Optimized blood management for elective orthopaedic surgery

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OPTIMIZED BLOOD MANAGEMENT FOR
ELECTIVE ORTHOPAEDIC SURGERY

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OPTIMIZED BLOOD MANAGEMENT FOR ELECTIVE ORTHOPAEDIC SURGERY

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht
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volgens het besluit van het College van Decanen
in het openbaar te verdedigen op
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Gabriel Garcia Marquez 2003

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CHAPTER 1

INTRODUCTION PURPOSE AND AIMS OF THE STUDY

INTRODUCTION

Next to pain and deep venous thrombosis, blood loss is one of the most important complications in elective orthopaedic surgery. Although blood transfusions have been used for many years to treat this complication, much remains unclear regarding indications, risks and side effects.

In the 20th century a series of discoveries dramatically improved the safety of blood transfusion, to the point where, after World War II, blood transfusion seemed a safe procedure (1). Then, during the middle of the 70's of the last century, it appeared that pre-transplant blood transfusion induced an immunologic reaction in the acceptor (2,3). In fact, every blood transfusion should be considered a "organ transplant", albeit a temporary one (4). Other immunomodulatory effects are an increase in cancer recurrence and possibly an increased infection incidence observed in patients receiving blood transfusions. In the middle 80's physicians and patients became more aware of the possible infection risks associated with blood transfusions (HIV, HepC, vCVJD etc.). This awareness, as well as a persistent shortage of donor blood, was a major reason for a re-evaluation of the indications for and alternatives to transfusion of allogeneic blood. It has come to be realized that it is not necessary to transfuse a patient unless the blood loss has deleterious effects on the oxygen supply to the tissues. As a result, the transfusion trigger has shifted from an "optimal" haemoglobin level (10 g/dl) (5) to that level of haemoglobin necessary to meet the patient's tissue oxygen demands (6,7). However, how to determine this level is still a matter of debate.

At this time, we find ourselves in the interesting situation where blood transfusions are safer than ever before, yet, people have become highly concerned about their risks. Blood transfusions are unlikely ever to be completely safe (8), and therefore transfusions should only be given when truly necessary. Other reasons to be reluctant with blood transfusions are altruism, scarcity and financial motives.

One of the main issues in this field, then, is to determine by what means we can avoid transfusions altogether. In addition, if blood has to be given, what blood transfusion management will make the practice as safe and effective as possible? This thesis will address several of these issues.

HYPOTHESIS

Our general hypotheses are as follows: (1) Blood transfusions should be minimized as, even in the absence of major complications, they detrimentally affect postoperative recovery; (2) the optimal manner to minimise the need for transfusion is by a multi-modal approach.

AIMS OF THE STUDY

In order to test our general hypotheses, we will address the following issues:

1. If a blood transfusion is required, what effect does this have on infections and duration of hospitalisation after elective major orthopaedic surgery?
2. Perioperative transfusions can be minimized by a variety of approaches.
 - a. Alternatively, transfusions are likely to be decreased if perioperative blood loss is limited. Whereas this is mostly a surgical issue, we will investigate one approaches to this issue of relevance to the anaesthesiologist: affecting perioperative blood loss by using different (routinely used) NSAID's?
 - b. Optimisation of the pre-operative haemoglobin will result in a decreased need for transfusion. We will investigate if it is possible to reduce blood transfusions by optimisation of the pre-operative haemoglobin concentration using epoetin alpha, and, if so, determine the optimal dose regimen?
 - c. Can perioperative transfusion rates be influence by re-infusion of the patient's own blood postoperatively?
 - d. Although no universally applicable transfusions triggers exist, can an approach be designed that is safe and ensures sufficient oxygen delivery to all tissues? What are the effects of transfusion guidelines on the transfusion incidence in clinical practice?
3. How effective can blood transfusion management be?

ORGANIZATION OF THE THESIS

The thesis is organized as follows.

In order to place our investigations in context, we will briefly review the developments in blood transfusion up to the present time. Chapter 2 will provide a historical overview of the concept of transfusion, whereas Chapter 3 will focus spe-

cifically on the issue of hemovigilance—a recent development attempting to assure optimal use and maximal safety of blood transfusion.

In Chapter 4 we will address the first part of the hypothesis, and present evidence that transfusion per se is a predictor of prolonged hospital stay and wound closure disturbances.

The next series of chapters will address the second part of the hypothesis, investigating different approaches to minimization of blood transfusion. Chapter 5 presents the results of the implementation strict transfusion guidelines. Then two chapters investigate the role of non-steroidal anti-inflammatory drugs in peri-operative blood loss: Chapter 6 determines the effect of ibuprofen, and Chapter 7 investigates if use of cox-2 selective compounds may be beneficial in this setting. The next two chapters address the use of pre-operatively administered erythropoietin. Chapter 8 presents results of an international multicenter trial investigating the effects of erythropoietin administration on perioperative outcome. Chapter 9 calculates the optimal dosage for the individual patient. Chapter 10 looks at a post-operative approach to minimizing transfusions: the re-infusion of drain blood.

The practical application of this multi-modal approach is presented in Chapter 11, in the form of algorithms that can be applied by the practicing physician. Finally, in Chapter 12, we discuss the findings and summarise the thesis.

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CHAPTER 2

A BRIEF HISTORY OF BLOOD AND BLOOD TRANSFUSION

As common as the concept of the blood circulation may now appear to us, it has a long and convoluted history behind it. Similarly, the concept of transfusing blood of one human into another did not suddenly appear on the scene, but developed slowly—with some catastrophes along the way. In this chapter, we will briefly trace these developments through time.

BLOOD AND THE CIRCULATION

The Egyptians and Greeks

For centuries people saw blood as a magical substance, a “humor” whose ebb and flow in the body mirrored the balance of the elements in the universe. That belief was reflected in the system of humoral medicine, developed by the Greeks, in which health was maintained by bloodletting, among other things. But even the Egyptians, as early as 2500 BC, used bleeding to treat patients, as seen on contemporary illustrations, where patients were bled from foot and neck.

In 500 BC the Greek thinker Alcmaeon of Croton practiced animal dissection, and observed that arteries and veins are dissimilar. Later in 450–400 BC Empedocles, a Greek philosopher in Sicily, believed that the organ of sense is the heart and theorizes that all matter is comprised of four “roots” (or elements) – earth, fire, air, and water (1).

Hippocrates

Influenced by the ideas of Empedocles, Hippocrates, the pre-eminent physician of antiquity, postulated that, similar to the four elements, the body is comprised of four humors – blood, phlegm, black bile, and yellow bile – and that their imbalance causes disease. In addition to this “humoral theory”, Hippocrates and his followers set forth tenets that form the basis of much of Western medicine: disease results from natural as opposed to magical causes, patients should be observed and symptoms of disease should be noted, and physicians should adhere to a strict ethical code of conduct.

Prior to the time of Hippocrates (460 to 377 B.C.), all illness was attributed to one disease with variable symptoms. Careful clinical observations by Hippocrates led to the recognition of specific disease states with identifying symptoms. It was

during this time that the concept of body humors developed. The four fluid substances of the body were blood, phlegm, yellow bile, and black bile. Health depended on the proper balance of these humors. Bloodletting was, therefore, a method used for adjusting one of the four body humors to proper balance. This clinical concept led to the decline in the doctrine of evil spirits in disease.

Aristotle

The Greek philosopher Aristotle (350 BC) believed that the heart was the central organ of the body and therefore the seat of the soul. He conducted dissections of many different animals and described their anatomical structures. Based on his observations, Aristotle presumed that the heart was a three-chambered organ, even in humans. Around 300 BCE, in Alexandria, Egypt, Herophilus of Chalcedon, one of the first Greek anatomists to publicly dissect human cadavers, determined that arteries are thicker than veins, and carry blood.

Claudius Galenus

Through his studies of anatomy, successful treatment of patients, and voluminous writings on medicine and the philosophy of medicine, Claudius Galenus (130–200 BC), known as Galen, became one of the most important physicians in history, second only to Hippocrates in influence. In his fourteenth year Galen attended lectures given by Stoic, Platonic, Peripatetic, and Epicurean philosophers from Pergamon. In 157 Galen returned to Pergamon, where he “had the good fortune to think out and publicly demonstrate a cure for wounded tendons” which gained him, in 158, the position of physician to the gladiators. He was reappointed annually until the outbreak of the Parthian War in 161. The traumatic injuries of the arena provided Galen with excellent opportunities to extend his knowledge of anatomy, surgery, and therapeutics, and throughout his life he drew on this fund of experience to illustrate his arguments. Dissecting and experimenting on animals, he proved that arteries contain blood, but he also suggested that the systems of arteries and veins are completely distinct, and that blood forms in the liver, travels through the veins to all parts of the body, and passes between the ventricles through pores in the septum. His ideas, not all of which are correct, formed the core of the medical canon for centuries. Galen believed that the Hippocratic writings were never wrong – merely obscure – and he saw his own work as the extension and clarification of the Hippocratic corpus (2,3,1).

The perception of the circulation developed much later, and very slowly. In the mid-1200s the eminent Cairo physician and author Ibn al-Nafis discovered and described the pulmonary circulation, the flow of blood to and from the lungs. Again much later in 1553, unaware of al-Nafis' findings, the Spanish physician and theologian Michael Servetus suggested that blood flows from one side of the heart to the other via the lungs instead of through the wall between the ventricles, in contrast to Galen's theory. He was burned at the stake as a heretic for denying the Trinity. Fabricius, the anatomist from Padua, in 1603 published his work "On the Valves in Veins" featuring the first drawings of vein valves. And then in 1628 the British physician William Harvey published his masterwork "Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus" (Anatomical Essay on the Motion of the Heart and Blood in Animals), in which he explained that blood circulates within the body and is pumped by the heart. "De Motu Cordis", which elicited great criticism, is the culmination of Harvey's years of experiments on animals – and even on the surface veins of arms of living subjects (4,1).

TRANSFUSION

Animal transfusion

It has been suggested the early Egyptians may already have performed blood transfusions. It appears, however, that this may have been an incorrect interpretation of the fact that Egyptian kings bathed in human blood as a cure for elephantiasis. Although there are descriptions of a blood transfusion of Pope Innocent VIII (1432–1492), these are of doubtful validity. In 1657 Christopher Wren performed the first intravenous drug injection. Once this technique became available, it was Richard Lower in 1665 who performed the first recorded blood transfusion in animals. With a crude syringe made of goose quill and bladder, he connects the jugular vein of a dog he had bled to the neck artery of second dog, thereby resuscitating the former (5,6,1).

Mammalian blood transfusion to man

In June of 1667, the French physician Jean-Baptiste Denis transfused nine ounces of lamb's blood into a teenage boy suffering from a persistent fever. He attached the lamb's carotid artery to a vein in the boy's forearm, without the

patient suffering any negative consequences. Denis used the procedure on several other patients, until the death of Antoine Mauroy, whom Denis transfused twice with calf's blood in December of the same year. Antoine Mauroy was a middle-aged man suffering from mad rages. Denis believed that by transfusing the blood of a calf into the man the man would assume the placid nature of the calf (7,8). The experiment appeared to work: the toxicity of the transfused blood probably made the subject very ill and therefore very placid. It is now believed that the man was in fact suffering from syphilis, which induced his violent behaviour. The symptoms of the syphilis would also have been relieved by the high fever that the toxic blood would have induced. Eventually the man died and Denis was arrested for his murder. Further investigations revealed, however, that the man had not in fact died from the blood but from cyanide placed in his food by his wife. Denis was eventually exonerated, but, 10 years later, the procedure was prohibited by law in France as well as in Italy and was also forbidden by the Royal Society of Medicine in England (9,1).

