Emergency Transfusion for Acute Severe Anemia: A Calculated Risk

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An editorial about a case report is unusual, but no more so than the case reported by Dai et al.[1] in this issue of the journal. They report survival, without apparent sequelae, of a 53-year-old man with a hemoglobin concentration as low as 0.7 g/dL (hematocrit 2.2%) for several hours. Despite the presence of a low fibrinogen concentration and an elevated partial thromboplastin time (not discussed here), successful management was facilitated by surgical control and minimal intraoperative blood loss. The reported nadir hemoglobin concentration may be the lowest known during acute anemia associated with survival, the previous apparently being 1.1 g/dL reported by Zollinger et al.[2] This raises 2 important questions: (1) How is this possible? and (2) What alternatives are possible when crossmatched erythrocytes are not available?

It is not possible to know accurately the hemoglobin concentration that is associated with mortality or serious morbidity, because prospective experiments in humans with those end points are impossible and data from laboratory animals cannot be extrapolated to humans because of potentially important differences among species. Retrospective analyses of hospital databases[3,4] and case reports[5] regarding mortality associated with severe acute anemia have suggested that the median value is <5 g/dL. In a recent reexamination of those data, it was estimated that the median hemoglobin concentration associated with anemia-induced mortality is approximately 2.5 g/dL (R. B. Weiskopf, unpublished data, 2010). Cardiovascular disease increases that value[3] (also R. B. Weiskopf, unpublished data, 2010). Retrospective examination of other databases relating preoperative hemoglobin concentration to postoperative mortality does not provide useful information because they do not separate those not transfused, nor are they able to account for the rationale for lack of transfusion or provide the hemoglobin concentration at death.[6–8] Adequately powered prospective randomized clinical trials in adults[9] and children[10] in intensive care units have not found different mortality rates between those transfused with "restrictive" or "liberal" strategies that resulted in hemoglobin concentrations of approximately 8.5 and 10.5 g/dL.

Considering that the human mean fatal hemoglobin concentration is approximately 2.5 g/dL, and that this case report documents a hemoglobin concentration that is lower than previously known during acute anemia, it may seem difficult to understand survival. Nevertheless, there are data to assist in the explanation of this seemingly exceedingly improbable event. The patient's fraction of inspired oxygen (F_{IO_2}) was nearly 1.0 throughout the 12 hours of surgery. Similarly, in the case reported by Zollinger et al.,[2] F_{IO_2} was 1.0 and Pa_{O_2} >400 mm Hg at the time of the nadir hemoglobin concentration. Classic thought is that the amount of oxygen dissolved in plasma (the solubility of oxygen in plasma is 0.0031 mL/dL/mm Hg O_2) is too little to be of physiologic consequence. Whereas that may be so during ordinary circumstances with an F_{IO_2} of 0.21, dissolved oxygen can be of substantial benefit during severe anemia, when the F_{IO_2} and Pa_{O_2} are high. Hyperoxia reduces mortality of pigs subjected to acute severe anemia and maintained at their critical hemoglobin concentration.[11] In healthy humans, breathing oxygen reverses the neurocognitive deficits[12] and increased P300 latency (the neurophysiologic correlate)[13] induced by severe anemia. High Pa_{O_2} in healthy humans decreases the heart rate response to acute severe anemia[12] (also J. Feiner, et al., unpublished data, 2010), and oxygen supplementation decreases heart rate after abdominal surgery.[14] The physiologic effect of a Pa_{O_2} in excess of 400 mm Hg has been estimated to be equivalent to approximately 3 g/dL hemoglobin[12] (also J. Feiner, et al., unpublished data, 2010). Thus, the physiologic effect of breathing oxygen when added to the patient's native hemoglobin of 0.7 g/dL produced a heart rate equivalent to nearly 4 g/dL hemoglobin, a value associated with approximately 80% survival (R. B. Weiskopf, unpublished data, 2010). Provision of a high F_{IO_2} can be a useful "bridge" until red cells are available for transfusion.

