Is the Whole Greater Than the Sum of Its Parts? The Implementation and Outcomes of a Whole Blood Program in Ecuador

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Abstract

Background. Hemorrhagic shock is a major cause of mortality in low-and-middle-income countries (LMICs). Many institutions in LMICs lack the resources to adequately prescribe balanced resuscitation. This study aims to describe the implementation of a whole blood program in Latin America and discuss the outcomes of the patients that received whole blood (WB).

Methods. We conducted a retrospective review of patients resuscitated with WB from 2013-2019. Five units of O+ WB were made available on a consistent basis for patients presenting in hemorrhagic shock. Variables collected included: sex, age, service treating the patient, units of WB administered, units of components administered, admission vital signs, admission hemoglobin, Shock Index, intraoperative crystalloid and colloid administration, symptoms of transfusion reaction, length-of-stay and in-hospital mortality.

Results. The sample includes a total of 101 patients, 57 of whom were trauma and acute care surgery (TACS) patients and 44 of whom were obstetrics and gynecology patients. No patients developed symptoms consistent with a transfusion reaction. Average shock index was 1.16 (±0.55). On average, patients received 1.66 (±0.80) units of whole blood. Overall mortality was 14/101 (13.86%) in the first 24 hours and 6/101 (5.94%) after 24 hours.

Conclusion. Implementing a WB protocol is achievable in LMICs. Whole blood allows for more efficient delivery of hemostatic resuscitation and is ideal for resource-restrained settings. To our knowledge, this is the first description of a whole blood program implemented in a civilian hospital in Latin America.

Background

Hemorrhagic shock kills an estimated 1.9 million people annually worldwide. Prompt management of hemorrhagic shock is essential. Several decades of experiences have shown that extensive volume resuscitation with crystalloid can lead to an exacerbation of the “lethal triad,” of trauma-induced coagulopathy, hypothermia and acidosis; this phenomenon has been recently modified to include hypocalcemia, and therefore has been termed the “lethal diamond.” Evidence over the past decade suggest a more balanced resuscitation involving the replacement of lost blood with a 1:1:1 transfusion with packed red blood cells (pRBCs), fresh frozen plasma (FFP) and platelets, mimicking the whole blood (WB) that is lost. Adherence to a 1:1:1 ratio, however, remains challenging even in high resource settings. Many regions of the world do not have the blood bank capabilities to adequately supply and respond to the challenging demands for providing and sustaining a timely and efficient 1:1:1 resuscitation strategy. As such, there has been renewed interest in WB transfusion programs as an initial approach to damage control resuscitation (DCR).

Hospital Vicente Corral Moscoso (HVCM) is a public hospital located in Southern Ecuador and serves as a referral center for more than 2 million inhabitants. A WB transfusion program was implemented in
2013 to address the issue of inadequate hemostatic resuscitation for patients in hemorrhagic shock. The aim of this paper is to describe the logistics of the implementation of a WB transfusion protocol at our institution, review the outcomes of exsanguinating trauma and obstetrics and gynecology populations who received WB and demonstrate the feasibility of a WB program in a low-and-middle-income country (LMIC).

**Methods**

We performed a mixed methods analysis of the WB resuscitation program at the HVCM. In order to document the details of the program, we interviewed members of the blood bank staff, hospital administration, and clinical leadership of the hospital who were instrumental in establishing the program. In order to characterize the safety profile of WB transfusions in our program, we identified patients who received WB transfusion from 2013-2019. The following datapoints were collected: sex, age, service treating the patient, units of WB administered, units of components administered, admission vital signs, admission hemoglobin, Shock Index, intraoperative crystalloid and colloid administration, length-of-stay and in-hospital mortality. In trauma patients, the revised trauma score (RTS) was calculated. We also collected information suggestive of symptomatic acute transfusion during transfusion including evidence of rash, urticaria, fever, respiratory difficulty or hemoglobinuria. No labs were sent post-transfusion to detect subclinical transfusion reactions.

We used SPSS v 26 for statistical analysis. This study was approved by the ethical committee of our institution, Hospital Vicente Corral Moscoso, and the academic committee of research of the University of Azuay Medicine Faculty.

**Results**

*Whole Blood Transfusion Protocol at the HVCM*

Five units of type O+ WB were made available daily and released to patients presenting in hemorrhagic shock, as determined by the attending surgeon taking care of the patient. After the type O+ whole blood is dispensed, the blood bank then proceeds to type and cross the patient using Bio-Rad Saxo ID-Reader. The patient is transfused with WB until vital signs stabilized per the judgment of the attending surgeon, after which type-specific pRBCs and FFP are dispensed according to their availability in the blood bank. The resuscitation strategy at the HVCM is largely based on clinical exam, as tools such as thromboelastography (TEG) used at some institutions to guide blood-based resuscitation are not available.

