Form Approved
OMB No. 0704-0188

REPORT DOCUMENTATION PAGE

1a. REPORT SECURITY CLASSIFICATION: UNCLASSIFIED

2a. SECURITY CLASSIFICATION AUTHORITY

2b. DECLASSIFICATION / DOWNGRADING SCHEDULE

3. DISTRIBUTION / AVAILABILITY OF REPORT: This document has been approved for public release, distribution is unlimited.

4. PERFORMING ORGANIZATION REPORT NUMBER(S)

5. MONITORING ORGANIZATION REPORT NUMBER(S)

6a. NAME OF PERFORMING ORGANIZATION: Division of Military Trauma Research

6b. OFFICE SYMBOL (If applicable): SGRD-ULZ-M

7a. NAME OF MONITORING ORGANIZATION: US Army Research and Development Command

6c. ADDRESS (City, State, and ZIP Code): Letterman Army Institute of Research, Presidio of San Francisco, CA 94129-6800

7b. ADDRESS (City, State, and ZIP Code): Fort Detrick, Frederick, MD 21701-5012

8a. NAME OF FUNDING / SPONSORING ORGANIZATION

8b. OFFICE SYMBOL (If applicable)

9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER

8c. ADDRESS (City, State, and ZIP Code)

10. SOURCE OF FUNDING NUMBERS

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.
61102A	BS14	S14/BA	

11. TITLE (Include Security Classification): (U) Trauma and Military Applications of Blood Substitutes

12. PERSONAL AUTHOR(S): J.C. Bowersox and J.R. Hess

13a. TYPE OF REPORT: Final

13b. TIME COVERED: FROM ________ TO ______

14. DATE OF REPORT: 1993, March, 14

15. PAGE COUNT: 15

16. SUPPLEMENTARY NOTATION

17. COSATI CODES

FIELD	GROUP	SUB-GROUP

18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number): blood, combat, casualties, logistic requirements

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

To review potential clinical uses of erythrocyte substitutes in treating military battlefield casualties, with specific emphasis on combat injury rates and wounding patterns, resuscitation doctrine and logistic requirements. We reviewed published medical literature and unclassified documents from the U.S. Armed Forces Blood Program. Hemorrhage is the leading cause of death on the battlefield. Early intervention, with definitive treatment, could save up to 30% of soldiers who are killed in action or who die of wounds. Hemorrhage control and rapid volume expansion in appropriate casualties are the main priorities in pre-hospital resuscitation of battlefield casualties. The role for oxygen-carrying fluids in the initial management of military injuries is undefined; however, erythrocyte substitutes could reduce the logistic requirements for blood in field hospitals. In recent wars, outdating of stored blood resulted in 60-95% of units being discarded: 60% of 1.3 million pints in Vietnam and 95% of 120,000 pints in the Persian Gulf War. Safety, long storage life, light unit weight, and tolerance to environmental extremes are all characteristics that are necessary for erythrocyte substitutes to extend or replace the use of stored blood in treating battlefield casualties.

20. DISTRIBUTION / AVAILABILITY OF ABSTRACT: ☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS

21. ABSTRACT SECURITY CLASSIFICATION: UNCLASSIFIED

22a. NAME OF RESPONSIBLE INDIVIDUAL: J.R. Hess, COL, MC, Commanding

22b. TELEPHONE (Include Area Code): (415) 561-3600

22c. OFFICE SYMBOL: SGRD-ULZ

TRAUMA AND MILITARY APPLICATIONS OF BLOOD SUBSTITUTES

Jon C. Bowersox, M.D., Ph.D. and John R. Hess, M.D., M.P.H.
Letterman Army Institute of Research
Presidio of San Francisco, California 94129-6800

ABSTRACT

PURPOSE: To review potential clinical uses of erythrocyte substitutes in treating military battlefield casualties, with specific emphasis on combat injury rates and wounding patterns, resuscitation doctrine and logistic requirements.

METHODS: Review of published medical literature and of unclassified documents from the U.S. Armed Forces Blood Program.