Homologous blood transfusion

For the next 150 years, there was little interest in transfusion, but it is significant that Nuck in 1714 and Cantwell in 1749 declared that this procedure would be of value in severe haemorrhage. When interest in transfusion was revived by James Blundell in 1818 (10,11,12,13), it was to replace lost blood in puerperal haemorrhage, and after a series of experiments in which he had demonstrated that human blood loses none of its "vital properties" by passage through transfusion equipment. Blundell failed in his first four desperate attempts to save women on the point of death from postpartum haemorrhage, but he succeeded in five of the next six attempts.

It appears that the technique rapidly gained in popularity. In 1875, Landois (14), in a comprehensive monograph on transfusion, collected 347 cases in which human blood had been used and 129 cases in which animal blood had been used. By this time, important studies on the physiology of the blood were being performed by a number of qualified observers, and some physicians, such as Fordyce Barker, advocated transfusion "...not exclusively in those desperate cases where favourable results are hardly looked for but ... before patients have arrived at, and fallen into, this desperate condition"—a very modern-sounding concept. Techniques in use included transfusion with defibrinated blood, immediate transfu-

sion with pure blood, immediate transfusion from vein to vein, and immediate transfusion from artery to vein.

Although the indications and rationale of blood transfusion were by this time apparently quite well understood, the indications during the last quarter of the 19th century again became vague and irrational, the procedure was employed indiscriminately, and the number of severe reactions and fatalities increased. As a result, transfusion again began to be considered as a hazardous, and even a disreputable procedure, to be employed only as a last resort and in desperation.

During the first years of the 20th century, a blood transfusion was frequently a more difficult technical procedure, and sometimes a procedure fraught with greater risks, than a major operation. Its development as an effective and safe therapeutic method required solutions to a number of special problems.

BLOOD COAGULATION

The first efforts to overcome coagulation difficulties were made in 1835, with the use of defibrinated blood by Bischoff, and concluded in 1914 with the successful use of sodium citrate by Hustin, Weil, and Lewisohn (15,16).

BLOOD TYPES

The way was opened to a solution of the vexing problem of agglutination and haemolysis from admixture of incompatible bloods, when Landsteiner (17) in 1900 published his epochal work on the identification of blood groups, based on his previous demonstration of the presence of isoagglutinating and isoagglutinable substances in the blood. Jansky in 1907 and Moss 3 years later, without knowledge of Jansky's studies, worked out the reciprocal agglutinating reactions of the four blood groups and classified them accordingly. The confusion that arose because of differences in nomenclature was eliminated after World War I, when the numbers previously used to designate blood groups were replaced by the letters A, B, AB, and O, each group being designated by the agglutinogens in Landsteiner's original scheme.

Communications in the early years of the 20th century were often slow, and foreign medical literature had only a limited circulation in the United States. No practical use, therefore, was made of Landsteiner's work until 1907, when Ottenberg (18), at Mount Sinai Hospital in New York, was the first to match donor and recipient before giving blood and thus made transfusion a safe procedure from the standpoint of compatibility. The validity of Ottenberg's work was not immediately realized; his offer to perform compatibility tests for the surgeon at his own hospital had no general acceptance for almost 5 years because such tests were considered unnecessary or misleading. In 1911, Ottenberg demonstrated that it was safe to use as a donor a person whose serum agglutinated the recipient's red cells, but unsafe and dangerous to use one whose red cells were acted upon by the recipient's serum. This demonstration eventually led to the widespread employment of group O donors as universal donors, since the red blood cells of this blood group are not agglutinable by the serum of any other blood group.

TECHNICAL DIFFICULTIES

Until 1913, direct transfusion was used to the exclusion of any other technique. This was a difficult and time-consuming method, requiring a specially trained team to carry it out and totally unsuited for use in sudden emergencies. In 1891, von Ziemssen of Munich had performed transfusion by the syringe technique but his report attracted no attention and when Lindeman (19) described it in 1913, it was, for all practical purposes, a new method. With this technique, no dissection of blood vessels was necessary in either donor or recipient, and the exact quantity of blood transfused was known. The technique, however, required a trained team of at least four persons and the use of a large number of expensive syringes. Also, rapid injection of the blood was mandatory. In 1915, Unger (20) introduced an apparatus based on the principle of the two-way stopcock, which overcame many of these difficulties. Dozens of variations of this apparatus were introduced during the next 15 years.

INFECTION

Infection ceased to be a major problem after first antiseptic, and then aseptic techniques came into general use, and as long as transfusion was employed on

in hospitals and on what amounted to elective indications. The open containers originally used to collect blood for indirect transfusion first became impractical, and then a real source of danger, when indications for transfusion were extended.

BLOOD STORAGE

From the First to the Second World War, scientists and physicians made rapid progress in the large-scale storage and use of blood. War was not an incidental factor to these developments, as it created unprecedented demand for the life-saving fluid. Much as the Spanish Civil War was a prelude to World War II, so was blood first transported to the front lines of battle in Spain. By the time war had spread through Europe, the Allied forces were aided by a well-organized blood supply. Even prior to U.S. military involvement, two Americans had revolutionized the storage and distribution of blood.

A plasma shortage in Britain during World War II prompted the U.S. to organize the Plasma of Britain campaign, run by Dr. Charles Drew from a central laboratory at Presbyterian Hospital in New York. Building on techniques he had already developed to separate and preserve blood plasma, which he considered to be a viable substitute for whole blood, Dr. Drew devised a modern and highly sterile system to process, test, and store plasma for shipment overseas by the Red Cross.

Searching for a durable substitute for liquid plasma, Harvard biochemist Edwin Cohn invented a method to separate out its different proteins (or fractions). In a series of steps that are repeated, with slight variations in temperature and chemical conditions, plasma is mixed with the solvent ethyl alcohol and centrifuged. Through this process, dubbed fractionation, Cohn and his team were able to isolate the plasma components fibrinogen (Fraction I), gamma globulin (Fraction II and III), and albumin (Fraction V). Each of these fractions was thought to have different therapeutic properties. After World War II, the science of blood reached new heights - and setbacks. The invention of the plastic blood-collection bag greatly reduced the external contamination of donated blood; the commercial introduction of Rh immunoglobulin saved the lives of many Rh-positive babies born to Rh-negative mothers; and the development of Factor VIII concentrate offered hemophiliacs a new lease on life. Yet these improvements were soon overshadowed by contaminated blood supplies. Hepatitis and, more drastically and

fatally, the HIV virus were transmitted to many transfusion recipients and haemophiliacs, the very people who had come to rely on the blood of others. As a result of new policies responding to this tragedy, blood supplies are now safer than ever before.

At the same time, these issues have made it clear that – whatever the safety nets in place – blood should only be transfused when necessary. The remaining chapter of this thesis will address various approaches to this issue.

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CHAPTER 3

РАБОЧИЙ ЛИСТ

INTRODUCTION

Transfusion of blood and blood products can give rise to many complications. Although these risks are slowly declining, they still have to be considered as potential fatal. In this chapter we will review the main complications of blood transfusions. The approaches taken to prevent such complications are grouped together under the term “haemovigilance”.

We will discuss the following issues:

1. Infectious complications
2. Transfusion reactions:
 - a. Haemolytic
 - b. Febrile non-haemolytic
 - c. Allergic
 - d. Non-immune haemolysis
3. Post-transfusion purpura
4. Transfusion-associated graft-versus-host disease
5. Transfusion-related acute lung injury
6. Transfusion-related immunomodulatory effects
 - a. Renal graft survival
 - b. Crohn's disease
 - c. Recurrent spontaneous abortion
 - d. Tumour recurrence
 - e. Postoperative infections

Finally, we will discuss the concept of haemovigilance systems.

INFECTIOUS COMPLICATIONS OF TRANSFUSION

Whilst transmission of syphilis and hepatitis B virus (HBV) have been recognized for many years, it was the identification of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) that opened many eyes not only to the potential of transfusion as a route of infection, but also to its efficiency in the transmission of a whole range of infectious agents. Viruses, bacteria and protozoa have been clearly demonstrated to be transmitted by transfusion of blood and blood products. Fungi have not been reported to have been transmitted and there is uncertainty over whether prions are actually transmitted by transfusion of blood and blood products (table 1). There are four main properties that generally

Table 1 Infections agents who are reported to have been transmitted by blood transfusion.

Viruses	Hepatitis viruses	Hepatitis A virus (HAV)
		Hepatitis B virus (HBV)
		Hepatitis C virus (HCV)
		Hepatitis D virus (HDV) (requires co-infection with HBV)
	Retroviruses	Human Immunodeficiency virus (HIV) 1 + 2 (+ other subtypes)
		Human T-cell leukaemia virus (HTLV) 1 + 2
	Herpes viruses	Human cytomegalo virus (CMV)
		Epstein-Barr virus (EBV)
		Human Herpes virus 8 (HHV-8)
	Parvovirus	Parvovirus B19
Bacteria	Miscellaneous viruses	GBC-C
	Endogenous	Treponema Pallidum (syphilis)
		Borrelia Burgdorferi (Lyme disease)
		Brucella melitensis (Brucellosis)
		Yersinia enterocolitica / Salmonella spp.
	Exogenous	Environmental species – Staphylococcal spp. / pseudomonas / Serratia spp.
		Rickettsia rickettsii (Rocky Mountain spotted fever)
	Rickettsiae	Coxiella burnetii (Q fever)
		Plasmodium spp. (malaria)
Protozoa		Trypanosoma cruzi (Chagas' disease)
		Toxoplasma gondii (toxoplasmosis)
		Babesia microti/divergens (babesiosis)
		Leishmania sp. (Leishmaniasis)

need to be met for an agent to be transmitted by transfusion; it should give rise to an asymptomatic infection; be present in the blood stream; transmitted parenterally; and it should be able to survive during storage of the blood.

1. The agent must be capable of giving rise to asymptomatic infection in the infected potential donor. In the presence of an adequate selection and ques-

tioning procedure the infected donor will be presumed healthy, and will be bled.

2. To transmit the disease, the infectious agent must be present in the blood or blood products. It must be carried free in the plasma or be present in the leucocytes or erythrocytes which will be transfused.
3. Only those infectious agents that are transmitted parenterally are considered transfusion-transmissible infectious agents (TIA).
4. Blood and blood products are stored under a number of different temperatures, and the infectious agent present has to survive these storage conditions in order to infect the recipient.

Bacterial infections are mostly caused by asymptomatic bacteraemia, skin contamination at the phlebotomy site or contamination during processing of the blood products.

The risk of a TIA can be reduced by several approaches. Although laboratory screening for a specific set of markers of infection is important, even more important is identification and deferral of potential high risk donors. Because a window period exist between infection and the detection in the screening test, donors of the high risk group have a greater risk of transmission of the infectious agent to the blood product pool.