As important as the above information may be, it is perhaps more important to know the hemoglobin concentration that is associated with significant morbidity than that associated with mortality, because clinicians would prefer to prevent the former before it results in the latter. The brain seems to be more sensitive to acute anemia than is the heart (R. B. Weiskopf, unpublished data, 2010). Healthy humans have degraded neurocognitive function

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at a hemoglobin concentration of 6 g/dL[12,15] and increased latency of the encephalographic P300 wave[13] that is associated with cognitive dysfunction[16] and defective information processing.[17] Prospective randomized clinical trials have not identified the low hemoglobin concentration that results in an increased morbidity or decreased function compared with that at a higher concentration.[9,10,18] The hemoglobin concentrations in those trials were apparently insufficiently low and different from the "liberal" transfusion group to be able to detect any differences.

The patient described by Dai et al.,[1] experiencing hemorrhagic shock as the result of an uncontrolled severed axillary artery, was not transfused with erythrocytes for 12 hours because crossmatched compatible blood was not available at that institution. The patient's ABO Rh type was B negative, with an unknown transfusion history, and the hospital blood bank's policy was to withhold Rh-positive blood without knowledge of the absence of anti-D antibodies in the potential recipient. Clinically significant anti-D antibodies do not arise in Rh-negative individuals unless exposed to that antigen by previous transfusion or pregnancy. One may be left with an incorrect impression that under these conditions there are no viable options. Delay in availability of crossmatched compatible erythrocytes is not extremely rare owing to the presence of a single antibody to a donor antigen, or unusual combinations of more than 1 of these. Furthermore, in circumstances of massive hemorrhage in an individual or of mass casualty, the availability of crossmatched compatible erythrocytes may be inadequate. Thus, familiarity with appropriate alternatives can be of benefit to clinicians to enable informed decisions and to facilitate communication with a physician of the blood bank or transfusion service during these circumstances.

For usual transfusions, red cell preparations undergo crossmatching of donor red cells and recipient's serum to ensure absence of immunohematologic incompatibility to avoid ensuing antigen-antibody–mediated hemolysis (although an increasing number of blood banks now only confirm the recipient's ABO type and proceed with type-specific red cells if the antibody screen is negative). In the absence of sufficient time to perform a crossmatch (approximately 30–45 minutes at most institutions) or the availability of crossmatched compatible blood, alternatives are possible.

In the United States (US), the Food and Drug Administration mandates "procedures to expedite transfusion in life-threatening emergencies" of blood and blood components when clinical circumstances so warrant.[19] Other organizations that certify blood banks, such as the American Association of Blood Banks and the College of American Pathologists, require that an institution's blood bank have a written policy for such release.[a,20] However, specific details are not mandated, and policies and procedures differ among institutions. It is possible to have emergency-release erythrocytes delivered from the institution's blood bank to the operating room within very few minutes.[21] Some active trauma centers maintain a supply of type O red cells in the immediate vicinity for even more rapid availability. Operating room personnel may be well advised to become familiar with policies and practices at their institution, and discuss changes to meet clinical needs, as necessary.

Deciding among options requires an assessment of the relative risks. The risks of not transfusing (anemia) are summarized above. The risks of erythrocyte components (in addition to the risks attached to all units of blood, independent of compatibility testing, such as potential transmission of viruses, parasites, and bacteria; transfusion-related acute lung injury; immunomodulation; and others, the current estimates of risk of transmission of human immunodeficiency virus or hepatitis C virus are ≤1 per 1 million units,[22] for hepatitis B virus approximately 1 per 300,000 U[23]; transfusion-related acute lung injury induced by packed red cells has been reported[24]; however, the risk is unquantified, but low because of the small amount of contained plasma) depend on both the specific component and the recipient. The risks accrue from potential incompatibility between red cell antigens and serum antibodies. In Vietnam, the US forces transfused ≥100,000 units of "universal donor"[25,26] supplied as O-positive whole blood[28,29] with low anti-A and anti-B titers[29] without a single fatality from transfusion reaction (I calculate the 95% upper confidence limit for a zero incidence as 3.0/100,000 units; and the 99% confidence interval as 4.6/100,000 units).[27] However, the vast majority of these were transfused in relatively young males who were unlikely to have been transfused previously. Previous transfusion or pregnancy of the recipient increases the possibility of recipient antibody development and the consequent risk. Data regarding antibodies to red cell antigens in hospitalized patients[28] and antigen frequency in the population[30] would seem to suggest that for this population an intravascular hemolytic transfusion reaction might occur with an approximate frequency of 1 to 6 per 10,000 transfusions. Although adverse events have been reported after the transfusion of type O whole blood to recipients with other blood types, these have been attributed to high titers of anti-A and/or anti-B antibodies in the donor plasma. Whole blood continues to be used by the military on occasion in combat zones, generally as type specific. Currently, in civilian practice, whole blood is not used for this purpose. "Emergency-release" "blood" currently is most often supplied as type O-negative erythrocytes, although some institutions may issue O-positive red cells instead to conserve their supply of the former (for transfusion to women with potential for childbearing, to prevent them from developing anti-D antibodies that could cause hemolytic disease of the newborn). Inasmuch as packed red cell preparations contain ≤10% of the plasma of whole blood (Hirschler N. Personal communication. President/CEO, Blood Centers of the Pacific, San Francisco; and Clinical Professor, University of California, San Francisco, 2010), this risk is greatly reduced, and there are no reports of fatal hemolytic reactions after their use as "universal donor."