RESULTS: Hemorrhage is the leading cause of death on the battlefield. Early intervention, with definitive treatment, could save up to 30% of soldiers who are killed in action or who die of wounds. Hemorrhage control and rapid volume expansion in appropriate casualties are the main priorities in pre-hospital resuscitation of battlefield casualties. The role for oxygen-carrying fluids in the initial management of military injuries is undefined; however, erythrocyte substitutes could reduce the logistic requirements for blood in field hospitals. In recent wars, outdating of stored blood resulted in 60-95% of units being discarded: 60% of 1.3 million pints in Vietnam and 95% of 120,000 pints in the Persian Gulf War.

CONCLUSIONS: Safety, long storage life, light unit weight, and tolerance to environmental extremes are all characteristics that are necessary for erythrocyte substitutes to extend or replace the use of stored blood in treating battlefield casualties.

INTRODUCTION

Hemorrhagic shock is the leading cause of death in soldiers injured on the battlefield. In contrast to injuries that cause extensive destruction of the central nervous system or other vital organs, the lethal insult in hemorrhagic shock is blood loss. Hemorrhage results in depleted intravascular volume, decreased oxygen transport to tissues, and decreased removal of metabolic waste products. Replacing intravascular volume by fluid resuscitation is highly effective in treating hemorrhagic shock.

Crystalloid solutions expand the circulating blood volume, restore tissue perfusion, and reverse cellular ischemia. Oxygen-carrying solutions are not required until the casualty has acutely lost 30-40% of the circulating blood volume (1500-2000 ml in the average adult). Erythrocyte transfusions are safe and highly effective in restoring oxygen-carrying capabilities after severe hemorrhage.

Potential applications of erythrocyte substitutes exist in military trauma when blood is not normally available (pre-hospital settings); when blood is available, but the time required for procurement would jeopardize patient survival (emergency treatment area, unexpected massive blood loss in the operating room); and when blood is available, but the demand exceeds the supply (mass casualty situations). In this paper, we review the epidemiology of military trauma, the use of blood in field surgical facilities, and current indications for blood transfusions in trauma.

EPIDEMIOLOGY OF MILITARY TRAUMA

The incidence of wounds in battle depends on the type of military action. For example, units engaging in offensive operations sustain more casualties than units defending a position. The lethality of wounds also depends on battlefield conditions and weapons systems [1]. More gunshot and booby trap wounds occur during jungle warfare (e.g., Vietnam) than in large-scale, conventional battles (e.g., the Persian Gulf War), in which fragmentation injuries predominate.

Approximately 20% of casualties are killed in action (KIA). They die on the battlefield before reaching a field hospital. This category corresponds to dead on arrival (DOA) in civilian trauma. The proportion of casualties KIA has remained unchanged throughout all the wars Americans have fought since the Civil War. In contrast, the percentage of casualties who reach a hospital, but then die of wounds (DOW) has decreased steadily (Figure 1) [2-4].

Over 50% of casualties who are killed in action bleed to death. Although massive truncal hemorrhage accounts for most of these deaths, one analysis indicates as many as 22% of injuries were in regions in which hemorrhage could have been controlled by rapid application of first aid [1].

Decreasing the time required to evacuate wounded combatants from the battlefield should also affect the percentage of casualties who die on the battlefield [5], however, a greater proportion of casualties will likely die of wounds in field hospitals. Although overall hospital mortality has decreased with more rapid evacuation, those casualties who die usually do so shortly after arriving at the hospital. Hemorrhage and neurological injuries account for the overwhelming majority of hospital deaths, whereas the incidence of lethal sepsis and pulmonary failure has declined [6-8].

The severity of wounds sustained in combat follows a bimodal distribution (Figure 2) [2]. Most casualties are either killed outright or they sustain survivable, frequently minor wounds. Those who are hospitalized generally require emergency surgery to control hemorrhage or to manage soft tissue injuries, gastrointestinal injuries or brain injuries. In Vietnam, 45-92% of casualties were operated on shortly after admission [6-8].

BLOOD TRANSFUSIONS IN MILITARY TRAUMA

Blood transfusions and intravenous fluid infusions have been shown to be lifesaving in combat casualties since World War I. Military doctrine has been developed to provide large quantities of blood to field hospitals, and a well organized logistics network (U.S. Armed Forces Blood Program) has been established to accomplish this task.

Blood is used to resuscitate casualties in severe shock, to replace blood perioperatively and to correct subsequent anemia in casualties with deficits in red cell mass after fluid replacement with crystalloid solutions. Most casualties who receive blood transfusions have hemorrhage requiring surgical control.