HAEMOLYTIC TRANSFUSION REACTIONS

Most prominent are the acute and delayed haemolytic transfusion reactions (HTR). HTR result from immune-mediated destruction of transfused incompatible packed red blood cells (PRBC). Acute haemolytic transfusion reactions (AHTR) occur within 24 hr after the transfusion, whereas the delayed haemolytic transfusion reaction (DHTR) typically occurs 5–7 days after the transfusion (1). HTR are caused by immunological incompatibility between blood donor and recipient. The haemolysis can be predominantly intravascular and characterized by gross haemoglobinaemia and haemoglobinuria, or extravascular when the only feature may be the decrease in haemoglobin. Most ABO-incompatible transfusions are due to errors in identification of the patient, or to errors in the system of release or administration of the blood products (2) (figure 1). Estimates of ABO-incompatible transfusions vary and may be underestimated, but two recent surveys have found a frequency of 1 in 30.000 transfu-

Figure 1 From SHOT Annual Report 2000 / 2001, These are accumulated data from 5 years of SHOT reporting on serious transfusion complications in the UK Distribution of errors in IBCT cases 1996/97 - 2000/01 (no. cases=699, no. errors=1200) Incorrect Blood Component Transfusion is still the largest category in Transfusion Related Complications. As the figure shows, errors are being made in the whole process. Like in previous years multiple errors were implicated in many “wrong blood” incident, up to 7 errors (n=2) are reported.

sions (3,4). Not all ABO-incompatible transfusions cause morbidity and mortality; However, as little as 30 ml group A cells given to a Group O recipient can be fatal. Less frequent, Kell, Kidd and Duffy antibodies can be responsible for haemolytic transfusion reactions.

FEBRILE NONHAEMOLYTIC TRANSFUSION REACTIONS

Febrile Nonhaemolytic Transfusion Reactions (FNHTR) are suspected in recipients of blood components who experience an increase in temperature of 1 °C or more in the absence of other identifiable causes for the fever. They are the most common encountered transfusion reaction (5). FNTHR are generally self-limited, but the recipient may experience anxiety and discomfort. Because the clinical presentation of fever and chills may represent a life-threatening AHTR, the first step is to discontinue the transfusion. If transfusion is still required following resolution of a reaction, other PRBC should be issued.

ALLERGIC TRANSFUSION REACTIONS

Mild allergic reactions may present as generalized urticaria, pruritis, and flushing, whereas more severe reactions are characterized by stridor, wheezing, dyspnoea and cyanosis, up to circulatory instability and anaphylaxis. Restarting the infusion is not recommended.

NONIMMUNE HAEMOLYSIS OF RBC

Non-immune haemolysis involves destruction of RBC within the circulation due to osmotic, thermal chemical or mechanical damage. These are rarely life-threatening and mostly preventable.

POST-TRANSFUSION PURPURA

Post-Transfusion Purpura (PTP) is a self limiting thrombocytopenia that develops 5–10 days after transfusion of blood components containing platelet antigens. PTP is a rather rare complication of transfusion, but can account for mortality due to intracranial haemorrhage during extreme thrombocytopenia (6).

TRANSFUSION-ASSOCIATED GRAFT VERSUS HOST DISEASE

TA-GVHD is a rare complication of allogenic transfusion, but is likely to be underreported. The mortality is presumed to be higher than 90%. TA-GVHD is caused by replication of competent donor lymphocyte in the cellular blood product, which engraft and lead to immune-mediated destruction of host tissues. The development of TA-GVHD reflects the inability of recipients's immune system to reject the transfused lymphocytes (7).

TRANSFUSION RELATED ACUTE LUNG INJURY

Transfusion related lung injury (TRALI) is a syndrome of acute hypoxia due to non-cardiogenic pulmonary edema. The syndrome is clinically indistinguishable from adult respiratory distress syndrome (ARDS). TRALI is thought to contrib-

ute significantly to mortality in 5 to 10 percent of patients who experience the reaction and is the third leading cause of transfusion-related mortality. Symptoms typically commence within 1 to 2 hours of transfusion but can occur as late as 6 hours. The syndrome has been described following infusion of any plasma-containing blood component, including RBCs, whole blood, FFP, cryoprecipitate, apheresis platelets, platelet concentrates. TRALI was first recognized as a discrete clinical entity almost 20 years ago (8). Before that time, there were several reports of noncardiogenic pulmonary edema, associated with transfusion, which were likely TRALI reactions. These reactions were given descriptive names such as noncardiogenic pulmonary edema, pulmonary hypersensitivity reaction, and severe allergic pulmonary edema.

Although the exact mechanism of lung injury in TRALI is not completely understood, the preponderant evidence favors an antigen-antibody-mediated model. The exact manner in which antibodies trigger a TRALI reaction has not been determined. The assumption has been that granulocytes with adherent antibodies localize in the pulmonary microvasculature and release cytokines locally, resulting in increased vascular permeability and pulmonary edema.

TRALI needs to be recognized as a serious consequence of transfusion, and must be diagnosed, reported, and managed appropriately (9). Evaluation should include a thorough search for an antibody-antigen reaction. Donors directly implicated in a case of TRALI should be deferred from donating plasma-containing blood components.

TRANSFUSION IMMUNOMODULATORY EFFECTS

One fascinating development has been the discovery of the effects of transfused blood products on the immune system. A number of such effects have been described, some of them beneficial, others decidedly detrimental.

Enhanced renal allograft survival

The beneficial effect of prior transfusion on renal allograft survival was described more than 20 years ago. It became standard policy to expose patients on the transplant waiting list to multiple transfusions. Still, the exact mechanism of the beneficial effects has not been elucidated.

Crohn's Disease

Some retrospective studies have shown a significant benefit (i.e. decrease in relapse rate) in patients with Crohn's disease receiving blood transfusions (10,11). However, this has not been demonstrated in all investigations (12).

Recurrent spontaneous abortion

Women with recurrent spontaneous abortion have been treated with infusion of their partner's or third-party leucocytes in order to induce immunological tolerance of the foetus. Although some studies in the past showed possible effects, subsequent randomised trials showed no effect (13).

Tumour recurrence

Over 70 clinical studies have examined the possible effect of transfusion on recurrence of a number of cancers. Meta-analysis of these studies suggests a deleterious effect of blood transfusions on cancer recurrence rate (14,15). Still, adequate randomised controlled trials have to be performed before this issue can be considered certain.

Postoperative infections

The evidence for transfusion as an independent risk factor for infection commonly seen after elective surgery is increasing (16,17).

HAEMOVIGILANCE SYSTEMS

The aim of haemovigilance is to detect and to analyse all unwanted effects of blood transfusion in order to correct their cause and to prevent recurrence, and to improve the safety of blood transfusion. Haemovigilance is defined as: "a set of surveillance procedures covering the whole transfusion chain (from the collection of blood and its components to the follow-up of its recipients), intended to collect and assess information on unexpected or undesirable effects resulting from therapeutic use of labile blood products, and to prevent their occurrence and recurrence"(18). The term was probably created in France and has Greek and Latin roots: haema ("blood"), and vigilans ("paying a particular attention to").

Table 2 SHOT Annual Report 2000/2001: Overall mortality/morbidity figures by fully analysed questionnaires 1996/97 – 2000/01 (n=1148) These are accumulated data from 5 years of SHOT reporting on serious transfusion complications in the UK. The tables shows data on transfusion complications concerning: Incorrect Blood Component Transfused, Acute Transfusion Reaction, Delayed Transfusion Reactions, Post Transfusion Purpura, Transfusion-Associated Graft Versus Host Disease, Transfusion Related Acute Lung Injury and Transmission Transmitted Infections (UC¹ = Un Classified).

	Total	IBCT	ATR	DTR	PTP	TA-GVHD	TRALI	TTI	UC ¹
Minor or no morbidity	819	566	121	103	24	0	0	0	5
Major morbidity	165	69	3	18	11	0	49	24	0
Death definitely attributed to transfusion	38	5	2	4	1	13	6	7	0
Death probably attributed to transfusion ²	3	1	0	0	0	0	2	0	0
Death possibly attributed to transfusion	21	5	4	1	1	0	10	0	0
Death unrelated to transfusion	90	56	13	14	3	0	3	1	0
Outcome unknown	12	6	3	1	0	0	0	0	2
Totals	1148	699	146	141	40	13	70	32	7

Haemovigilance, as a safety concept, appeared in the beginning of the 1990s in France, and the first nation-wide mandatory haemovigilance sytem was set up in 1992 in the same country. The United Kingdom followed in 1996 with the voluntary “Serious Hazards of Transfusion” (SHOT) steering group (<http://www.shot.demon.co.uk/>) (table 2).

On the European level, haemovigilance was accorded interest around 1995. The European Council published its resolution of June 2, 1995 and a communication on “Blood Safety and Self-Sufficiency in the Community” with the aim to improve public confidence in the safety of blood supply. The results of the project should be threefold: a. identify objectives, methods and means related to the establishment of a Community-wide haemovigilance network which would also serve to improve exchange of information between the Member States; b. promote co-operation between Member States on the systematic monitoring of risks and hazards associated with blood collection and transfusion and provide guidance in this respect; c. determine the measures that add value to the actions and

measures of Member States and which need to be proposed to the European Commission in order to enhance the safety of the blood chain. In Paris, on the 16th of July 2001 the European Haemovigilance Network (EHN) was started (<http://www.ehn-org.net/>). In order to continuously improve safety in blood transfusion, the EHN advocated the following:

Member States should introduce and maintain efficient haemovigilance systems that: collect data on side effects / adverse events in recipients, during and after transfusion of blood and blood components gather data on incidents in donors, during and after donation, as well as epidemiological data on donors (especially in relation with incidence and prevalence rates of infectious diseases markers).

Rapid Alert / Early Warning should be incorporated in the haemovigilance system to allow instant reaction in case of emerging threat to the blood supply, of any kind.

In 1996 the Dutch Inspectorate of Health enquired whether a national surveillance system for haemovigilance could be developed for the Netherlands. This request was inspired by the United Kingdom's initiative to install a reporting system for SHOT. An independent foundation named Transfusion Reactions In Patients (TRIP) was established, owned by the professional medical societies engaged in blood transfusion. TRIP was formally launched at the 5th European Haemovigilance Seminar in Amsterdam on February 6–7, 2003. The TRIP office has the aim to anonymously collate, register, analyze and report on the safety of blood transfusion (table 3). In addition, TRIP aims to enhance the safety of blood transfusion by educational programs on this topic. The TRIP program closely resembles the British SHOT system, in being a voluntary system supporting professionals and in its focus on serious adverse events. It is recognized that underreporting may exist, but it is felt that in the Netherlands a voluntary system would be more productive than a compulsory system. TRIP holds the view that the correct and optimal use of blood is as important for blood transfusion safety as is the prevention of adverse events.

Table 3 The list of transfusion complications TRIP requests hospitals to report to them.

1. Incorrect blood product transfused
2. Acute Haemolytic Transfusion Reaction
3. Delayed Type (Haemolytic) Transfusion Reaction
4. Allergic Reaction
5. Bacterial Contamination
6. Transfusion-related Lung Injury (TRALI)
7. Transfusion-associated Graft Versus Host disease (TA-GVHD)
8. Post-transfusion Purpura (PTP)
9. Post-transfusion Viral Infection
10. Post-transfusion malaria and other parasitic infection
11. Circulatory Overload
12. The 'novel' appearance of antibodies to blood group antigens or HLA
13. Non-haemolytic febrile transfusion reactions >? OC

CONCLUSION

Although a blood transfusion has never been safer, transfusion still accounts for some major morbidity and mortality. In this aspect haemovigilance systems have an important function in safeguarding transfusion medicine. Errors have to be prevented and improvement in the use of blood products might be achieved through an audit process based on simple indicators, providing the responsible clinician with continuous feedback of results obtained.