**Blood donation and collection:** Whole blood is obtained through voluntary unpaid donation or replacement donation. The blood must be collected in no more than 12 minutes with constant manual or mechanical activation so as to prevent the activation of the clotting cascade. The use of aseptic technique is paramount for quality control and prevention of bacterial contamination. The sterile material utilized in this process is disposable. The extraction bags are quadruple bags including CPD+SAG-
Manitol BUFFY-COAT, and the filtration system is used only when the blood is fractionated into components.

**WB processing, storage and administration:** After a unit of blood is donated, it is quarantined for 8 hours during which time the ABO type and Rh (D) type is determined. The WB is screened for the following serologic markers according to World Health Organization (WHO) standards: Syphilis, Hepatitis C, Hepatitis B, and HIV. Plasma antibody titers are not measured prior to the transfusion of WB. If the blood tests negative for infectious diseases, it is stored at 4-6°C and available for 48 hours. As such, the product dispensed at the HVCM is considered cold, fresh whole blood.

Leukoreduction is not routinely performed on the units of WB due to the inability to preserve platelets. After 48 hours, if the blood is not utilized, it is fractionated into components. The packed red blood cells and frozen plasma are then made available for up 35-42 days and one year respectively. Platelets are not available to patients at the HVCM after fractionation. Given the relative scarcity of blood products in the region, the platelets obtained through fractionation are primarily sent to the local cancer hospital. The blood bank stock is then replaced by the aforementioned methods.

**Outcomes of Patients Managed with WB:**

| Variable                          | Trauma and Acute Care Surgery, n (%) | Obstetrics and Gynecology, n (%) |
|-----------------------------------|--------------------------------------|----------------------------------|
| Age (years)                       |                                      |                                  |
| ≤18                               | 5 (8.8)                              | 2 (4.5)                          |
| 19-39                             | 32 (56.1)                            | 39 (88.6)                        |
| 40-64                             | 15 (26.3)                            | 3 (6.8)                          |
| ≥65                               | 5 (8.8)                              | 0 (0.0)                          |
| Gender                            |                                      |                                  |
| Male                              | 45 (78.9)                            | 0 (0.0)                          |
| Female                            | 12 (21.1)                            | 44 (100.0)                       |
| Number of WB units transfused in the first 24 hours |                                      |                                  |
| 1                                 | 26 (45.6)                            | 22 (50.0)                        |
| 2                                 | 23 (40.4)                            | 20 (45.5)                        |
| 3                                 | 6 (10.5)                             | 2 (4.5)                          |
| 4                                 | 1 (1.8)                              | 0 (0)                            |
| 6                                 | 1 (1.8)                              | 0 (0)                            |
| Blood Type                        |                                      |                                  |
| A+                                | 0 (0)                                | 2 (4.5)                          |
| AB+                               | 1 (1.8)                              | 0 (0)                            |
| O+                                | 56 (98.2)                            | 42 (95.5)                        |
Table 1. Demographics of patients receiving whole blood transfusion (n=101)

One-hundred-and-one TACS or obstetrics and gynecology patients were identified as receiving resuscitation with WB. Fifty-seven patients presented to the TACS service, and 44 patients presented to the obstetrics and gynecology service with an average shock index of 1.16 (±0.55) (Table 1). Admission vital signs and laboratory values can be found in Table 2.

|                               | Trauma and Acute Care Surgery (SD) | Obstetrics and Gynecology (SD) |
|-------------------------------|------------------------------------|---------------------------------|
| Systolic blood pressure (mmHg)| 96.00 (±30.62)                     | 99.59 (±23.68)                  |
| Mean arterial pressure (mmHg) | 69.11 (±22.98)                     | 71.44 (±17.63)                  |
| Heart rate (beats per minute) | 100.82 (±26.23)                    | 102.50 (±23.91)                 |
| Respiratory rate (breaths per minute) | 21.79 (±6.47)                  | 20.84 (±3.62)                  |
| Temperature (Celsius)         | 35.88 (±1.72)                      | 35.90 (±1.89)                   |
| Glasgow Coma Score (GCS)      | 11.32 (±4.85)                      | 14.45 (±1.98)                   |
| Shock Index                   | 1.16 (±0.53)                       | 1.14 (±0.58)                    |
| Hemoglobin (ug/dL)            | 10.19 (±3.13)                      | 8.85 (±2.43)                    |
| Crystalloid administered in the operating room (mL) | 2203.13 (±1667.03)            | 1497.94 (±778.78)               |
| Colloid administered in the operating room (mL) | 483.28 (±426.88)                | 400.06 (±438.62)                |
| Estimated blood loss (mL)     | 1856.40 (±1577.35)                | 1569.49 (±1115.63)              |