In Vietnam, 46% of all casualties admitted to field hospitals received blood transfusions [9]. Similar percentages were reported in the Falkland Islands campaign (64%) [10], and during the civil war in Lebanon (50%) [11]. In a recent report from the International Committee of the Red Cross (ICRC) only 16% of casualties treated in ICRC field hospitals in Thailand, Pakistan, and Afghanistan were transfused, however, almost 70% of the casualties in this series arrived at hospitals more than six hours after being wounded [12].

The number of units of blood transfused per hospitalized casualty has been reported as 1.5-2 units during World War II, Korea, and Vietnam. This number is meaningless, however, because all hospitalized patients were included in the denominator, whether or not they were hospitalized for wounds. For planning purposes, a more useful figure is the number of units transfused per casualty receiving blood. In Vietnam, patients were transfused with an average of 4.3 units [9]. Similar values were reported from Lebanon (4.6 units/casualty) [11]; however, only 2.9 units/casualty were administered by the ICRC field hospitals [12].

The amount of blood administered in field hospitals has depended on individual clinical practices and on the nature of the wounds. In general, very few casualties have received single unit transfusions in any study, which reflects the use of blood in resuscitating severely hemorrhaging casualties before bleeding could be surgically controlled. In one series of 1,963 casualties in Vietnam, no patient received a single unit transfusion [6]. Injuries caused by land mines required more blood than those caused by gunshot wounds or fragments from bombs and rockets.

Universal donor (Type O, Rh positive) blood was widely used before 1966; most blood used subsequently has been fully cross-matched. The administration of universal donor blood is extremely safe; more than 100,000 units were given in Vietnam without a single fatal hemolytic transfusion reaction. Typing and cross-matching, however, can be performed within 20 minutes [13]. For casualties requiring multiple units, administering low titer, type O or type-specific blood prevents the risk of antibody transfer that can occur from the anti-A and anti-B antibodies present in normal titer, type O blood.

INDICATIONS FOR TRANSFUSION

Clinical criteria for erythrocyte transfusions are not well delineated. The awareness of infectious risks and a better understanding of oxygen delivery has led to much more judicious use of blood in 1993 than was practiced 40 years ago. Anecdotal descriptions of blood transfusions in the Korean War report casualties being transfused to hematocrits of around 40% [14]. Pre- and post-transfusion hematocrits have not been reported for individual casualties, nor have specific "transfusion triggers" for battlefield casualties been well established.

NATO doctrine for wartime blood transfusion follows guidelines established by the American College of Surgeons for the Advanced Trauma Life Support (ATLS) course [15-17]. Blood transfusion is indicated for casualties with evidence of ongoing hemorrhage in the presence of shock and for those casualties whose vital signs either fail to respond or respond only transiently to volume infusion. Guidelines have also recommended administering blood to casualties bleeding more than 100 ml/min.

Clearly, more objective criteria are required. The first therapeutic objective in bleeding patients is to control hemorrhage. Controlling hemorrhage is the primary modality for preventing the consequences of blood loss and will immediately reduce subsequent transfusion requirements. Although this fact would seem intuitively obvious, as many as 20% of all casualties who died on the battlefield in Vietnam could have been saved by simple first aid measures to stop bleeding [1]. In some casualties, however, blood loss cannot be controlled without surgery. It is these casualties who require aggressive resuscitation to prevent death.

In patients with ongoing hemorrhage or severe blood loss, the most important immediate objective is to ensure adequate perfusion of cells and tissues. There is usually abundant reserve in the body's oxygen delivery system in young people, thus volume replacement with oxygen-carrying solutions is generally not required in the initial phase of resuscitation. Restoring intravascular volume with crystalloid or colloid solutions increases perfusion and restores oxygen delivery to peripheral tissues. Even in the absence of oxygen delivery, maintained perfusion prevents cell death by removing toxic metabolites and by delivering substrates for anaerobic metabolism to tissues.

The minimally acceptable hemoglobin concentration is an individual characteristic that depends on non-hemoglobin variables, including the ability to increase cardiac output, tissue oxygen demand, pH, the ability to oxygenate available hemoglobin, and the adequacy of perfusion to critical vascular beds [18]. An oxygen extraction ratio of greater than 50% [19] or a mixed venous oxygen saturation of less than 67% (mixed venous oxygen content = 35 mm Hg) [20] have been suggested as critical levels for transfusion.