This can only be achieved if as much incidents are reported as possible, and is only possible if all prescribing physicians are aware of the complications of blood transfusion and are willing to report to the haemovigilance systems.

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CHAPTER 4

THE IMPACT OF A BLOOD PRODUCT TRANSFUSION PROTOCOL ON REQUIREMENT FOR RED BLOOD CELL TRANSFUSIONS

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ABSTRACT

National guidelines for the clinical practice of red blood cell transfusions have been transformed at the Sint Maartenskliniek into a protocol. Pretransfusion hemoglobin level is the sole indicator of need for red blood cell transfusions. In combination with other factors, such as technique of anesthesia and use of COX-2 selective NSAID's, the guidelines for clinical practice did reduce the need for red blood cell transfusions by 50% ($p < 0.001$).

INTRODUCTION

Blood loss is a common complication during orthopaedic surgery and often requires homologous blood transfusion (HBT). With a HBT, a patient is exposed to transfusion-related infections, transfusion reactions, the effects of immunomodulation, and potential complications due to human errors in the administration of the packed red blood cells (PRBC) (1). At the same time, PRBC are donated voluntarily (in the Netherlands) and the pool of PRBC in the Netherlands is not infinite. These were the reasons to develop a nationwide consensus for PRBC transfusions in the perioperative period. This nationwide consensus resulted in a transfusion protocol for our hospital in which the haemoglobin concentration was the sole indication for HBT. In this study we investigated the HBT ratio before and after the introduction of the new protocol.

PATIENTS AND METHODS

We based our HBT protocol on the national consensus agreement for transfusions(1). A HBT would only be administered if the haemoglobin concentration of the patient was known (unless active bleeding occurred). Although in the intra- and postoperative phase a haemoglobin concentration of at least 8.8 g/dl was advocated, a lower haemoglobin concentration (8 g/dl) was accepted as transfusion trigger, as patients in the perioperative phase are frequently haemodiluted with crystalloids or colloids. For the cardiac compromised patients we accepted 10.4 g/dl as trigger, and for patients who predonated autologous blood we accepted 11.2 g/dl.

Table 1 Transfusion protocol.

All patients in the post-operative phase

Within 4 hours after the operation	More than 4 hours after the operation
Hb > 8 g/dl = 0 packed cells	Hb > 8 g/dl = 1 packed cells
Hb < 8 g/dl = 1 packed cells	Hb < 8 g/dl = 2 packed cells
Hb < 7.2 g/dl = 2 packed cells	Hb < 7.2 g/dl = 3 packed cells
Cardiac compromised patients	
Within 4 hours after the operation	More than 4 hours after the operation
Hb < 8.8 g/dl = 1 packed cells	Hb < 8 g/dl = 2 packed cells
Hb < 8 g/dl = 2 packed cells	Hb < 8 g/dl = 3 packed cells
Hb < 7.2 g/dl = 3 packed cells	Hb < 7.2 g/dl = 3 packed cells
Patients who predonated autologous blood	
Hb < 11.2 g/dl = 1 packed cells	

This protocol was introduced in May 1996 in our Postoperative Care / Intensive Care Unit (PACU/ICU), and after September 1997 it was applied hospital-wide (table 1). After the introduction of the protocol a HBT was not delivered unless known haemoglobin concentration was available which met the transfusion trigger. Since 1991 our hospital, specialized in elective orthopaedic surgery, has maintained an extensive database of all variables concerning blood loss, operation, duration, surgeon, anaesthesia etc. The data about HBT is retained for at least 10 years after delivery of the PRBC. These databases were merged for the period of January 1, 1998, until September 30, 1998. We compared three periods: (1) Period A, the old situation From January 1995 until May 1996; (2) Period B, from June 1996 until August 1997, when the protocol was only implemented on the PACU/ICU; and (3) Period C, from September 1997 until September 1998 when the protocol was implemented hospital-wide. The number of HBT was compared in these three periods. Proportions were analysed with statistics Chi-square and Fisher's exact test. A p-value of less than 0.05 was presumed significant.

RESULTS

In Periods A, B and C, respectively 4620, 5703 and 4264 patients were compared for the incidence of blood transfusions. Patient populations and types of

Table 2 Results.

	Period A	Period B	Period C
Operations	4620	5703	4264
Type anaesthesia:			
- General [%]	38	37	39
- Neuraxial [%]	56	55	56
- Peripheral nerve [%]	6	17	11
Male [%]	39	39	39
Age [yr.]	40.6	37.1	42.5
Operation time [min.]	48	49.1	50.1
Blood loss [ml.]	251	206	189
Units packed cells [n]	2218	1882	981*
Packed cell usage per operation [n]	0.48	0.33	0.23*

Type of anaesthesia, more combinations can be possible (* = $p < 0.001$).

Figure 1 Packed red cells per operation.

operation in the 3 patient groups were comparable (table 2). The mean consumption of PRBC per operation was 0.48 in period A, 0.33 in period B and 0.23 in period C. The differences between period A and B, period A and C, and period B and C were significant ($p < 0.001$) (figure 1). The mean blood loss per operation showed a tendency to decrease, respectively 251 ml, 206 ml and 189 ml for the periods A, B, and C (figure 2).

Figure 2 Mean blood loss.

DISCUSSION

The options to reduce HBT are numerous. Examples include transfusion guidelines, perioperative blood saving techniques, novel surgical techniques, anticoagulation management, autologous predonation and the perioperative use of erythropoietin (2). The responsibility for determining the indication for the administration of a blood transfusion rests with the transfusion commission, surgeons and anaesthesiologists. In our hospital the responsibility for transfusion guidelines and perioperative cell saving techniques is delegated to the anaesthesiologists, whereas the responsibility for operative technique and anticoagulation management rests with the orthopaedic surgeons. In absence of a known transfusion trigger, feedback with the prescribing physician is essential for maintenance of a transfusion protocol. Guidelines for autologous predonations and preoperative administration of erythropoietin are changing, but since the year 2000 erythropoietin is registered for pre-operative use in major orthopaedic surgery for patients with a haemoglobin concentration less then 13 g/dl.

Of course is it not possible to maintain all confounding factors constant that can affect per-operative blood loss during a period of evaluation as long as the present study. Several important factors changed in our hospital during the evaluation period. Changes occurred in the surgical staff, and the percentage of loco-regional anaesthesia increased. Also, during the evaluation period the introduction of more COX-2 selective NSAID's took place. Undoubtedly, these other factors are likely to be to some extend responsible for the decreased blood loss and

thus for decreased perioperative transfusion requirements (3,4). Still, our study shows clearly the benefits of employing strict perioperative transfusion guidelines, as a 50% decrease in PRBC transfusions was seen during the observation period compared to the 25% decrease in blood loss during the same periods.

Perioperative transfusions are responsible for 60% of all transfusions in the Netherlands. For 40% of these, the indication were poorly specified: blood loss, routine practice, cardiovascular changes, weakness or fatigue were cited. Current guideline, as well as the results of the present study, indicate that in the perioperative period a patient should only be transfused if the haemoglobin concentration is known (5).

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CHAPTER 5

PERIOPERATIVE BLOOD
TRANSFUSIONS AND DECREASED
WOUND HEALING AFTER
REPLACEMENT SURGERY
EFFECTS ON DURATION OF
HOSPITALIZATION

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Submitted.

SUMMARY

Patients who receive any homologous blood transfusion (HBT) after major orthopaedic surgery have a longer duration of hospitalisation (DOH), which can not be explained by a greater incidence of infections in the transfused patients. To determine if minor wound healing disturbances (WHD) are increased by HBT, and if such disturbances are correlated with DOH, we performed an observational study in 444 consecutive patients scheduled for elective primary hip surgery. Transfusion, wound and infection parameters were collected at five time points during treatment. Of the 444 consecutive patients studied, 92 received blood transfusions during their perioperative course, and 352 did not. Thirty-one percent of transfused patients developed WHD vs. 18% of the non-transfused group ($p<0.05$); HBT was the only significant predictor for development of WHD. DOH was prolonged in transfused patients (12.3 vs. 9.8 days), and could be predicted by four significant variables: requirement for blood transfusion (adds 2.71 ± 0.47 days), presence of WHD (adds 1.25 ± 0.45 days), duration of operation (adds 0.2 ± 0.08 days/ 10 min), and patient age (adds 0.9 ± 0.16 days/ 10 years). These data suggest that HBT may increase the incidence of WHD, and that prevention of HBT may be of relevance in limiting duration of admission after elective orthopaedic surgery.

Keywords. blood transfusion, immunomodulation, infections, wound disturbance.

IMPLICATION STATEMENT

Homologous blood transfusion during elective orthopaedic surgery is associated with an increase in minor wound healing disturbances. Requirement for transfusion and present of wound healing disturbances are the main factors predicting duration of hospitalisation in these patients.

INTRODUCTION

Perioperative blood loss is still a major problem in elective orthopaedic surgery. Homologous blood transfusion (HBT) is the standard approach to treat potentially detrimental decreases in haemoglobin (Hb) concentration. However, HBT

is associated with various adverse events, including febrile reactions induced by leukoagglutinins and transmission of infectious diseases. Moreover, HBT has an immunomodulatory effect, which is hypothesized to increase the frequency of postoperative infections (1,2). This issue is far from resolved, as observational cohort studies comparing patients who had or did not have transfusions produced conflicting results (3,4,5,6). A recent meta-analysis found no evidence that autologous versus homologous blood transfusion reduced postoperative infections (7). In a similar fashion, recent randomised controlled trials on the effect of leukocyte-depleted blood transfusions yielded conflicting results as to the frequency of postoperative infections (8,9,10,11,12,13,14,15).

Nonetheless, the clinical observation that patients who receive any HBT after major orthopaedic surgery do stay in the hospital significantly longer is undisputed (16). As postoperative infections are relatively rare (1–3%), and as the role of HBT herein is not yet established (17), other factors are likely to be responsible for the prolonged hospital stay. A host of other factors (age, length of surgery, use of implants etc.) might influence the incidence of post-operative infections as well, and, in addition, the endpoint of frank wound infection may not be an appropriate one. Less severe types of wound healing disturbance could occur after transfusion and lead to subsequent complications or prolonged hospitalisation. To address these issues we undertook this prospective observational study. In 444 patients who underwent elective total hip arthroplasty, we studied (among other parameters) the frequency of HBT, wound disturbances, superficial and deep wound infections, and length of hospital admission.