Anti-A and anti-B antibodies persist for a variable time after transfusion of type O blood to someone with another ABO type.[31] Consequently, it has been recommended to assess these titers in the recipient after transfusion of type O

[a]College of American Pathologists. Transfusion. Medicine Checklist. Edition 671, 2010. Available at www.cap.org.

before switching back to the patient's hereditary ABO type when the crossmatch is compatible, although the exact satisfactory titer has not been determined.[31]

If it is determined that transfusion can wait a few minutes longer, another alternative is possible. If a type and screen (for unexpected antibodies in the recipient's serum) is negative, use of type-specific blood has generally been considered acceptable. Combining examinations of 2 reports from 1 large institution totaling 141,286 crossmatches, the incidence of a clinically significant antibody in a general hospitalized population was 1.2 per 10,000 units transfused,[32,33] which I calculate to have a 99.99% upper confidence limit of 2.8 per 10,000 units. Furthermore, all antibodies were weakly positive and would have been unlikely to have caused an immediate hemolytic transfusion reaction, although delayed hemolysis would have been possible. At a different institution, examination of 12,848 type and screens in a single year found 11 recipient antibodies that were not detected (incidence of 8.6 of 10,000 recipients).[28] Only 1 of these missed antibodies is associated with clinical hemolytic transfusion reactions (with an antigen of low frequency of approximately 0.0038), resulting in my calculated risk (with 99.99% confidence[b]) of a hemolytic transfusion reaction of no more than 2.2 per 1 million transfusions when relying on a type and screen without a crossmatch. Thus, performing an "immediate spin crossmatch" (sometimes called "quick spin") to verify patient ABO type should allow for provision of red cells within 5 to 10 minutes. However, this does not apply to neonates because the screen may not detect passively transferred ABO immunoglobulin G antibodies.

In the absence of a previously performed type and screen, other remaining options include performing a type and screen, or dispensing with the antibody screen and proceeding with transfusion of type-specific cells. Several reports of relatively small civilian experiences have failed to note a single case of hemolytic transfusion reactions after "emergency" transfusion of type-specific units.[29,34–36]

However, there is significant question whether requesting and transfusing type-specific red cells is safer than type O in emergency situations.[29,37] It was noted in the Vietnam experience that the incidents of hemolytic transfusion reactions when using type-specific blood occurred in clusters when mass casualties were treated.[25,26,29,31] This has led to the supposition that human error induced by the need for speed and multiple simultaneous procedures and transfusions, misaligning recipients, recipients' blood samples, and donor units resulted in major incompatibilities.[29]

Different considerations apply to the Rh system. Transfusion of Rh-positive red cells to a patient who is Rh negative, but does not have anti-D antibodies will not result in the rapid destruction of red blood cells unless the patient forms antibodies to the D antigen, which usually takes >4 weeks. Anti-D antibody rarely fixes complement and thus, transfusion of Rh-positive red blood cells to an Rh-negative patient with anti-D antibodies rarely results in intravascular hemolysis.[38] Thus, in the absence of other alternatives in an exceptional critical circumstance, after consultation with a physician of the blood bank or transfusion service, it may be acceptable to transfuse Rh-positive red blood cells to a recipient who has anti-D antibodies.