Because these values are not readily available in most emergency situations, hemoglobin concentrations have been used to identify casualties requiring blood transfusion. As hemoglobin concentrations of less than 10 g/dl result in decreased oxygen delivery to the myocardium, this value has been identified as an indication for erythrocyte transfusion [21]. In fact, these data were derived from older patients with preexisting cardiovascular disease and do not necessarily correlate with adverse outcome in young trauma patients with abundant cardiac reserve. Animal studies have shown that hemoglobin concentrations of 5 g/dl after exchange transfusion are well tolerated [22]. More recent recommendations suggest hemoglobin concentrations below 7 g/dl [17] to 8 g/dl [12] as "triggers" for transfusion.

Hemoglobin concentrations or hematocrits do not accurately reflect the intravascular volume status in the acutely hemorrhaging trauma patient. In the Danang Naval blood utilization study, the mean admission hematocrit was 36.5 ± 5.3% [23]. Furthermore, military trauma casualties may require greater hemoglobin levels than anemic volunteers or animals who are otherwise healthy. Additional encroachments on tissue oxygen supply may result from increased cellular metabolic requirements, arterial hypoxemia, or alkalosis. Also, the potential for close medical monitoring is limited in the austere settings of field hospitals, and the availability of other supportive measures, such as ventilators, is limited [20].

PLANNING FOR MILITARY BLOOD USE

At the height of the Cold War, plans for military blood use were based on scenarios of high-intensity combat involving field armies with millions of soldiers on the plains of northern Europe. Blood requirements of more than 100,000 units a day were predicted. At that rate, blood use would have been more than three times the sustained yield of the entire U.S. blood banking system. Additional logistic constraints requiring that blood be available on short notice and that it not monopolize limited airlift capabilities became the driving forces in the development of alternatives to liquid blood. As the Soviet military threat has diminished, U.S. military blood requirements have been markedly reduced.

Estimates of blood use based on previous U.S. military experience suggest far more modest blood requirements. Even the largest demands for blood faced in 1968, when 476,000 units were shipped to Vietnam [24], or in 1990, when 120,000 units were shipped to the Persian Gulf [25], represent less than 4% or 1%, respectively, of the annual blood supply in the United States (Figure 3). Although 60% of the blood shipped to Vietnam and 95% of the blood sent to the Persian Gulf became outdated, the costs to provide guaranteed availability are willingly borne by military planners.

POTENTIAL ROLES FOR ERYTHROCYTE SUBSTITUTES IN MILITARY TRAUMA

Potential military uses of erythrocyte substitutes are to replace blood for transfusion therapy and to extend the availability of oxygen-carrying solutions to applications for which blood is not currently available. To replace blood, erythrocyte substitutes must compare favorably to blood in terms of safety, efficacy, durability, and cost effectiveness. When used to extend the availability of oxygen-carrying solutions, erythrocyte substitutes must meet the same criteria, as well as show a therapeutic advantage compared with standard crystalloid resuscitation solutions.

The safety of both universal-donor and type-specific blood is well documented, as is erythrocyte viability and survival in banked blood. The efficacy of erythrocyte transfusions in managing hemorrhagic shock has been well substantiated for over half a century. Therefore, for erythrocyte substitutes to be competitive as a blood replacement, there must be significant advantages in lower cost, less volume and weight per unit dose, and less stringent storage requirements.

Extending the role of oxygen carrying solutions with erythrocyte substitutes to pre-hospital resuscitation of hemorrhagic shock will also require documentation of the advantages of an oxygen-carrying solution over crystalloid solutions in casualty survival rates and morbidity. In scenarios in which evacuation times to definitive care are rapid, justifying a therapeutic advantage of erythrocyte substitutes will be difficult unless they are very safe. Erythrocyte substitutes could be beneficial to medical units supporting airborne and special operations units with limited capabilities for providing definitive care to large numbers of casualties.

The opinions and assertations contained herein are the private views of the authors and are not to be construed as official nor do they reflect the views of the Department of the Army or the Department of Defense (AR360-5).

REFERENCES

1. RF Bellamy: The causes of death in conventional land warfare: implications for combat casualty care research. Milit. Med., 149:55-62 (1984).