PATIENTS AND METHODS

We performed an observational study in 444 consecutive patients hospitalised to undergo total hip replacement in the St. Maartens Hospital, Nijmegen, The Netherlands. The hospital's Institutional Review Board approved the study, and all patients gave written informed consent after having received information and explanation of the study. Inclusion criteria included: planned elective primary total hip arthroplasty; age at least 18 years; living in The Netherlands or otherwise available for follow-up for at least 6 weeks post-surgery. Exclusion criteria were: any infection of any body system at screening as determined by symptoms, by erythrocyte sedimentation rate (ESR) >20 mm (unless known to be pre-existent); any blood transfusion received in the six weeks before surgery; any surgery

in the six weeks before surgery. Patients who donated autologous blood before surgery were excluded from the study. During admission patients received standard care according to hospital protocol. Transfusions of packed red blood cells were administered according to the following transfusion triggers: Hb <8.1 g/dl (5.0 mmol/l) during surgery and until 4 hours post surgery; and Hb <8.9 g/dl (5.5 mmol/l) more than 4 hours post surgery. For subjects suffering from cardiovascular disease all transfusion triggers were increased by 0.8 g/dl (0.5 mmol/l). Packed red blood cells were supplied by the local blood bank and consisted of buffy coat-depleted red cells, mean volume 320 ml, Hb 17.8 g/dl, Ht 0.58 leukocytes 0.4×10^9 /l.

DATA COLLECTION

Data were collected at five time points during treatment: 1: last week prior to surgery (screening); 2: on the day of surgery (POD0); 3: one day after surgery (POD1); 4: four days after surgery (POD4); 5: at discharge.

At all these time points, we recorded vital signs, any signs of infection present and other relevant parameters. In addition, the following data were collected at specific time points: At screening: informed consent, medical history, physical examination, use of antibiotics, transfusion information over the past 3 months (including pre-transfusion Hb, volume and type of product transfused, and routine clinical laboratory tests (including at least: Hb, ESR, white blood cell count and differentiation, serum pre-albumin and C-reactive protein).

At POD0: all routine clinical postoperative assessments, name of the surgeon, Hb level.

At POD1: blood loss, transfusion data (including units and type of blood products given and Hb before transfusion), any blood saving techniques used, medications used.

At POD4: serum pre-albumin and pre-transfusion Hb (only if transfused). At discharge: blood loss, transfusion data (number of units, type of blood products), and length of hospitalisation.

In addition, during and after surgery until discharge all relevant medical events were documented in a database: infections, wound leakage, superficial wound disturbances, haematomas etc. Wound and urinary tract infections were defined by the presence of a positive culture. Classification of infection as “deep” required joint involvement. Wound disturbance was defined by erythematous inflammation of more than 1 cm, wound fluid discharge, purulent suture, wound dehiscence, blister and/or any degree of wound necrosis. Moreover, certain events were recorded at any moment during the follow-up period: postoperative infections, withdrawal from study (including reason of withdrawal) and death (including cause of death).

STATISTICAL ANALYSIS

Descriptive statistics were used when appropriate. The occurrence of wound disturbances in relation to receiving blood transfusion and other potentially related factors were calculated with logistic regression analysis. For this purpose use of transfusion and gentamycin cement were coded as binary variables (yes or no), other factors were handled as a continuous variables.

First the effect of each variable was calculated with univariate analysis. Then, using stepwise conditional back and forward selection of variables, multivariate analysis was performed. The effect of variables on the duration of hospitalisation was calculated using linear regression analysis. For this purpose the duration of hospitalisation was log-normalized. A similar uni- and multivariate analysis approach was used.

RESULTS

Differences between transfused and non-transfused patients

Of the 444 consecutive patients studied, 92 received blood transfusions during their peri-operative course, and 352 did not. A comparison between these two groups is provided in table 1. There were significant differences between these groups in gender distribution, length, weight, pre-operative Hb, ESR and pre-albumin levels, operation duration, peri-operative blood loss, total blood loss, and duration of hospitalisation. Of these, the differences in pre-operative

Table 1 Characteristics of transfused and non-transfused patients.

Group statistics (mean)	Total	No transfusion	Transfusion	p
Patients	444	352	92	
Blood transfusions	0.36 (0.83)	0 (0)	1.7 (1.0)	
Age (years)	63.3 (11.9)	63.1 (11.2)	64.2 (14.5)	N.S.
Sex (% male)	34 (47.3)	39 (49)	13 (34)	<0.001
Length (cm)	169 (8.9)	171 (8.9)	167 (8.6)	<0.05
Weight (kg)	77.6 (14.4)	79 (13.8)	72 (15.4)	<0.001
ESR (mm in 1 st hour)	15.3 (11.8)	14.5 (11.1)	18.3 (13.8)	<0.05
Pre-albumin (mmol/l)	281 (55.7)	285 (56.2)	266 (51.4)	<0.05
CRP	6.23 (9.7)	6.25 (9.6)	6.17 (9.8)	N.S.
Pre-operative Hb (mmol/l)	8.47 (0.77)	8.6 (0.72)	8.0 (0.75)	<0.001
Operation time (min)	73 (22.7)	71 (19.5)	80 (31.6)	<0.05
Peri-operative blood loss (ml)	591 (363)	540 (274)	789 (551)	<0.001
Total blood loss (ml)	975 (511)	922 (431)	1185 (716)	<0.001
Gentamycine cement used (%)	15 (36)	14 (34)	21 (41)	N.S.
Wound disturbance (%)	21 (40)	18 (39)	31 (47)	<0.05
Positive wound culture (%)	2.25 (15)	1.99 (14)	3.26 (18)	N.S.
Deep infection (%)	1 (8)	1 (8)	1 (10)	N.S.
Urinary tract infections (%)	3.6 (17)	3.69 (19)	3.26 (18)	N.S.
Mean hospital stay (days)	10.2 (4.1)	9.8 (3.5)	12.3 (5.3)	<0.001

ESR, pre-albumin levels, and length were considered to be so small as to be clinically insignificant. As expected, there were no significant differences in the rate of positive wound cultures or the incidence of deep infection (1% in each group). Nonetheless, the clear trend for increased incidence of positive cultures (1.99 in the non-transfused group vs. 3.26 in the transfused group) suggested that a more detailed analysis of wound healing disturbances would be warranted.

Association of transfusion with wound disturbances

Comparing the incidence of wound disturbances between the two groups, we found a clear difference: 31% of the transfused group developed a wound distur-

Figure 1 Percentages of wound healing disturbances in transfused vs. non-transfused patients. Patients were divided three subgroups, sustaining peri-operative blood loss of 0–700 ml (Group I), 701–1000 ml (Group II), or greater than 1001 ml (Group III).

Figure 2 Length of hospital admission in transfused vs. non-transfused patients, divided into subgroups according to perioperative blood loss volume, 0–700 ml (Group I), 701–1000 ml (Group II), or greater than 1001 ml (Group III).

bance vs. 18% of the non-transfused group ($p < 0.05$, figure 1). To determine whether the amount of peri-operative blood loss affected this relationship, we divided the group into three subgroups, sustaining blood loss of 0–700 ml, 701–1000 ml, or more than 1001 ml, respectively. For each of these subgroups we observed essentially the same proportion in the incidence of wound disturbances as was found for the groups as a whole (figure 1). However, since the study was not powered for this analysis, the correlation between transfusions and wound disturbances did not reach statistical significance in these subgroups.

Association between duration of hospitalisation and transfusion

As a group, transfused patients stayed significantly longer in the hospital than non-transfused patients ($p < 0.001$). In addition, the differences in hospitalisation duration (9.8 vs. 12.3 days) suggest a potential major economic impact. However, many factors can affect this important but broad outcome measure. We therefore determined if the duration of hospitalisation was affected by the amount of perioperative blood loss per se. As indicated in figure 2, when the patients were subdivided by amount of perioperative blood loss, we observed (1) that duration of hospitalisation was essentially unaffected by blood loss, and (2) that a similar difference in hospitalisation duration between transfused and non-transfused patients was maintained among the subgroups. Indeed, although the study was not powered to detect significant differences in this sub-analysis, the difference between transfused and non-transfused patients did reach significance in those patients who lost more than 700 ml of blood perioperative.

Univariate and multivariate analysis

The requirement for blood transfusion was not the only difference between the two study groups, and some of these other significant factors may also be responsible in part for the increased incidence of wound disturbances. However, many of the factors that showed significant differences between transfused and non-transfused patients can be logically linked to red cell loss, and thereby to transfusion requirement. For example, male gender, greater height and weight, and a higher pre-operative Hb are all associated with a greater red cell mass, and these patients will therefore tolerate more red cell loss before transfusion triggers are reached. Similarly, longer duration of operation and greater blood loss are logically correlated with transfusion incidence. To analyse this more formally, we performed univariate and multivariate analysis across these factors, and deter-

Table 2 Odds ratios between patient variables and wound disturbances, according to univariate analyses.

	Odds Ratio (per unit)	95 % Confidence Interval
Blood transfusion (yes vs no)	2.095	1.239 - 3.542
Age	1.005	0.985 - 1.025
Sex (male vs female)	1.199	0.739 - 1.947
Length	0.997	0.971 - 1.023
Weight	1.009	0.993 - 1.025
ESR	1.017	0.988 - 1.035
Pre-alb	0.997	0.993 - 1.002
CRP	1.003	0.978 - 1.029
Pre-operative Hb	1.020	0.743 - 1.401
Operation time	1.010	1.001 - 1.020
Per-operative blood loss	1.000	0.999 - 1.001
Total blood loss	1.000	1.000 - 1.001
Gentamycin cement (yes vs no)	1.333	0.717 - 2.248

mined which of the variables are best predictive of the development of post-operative wound healing disturbances (table 2). With univariate analysis, blood transfusion was clearly the main factor associated (odds ratio 2.1). With back and forward stepwise modelling with multivariate analysis blood transfusion appeared the only statistically significant variable to appear in the model.

Predicting duration of hospital stay

Based on these data, we developed a regression model to predict duration of hospital stay from the factors analysed in this study. Duration of stay could be predicted by four significant variables (table 3): requirement for blood transfusion, presence of wound disturbances, duration of operation, and patient age. Whereas each 10 additional years of age adds 0.9 ± 0.16 days to hospital stay and each 10 minutes additional operation duration adds 0.2 ± 0.08 days to hospital stay, the effects of wound disturbance and transfusion are much more pronounced: the presence of wound disturbances adds 1.25 ± 0.45 days, and the requirement for transfusion adds 2.71 ± 0.47 days to hospital duration.

Table 3 Regression model for Duration of Hospitalisation in days.

	β	95% Confidence Interval	p-value
Age (days per 10 years)	0.9	0.6 - 1.2	<0.001
Operation time (days per 10 min.)	0.2	0.05 - 0.36	0.011
Wound disturbance (days if present)	1.25	0.36 - 2.14	0.006
Transfusion (days if given)	2.17	1.26 - 3.1	<0.001

P-value based on the regression model with log normalized duration of hospitalisation as independent variable.

DISCUSSION

The deleterious clinical effects of perioperative HBT in elective orthopaedic surgery are well established (18,19,16). However, the precise impact and mechanisms of these effects are much less clear. It has been postulated that HBT increases postoperative infections through immunomodulation. To test this hypothesis numerous observational studies have been performed, investigating rates of cancer recurrence (3,5) and postoperative infections in patients who had received perioperative HBT (3,4,5,6). These studies, however, have produced conflicting results. Controlled trials on this subject have also not resolved the issue (8,9,10,11,12,13,14,15). As the bulk of these studies involve patients undergoing gastrointestinal surgery, the role of HBT in development of adverse effects is even more unclear in elective orthopaedic surgery patients.

