decrease mortality in trauma patients by a recent randomized controlled trial (CRASH-2 investigators).[5] The rate of transfusion-related complications (e.g., volume overload, acute lung injury) were not reported. These complications tend to occur later in the resuscitation (> 6 h later) and may significantly contribute to patient morbidity and mortality. It would have been interesting to see how many of the surviving patients who received 1:1 resuscitation experienced such complications and to learn more about these patients. The potential benefit and safety of the high ratio approach may differ among populations. For example, previous studies have shown that women, patients with blunt (v. penetrating) injuries and those with traumatic brain injuries benefited less from high plasma:RBC ratio transfusion.[6–8]

While the PROMMTT study adds further evidence to support transfusions with higher plasma:RBC transfusions, further studies are needed, especially regarding how to efficiently identify the patients who will benefit from early administration of the therapy. Future studies looking at the infusion rate of each component on mortality will also help clarify this question further. Clinicians cannot be confident, however, that by administering enhanced ratios of plasma and platelets that they will influence the mortality of their seriously injured patients, and a randomized controlled trial is still urgently required. The Pragmatic, Randomized, Optimal Platelet and Plasma Ratios (PROPPR) is a Phase III trial designed to evaluate the difference in 24-hour and 30-day mortality among patients predicted to receive massive transfusion (defined as receiving 10 or more units of RBCs within the first 24 h) has been completed, and the results are imminently expected; they may greatly advance this critical area of practice.

Competing interests: None declared.

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