2. RF Bellamy, PA Maningas, JS Vayer: Epidemiology of trauma: military experience. Ann. Emer. Med., 15:1384-1388 (1986).

3. ME Carey: Learning from traditional combat mortality and morbidity data used in the evaluation of combat medical care. Milit. Med., 152:6-13 (1987).

4. RM Garfield, AI Neugut: Epidemiologic analysis of warfare. J. Am. Med. Assoc., 266:688-692 (1991).

5. DD Trunkey: Overview of trauma. Surg. Clin. North Am., 62:3-7 (1982).

6. WG Byerly, PD Pendse: War surgery in a forward surgical hospital in Vietnam: a continuing report. Milit. Med., 136:221-226 (1981).

7. JJ McNamara, JF Stremple: Causes of death following combat injury in an evacuation hospital in Vietnam. J. Trauma, 12:1010-1012 (1973).

8. K Arnold, RT Cutting: Causes of death in United States military personnel hospitalized in Vietnam. Milit. Med., 143:161-164 (1978).

9. JA Mendelson: The use of whole blood and blood volume expanders in U.S. military medical facilities in Vietnam, 1966-1971. J. Trauma, 15:1-13 (1975).

10. MD Jowitt, RJ Knight: Anaesthesia in the Falklands campaign. Anaesth., 38:776-783 (1983).

11. CK Allam, RE Nassif, SY Alami: Disaster transfusion experience. Mid. East. J. Anesth., 7:147-152 (1983).

12. B Eshaya-Chauvin, RM Coupland: Transfusion requirements for the management of war injured: the experience of the International Committee of the Red Cross. Br. J. Anaesth., 68:221-223 (1992).

13. WP Monaghan, DR Levan, FR Camp Jr.: Military blood banking: blood transfusion aboard a naval hospital ship receiving multiple casualties in a combat zone, a controlled medical environment. Transfusion, 17:473-478 (1977).

14. WH Crosby: Acute anemia in the severely wounded battle casualty. Milit. Med., 153:25-27 (1988).

15. TE Bowen, RF Bellamy (eds.): Emergency War Surgery. Washington, D.C., U.S. Government Printing Office, pp. 134-148 (1988).

16. Advanced Trauma Life Support Course for Physicians. Chicago, American College of Surgeons, pp. 59-73 (1989).

17. Combat Casualty Care Guidelines: Operation Desert Storm. Washington, D.C., Office of the Surgeon General, pp. 30-33, 120-122 (1991).

18. P Lundsgaard-Hansen: Treatment of acute blood loss. Vox. Sang., 63:241-246 (1992).

19. DK Wilkerson, AL Rosen, SA Gould, LR Sehgal, HL Sehgal, GS Moss: Oxygen extraction ratio: a valid indicator of myocardial metabolism in anemia. J. Surg. Res., 42:629-634 (1987).

20. P Lundsgaard-Hansen, JE Doran, B Blauhut: ıs there a generally valid, minimally acceptable hemoglobin level? Infusiontherapie, 16:167-175 (1989).

21. LSC Czer, WC Shoemaker: Optimal hematocrit value in critically ill postoperative patients. Surg. Gynecol. Obstet., 147:363-368 (1978).

22. F Levine, A Rosen, LR Sehgal, S Gould, W Sehgal, G Moss: Physiologic effects of acute anemia: implications for a reduced transfusion trigger. Transfusion, 30:11-14 (1990).

23. BG Mc Caughey, J Garrick, LC Carey, JB Kelley. Naval Support Activity Hospital, Danang, casualty blood utilization: January to June 1968. Milit. Med., 153:181-185 (1988).

24. FR Camp Jr., NF Conte, JR Brewer: Military Blood Banking 1941-1973. Fort Knox, KY, U.S. Army Medical Research Laboratory, p. 20 (1973).