In the present prospective observational study we found that HBT is associated with prolonged hospital admission. We found that this prolonged admission is not a straightforward consequence of an increased postoperative infection rate. Deep infections, which have high morbidity (20), occurred at similar rates in both transfused and non-transfused patients. Other infections tended to be increased in the transfused group, but this did not reach statistical significance. However, HBT was the sole significant predictor of the development of wound healing disturbances, and together these two factors were the main predictors of prolongation of hospitalisation (figure 1). No significant influence on wound disturbance and hospitalisation was found, either by univariate or multivariate analysis, of age, sex, length, weight, operation duration, blood loss or the use of gentamycin cement.

As this was an observational study, the mechanism by which wound healing disturbances and length of hospital stay are related was not studied in detail. A direct effect of tissue hypoxia as a consequence of decreased Hb seems unlikely. The effect (both on wound disturbances and on hospital admission duration) was evenly distributed among three subgroups with varying volumes of blood loss (figure 1). Frank anaemia can delay wound healing in experimental animals (21,22), but this did not play a role in our patient series. It is conceivable that sub clinical bacterial infection is responsible for disturbed wound healing, but then one would expect to find a concomitant increased body temperature. An alternative explanation might be that HBT induces a small but significant delay in wound healing. Experimental studies have shown that the immunomodulatory effects of HBT (23) might lead to a decrease in pro-angiogenic factors that are essential for wound healing, such as interleukin-8 (24).

Although the nature of the observed wound disturbances remain unclear and warrant further investigation, the more pragmatic conclusion we reach from our data is that prevention of HBT may be of relevance in limiting duration of admission after elective orthopaedic surgery. If this is indeed the case measures to prevent perioperative blood loss, cell saving techniques and methods to enhance preoperative Hb (such as erythropoietin) might be attractive treatment options (25).

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CHAPTER 6

DOES IBUPROFEN INCREASE
PERIOPERATIVE BLOOD LOSS
DURING HIP ARTHROPLASTY?

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SUMMARY

Background. This study was designed to determine whether a prior exposure to NSAID's has the potential to increase perioperative blood loss after major orthopaedic surgery.

Methods. Patients (n=50) scheduled for total hip surgery were allocated to two groups (double blind, randomised manner). All patients were pre-treated during 2 weeks before surgery: Group I with placebo drug, and Group II with ibuprofen. For surgical anaesthesia, all patients were injected intrathecally with 20 mg bupivacaine dose plus 0.1 mg morphine in a total volume of 4 ml. The presence of severe adverse experiences caused 8 patients of the ibuprofen group and 6 of the placebo group to stop their participation in the trial.

Results. The perioperative blood loss increased by 45% in the ibuprofen group comparing placebo. The total blood loss in the ibuprofen group was 1161 ml (SD±472 ml) versus 796 ml (SD±337 ml) in the placebo group.

Conclusion. Pre-treatment with ibuprofen before elective total hip surgery increases the perioperative blood loss significant. Early discontinuation of non-selective NSAID's is advised.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (= NSAID's) are used in the perioperative period for analgesia and reduction of oedema in the surgical field. Beside these benefits there are some unwanted side effects of NSAID's: reduction of renal blood flow, gastric complaints and increase of blood loss during surgery by influencing the coagulation cascade.

NSAID's are widely used in orthopaedic surgery, and ibuprofen is a very commonly used NSAID in the Netherlands. There is concern over the perioperative use of NSAID's since they have the potential to increased perioperative blood loss related to their mechanism of action.

We wish to assess the effect of ibuprofen in every day's practise on perioperative blood loss in patients having hip arthroplasty, and started a randomised double-blinded placebo controlled study.

MATERIALS AND METHODS

The ethical committee of our hospital approved the study and a written informed consent was obtained from all patients. To exclude as much as possible external factors we included in this study patients that undergo first elective total hip replacement surgery for coxarthrosis by intrathecal anaesthesia. Patients were allocated and randomised to two groups in a double-blind manner two weeks before surgery. All patients were pre-treated during a 2-week period before surgery: one group with placebo drug, and the other group with ibuprofen 600 mg. Both placebo and ibuprofen 600 mg (total 1800 mg) were given orally three times a day. The pharmacist prepared identical tablets and was only aware of the type of pre-treatment. Patients using any NSAID's, aspirin and or anticoagulants before starting the trial were excluded from participation. Also patients with a history of peptic ulcer disease, renal dysfunction or allergy to any NSAID were excluded.

At the day of surgery, all patients were premedicated with 7.5 mg midazolam orally one hour before spinal anaesthesia. Spinal anaesthesia was performed in each of these patients by administering 20 mg bupivacaine plus 0.1 mg morphine solved in 4 ml.

The following fluid replacement regimen was used: 500 ml glucose 2.5% / NaCl 0.9% solution after inserting the intravenous line and before starting surgery. A continuous drip was given of the same solution, during surgery 250 ml/hour and after surgery 100 ml/hour. A colloid solution (Gelofusine) was added in the same volume amount as blood loss was counted which a maximum of 2.5 litre per 24 hours.

Adequate sedation was provided at patient's request during the procedure: the anaesthesiologist administered 1 mg midazolam at the minimum interval of 5 minutes until the patient indicated that the desired sedation was reached. Non-invasive blood pressure, heart rate (ECG), transcutaneous oxygen saturation, and respiratory rate were continuously monitored during anaesthesia and in the intensive care unit during the first 24 h after surgery.

Peri-operative blood loss

All operations were performed by one single orthopaedic surgeon. The prophylaxis against thromboembolism was started in all patients the evening before surgery with 3 mg acenocoumarol. At the day of surgery 2 mg acenocoumarol was given just 24 hours after the first dose. The third dose of acenocoumarol was given after the trial was finished. Peroperative blood loss was measured by operating nurses unaware of the NSAID's given. Total blood loss was calculated by taking into account the volume in the suction containers, the weight of the surgical sponges and the irrigation fluid used.

In the postoperative phase all patients stay at an intensive care unit, which is our normal policy. The volume of blood in a high vacuum wound drainage containers was collected and measured twenty-four hours after surgery. The transfusion trigger for homologous packed cells was a haemoglobin level below 8 g/l in the whole postoperative period.

Statistical analysis

Student t-tests were used to identify the sources of differences between the groups. A p-value < 0.05 was considered as statistically significant.

RESULTS

Demographic data are given in table 1. The two groups did not differ for age, height, weight or gender. Likewise other variables, e.g. preoperative use of beta blockers, percentages of patient's which got sedation during surgery, use of cementation, and blood pressure drop (>25% decrease in mean arterial pressure after cementation) showed no differences among the groups. Also there was no difference between the duration of surgery between both groups.

The presence of (severe) adverse effects or an increase of pain caused 8 patients of the ibuprofen group and 6 of the placebo group to stop their participation in the trial (see for details table 2).

Table 1 Demographic data.

Group	Ibuprofen	Placebo
n	17	19
Age (years)	63 (12)	59 (14)
Height (cm)	170 (8)	169 (11)
Weight (kg)	74 (13)	72 (14)
Gender (m/f)	6/11	5/14
Duration of surgery (minutes)	67 (25)	67 (18)

Age, height, weight and duration of surgery are given as mean values, standard deviation between arrows. n=number of patients, m=male, f=female.

Table 2 Reasons to stop the trial.

	Ibuprofen	Placebo
Lack of efficacy, increase of pain	2	2
Gastric acid	3	1
Nausea	3	3
Total	8	6

Table 3 Per and postoperative blood loss.

Group	Ibuprofen	Placebo
Blood loss during surgery	700* (367)	416 (203)
Blood loss 24 h after surgery	461 (312)	380 (169)
Total blood loss	1161** (472)	796 (337)

Blood loss is given as mean (SD) value in ml. *= $p<0.01$, **= $p<0.05$. For details see text.

Peri-operative blood loss

The volumes of blood loss were significantly higher in patients pre-treated with ibuprofen than placebo. The volume of peroperative blood loss showed 40% more in the ibuprofen group (mean 700 ml) versus the placebo group (mean 416 ml), which is statistically different ($p<0.01$). The measured blood loss in the first twenty-four hours after surgery showed also a 17% higher blood loss in the ibuprofen group versus placebo group, which was not statistically different. The over all blood loss, perioperative blood loss plus the blood loss in the first

twenty-four hours after surgery, showed an increase of 45% ($p < 0.05$). See table 3. Our study had a 86% power to demonstrate a 45% difference in expected blood loss at a level of significance of $p = 0.05$. The number of homologous blood transfusions was 9 in the ibuprofen group and 6 in the placebo group (not statistically significant) during the whole period patient were in the hospital.

DISCUSSION

The main finding of this study is, that preoperative pre-treatment with ibuprofen showed a relevant increase in blood loss during and the first 24 hours after total hip replacement surgery. Besides the wanted anti-inflammatory, analgesic and antipyretic action of NSAID's this study demonstrates is also a common unwanted negative effect of NSAID's: increase of blood loss.

The anti-inflammatory, analgesic and antipyretic action of NSAID's are mediated through inhibition of prostaglandin synthesis by inhibiting cyclooxygenase. Cyclooxygenase is the major enzyme in the biosynthesis of prostanoids. Following the discovery in the early 1990s of an inducible isoform of COX it is now known that COX exists in at least two isoforms known as COX-1 and COX-2

COX-1 exists in the stomach, intestine, kidneys and blood platelets. COX-1 synthesizes the prostaglandins that regulate the normal physiologic processes involved in protecting the GI mucosa, maintaining renal function as well as vascular homeostasis. This role of COX-1 has been referred as "housekeeping" function. In contrast the inducible isoform COX-2, after expression induced by several cytokines or lipopolysaccharide, produces large amounts of prostanoids mainly contributing to the pathophysiological process of inflammation.

The therapeutic effects of NSAID's are largely the result of inhibition of the enzyme COX-2 whereas toxic effects (platelets, gastrointestinal and renal effects) are primary due to the inhibition of COX-1. In blood platelets this leads to a lack of thromboxane synthesis and impaired platelet aggregation. It has been suggested widely that NSAID's that selectively inhibit COX-2 have fewer side effects. The relationship between platelet aggregation, thromboxane production and serum concentrations of non COX-2 selective ibuprofen has been examined. A single dose of ibuprofen between 300 mg and 800 mg blocked platelet aggregation 2 hours after administration. However, the effect was lost within 24 hours.

After ibuprofen administration of 200 mg, 400 mg, and 800 mg in healthy volunteers, platelet aggregation was inhibited for 6, 8, and 11 hours respectively. These data and the half life time of ibuprofen (2 hours) suggesting to stop the oral use of ibuprofen 24 hours before surgery.

Although we tried to reduce as much possible confounding factors in our study (one type of surgery performed one single orthopaedic surgeon, blinded medications), the use of prophylaxis against thromboembolism by acenocoumarol could be a problem in the outcome of our study. The prothrombine time will change due to ibuprofen, and not to the use of a placebo. Other weaknesses of our study are: the technique of measuring blood loss, which is very difficult to get it really accurate and a relatively high drop out rate. The study was not probably powerful enough to show whether an increase in blood loss results in increase transfusion requirement or perioperative morbidity/mortality. These are much more important outcome measures for the patient compared with the actual measured blood loss. They are however much more difficult to measure and were therefore not primary endpoints of this study. In all, to reduce perioperative blood loss two ways are possible. First to stop NSAID's far enough before major orthopaedic surgery. For pain treatment to change NSAID's three days before surgery and replace the drugs to other analgesics, e.g. paracetamol or may be COX-2 selective anti-inflammatory agents, with a better safety profile concerning peroperative blood loss.

