Blood and War—Lest We Forget

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Early theories in medicine

The goals of treatment as a target for blood transfusion have evolved over time and included volume resuscitation, oxygen delivery, and hemostasis. These have accounted for the targets of a spectrum of volume resuscitation efforts, from saline to fresh whole blood.

Early surgery consisted of trephination, treatment of trauma, and bloodletting for the treatment of many syndromes. *The Iliad* describes 147 wounds, three-quarters of which led to death at the scene; treatment consisted of bandaging with herbs and bloodletting. At the peak of Greek civilization, Alexander the Great conquered what we now know as the Middle East and was the first to take scientists along with him because his teacher, Aristotle, was interested in the study of natural history. Alexander accommodated him by bringing leading worldly discoveries home.

In doing so, he collected new information and spread Greek medicine. The concept of research study during conflict was also established. Galen, a dominant figure during Roman domination of the world, started his medical training in the second century AD and studied at Alexandria. He dissected animals and established his observations based on misinterpretation of objective animal data. His writings became gospel and determined much of medical care for the next 1,500 years.[1]

Galen's theory of circulation described food going to the liver, blood emerging from the liver going into arteries, and blood crossing the heart and continuing into veins with pulsatile flow. Draining blood was viewed as therapeutic and applied for multiple conditions. The basis of bloodletting was established, consistent with the current understanding of cardiovascular physiology at the time.

Roman domination included most of the Middle East and Europe, and the concept of far-forward care was first demonstrated in early depictions of Roman military care, in frescoes of the time. The seat of Roman power ultimately shifted from Rome to Constantinople (Istanbul), and with this, Europe and Rome ultimately fell.

Over the next 200 years, what was known as the Roman Empire shifted to the influence of Islam. Latin turned into Arabic, Galen's readings and writings were endorsed by Avicenna, and bleeding continued to be the therapeutic treatment of choice.

Medicine returned to Europe in 1010 AD, when Constantine of Carthage, having studied medicine in Arabia, returned to Carthage and after being shunned, escaped to Salerno, where his Arabic was translated back into Latin. He sought refuge in a monastery and this established the first known medical school in Europe. With this, dissection reemerged and the term *chairman* evolved from the master dissector overseeing pupils.[1]

The emergence of circulatory theory

Despite these advances the incidence of injury and significant surgical bleeding was low. Public registry data from the 14th century shows infection overwhelmingly responsible for mortality and bleeding as a minor cause of mortality.[1] In the 16th century, the Barbers Company and Surgeons Guild were joined under a doctrine approved by Henry VIII and bloodletting, having been prohibited by monks during the previous two centuries, became the core business of barber surgeons. Reflecting the importance of this technique at the time, the second publication from the famous Guttenberg Press was a bloodletting calendar for practitioners at the time. In addition, they were given four executed criminals a year for dissection, and anatomic study was reestablished.

Paré described early involvement with gunshot wounds, and the practice of cautery for wounds was replaced by treatment with open dressings of turpentine and rosehips.[1] The basis of transfusion emerged with a better understanding of anatomy, as described by Vesalius, who used human dissection to create the *De Fabrica Humani Corporis*. This effort led to his subsequent professional ostracism, but established the basis of anatomy as we know it today and set the stage for additional research in circulatory physiology.

Galileo, known for his description of the universe and the relationships between planets orbiting the sun, originally started medical school and was the first to describe the timing of the pulse. This observation allowed Harvey to subsequently calculate the ejection volume per hour of blood. He realized that if Galen's theory of blood flow was correct, the human body would create 16 tons of blood in

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24 hours and this was impossible. This allowed him to establish his theory of circulation, published in 1628. He assumed that because Galen's theory was impossible to accept, blood must circulate. He died 4 years before capillaries were observed.[2]

Harvey was a member of the Experimental Philosophy Club at Oxford and Charles Wren, the architect, and Boyle, the chemist, were also members and did experiments based on Harvey's theories. They proved that injection of antimony or opium in dogs induced vomiting and sedation, respectively, demonstrating that intravenous injections circulated. A medical student of Wren and Boyle, Lower applied this concept and drained blood from a dog and resuscitated the bled dog with another dog, artery to vein, demonstrating that one animal can live with the blood of another.[3]

A classical moment in the history of blood transfusion

In 1667, Jean-Baptiste Denys transfused Antoine Maury with a lamb's blood, which led to calming of the patient, who suffered from known mental dementia. He described the first human hemolytic reaction (black urine), and after this demonstration, the technique spread to Europe.

