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ORIGINAL ARTICLE

Gastrointestinal Hemorrhage: Should We Transfuse Less?

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Abstract Although blood transfusion has an established place in the conventional management of acute upper gastrointestinal (GI) hemorrhage, there is growing evidence of adverse side effects of transfusion, both acute and later. An Ovid Medline literature search was performed to evaluate the significance and importance of these effects. Evidence of impaired hemostasis with repletion of blood volume in the acute phase was found in multiple studies and in uncontrolled studies in combat casualties. There are multiple large studies of a so-called immunosuppressive effect of transfused blood leading to increased infection rates and mortality dependent both on dose and on the age of the stored blood. In view of evidence of increased bleeding with early blood volume restoration and the growing evidence of so-called immunosuppressive effects of stored blood, there is a need to consider trials using a conservative utilization of blood in acute GI bleeding.

Keywords Blood transfusion · Gastrointestinal hemorrhage · Immunomodulation · Bacteramia · Nosocomial infection

Introduction

In the current management of acute gastrointestinal hemorrhage (GIH), blood transfusion plays a key role although the only small controlled trial showed that early transfusion within 24 hours abolished the hypercoagulable post-bleeding state with a significantly raised re-bleeding rate [1]. It is also widely believed that rapid restoration of intravascular volume is essential despite tenuous supporting evidence [2–5]. Among intensivists and anesthetists there is widespread recognition that allogeneic blood produces clinically significant immune depression [6, 7]. Although 40 years have passed since the observation that prior blood transfusion enhances renal transplant retention [8] by immune depression, there is little discussion of this and other adverse effects of transfusion in the management of gastrointestinal hemorrhage. However, the American College of Gastroenterology has recently published guidelines recommending that in bleeding varices blood transfusion should aim at a Hb level of 8 g% and that "vigorous resuscitation with saline should generally be avoided" [9]. It is proposed to review the evidence for an immunosuppressive effect of allogeneic blood, to evaluate the evidence for a vigorous approach to blood transfusion in GIH, and to determine whether these two approaches can be reconciled. This article is subdivided to address several pertinent questions.

If Immunomodulation Occurs, Does It Affect Outcomes?

There seems to be little doubt that in the intensive care area the use of allogeneic blood is associated in certain circumstances with an increase in mortality rate. There are several large intensive care unit (ICU) studies available. In a report of 3,514 patients in 146 European centers, logistic regression analysis showed that blood transfusion increased the odds ratio (OR) of death to 1.37 (95% CI 1.02–1.89)

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[10]. When 516 transfused patients were matched with 516 nontransfused by their propensity scores, it showed that the mortality (MR) of the transfused patients was 27.7% versus 17.1% in the nontransfused ($P = 0.02$). The survival curves crossed at 10 days; before that the nontransfused patients had excessive deaths; after that the MR was higher in the transfused group. Another multicenter nationwide US review of 4,892 patients in 213 hospitals led to several conclusions [11]. Statistical analysis comparing the transfused with closely matched nontransfused patients showed a higher MR in those transfused, with a dose–response relationship. The OR for death rose from 1.48 for those receiving 1–2 units to 2.67 for 3–4 units to 4.01 for more that 4 units ($P < 0.0001$ for the latter two). In a study of 2,085 adults in ICU in an institution, 21.5% received blood transfusion; multivariate analysis corrected for survival probability found a higher incidence of nosocomial infection in those transfused ($P < 0.0001$) [12]. In these early studies, major issues of comparability of groups, the validity of propensity scores, and indices of survival probability all loom large to cast doubt on the strength of the conclusions. The most decisive study available so far is the TRICC trial—the Transfusion Requirement in Critical Care Investigation—of the Canadian Critical Trials Group [13]. In this trial, 838 critically ill patients with euvolemia after initial treatment and hemoglobin estimations less than 9 g% within 72 hours of admission to the ITU were randomly assigned—418 to a restricted transfusion strategy in which red cells were given if the hemoglobin fell below 7 g% and maintained between 7 and 9 g%, and 402 patients to a liberal transfusion strategy in which the hemoglobin was maintained between 10 and 12 g%. The overall difference in MR (18.7% vs. 23.3%) was not significant. However, one major group did benefit from the restricted transfusion approach, i.e. those aged less than 56 years without cardiovascular disease (MR 18.7% vs. 16.1%, $P = 0.05$). The findings of the TRICC trial, that those under 56 years without cardiovascular disease and APACHE scores of less than 20 have a statistically better outcome, may have relevance; however, caution is needed given the different indications for transfusion between the groups.