25. Personal communication. Lieutenant Colonel Michael Ward, U.S. Armed Forces Blood Program Office.

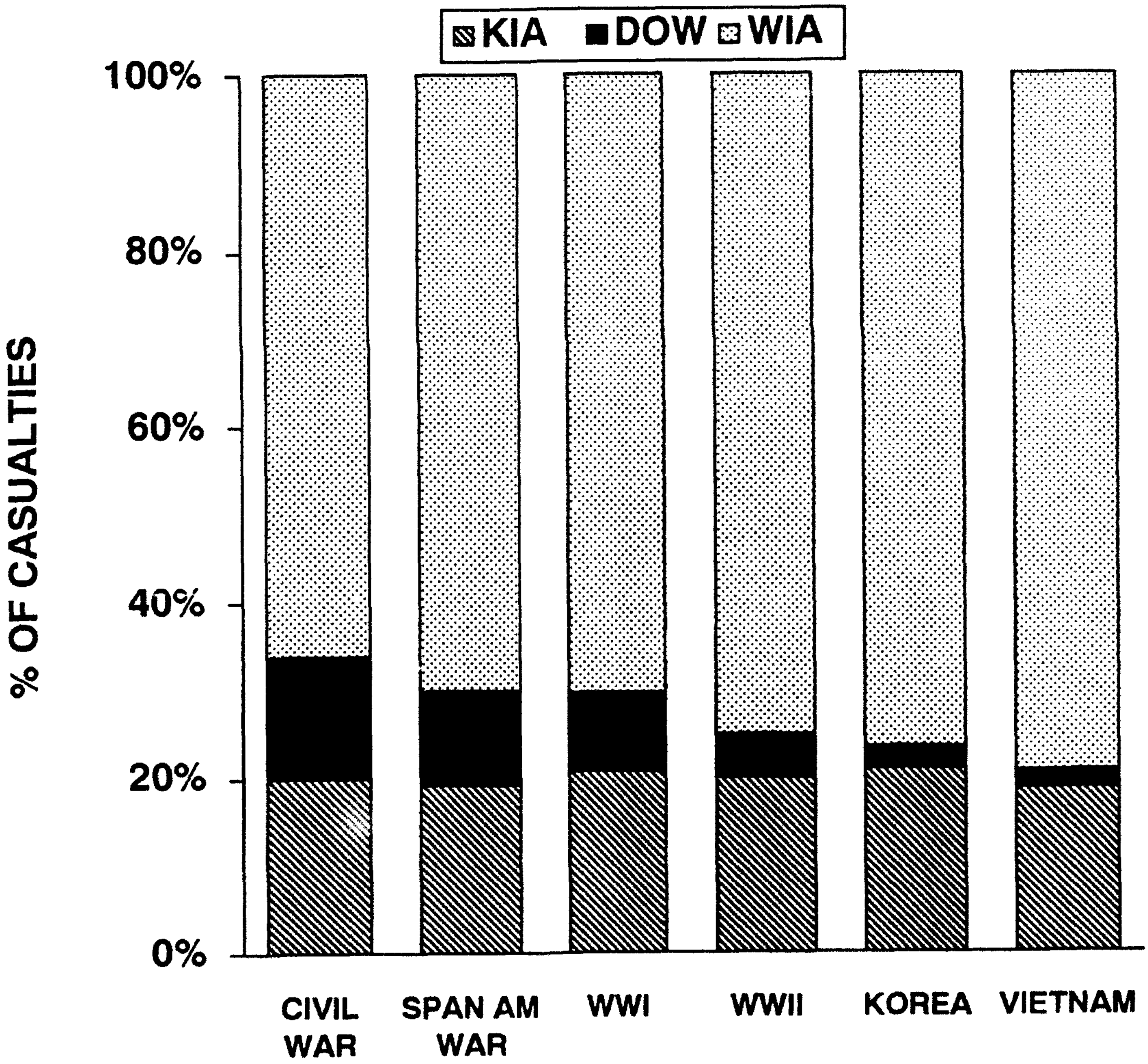
26. EL Wallace, DM Surgenor, HS Hao, J An, RH Chapman, WH Churchill: Collection and transfusion of blood and blood components in the United States, 1989. Transfusion, 33:139-144 (1993).