The practice continued to be controversial and Denys' patient returned for two subsequent transfusions; the third led to his death and caused the patient's wife to sue Denys. Denys was absolved at trial but the French Parliament banned the practice and the Pope subsequently followed suit. As a result, transfusion as a medical practice went dark for 150 years.[4]

Bloodletting returned and ruled, and the *Lancet* journal is named after the instruments used for this treatment. Benjamin Rush was sued for this practice in Philadelphia, during his treatment of the malaria epidemic of 1799. George Washington was bled four times in the last 2 days before his death, and William Osler continued this practice into the early 20th century.[2]

Early transfusion

Blundell, an obstetrician at Guys Hospital, transfused patients after obstetric hemorrhage. His first four patients died, but in 1829 he had an initial survivor and blood transfusion was reestablished. There was little record of blood transfusion during the Civil War.

The history of saline solution as a volume replacement began developing in the early 19th century. The use of saline resuscitation evolved from observations during cholera epidemics, which described concentrated dark blood that suggested loss of fluid and electrolytes.[5,6] In 1832 the infusion of normal saline was associated with a reduction in mortality.[7-10] This was followed 50 years later by Ringer, who described subcomponents of electrolytes and their effect on myocardial activity in an in vitro heart model.[11] The first use of saline in a resuscitation effort instead of blood for obstetric hemorrhage was in 1898.[12]

The use of acacia, a carbohydrate colloid, with saline and hypertonic saline solutions emerged during World War I. The concept of a postoperative or perioperative drip was introduced by Matas in 1924.[13] Hartman[14] described the addition of lactate and the debate regarding sodium chloride and lactated Ringers emerged during the 1950s and 1960s.[15]

Beginning of rapid progress

The first transfusion in the United States was probably carried out by Alex Carrel working at the Rockefeller Institute, having been recruited by Flexner to investigate techniques of vascular anastomosis. Carrel had concerned himself with this when, as a medical student in France, he witnessed the death of a patient with a portal vein injury.

In 1908 he was summoned by Lambert (who had brothers who were surgeons) and asked to help with Lambert's child, who suffered from acute anemia associated with childbirth. Carrel, despite having no license, went to Lambert's apartment and sewed the father's radial artery to the baby's saphenous vein and they witnessed father-to-daughter transfusion, which subsequently saved the baby's life. He celebrated the child's birthday 21 years later.[2]

Transfusion was popularized, and direct transfusion (a surgical procedure) was required because anticoagulation and technical problems precluded successful use of any other technique. Dr George Crile established the most commonly used technique, but it was still accompanied by a 35% hemolytic transfusion reaction. It was, by today's standards, one of the most expensive surgical procedures performed at the time.

A landmark in making transfusions more widely available occurred through Landsteiner's discovery of ABO compatibility and simplification of testing by Ottenberg at Mount Sinai.[3] This reduced hemolysis to essentially zero when blood was adequately tested. At the same time, Lewisohn, in 1915, demonstrated that anticoagulation with sodium citrate allowed the technique of blood transfusion to be as simple as, and equal to, saline infusion. This opened the door for longterm storage. It was the critical reason that blood could, for the first time, be widely used toward the end of World War I.[2]

Use of blood during war

During the beginning of World War I, the etiology of shock was debated. The prevailing theory was that circulating shock factors, as part of the neuroendocrine response, were responsible for the shock syndrome, as advocated by Cannon and Crile. Volume resuscitation was done primarily with crystalloid and acacia. Robertson was the first to introduce citrated type O blood in curing casualties well after the start of World War I.[3] Cannon, a physician and physiologist at Harvard, subsequently published extensive literature on traumatic shock, based on his theory that a dilated capillary region led to entrapment and this caused hypovolemia. In addition, Cannon and colleagues[16] observed that the injection of fluid increased blood pressure, which was dangerous in itself, and they demonstrated that blood pressure could "pop the clot" and aggravate bleeding, begging the question whether volume resuscitation was appropriate at all.

In 1918 the US adopted citrated blood and a postwar evaluation demonstrated that blood was better than gum acacia and salt solution. It was noted that if blood was grouped using techniques of Ottenberg, no serum reaction occurred. To quote a battlefield surgeon at the time "slight as my experience has been with this method of blood transfusion, I know that at this hospital we save lives by its use, which would have otherwise have been lost."[3]

An interesting quote by Walter Cannon after an analysis of his experience in World War I noted that fundamentally, research in this area had been accompanied by ignorance. "One reason for our ignorance is the relative irregularity of the appearance of shock ensuing in life and the consequent difficulty of pursuing persistent studies. The circumstances of war however, are such to permit at times systematic examination of large numbers of shock cases instead of infrequent single cases as in civilian life. With such opportunity theoretic consideration should be set aside."[16]

After World War I, Keynes, the brother of the famous economist, set up a blood bank at St Bartholomew's hospital in London, and the US had several similar efforts, using the concept of "donors on the hoof," in which citizens were on call to donate blood based a prescreening system.[17]