More recently an enormous study from the Cleveland Clinic compared various outcomes in transfused cardiac surgery patients on the basis of the age of the transfused blood. This included 2,822 patients who received 8,802 units of blood stored for less than 14 days (mean 11 days) and 3,130 patients receiving 10,782 units stored for more than 14 days (mean 20 days). The differences were stark, although preoperatively the two series were evenly matched [14]. Those receiving the older blood had higher in-hospital mortality rates (2.8% vs. 1.7%), prolonged intubation rate (9.7% vs. 5.6%), renal failure (2.7% vs. 1.6%), and sepsis or septicaemia (25.9% vs. 22.4%). Mortality at one year was 11% vs. 7.4% (all differences highly significant). No data were given on the number of units individually transfused. A contrary view of 2733 CABG patients showed benefit on univariate analysis but no benefit of short storage blood on multivariate analysis [15].

A partial explanation of these changes might be in another recent study of the biochemical changes in stored blood and their physiological consequences, although these findings have been challenged [16, 17]. Blood from 15 volunteers was assayed regularly from 0 to 6 weeks. Two major findings emerged. Nitric oxide (NO) levels fell to one third to one quarter of basal levels by 3 hours and remained down. Simultaneously, red blood cell deformability decreased, restricting the ability of red blood cells to squeeze through the slightly narrow capillaries of the hypoxic state.

It is known that red cells in hypoxic states are able to synthesize NO to produce capillary vasodilatation. Stored blood impairs tissue oxygenation by four mechanisms: lack of NO to produce vasodilatation, impaired oxygen release due to reduced 2–3 DPG levels, and increased red cell rigidity which impairs perfusion. Finally, the studies showed that NO deficient red cells will scavenge NO from the patient's native red cells, further impairing tissue perfusion. These may be part of a growing evidence of major adverse effects from the "storage lesion" in banked blood [18].

How Is Immunomodulation Manifested?

There is evidence of three acute manifestations. The first came two decades ago with a report of increased of postoperative infection associated with blood transfusion in colorectal cancer surgery [19]. Since then there have been many such reports concerning elective surgery and trauma [20–25]. Such studies are difficult if not impossible to evaluate because of the problem of measuring factors such as shock, anesthesia, tissue damage, and hemorrhage. Also, when such patients go to surgery after multiple transfusions, postoperative infections are very frequent [26]. Although there are many reports of individual units with a MR of 15% after urgent surgery, most due to infection, currently the UK figure is 30% [27].

The second manifestation is blood stream infection. A prospective study of 84 patients who developed a blood stream infection matched 2:1 with 167 controls in a large general hospital showed, using conditional logistic regression, that the predictors of blood stream infection were: (a) blood transfusion within the prior week with OR 5.14 (95% CI 1.74–15.2) and (b) the presence of a central line (OR 2.74, 95% CI 1.28–5.8) with recent surgery (OR

0.3, 95% CI 0.12–0.79) and antibiotic prophylaxis (OR 0.38, 95% CI 0.16–0.98) being protective.

This study, embracing all parts of the hospital and considering factors such as steroid use and immunosuppressive diseases, avoided many of the problems inherent in studies of possibly inadequately controlled ICU patients [28]. Another study encompassed 8,578 (98%) adult cardiac surgery patients during 1998–2003 in the United Kingdom, and detailed analysis showed ORs of 3.38 (2.6–4.4) for infection and 3.35 (2.68–4.35) for ischaemic events in transfused versus nontransfused patients with increased length of stay. Transfused patients stayed longer, cost more, and were more likely to die up to more than a year after surgery [29].

More recently, in a prospective study of 361 critically ill trauma patients of whom 55 developed blood stream infection, statistical analysis produced nine predictors of blood stream infection including a blood transfusion of more that ten units, presence of a central line, use of immunosuppressive agents, and preexisting infection [30]. There is also evidence of pneumonia as an increased hazard after blood transfusion. This is especially true for ventilator-related pneumonia and for patients having coronary artery surgery with a dose–response relationship between the amount and age of blood transfused and risk [31–33]. While the relevance of these findings to acute GIH may appear tenuous, those with experience of bleeding cirrhotic patients will recognize the high frequency of nosocomial infection, especially pneumonia, developing in such patients.

Long Term Tumor Effects and Tumor Recurrence

The literature on this is enormous, principally entailing studies of patients having surgery for malignancy and the role of transfusion in tumor recurrence; the issue remains unresolved. The problems with matching transfused to nontransfused patients as well as acquiring studies of adequate size and adequate follow-up have proven insurmountable [34–36].