The above issues (and the previously higher incidence of transfusion-transmitted infectious disease) have prompted the development of synthetic or semisynthetic oxygen carriers. Recently, the focus has been on potential use when blood is not available. However, a large randomized clinical trial with that goal in mind testing a hemoglobin-based oxygen carrier (HBOC) was not successful, having not met a noninferiority 30-day mortality end point when compared with standard care.[39] However, it should be noted that noninferiority margins are generally somewhat arbitrary, that the clinical trial missed the upper confidence limit of noninferiority by <1%, and that the overall mortality did not differ statistically between groups. The failure of that trial and previous HBOC trials[c,40] and the transient increases in serum troponin and lipase in a number of clinical studies[41,42] has led some to conclude that these are effects of the entire class of compounds (see refs. 41 and 42). Currently, there are no ongoing clinical trials in the US with HBOCs, although development of at least one HBOC is continuing in Europe.[43] Consequently, the potential option of use of HBOCs as a "bridge" until erythrocytes are available will not appear soon in the US. As noted above, a partial bridge, however, may be provided by administration of a high FIO_2.

What is the value of having reviewed this information? We still do not know when to transfuse red cells. We have no clinical measures that let us know of impending insufficient oxygenation as anemia progresses. Large studies or clinical trials will never be able to define that point for a specific patient with the specific circumstances at hand. Thus, until better measures are available, clinical judgment is required. Implicit in such judgment is the balance of risks of not transfusing versus transfusing using one of the options available. It is the transfusing clinician who must make that assessment, and choose among options, and, if appropriate, with consultation with a physician from the blood bank or transfusion service. In doing so, it is well to remember that clinical medicine does not include a condition of "no risk"; that even 99.99% confidence is but a probability and allows for a risk, albeit small, of adverse outcome, despite unreasonable societal expectations or demands of absence of medical risk, while not holding themselves to that same impossible standard. The clinician who faces these, at times, difficult assessments and responsibility can request and expect the appropriate component that she or he deems to best satisfy the solution that minimizes the attendant risk. The nature of providing anesthesia is minimization of risk, which at times requires selection among options, all of which entail some risk. To

[b]Calculation of confidence intervals of the result of multiplying 2 values, each with its own confidence interval, is not standard. My estimate likely somewhat underestimates the confidence interval, and thus likely overestimates the risk.

[c]Hemosol, news release. Available at: http://www.evalu8.org/staticpage?page=review&siteid=2657; 21 June 2003. Accessed August 4, 2009.

do so implies appropriate knowledge; decisions regarding if and when to transfuse and selecting among transfusion choices fits well with that professional paradigm.

—"Take calculated risks. That is quite different from being rash."—Gen. George S. Patton, III, letter to Cadet George S. Patton IV, 6 June 1944.

DISCLOSURE

The author has a relationship with or consults for the following companies and organizations that have an interest in erythrocyte transfusion: US Food and Drug Administration, US National Heart, Lung, and Blood Institute/National Institutes of Health, US Army, Sangart Inc., and CaridianBCT. The author was project/corporate VP and Executive Scientific Advisor at Novo Nordisk A/S 2005–2007. The NHLBI/NIH provides partial salary support for the author.

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Section Editor: **Michael J. Murray**

CASE REPORT

Intraoperative Management of Extreme Hemodilution in a Patient with a Severed Axillary Artery

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We present a case of extreme hemodilution in which appropriately crossmatched blood was not available. A 53-year-old man was admitted to our hospital because of hemorrhagic shock due to multiple stab wounds. His blood type was B, Rh negative, and his intravascular fluid volume was maintained with balanced salt solution and plasma substitutes, i.e., hydroxyethyl starch. His hemoglobin reached a nadir of 0.7 g/dL and hematocrit 2.2% before being transfused. No evidence of cardiac ischemia was noted and he was discharged in good condition. Extreme hemodilution can be successfully managed by maintaining a normal blood volume, 100% oxygen, and the use of plasma substitutes. (Anesth Analg 2010;111:1204–6)