Table 2. Admission vital signs and laboratory values of patients resuscitated with WB

On average, TACS patients received 1.75 (SD ±0.93) units of WB, and obstetrics and gynecology patients received 1.55 (SD ±0.59) units of WB. An average of 1.91 (SD ± 2.68) and 1.74 (SD ± 1.91) units of pRBCs were administered to TACS and obstetrics and gynecology patients respectively after WB. An average of 1.30 (SD ±2.59) and 0.84 (SD ±1.86) units of FFP were administered to TACS and obstetrics and gynecology patients respectively after WB. Platelets, as previously mentioned, are rarely available at our institution.

TACS Patients

Of the 57 patients on the TACS service, 47 were trauma patients and 10 were emergency general surgery patients. Average RTS in the trauma population was 6.06 (±1.89) and average shock index was 1.18 (±51). Of the 47 trauma patients, 24 suffered penetrating trauma and 23 suffered blunt trauma. Hemorrhage was localized in the abdomen in 12 (25.53%) patients, thorax in 11 (23.40%) patients, thorax
and abdomen in 6 (12.76%) patients, spine in 1 (2.13%) patient, neck in 1 (2.13%) patient, extremities in 10 (21.27%) patients, face in 2 (4.26%) patients, pelvis in 2 (4.26%) patients, and unknown in 2 (4.26%) patients as these patients expired prior to complete assessment.

The remaining 10 patients were emergency general surgery patients. Whole blood transfusion was utilized for intraoperative bleeding in a patient undergoing an open necrosectomy for infected pancreatic necrosis (n=1), a bowel resection for ischemic gut (n=1), a repair of an iliac artery aneurysm (n=1) and a repair of a ruptured abdominal aortic aneurysm (n=3). Whole blood transfusion was used for bleeding of the superficial femoral artery following the excision of a left groin mass (n=1), liver bed following a laparoscopic cholecystectomy (n=1), spleen following a splenic biopsy (n=1), and hypogastric artery following a spinal surgery (n=1).

Obstetrics and Gynecology Patients

Forty-four patients presented to the obstetrics and gynecology service, with an average shock index of 1.15 (±0.58). Thirty-six patients (81.81%) suffered post-partum hemorrhage either after cesarean section or vaginal delivery. Post-partum hemorrhage was found to be due to atony in 18 (50.0%) patients, retained products in 3 (8.33%) patients, mucosal tear in 4 (11.11%) patients, placenta accrete spectrum or placenta previa in 8 (22.22%) patients, and uterine rupture in 2 (5.56%) patients. One (2.78%) patient had bleeding from an extrauterine vessel following a c-section. The remaining 8 patients suffered hemorrhage due to a non-pregnancy-related gynecologic emergency (18.18%) including incomplete abortion in 3 (37.50%) patients, fibroids in 1 (12.50%) patient, ruptured ectopic pregnancy in 2 (25.0%) patients, post-operative bleeding after a hysterectomy in 1 (12.50%) patient, and a hemorrhagic ovarian cyst in 1 (12.50%) patient. The only mortality in this cohort expired due to complications related to hemorrhage from HELLP syndrome.

Length-of-stay in the intensive care unit was 4.79 (SD±5.85) days in TACS patients, and 1.84 (SD±2.77) days in obstetrics and gynecology patients. Length of stay was 13.07 (SD±15.33) days in TACS patients, and 5.86 (SD±4.56) days in obstetrics and gynecology patients (Figure 1).

Adverse Outcomes

Importantly, none of the patients in our series developed symptomatology consistent with acute transfusion reaction.