Meanwhile, Alfred Blaylock was beginning his career, joined Harrison at Vanderbilt, where both were chief residents, and studied the relationship of blood loss and cardiogenic shock. He collaborated with Vivian Thomas and did definitive shock studies before World War II, demonstrating the importance of volume loss as the most important cause of hypovolemic shock.[18]

In 1936 Elliott, a surgeon in North Carolina, demonstrated after separating blood into plasma and red cells, that plasma transfusion of a stab wound victim was life saving. He approached John Scudder, who was known for his studies of shock at Columbia and had been responsible for resuscitating the German pilots and crew with hypertonic saline solutions after the Hindenburg disaster in Lakehurst, NJ.[19] Dr Scudder was an advocate of the Blood Betterment Association in New York City and based on Dr Scudder's recommendations, Dr Charles Drew was asked to design a program for plasma therapy, which led to the collection of 9 million units for plasma preparation during World War II.[20]

Started initially as a program for Britain, which was initiated by Carrel, who moved back to France after retirement, the Americans were approached to help with the need for blood. It was realized that blood would not survive the journey to Europe because transatlantic flights at that time were not routine and the delay associated with transatlantic shipping would cause increased infection of the units shipped. As such, a shift to focus on plasma to support blood pressure was established.

Dr Edwin Cohn, concerned about infection risk of blood, had also embarked on a program known as Cohn fractionation and this led to the isolation of albumin. Dr IS Radvin was commissioned to take the first 50 bottles of albumin and test them 4 days after the invasion of Pearl Harbor. As such, plasma and albumin therapy was the fluid resuscitation of choice at the beginning of World War II.[2]

The National Research Council established the Committee on Transfusion, chaired by Walter Cannon toward the end of his career, and they concluded that shock is really a form of hemoconcentration and that plasma would, in fact, be more effective than blood. Despite this, the Subcommittee on Blood Substitutes had the contrary opinion that whole blood would be best as resuscitation during World War II. This was omitted from their minutes in their meeting in 1941 and was subsequently placed into meeting minutes 2 years later.[2]

It was Dr Churchill, a thoracic surgeon from Harvard, as part of an in-theater evaluation team, who studied resuscitation during his deployment and concluded that plasma was not the best blood substitute. He described the early effects of overzealous shock resuscitation and concluded that whole blood was necessary for someone to endure an operation. He attempted to convince command that a movement to blood was important. But this request was denied and as a result, he improvised and started a local blood bank in North Africa. His partner at Harvard in general surgery, Elliott Cutler, was also part of a study team deployed to study resuscitation and he shared the opinion that blood was needed. He worked to change the command's view. By the end of World War II blood transfusion had been established.[20]

Five years later, during the Korean conflict, the military blood program of World War II had collapsed and there was no blood available for the first 70 days in Korea. It was during this time, however, that the first changes in coagulation were reported, but these had little impact on resuscitation efforts.[21]

Civilian practice

Subsequent to Korea, the classic studies of Shires and Carrico described using a three isotope model that extracellular fluid repletion with crystalloid was essential for survival. Many studies compared crystalloid with colloid resuscitation and established that crystalloid solutions appeared superior.[15,22,23]

During the 1960s, blood was influenced significantly by economic factors. This was a time when collection was unregulated and fractionation was aimed at a market for drug use, Inappropriate collection became rampant and the result was that hepatitis emerged as a threat. Garrett Allen at Stanford demonstrated that slow heating killed hepatitis, and he collected plasma samples in Haight Ashbury to demonstrate how this could be prepared. He also lobbied the federal government about blood banking and ultimately was responsible for making a national agenda to control blood banking as we know it today.[2]

During this time, the use of fresh blood was described by George Sheldon and associates[24] under a model of the Irwin Blood Bank in San Francisco. He believed that the routine use of whole blood to meet transfusion needs was inappropriate and unnecessary. However, they maintained a population available for fresh whole blood use after massive transfusion.

Modern warfare

During the Vietnam War, the use of blood included early use of fresh whole blood. This was replaced with red cells and fresh frozen plasma, and at the peak of 1969, the blood program provided 36,000 units of blood per month to 100 surgical teams. Universal donor red cells in more than 100,000 transfusions showed no fatal transfusion reaction and this practice was moved into civilian practice after the war.

The first complete description of coagulopathy after massive trauma related to shock came from classic work by Simmons and colleagues;[25] they described the relationship of coagulopathy to shock and acidosis in 9% of massive transfusions. Collins[26] demonstrated that incremental blood volume loss requirements and their impact on volume, red cells, albumin, coagulation factors, and platelets were stepwise. He believed that treatment should be stepwise as well, and in the same order that blood volume replacement requirements dictated component loss. His perspective dominated transfusion practice in trauma patients for the next 30 years.