When patients with significant antibodies lose a massive amount of blood after severe trauma, blood transfusion can be delayed because of difficulty finding the same type of or compatible blood. During this period, the patient's survival relies on effective bleeding control and adequate fluid replacement to maintain intravascular fluid volume.[1,2] However, massive fluid infusion will inevitably result in significant blood dilution. It is uncertain to what extent and how long the human body can withstand extreme hemodilution.[3–5] We report the successful management of a patient in whom the hematocrit (Hct) decreased to 2.2% during a 12-hour surgery to repair lacerated left axillary vessels and brachial plexus nerves.

CASE DESCRIPTION

A 53-year-old man was admitted to our hospital because of hemorrhagic shock due to multiple stab wounds of the left upper limb and injuries to the left axillary artery and vein and the left brachial plexus nerves. His weight was approximately 70 kg and he was in general good health without any significant medical history or history of chronic systemic diseases. He had no history of chronic hypoxia or high altitude residence. On physical examination, he was conscious and slightly restless. His arterial blood pressure (BP) was 87/45 mm Hg, heart rate (HR) was 126 bpm, and respiration rate was 21 breaths/min. The left axillary artery was completely severed and bleeding profusely. The proximal portion of the artery was retracted, thus the bleeding could not be controlled by arterial clamping. To reach the proximal portion of the artery, the left clavicle was broken after the patient was anesthetized and the artery was clamped for temporary control of the bleeding. Additionally, the right jugular vein was catheterized. His initial hemoglobin (Hgb) and Hct were 0.9 g/dL and 3%, respectively, determined on an ADVIA 2120 (Bayer Corporation, Leverkusen, Germany). How much fluid he had received during transport to our hospital was unknown. Other laboratory studies revealed the following: oxygen saturation (Spo_2), 97%; central venous pressure, 3 cm H_2O; pH, 7.22; Pco_2,40 mm Hg; HCO_3^-, 16.2 mmol/L; base excess, −10.9 mmol/L; fibrinogen, 0.34 g/L; and partial thromboplastin time, 62.8 seconds. The patient's blood type was B, Rh negative.

The local blood bank did not have matched blood, and the blood banks in our hospital and local district will not distribute Rh-positive blood without knowing whether an Rh-negative patient has Rh antibodies. It was not certain whether the patient had a history of blood transfusion (he stated he was not certain) or Rh antibodies, and a test for Rh antibodies was not technically available in our hospital. No O-type Rh-negative red blood cells (RBCs) were available. While we attempted to locate matched blood, the circulating blood volume and BP were maintained by continuous infusion of balanced salt solution (BSS) and plasma substitutes; 2500 mL of BSS and 500 mL of hydroxyethyl starch (HES) (6% HES 130/0.4; Fresenius Kabi, Bad Homburg, Germany) were infused over the 2 hours between admission and start of surgery.

At the beginning of surgery, the patient's BP was 101/64 mm Hg, HR 98 bpm, and Spo_2 97%. The patient was anesthetized with slow IV injection of fentanyl 0.05 mg, droperidol 2.5 mg, propofol 60 mg, and succinylcholine 100 mg. The patient was tracheally intubated and rocuronium bromide, 4 mg IV, was administered. Ventilation was with 100% oxygen to maintain the P_{ETCO_2} at 30 to 36 mm Hg. Intraoperatively, anesthesia was maintained by 0.8% isoflurane inhalation and remifentanil infusion (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Fentanyl (0.05–0.10 mg) and rocuronium bromide (2 mg) were injected intermittently when necessary.