Overall mortality was 14/101 (13.86%) in the first 24 hours and 6/101 (5.94%) after 24 hours. The shock index of patients who expired in the first 24 hours and after 24 hours was 1.42 (SD±0.64) and 1.29 (SD±0.48), respectively. By comparison, patients who survived had an average shock index of 1.09 (SD±0.53). Of those patients that expired in the first 24 hours after transfusion, the cause of death was attributed to hemorrhage in 11 patients, 3 of whom arrested prior to any operative intervention, 6 of whom arrested in the operating room, and 3 of whom arrested shortly after surgery. The two remaining patients expired due to a subarachnoid hemorrhage and irreversible shock postoperatively. One death in the
maternal population occurred due to hemorrhage in a patient presenting with HELLP syndrome, severe preeclampsia and intrauterine fetal demise. The patient was found to have evidence of severe coagulopathy and a hepatic hematoma after undergoing a cesarean-section; this patient unfortunately arrested before to operative intervention could be undertaken.

Of the patients that 6 patients that expired after 24 hours, three suffered sepsis leading to multisystem organ failure. Two patients were declared brain dead and one patient suffered irreversible shock after blunt force trauma to the chest not responsive to treatment.

**Discussion**

The HVCM is at the forefront of using WB transfusion in patients with hemorrhagic shock in Latin America. Our experience shows that WB transfusion represents a feasible strategy for achieving hemostatic resuscitation in patients presenting in hemorrhagic shock, especially in LMICs. Of the patients resuscitated with WB, we do not describe any transfusion reactions.

The use of WB is not a new concept. Prior to the adoption of component therapy in 1970s, resuscitation of patients in hemorrhagic shock with WB was commonplace. Component therapy was popularized for logistical reasons and was never proven to be as efficacious as WB in hemorrhagic shock. Recent literature from the military suggest that WB may have superior or equivalent outcomes when compared to component therapy. Two retrospective combat casualty analyses compared the use of fresh whole blood to component therapy. One study described a mortality benefit in the WB group at 24-hours and 30-days, while the other found no statistically significant difference in mortality, death due to exsanguination, MSOF or sepsis. Nessen et al. showed that, in the experience with Forward Surgical Teams (FSTs) in Afghanistan, use of FWB in addition to RBCs and FFP was associated with improved in-hospital survival compared to RBCs and FFP alone. Within the civilian sector, retrospective analyses suggest superiority or equivalence of WB with regards to mortality and overall blood product use. The only randomized control trial in trauma patients, to our knowledge, compared modified whole blood (leukoreduced whole blood with additional platelet transfusion) with component therapy. After excluding patients with traumatic brain injury, a decrease in the use of component therapy was demonstrated in patients that received modified whole blood.

Whole blood has both, financial and logistical benefits compared to component therapy. Whole blood has the advantage of being easy to store, transport and administer to patients. Its use is ideal for resource constrained environments and pre-hospital settings, especially those that do not have ready access to all blood components, delivering the product that would otherwise require three bags in one bag. Moreover, when separated components are transfused, each unit contains an increased amount of anticoagulants and additives that contribute to a patient’s overall coagulopathy compared to one unit of whole blood. Spinella et al. found that, in patients receiving massive transfusion, those receiving component therapy received a median of 825ml of additional additives and anticoagulants compared to
the group resuscitated with WB\textsuperscript{18}. Additionally, it has been asserted that the administration of WB may actually be safer for patients with respect to risk of transmission of blood-borne diseases, exposing them to one donor instead of multiple donors \textsuperscript{28}.

Access to transfusion therapy and the “blood drought” creates significant barriers to safe surgery in LMICs\textsuperscript{29}. The use of WB is a potentially beneficial in countries where keeping up with 1:1:1 transfusion ratios is not feasible. In resource-limited settings such as our institution in Southern Ecuador, a WB program has allowed us to streamline the prompt and expeditious administration of all blood components at once thus ensuring higher concentrations of all primordial elements thereby securing hemostatic strategy for patients in hemorrhagic shock.

It must be noted that Cuenca, Ecuador provides a favorable setting for implementing a whole blood program as 80% population is type O+ and 2% is type O- \textsuperscript{30}. In our sample, most patients had type O+ blood. Due to the previously mentioned government initiative to reduce maternal mortality, the blood type of the obstetrics and gynecology patients was known prior to transfusion so as to prevent the possibility of Rh incompatibility. This likely contributes to why our sample has a slightly higher rate of O+ patients compared to the general population per the HVCM blood bank. The high incidence of type O+ blood in the population makes it easier to identify donors and makes it more likely that a patient receiving a type O+ transfusion will be receiving a transfusion from a donor with the same blood type. While this is an advantage to implementation in our setting, this may make the study less generalizable to other populations.