If Immunomodulation Occurs, What Causes It?

While this has little immediate relevance to the bleeding patient and much has yet to be learned, the evidence points to white cell products [37]. Cytokines liberated from white cells, colony stimulating factors, interferons, interleukin, and TNF leak into the plasma, with a myriad of effects paralleling the age of the blood. While this has led to major efforts to reduce the WCC content of blood, the effectiveness of these strategies is controversial [38] but favors leukodepletion [39].

Given that the conventional view is of liberal transfusion of crystalloid and blood, it is now difficult to evaluate the role for a restricted transfusion policy in GIH. There are two key issues.

What Is the Evidence that a Restricted Transfusion Policy Is Associated with Less Bleeding?

One of the earliest evaluations of this was of combat casualties in the North African and Italian campaigns by the US army in WW2. The official history noted "if operation could not be undertaken immediately, it was not necessary to achieve the improvement beyond a rising blood pressure of 80 mm Hg and a warm skin of good color" [40], blood was the only fluid capable of improving the patient, further bleeding might be provoked if the blood pressure was elevated more than was necessary to keep the patient out of shock, and "saline and dextrose solutions were not effective and could be dangerous".

The approach in Vietnam was different. The reduction in time to a surgical facility from 7 hours in WWII to 1.5 hours in Vietnam was associated with a reduction in mortality from 4% to 2%. In civilian life there are numerous studies of restricted transfusion in trauma patients but of limited scientific value and only one controlled trial [41]. This study of 598 patients with penetrating torso injuries and a pre-hospital BP of <90 mm randomized to either immediate on-site resuscitation or delayed resuscitation in hospital showed benefit from the latter approach. The MR was 30% vs. 38% ($P = 0.04$), with a complication rate of 23% vs. 30% ($P = 0.08$), and a shorter hospital stay ($P < 0.006$).

In the numerous animal studies two stand out: one is of pigs with a 5 mm aortic incision given Ringer's solution [42] and the other involves dogs with severed saphenous arteries given blood to maintain blood pressure. In both studies all of the transfused animals died, whereas all those left alone survived [43]. However, an enormous audit (the UK audit on upper gastrointestinal bleeding), a successor to the Rockall study [24], showed strong support. "For all Rockall scores the rate of re-bleeding is higher in the transfused group", but confounding can not be excluded (Table 8.1.3 of reference [31]).

Does Leaving the Patient with Low Hemoglobin and Blood Volume Put Them at Increased Risk in the Event of Re-Bleeding or Continued Bleeding?

Whilst there is a widely held view that in acute GIH patients, bleeding is continuous, the evidence from human and animal studies is that it is generally episodic and that a period of mild hypotension promotes hemostasis [44]. In a large study of 929 patients endoscoped within 24 hours of bleeding, only 12 (1.2%) were spurting.

While a restricted transfusion policy may seem heretical, it was promoted more than a half century ago by the late Morton Grossman, who, after stating that "there are no crucial data proving that blood transfusion decreases the mortality of hemorrhage from peptic ulcer", suggested that "in cases of severe bleeding, as a general rule, it is recommended that blood be given when the blood pressure falls below 90 mm or 100 mm Hg systolic, the pulse increases above 110–120 and the Hb is below 7 or 8 g per 100 ccs. The best and simplest physiologic and clinical symptom of the need for blood after the hemorrhage is dizziness or faintness on sitting up" [45].

Conclusion

For the present, the last word is likely to be the Cochrane Report on the role of blood transfusion [46]. This analyzed the only ten controlled studies of transfusion "triggers" in various settings: trauma, surgery, or, in one case, GIH. Mortality, morbidity, and length of stay did not appear to be adversely affected by the use of triggers of 8–9 g/dl, even 7 g/dl Hb. One can only echo the suggestion of the study group that additional studies be undertaken to evaluate the situation. In GIH the use of conservative trigger points will need caution in patients with cardiovascular disease.

In summary, there is a considerable and growing body of evidence to suggest that a less vigorous approach to transfusion in the immediate management of GIH might be beneficial. Consideration should be given to a controlled trial to clarify the problem. Such a study would need: adequate power; the inclusion of adults without major co-morbidities, preferably young adults <45 years; withholding of crystalloid infusion; restricting blood to those with a pulse greater than 110 bpm and a systolic blood pressure less than 110 mm Hg; and major endpoints of in-patient mortality and referral for surgery.

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