The surgical procedure included wound debridement, anastomoses of the left axillary artery and vein and the left

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Table 1. Summary of Hemoglobin Values and Fluids Administered from the Patient's Arrival in the Emergency Department to After Completion of Surgery

Time	Event	Hemoglobin concentration (g/dL)	Fluid administered
0	Arrival in ED	0.9	2500 mL BSS
1			500 mL HES
2	Start of surgery		2250 mL BSS
3			1750 mL HES
4			
5			
6			
7			
8	6th h of surgery	0.8	1500 mL BSS
9			1166 mL HES
10			250 mL $NaHCO_3$
11			1000 mL plasma
12	10th h of surgery	0.7	750 mL BSS
13			584 mL HES
			600 mL PRBCs
14	Immediately postoperatively (surgery lasted for 12 h)	4.7	
	Total fluids administered from arrival in the ED to immediately after surgery		7000 mL BSS
			4000 mL HES
			250 mL $NaHCO_3$
			1000 mL plasma
			600 mL PRBCs

ED = emergency department; BSS = balanced salt solution; HES = hydroxyethyl starch; PRBCs = packed red blood cells.
Note: In the first 8 h postoperatively, the patient was transfused with 850 mL PRBCs and the posttransfusion hemoglobin concentration was 8.7 g/dL. Intraoperative blood loss was minimal.

brachial plexus nerves, left clavicle fixation, and the repair of multiple lacerations of the left upper extremity. The operation lasted 12 hours. Intraoperatively, the patient was infused with 4500 mL of BSS, 3500 mL of HES, 250 mL of 5% sodium bicarbonate, and 1000 mL of type B, Rh-negative plasma. His hemodynamic variables intraoperatively were: BP, 70 to 110/40 to 70 mm Hg; HR, 80 to 110 bpm; Spo_2, 98% to 100%; and central venous pressure, 9 to 15 cm H_2O. At the sixth hour of surgery, the patient's Hgb was 0.8 g/dL, Hct, 2.6%; pH, 7.32; Pco_2, 43 mm Hg, HCO_3^-, 21.9 mmol/L; and base excess, −4 mmol/L. At the 10th hour of surgery, the Hgb was 0.7 g/dL and Hct was 2.2%. At the 11th hour of surgery, type B, Rh-negative blood arrived and blood infusion was started. In the next hour, 600 mL of packed RBCs was transfused. After the transfusion, the patient's Hgb and Hct were 4.7 g/dL and 14.1%, respectively. Throughout the procedure, the patient was continuously monitored by electrocardiograph and there was no evidence of myocardial ischemia or cardiac arrhythmias, except for sinus tachycardia. His nasopharyngeal temperature was maintained between 34.5°C and 35.5°C during the operation. Intraoperative blood loss was minimal and urine output was 3900 mL. In total, 12,250 mL of fluid was infused from the patient's arrival in the emergency department to the completion of surgery; 2500 mL of salt solution and 500 mL of HES were infused preoperatively, and 4500 mL of salt solutions, 3500 mL of HES, 250 mL of $NaHCO_3$, and 1000 mL of plasma were infused intraoperatively. A summary of Hgb values and fluids administered is presented in Table 1.

Once the surgery was successfully completed, the patient was taken to the intensive care unit for further care. Immediately postoperatively, he was conscious and could open his eyes when he was transferred from the operating room. Ventilation was continued with 50% oxygen until approximately 19 hours postoperatively when the patient was tracheally extubated. An additional 850 mL of type B, Rh-negative packed RBCs was transfused 8 hours postoperatively. Posttransfusion, his Hgb was 8.7 g/dL and Hct was 26%. Other laboratory studies revealed a prothrombin time of 20.7 seconds (normal range, 11–15 seconds), fibrinogen of 1.8 g/L, partial thromboplastin time of 34.5 seconds, and normal thrombin time, blood urea nitrogen, and serum creatinine.

The patient's urine output remained good and on postoperative day 3 the patient was transferred to the general surgery ward. His postoperative course was without complications and there was no evidence of brain injury. He was discharged 20 days after surgery in good condition, i.e., consciousness level was normal, the function of each organ was normal, partial function of the left arm was restored, the wound was healed, and he could walk without assistance.