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CHAPTER 7

COX-2 SELECTIVITY OF NSAIDS AND
PERIOPERATIVE BLOOD LOSS IN END
SURGERY: A RANDOMISED
COMPARISON OF INDOMETHACIN
AND MELoxicAM

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SUMMARY

Background. In this prospective randomised study we tested the hypothesis that use of more cyclooxygenase-2 (COX-2)-selective non-steroidal anti-inflammatory drugs (NSAID's) can reduce perioperative blood loss as compared with non-selective NSAID's.

Methods. Data from 200 patients who underwent total hip replacement were studied. Two NSAID's were compared: indomethacin 50 mg (n=82) and meloxicam 15 mg (n=86). Both NSAID's were given orally one hour before surgery.

Results. The two groups were not different with respect to age, gender, ASA class or duration of surgery. When indomethacin was used preoperatively, intraoperative blood loss was 623 ± 243 ml (mean $\pm$ SD) and postoperative blood loss 410 ± 340 ml. After meloxicam these values were 524 ± 304 ml and 358 ± 272 ml, respectively. Total perioperative blood loss after meloxicam was 17% ($p < 0.05$) less than that observed after indomethacin.

Conclusion. Perioperative blood loss after meloxicam is less than after indomethacin. These in vivo findings are consistent with in vitro results using selective COX-2 NSAID's.

Keywords. Anti-inflammatory Agents, Non Steroidal; Blood Loss, Surgical; Hip Replacement.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAID's) are used in the perioperative period for analgesia and reduction of oedema in the surgical field. However, they exhibit several side effects: reduction of renal blood flow, an increased incidence of gastric complaints and increased blood loss during surgery. These adverse effects result from inhibition of the physiologic formation by cyclo-oxygenase (COX)-1 of several prostanoids: PGE₂ and PGI₂ with a cytoprotective function, and thromboxane A₂, which is responsible for platelet aggregation. In contrast, newer COX-2-selective NSAID's such as meloxicam are considered to influence only the inflammatory response (oedema, pain and fever). We hypothesized that

this selectivity of action can be extrapolated to clinical practice, and that administration of a COX-2 selective NSAID would result in decreased perioperative blood loss as compared with administration of a non-selective compound. To test this hypothesis, we performed a randomised study in patients undergoing total hip replacement, and compared perioperative blood loss after use of one of two NSAID's: indomethacin and meloxicam.

METHODS

Patients (ASA 1–3) scheduled for total hip surgery using intrathecal anaesthesia were potentially eligible for the study. Patients with a history of peptic ulcer disease, renal dysfunction or allergy to any NSAID were excluded. The remaining patients were randomised to one of two groups: those receiving meloxicam 15 mg p.o. q.d., or those receiving indomethacin 50 mg p.o. t.i.d. The study was not masked. Patients were asked to stop use of any NSAID two weeks prior to surgery. In case of severe pain paracetamol was available if necessary. Patients who failed to stop the use of NSAID were excluded. The study was approved by the ethical committee of our hospital.

All patients were premedicated with 7.5 mg midazolam p.o. one hour before administration of intrathecal anaesthesia. At the same time the first dose of NSAID was given. Intrathecal anaesthesia (27 gauge pencil point needle) was administered using 20 mg bupivacaine plus 0.1 mg morphine dissolved in 4 ml. The anaesthesiologist administered midazolam (1 mg at intervals of no less than 5 min) until the patient indicated that adequate sedation was achieved. Fluid replacement was by protocol: 500 ml glucose 2.5% / NaCl 0.9% solution was administered after placement of an intravenous line and before starting surgery. The same solution was infused during surgery at 250 ml/h, and after surgery at 100 ml/h. A colloid solution (Gelofusine) was administered to match measured blood loss (see below), with a maximum of 2.5 litre per 24 hours. Non-invasive blood pressure, heart rate (electrocardiogram), oxygen saturation (SpO₂), and respiratory frequency were continuously monitored during anaesthesia and in the intensive care unit during the first 24 h after surgery.

Blood loss

One day before surgery, patients received acenocoumarol 3 mg. Intraoperative blood loss was measured by operating nurses unaware of NSAID given. Total blood loss was calculated by taking into account the volume in the suction containers, the weight of the surgical sponges, and the irrigation fluid used. In the postoperative phase all patients remained in an intensive care unit for 24 h, which is our normal policy. The volume of blood in a high vacuum wound drainage system was collected and measured for twenty-four hours after surgery.

Pain

In the post-operative period, all patients were treated with indomethacine 50 mg p.o. t.i.d., or meloxicam 15 mg p.o. q.d. If pain was present morphine was administered intravenously by patient controlled analgesia (PCA) pump. The settings of the PCA pump (BRAUN®, Melsungen, Germany) were: basal rate 0.0 mg/h, bolus dose 1.0 mg, bolus interval 5 min, maximum 30 mg per 4 h. Pain was evaluated using visual analog scores (VAS, ranging from 0 to 10, with 0=no pain and 10=most severe pain). For each individual patient we assessed the maximum VAS score in the 24 h period and cumulative VAS scores, quantified as area under the curve (AUC) of VAS scores during the 24 h period.

Statistical analysis

To detect a difference of 100 ml of blood loss during surgery (SD 250 ml) with an α error (2 sided) of 0.05 and a α error of 0.10, it was necessary to include 84 patients per group.

Analysis of interval scored data was performed using the Student t-test. Non-parametric techniques (Kruskal Wallis) were used when necessary. Proportions were analysed with Chi-square statistics and Fischer's Exact test. The α level for all analyses was set on $p=0.05$. Data are reported as means $\pm$ SD.

RESULTS

In total 200 consecutive patients consented to participate during the preoperative outpatient visit. However, at the time of admission 32 patients had failed to stop

Table 1 Demographic data and intra-operative factors.

Group	meloxicam	indomethacin
n	86	82
Age (years)	64 (10)	65 (10)
Height (cm)	168 (10)	171 (7)
Weight (kg)	75 (13)	77 (11)
Gender (m/f)	27/ 59	27/ 55
Duration of surgery (min)	67 (12)	69 (11)
MAP (mmHg)	105 (15)	107 (13)
Heart rate (beats/min)	74 (9)	75 (10)

Averaged data are shown as mean (SD). n=number of patients, m=male, f=female. MAP=mean arterial blood pressure.

Table 2 Intra- and postoperative blood loss.

Group	Meloxicam	Indomethacin
Blood loss during surgery	524** (304)	623 (243)
Blood loss 24 h after surgery	358* (272)	410 (340)
Total blood loss	882* (479)	1034 (486)

Values are shown as mean (SD) and expressed in ml. *= $p<0.01$, **= $p<0.05$ as compared with the indomethacin group. For details see text.

use of regular NSAID's, mainly because of pain. Of the remaining 168 patients, 82 were randomised to indomethacine and 86 were randomised to meloxicam. Demographic data of these remaining patients are provided in table 1. The two groups were similar with regard to age, height, weight, gender, mean arterial blood pressure and heart rate.

Blood loss

As indicated in table 2, blood loss was significantly greater in patients pre-treated with indomethacin than in those receiving meloxicam. The volume of intraoperative blood loss was 19% greater in the indomethacin group than in the meloxicam group ($p<0.01$). Likewise, blood loss in the first twenty-four hours after surgery was 15% greater in the indomethacin group than in the meloxicam

Figure 1 VAS pain scores 24 hours after surgery.

group ($p < 0.05$). As a result, total blood loss (i.e. intra-operative blood loss plus blood loss during the first twenty-four hours after surgery) was 17% greater in the indomethacin group than in the meloxicam group ($p < 0.05$).

Pain

VAS scores were less than 3 in the postoperative period in all patients in both groups (figure 1). Cumulative VAS scores were 6.1 for the indomethacin group and 5.3 for the meloxicam group ($p > 0.05$). Use of systemic morphine by PCA infusion pump was similar: 18 ± 9 mg in the meloxicam group and 18 ± 7 mg in the indomethacin group.

DISCUSSION

The major finding of our study is that pre-treatment with the COX-2 selective NSAID meloxicam results in less perioperative blood loss than use of the non-selective compound indomethacin. This data from clinical practice is consistent with in vitro studies that demonstrated the COX-2 selective action of meloxicam. Several limitations of the study should be kept in mind, however. We

did not stratify patients by surgeon, as routine audit data from our hospital show very similar levels of blood loss among the surgical staff. However, this is a potential confounder. In addition, we did not determine if the observed effects on blood loss had a significant impact on patient outcome or management (e.g. haemoglobin levels or transfusion requirements).

NSAID's are used widely in orthopaedic surgery, but concerns remain about their tendency to increase intraoperative blood loss. This side effect results from impairment of platelet aggregation by block of thromboxane formation, and could not be explained by an interaction between indomethacin and acenocoumarol. A breakthrough in the ability to separate the beneficial anti-inflammatory, analgesic and antipyretic action of NSAID's from these side effects resulted from better insights in their mechanism of action. NSAID's inhibit cyclooxygenase (COX), the major enzyme in the biosynthesis of prostaglandins. In the early 1990s it was recognized that the rate of prostaglandin synthesis could increase dramatically when the formation of a particular isoform of COX is induced by several cytokines or lipopolysaccharide. It is now known that COX exists in at least two isoforms, known as COX-1 and COX-2. COX-1 is found in the stomach, intestine, kidneys and platelets, and is essential for the synthesis of prostaglandins involved in important physiologic processes such as protection of the gastrointestinal mucosa, maintenance of renal function, and circulatory homeostasis. This role of COX-1 has been referred to as the "house-keeping" function. In contrast, the inducible isoform COX-2 produces large amounts of prostaglandins that mainly contribute to the pathophysiologic process of inflammation. Thus, the therapeutic effects of NSAID's are largely the result of inhibition of the enzyme COX-2, whereas adverse effects are primarily due to the inhibition of COX-1.

It has been suggested that NSAID's that selectively inhibit COX-2 have fewer side effects. An example is meloxicam, a NSAID derived from enolic acid which has a favourable COX-2/COX-1 ratio. This ratio translates into fewer effects on platelet aggregation in vitro. Indomethacin is a COX-2/COX-1 non selective NSAID when tested in vitro, but shows a slight preference for COX-2 when tested ex vivo. Studies in vivo show contradictory results on the effects of indomethacin on blood loss. In this study we compared 2 different NSAID's which inhibit the two COX- isoforms to varying degrees.

More relevant to clinical practice is the question whether these data from in vitro studies and animal experiments translate in a decreased volume of blood loss. The present study indicates that such is indeed the case: blood loss was approximately 20% less when meloxicam instead of indomethacin was used. However, whether this is of clinical significance and influences patient outcome remains to be determined. In addition, the potential beneficial effects of these compounds on blood loss should be weighed against potential detrimental effects (such as a potentially increased risk for cardiovascular events) before routine use can be recommended.

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CHAPTER 8

EFFECTS OF EPOETIN ALPHA ON BLOOD TRANSFUSIONS AND POSTOPERATIVE RECOVERY IN ORTHOPAEDIC SURGERY: THE EUROPEAN EPOETIN ALPHA SURGERY TRIAL (BEST)

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SUMMARY

Background and objectives. As preoperative epoetin alpha administration reduces transfusion requirements, it may prevent transfusion complications, such as postoperative infections due to immune suppression and thus hospitalisation time. This study tested the impact of preoperative epoetin alpha administration on postoperative recovery and infection rate.