During the late 1970s and 1980s, trauma systems developed quickly and this led to trauma centers seeing sicker patients, reflecting the comments of Walter Cannon 70 years earlier. Coagulopathy in civilian populations was noted.[27,28] The concept of early volume resuscitation doing harm by "popping the clot" was raised, and excessive crystalloid resuscitation after targeted, goal-directed therapy became a controversial entity because it might contribute to postresuscitation complications.[29]

An Institute of Medicine report in 1999, which evaluated fluid resuscitation, raised concerns with lactated Ringers and colloid because of proinflammatory effects and increased mortality, while restimulating interest in hypertonic saline and hemoglobin solutions, as well as other designer fluids, for their effect on the early inflammatory response.[30]

This time period was also accompanied by the emergence of the concept of damage control, a practice introduced into civilian practice in patients with hypothermia, acidosis, and coagulopathy. Overzealous resuscitation and attempts at definitive surgical treatment led to the realization that damage control or restoration of integrity and temporary control using different operational logistics allowed restoration of the patient's physiology and subsequent return for definitive care, with an increase in survival.[31]

Modern treatment of coagulopathy

Triggers for treatment of coagulopathy have been debated extensively in the last 15 years. The role of platelets was questioned by a group in Seattle and their statement after a clinical trial suggested that prophylactic platelet administration was not warranted as a routine measure to prevent massive transfusion microvascular nonmechanical bleeding. Similarly, the role of fresh frozen plasma (FFP) was believed to be unnecessary as supplementation after massive transfusion.[32,33]

A series of evaluations by Lucas and Ledgerwood and colleagues[34,35] found that the effects of colloid resuscitation and coagulation were significant, but that FFP resuscitation did not restore coagulation activity. A subsequent study revealed that after patient care was found to be compromised by the previous strategy, FFP was necessary beyond one blood volume.

Despite this, the consensus of blood bankers at the time was that measures of coagulation and platelet counts were essential to guide incremental component therapy and that plasma, platelets, and cryoprecipitate should not be given without specific indications and only after measurement. Trauma center algorithms were based on this strategy and continued with this despite emerging evidence that a significant number of patients had significant coagulopathy.[36]

In 1999, Cinat and coworkers,[37] at a Level I trauma center, described several elements improving outcomes after damage control methods and suggested the importance of the FFP to RBC ratio. Similarly, Brohi and associates[38] described the existence of early coagulopathy and suggested the importance of screening.

The Iraqi conflict

By the beginning of the war in Iraq, far-forward surgical care, including damage control surgery, was introduced and the use of fresh whole blood initially for massive transfusion was practiced. This precipitated a subsequent movement to "virtual" fresh whole blood and a commitment was made to study this in the battlefield.[39] Early analysis demonstrated that incremental improvements in mortality were associated with a movement of a transfusion strategy that achieved an FFP to RBC ratio of 1:1.[40] There have now been several studies to confirm this observation and a more recent evaluation in civilian trauma centers showed more plasma and platelets are associated with better survival. Selecting patients to undergo this type of therapy remains a challenge, but some recent studies suggest prehospital physiologic and laboratory factors can be used to predict the patient at risk.[41,42]

In summary, moving back toward reconstituted whole blood seems very promising in select patients and represents a return to a practice almost 350 years old. A recent initiative for critical bleeding in trauma evaluated animal models and the mechanism behind this problem. This has led to a multidisciplinary consensus statement about current knowledge in this area.[43-46]

A world survey of trauma centers in the US and Europe evaluating senior clinicians' current practice protocols has demonstrated that a protocol to address these specific factors, including an RBC to FFP ratio, are currently used in only about one-third of trauma centers. A prospective randomized trial is warranted and plans are underway to test this important hypothesis.[47]

The act of transfusion has gone from being feasible to being concerning over infectious complications and potential fears about toxicity. It is known that trauma leading to hemorrhage and shock is associated with an acute coagulopathy of trauma because of factor consumption, fibronolysis, and augmentation by acidosis and hypothermia. For some patients, this is critical to survival and early repletion with reconstitution toward whole blood may be critical.

Although we have traditionally resuscitated over the last 50 years with crystalloid, it may be more appropriate to think of resuscitation with reconstituted whole blood. This still needs to be worked out.

There is a subgroup of patients that has been present throughout wars, which we have trouble seeing in civilian practice, and for which we need better indicators of early coagulopathy. Protocols for identifying these patients and for treating these patients are inconsistent within and across trauma centers, but targeting correction may increase survival. Current practice with incremental coagulopathy component correction is probably out of date and out of fashion. Reconstitution of blood and the use of adjuvant therapy are likely to save lives, and research and evaluation of protocols are needed so this is done correctly.

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