The context for transfusion of patients in our region is distinct from the literature that typically recommends transfusion at a hemoglobin of 7g/dL \textsuperscript{31}. Located at 2,560 meters above sea level, the average hemoglobin in this population is higher than at lower altitudes. A study of hemoglobin levels published in Colombia described the average hemoglobin of those living at 2,600 meters to range between 14.6-15.2g/dl in women and 16.8-17.4g/dl in men \textsuperscript{32}. As such, patients at our institution are often transfused at a higher threshold, typically 9-10ug/dL.

The primary concern with the transfusion of group O whole blood to non-group O recipients involves the possibility of minor ABO mismatch. Minor mismatch occurs when the anti-A and anti-B antibodies found in group O WB cause hemolysis in a non-group O recipient. This is typically mitigated by transfusion of only type-specific whole blood or through the transfusion of whole units with lows titer of antibody (most commonly <256 by the saline dilution, immediate spin method), known as low-titer O whole blood (LTOWB) \textsuperscript{16}. Numerous studies documented the safety of LTOWB, demonstrating that it does not increase risk of transfusion reaction\textsuperscript{15,16,20,21,28,33,34}.

However, at the HVCM, anti-A and anti-B titers are not measured prior to administration of blood products. Data supporting the transfusion of untitered whole blood is scarce in the literature. In a safety analysis of the transfusion of stored whole blood, Yazer et. al found that there was no statistically significant difference in the amount of incompatible plasma transfused in a unit of whole blood compared to the
amount of incompatible plasma transfused in any unit of platelets (p=0.38) \(^{23}\). Additionally, while group AB is considered to be the “universal plasma donor,” the military permits group A plasma to be dispensed in emergencies as group A individuals do not tend to make high anti-B antibodies and B red cells express the B antigen at a low density\(^{35}\). Sperry et. al. recently demonstrated a rate of adverse events possibly related to transfusions of 2.2% in a description of AB plasma and A plasma with low-titer B antibodies administered to patients in hemorrhagic shock in the pre-hospital setting \(^{36}\). The blood types of the patients in our sample were predominantly type O+, with a smaller percentage of AB+ and A+ individuals. No group B individuals were in our sample. Severe intravascular hemolytic transfusion reactions caused by minor mismatch are a relatively rare phenomenon \(^{19}\) that may be difficult to detect in an otherwise critically ill patient, and may not have been detected with the \(n\) of 93 in our series. While, again, we do not report any patients that developed symptomatology that was recognized as a hemolytic transfusion reaction, hemolysis labs post-transfusion were not routinely ordered. Several studies have documented that whole blood does not have evidence of increased hemolytic reactions with administration of up to 4 units \(^{20,21,37}\).

This study is limited in that it is a single-institution and retrospective study. While more patients were identified than described, many files were unable to be located in medical records. The documentation at the HVCM continues to be written by hand, and many of the patient charts in medical records are missed pages or written illegibly.

**Conclusion**

In summary, our experience demonstrates that whole blood administration in patients presenting with hemorrhagic shock can be an achievable alternative therapy to 1:1:1 resuscitation especially in limited resource settings, wherein access to all blood products may not be feasible. Further studies comparing whole blood to component therapy in this population are needed. To our knowledge, this is the first description of a whole blood program implemented in a civilian setting in Latin America.

**Abbreviations**

- WB=Whole Blood
- LMIC=Low- and middle-income country
- DCR=Damage control resuscitation
- HVCM= Hospital Vicente Corral Moscoso
- RTS=Revised Trauma Score
- WHO=World Health Organization
- TACS=Trauma and Acute Care Surgery
- pRBCs=Packed red blood cells
- FFP=Fresh frozen plasma
• Thrombo-elastography = TEG

Declarations

Ethics approval: This study was approved by the ethical committee of our institution, Hospital Vicente Corral Moscoso, and the academic committee of research of the University of Azuay Medicine Faculty.

Consent to Participate: This is a retrospective study. Patients cannot be easily identified given the information extracted from the charts.

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Competing Interests: The authors have no competing interests to declare.

Availability of data: The data collection sheet is provided in the electronic supplementary material. All identifying patient information has been removed for privacy.

Author contributions

• Data collection, data analysis, manuscript writing: AH
• Data collection, manuscript writing: MGA
• Data collection, data analysis: JRN, DSA, SGPP
• Critical review of manuscript: NFL, RPA, HAS, LFC, CCA
• Critical review of manuscript, final approval of manuscript for submission: JCP, JCSM

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**Figures**
Figure 1

(A) One unit of type O+ whole blood. (B) The three components after whole blood is fractionated. At our institution, whole blood is available for 48 hours, after which it is fractionated into components.

Supplementary Files
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