DISCUSSION

In this report, we have described the successful management of a patient with extreme hemodilution until appropriately matched blood was available. Clinically, at Hct levels <20%, blood oxygen transport and supply to tissues and organs are affected.[3] Experiments with animals[4] and humans,[5] however, have indicated that as long as normovolemia is maintained, adequate systemic oxygenation can still occur even with a Hct as low as 5% to 10%. Sugimoto et al.[6] reported the case of a 45-year-old woman with massive intraoperative bleeding in whom cardiac ischemic changes were not evident until the Hgb level reached 2.0 g/dL. Zollinger et al.[1] reported a case of massive intraoperative blood loss resulting in a nadir Hgb of 1.1 g/dL that lasted for 30 minutes, which may to be the lowest reported Hgb level in a human. In our case, the patient's Hct reached a low of 2.2% without any evidence of

myocardial ischemia or rhythm abnormalities except for sinus tachycardia. A number of retrospective database analyses, however, have shown that mortality increases significantly when Hgb levels reach 6 to 7 g/dL or less.[7–9] In addition, the brain is very sensitive to acute anemia, and cognitive function has been shown to be impaired when Hgb levels reach 6 to 7 g/dL.[10,11]

Based on our experience and review of the literature, we have identified variables that we believe are critical to managing a patient with extreme hemodilution. Maintaining a normal fluid volume was the most important step in resuscitation of massive bleeding. As studies and case reports have indicated, if an effective circulating blood volume and BP can be maintained, and 100% oxygen administered, adequate systemic oxygenation can be maintained providing Hgb concentration has not decreased below a critical level.[1,2,4,5] Although the Hgb level was extremely low, the patient had normal circulation, blood gas analysis, and urine volume. After the operation, he immediately woke up and recovered successfully with normal organ functions, suggesting that hypoxic organ dysfunction did not occur. Deep anesthesia and decreased body temperature can minimize oxygen consumption and increase the available oxygen in arterial blood.[12] Because the room temperature in the operating room was low, other strategies had not been taken to reduce the patient's temperature. While maintaining an effective circulating blood volume and BP, administration of vasoactive drugs such as dopamine and cardiac stimulants such as Cedilanide can reduce HR and further maintain BP as well as increase organ perfusion and promote diuresis.[1] The deterioration of cardiac function (including cardiac arrhythmia and myocardial ischemia) due to increased cardiac work load and oxygen consumption by these 2 drugs did not occur in our patient.

In the Chinese Han population, only 0.3% to 0.4% of individuals are Rh negative.[13] However, the detection of anti-D antibodies in Rh-negative individuals who have previously received Rh-positive RBCs is reported to be approximately 21% to 22%.[14,15] In emergency situations, Rh-positive RBCs may be transfused for Rh-negative patients who have no history of exposure. We did not know whether the patient described in this report had anti-D antibodies. However, even if he did, there would have been a significant decrease of antibody titer because of the large amount of fluid infused resulting in hemodilution. In this circumstance, the infusion of Rh-positive blood is not likely to cause a fatal hemolytic reaction, and the probability of any hemolytic reaction is much less than 21% to 22%. Our patient's Hgb was only 0.7 g/dL. According to the formula: blood oxygen content per 100 mL = $1.34 \times \text{Hgb} \times \text{Sao}_2 + (\text{Pao}_2 \times 0.003)$, the normal blood oxygen content is approximately 20 mL/dL. Our patient's blood oxygen content was $1.34 \times 0.7 \times 100\% + (500 \times 0.003) = 2.4$ mL/dL. Theoretically, it is impossible to survive without a blood transfusion in such a situation and the mortality rate should be 100%. Based on this analysis, a blood transfusion, even if crossmatched blood was not available, should have been administered. However, because of our departmental policies, a transfusion could not be performed. In this case, the patient's vital signs were stable and he was able to survive until appropriately crossmatched blood could be given. Although much research has been directed toward the development of artificial blood substitutes, their clinical use does not seem to be forthcoming.[16]

In summary, extreme hemodilution can be successfully managed by maintaining a normal blood volume, 100% oxygen, hypothermia, and the use of plasma substitutes until homologous blood is available. If unable to maintain the BP, cardiac stimulants may be useful and transfusion of heterogonous blood should be considered.

AUTHOR CONTRIBUTIONS

JQD helped with data collection and analysis, and drafting the manuscript; WFT helped with drafting the manuscript; and ZY and RHL helped with data collection and manuscript preparation.

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