FIGURE LEGENDS

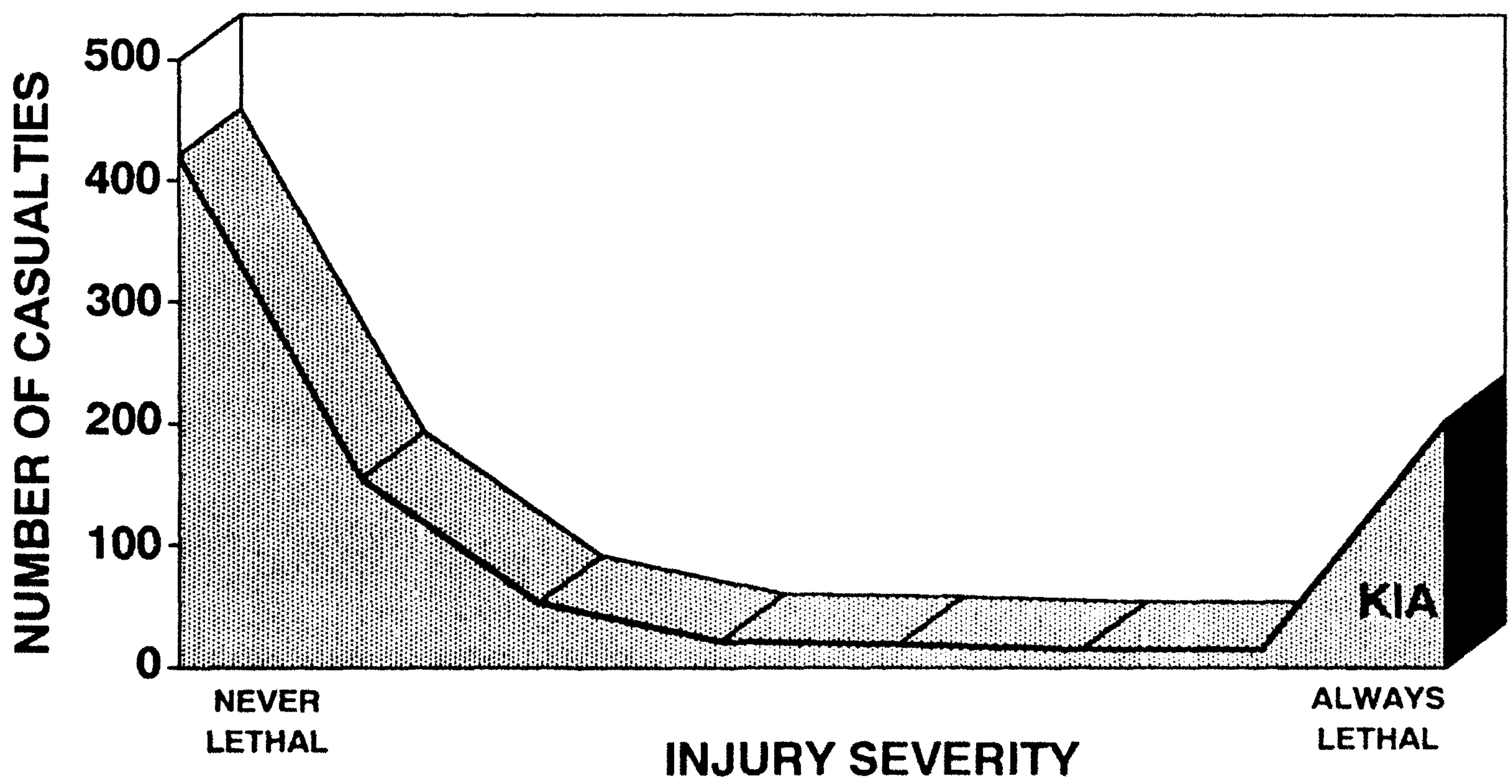
Figure 1. Distribution of casualties in American wars. The decrease in casualties dying of wounds (DOW) correlates with shorter evacuation times to field hospitals.

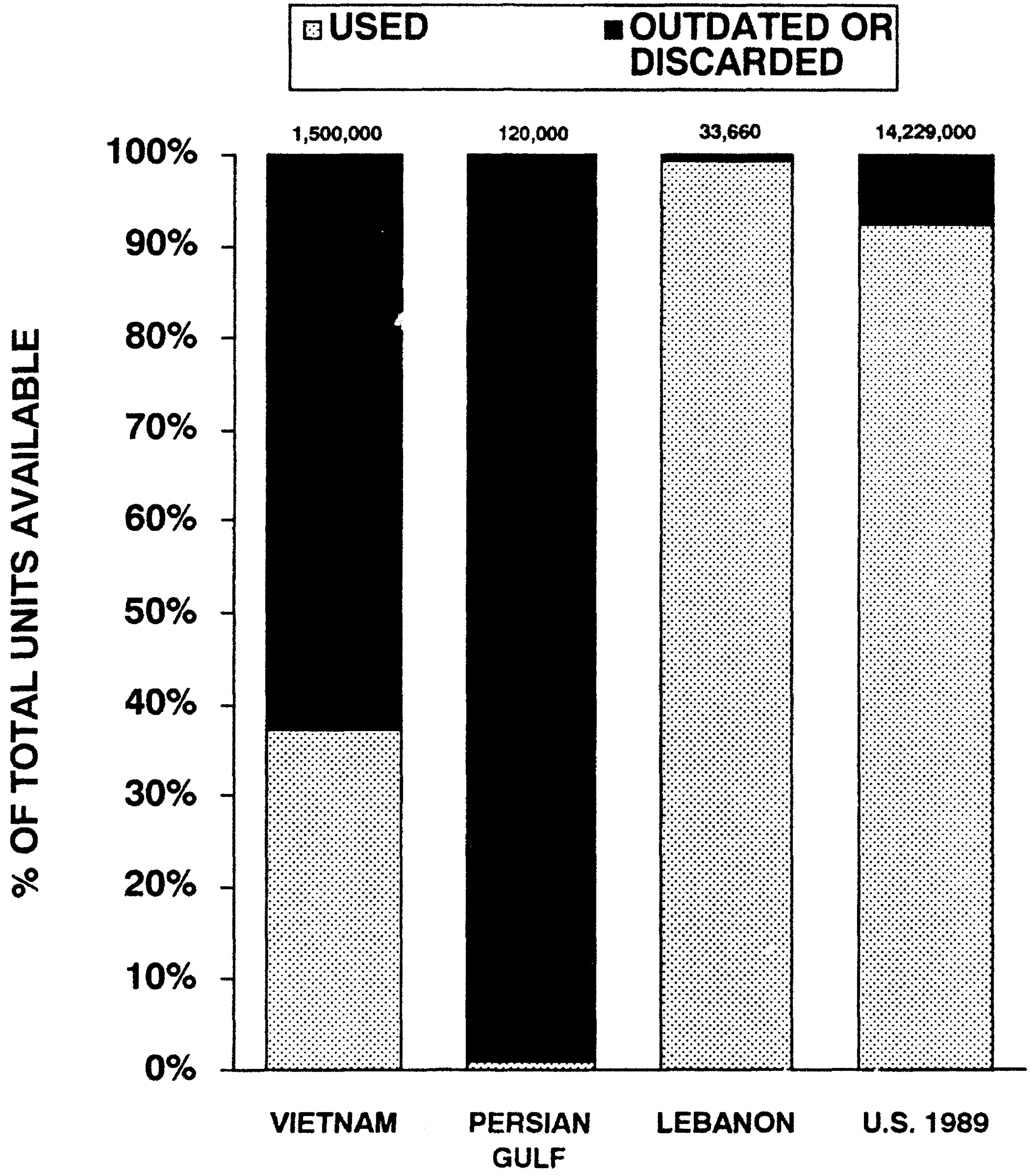
Figure 2. Bimodal distribution of injury severity from wounds sustained in combat. Injuries identified as *never lethal* are "carded for record only" and not admitted to a hospital. Injuries identified as *always lethal* are killed in action. Earlier treatment and evacuation could potentially reduce the *always lethal* peak.

Figure 3. Patterns of blood use in recent conflicts, compared to the total U.S. blood supply in 1989 [26]. The high percentage of units outdated or discarded in the Vietnam and Persian Gulf Wars reflects the need to position adequate blood to meet anticipated needs far from the continental U.S.



KIA
DOW
WIA
100%
80%
60%
40%
20%
0%
% OF CASUALTIES
CIVIL WAR
SPAN AM WAR
WWI
WWII
KOREA
VIETNAM


NUMBER OF CASUALTIES
500
400
300
200
100
0
NEVER LETHAL
ALWAYS LETHAL
INJURY SEVERITY
KIA



USED
OUTDATED OR DISCARDED
1,500,000
120,000
33,660
14,229,000
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
% OF TOTAL UNITS AVAILABLE
VIETNAM
PERSIAN GULF
LEBANON
U.S. 1989