Methods. In a randomised controlled trial in orthopaedic surgery patients the effects of preoperative administration of epoetin alpha (EPO) and best standard of care (BSC) were compared in a daily life setting in six countries. Haemoglobin (Hb) values, transfusions, time to ambulation, time to discharge, infections and safety parameters were evaluated in patients with preoperative Hb values 10–13 g/dl (on-treatment population: EPO n=460, BSC n=235), from study entry until 4–6 weeks after surgery. Outcome was also compared in patients with and without transfusions.

Results. EPO-treated patients had higher Hb values from the day of surgery until endpoint ($p<0.001$; not different at baseline) and lower transfusion rates (12% vs. 46%; $p<0.001$). EPO treatment delivered no significant effect on postoperative recovery (time to ambulation, time to discharge, infection rate). Time to ambulation and time to discharge were, however, longer in transfused than in not-transfused patients ($p<0.001$). Side effects in both groups were comparable.

Conclusions. Epoetin alpha increases perioperative Hb in mild-moderate anaemic patients and reduces transfusion requirements. Patients receiving blood transfusions require a longer hospitalisations than not-transfused patients. An explanation for the absence of clear effects of epoetin alpha on postoperative recovery is postulated.

INTRODUCTION

Hip and knee replacement surgery are associated with large blood losses, frequently exceeding 700 ml. As a consequence blood transfusions are frequently required during and after orthopaedic surgery. Apart from the possible serious complications and side effects, such as ABO incompatibility and HIV or hepatitis infections, allogeneic transfusions may also have other complications, such as allo-immunization and immune modulation, which may be responsible for the rise in postoperative infections and possibly increased length of hospitalisations that have been reported in transfused patients.

Minimizing the number of allogeneic blood transfusions by blood management measures is becoming more and more general practice. Such measures may include introduction of transfusion protocols that define low transfusion triggers (haemoglobin values at which patients may receive an allogeneic blood transfusion), preoperative autologous blood donations, cell saving, haemodilution techniques, tranexamic acid administration or elevation of the preoperative haemoglobin (Hb) value by means of preoperative epoetin alpha injections.

This last method has proven to increase preoperative Hb in patients with a Hb lower than 13 g/dl at screening, as well as to reduce the need for allogeneic blood transfusions and to increase the perioperative Hb. However, possible changes in infection rate and postoperative recovery after epoetin alpha administration have not been studied yet in a daily life population of orthopaedic patients. This question was addressed by an international, randomised study were to investigate the effects of preoperative epoetin alpha administration on perioperative haemoglobin levels, and its effects on allogeneic perioperative transfusion requirements in mild to moderate anaemic patients, scheduled for major elective orthopaedic surgery. Secondly, the effect of epoetin alpha on postoperative infections and recovery was monitored in the perisurgical setting.

METHODS

A prospective, open, randomised phase IV trial was conducted in the Netherlands, France, Germany, Sweden, Belgium and Australia. Patients scheduled for elective major orthopaedic surgery (hip, knee, spine, primary or revision) and with a preoperative Hb value between 10–13 g/dl were included. Spine surgery included spinal fusion of at least three segments. All patients received best standard of care (BSC). Patients were randomised in a 1:2 ratio to receive either BSC alone or BSC and epoetin alpha (EPO: 40,000 IU once weekly for 3 weeks before surgery and on the day of surgery + oral iron). This ratio was chosen in order to improve trial acceptability and participation by the patients. Patients in the BSC group could also take iron orally or receive it by intravenous injection, if this was part of usual standard care in the hospital. All patients, irrespective of their group allocation, received blood transfusions when needed. Blood transfusions were only be given according to the hospital transfusion protocol. If no transparent local protocol was available, transfusion with packed cells could only be given

during and after surgery if the Hb had dropped below 8.0 g/dl. Before any blood transfusion, the Hb value was recorded.

Patients were evaluated for Hb values from study entry until 4–6 weeks after surgery. Other parameters were blood transfusions (peroperative and postoperative; type of transfusion; numbers of patients transfused and numbers of units transfused), time to ambulation, time to discharge from hospital, postoperative infections, therapeutic antibiotics use and safety parameters.

Evaluations were carried out at study entry, just before surgery, one day after surgery, at discharge from hospital and at follow-up (planned at 4–6 weeks after surgery).

A patient was considered to have an infection when one of the following items existed:

- wound infection: redness, purulent exudate or positive culture of wound fluid;
- wound abscess: drainage of abscess or spontaneous discharge of pus;
- abscess or infected haematoma in surgical area or near implantate. Positive culture after collection of pus or re-exploration;
- urinary tract infection: abnormal urine sediment with white blood cells and/or a positive urine culture and/or clinical signs;
- respiratory tract infection: clinical signs and/or a positive sputum culture leading to treatment with antibiotics;
- pneumonia: clinical or radiological signs of a pulmonary infiltrate;
- septicæmia: typical clinical signs, fever, and positive blood culture.

Infections were checked by culture. A raised temperature in itself was not indicative of infection.

Time to ambulation was defined as the number of days between surgery and the first day that the patient was able to get out of bed and walk around in the room, with or without support.

Time to discharge was defined as the number of days between surgery and discharge from the hospital where surgery was performed. This implies that there was no correction for hospitalisation for social reasons or for early recovery protocols. The investigators assumed that randomisation should correct for these phenomena.

An intention-to-treat (ITT) analysis was performed in all patients who were included in the trial and had a study evaluation on the day before surgery. The on-treatment population was defined as those patients included in the trial who underwent surgery. Statistical analysis was two-tailed and on an $\alpha = 0.05$ level, using Wilcoxon's two sample test, Fisher's Exact test and Pearson's Chi-square test. The actual tests are mentioned with the results.

Apart from differences between both treatment groups, also differences between transfused and not-transfused patients were tested. In order to exclude the influence of variations by country (heterogeneity in blood saving methods, anaesthesia methods, standard hospitalisation periods, etc.) a large and homogenous part of the study population was analysed separately for postoperative infections and recovery data. This population consisted of primary hip replacement arthroplasty patients from one country: the Netherlands ($n=431$).

The study was approved by the Institutional Review Board and Local Ethics Committees. All subjects gave informed consent prior to study entry.

RESULTS

In the study 733 patients were enrolled: 487 in the EPO group and 246 in the BSC group. The ITT population amounted to 704 patients (467 EPO; 237 BSC) and the actual surgery population to 695 (460 EPO; 235 BSC). See table 1 for the division of patients over the participating countries.

Patient characteristics

There were no differences between both treatment groups regarding age, height, weight, blood pressure, sex, type of surgery, type of anaesthesia and percentage of patients with rheumatoid arthritis or patients possibly having infections (table 2). In both groups 90% of patients were female; mean age was 67 years. Mean systolic and diastolic blood pressures were 146 and 82 mmHg, respectively, 19% of the patients having a high blood pressure (defined as systolic pressure >160 mmHg or diastolic pressure >95 mmHg); 16% had rheumatoid arthritis, 8% had elevated CRP or BSE and 90% was considered as not having a potential infection.

Table 1 Number of patients by country (ITT population).

Land	EPO n=467	BSC n=237	Overall n=704
Australia	6	2	8
Belgium	11	6	17
France	54	27	81
Germany	44	22	66
Netherlands	334	171	505
Sweden	18	9	27
Total	467	237	704

Table 2 Patient characteristics (ITT population). No significant differences between groups.

Characteristic	EPO n=467	BSC n=237	Overall n=704
Age (years)	67.0±11.0	66.7±10.8	66.9±10.9
Height (cm)	164.54±8.4	164.54±7.0	164.54±7.9
Weight (kg)	72.4±13.4	72.9±12.5	72.6±13.1
Sex (% female)	89.9	89.5	89.8
Hypertension (%)	20.8	14.3	18.6
MBP (mean systolic/mean diastolic, mmHg)	147/82	145/82	146/82
RA (%)	16.1	16.0	16.1
% with elevated BSE or CRP	9.0	7.2	8.4

Table 3 shows types of surgery and types of anaesthesia, which did not differ between groups either: 61% underwent primary hip replacement arthroplasty, 27% primary knee replacement arthroplasty, 9% a revision hip or knee replacement arthroplasty and 3% had spine surgery. In most patients (69%) spinal anaesthesia was used; others had general anaesthesia (27%) or mixed forms (2%). Only 2% had local anaesthesia. In the BSC group 77% of the patients were on oral iron therapy before surgery; in the EPO group 99%.

Table 3 Type of surgery and type of anaesthesia (% of patients; surgery population).

Type of surgery or anaesthesia	EPO n=460	BSC n=235	Overall n=695
Primary hip surgery	60	62	61
Primary knee surgery	28	26	28
Revision hip/knee surgery	8	9	9
Spine surgery	3	3	3
Unilateral surgery	97	96	97
Bilateral surgery	3	4	3
General anaesthesia	26	29	27
Spinal anaesthesia	70	68	69
Local/mixed anaesthesia	4	4	4

Hb values

Hb values at screening were 12.2±0.7 g/dl in the BSC group and 12.3±0.7 g/dl in the EPO group (mean±s.d.). Hb increased to 14.3±1.2 g/dl (+2.1) on the day of surgery in the EPO group, but did not increase in the BSC group (+0.1). Except for the screening visit, Hb values were different between treatment groups at each time point (p<0.05; Wilcoxon two-sample test). On the day after surgery, Hb was decreased in both groups: to 11.4±1.4 g/dl in the EPO group and to 9.7±1.2 g/dl in the BSC group. Hb increased to 12.3±1.0 g/dl and 11.9±0.9 g/dl at follow-up (4–6 weeks after surgery) in the EPO and BSC group, respectively (figure 1).

Transfusions

In the EPO group 12% of patients received at least one blood transfusion; in the BSC group 46% (p<0.05; Fisher’s Exact test; figure 2 and 3). In most cases, these were allogeneic transfusions: 9% of EPO patients and 37% of BSC patients received only allogeneic transfusions (p<0.05; Fisher’s Exact test). 3% of EPO patients and 9% of BSC patients received autologous transfusions (only autologous or mixed transfusions) (p<0.05; Fisher’s Exact test).

The composition of the transfusions (autologous blood, allogeneic packed cells, allogeneic whole blood, mixed transfusions) was not different between treatment

Figure 1 Hb values.

Figure 2 Percentage of patients receiving transfusions.

groups (figure 3): 73 and 78% in the EPO and BSC groups, respectively, were allogeneic transfusions. For autologous blood, this was 23 and 16% respectively.

Transfusion needs were lowest in spine surgery patients (table 4).

The transfused quantities in both treatment groups were similar. The number of transfusions per transfused patient was not different between treatments (1.25 ± 0.51 and 1.42 ± 0.70 for EPO and BSC, respectively) (NS: $p=0.141$; Wilcoxon two-sample test). The number of units transfused per transfused patient was 2.36 ± 1.95 and 2.41 ± 1.24 , respectively (NS: $p=0.126$; Wilcoxon

Figure 3 Percentage of patients receiving transfusions and type of transfusions by treatment.

Table 4 Percentage of transfused patients by type of surgery (surgery population).

	EPO n=458	BSC n=235	Overall n=693
Primary hip surgery	12.0	47.9	36.4
Primary knee surgery	10.8	41.0	30.2
Revision hip/knee surgery	21.1	50.0	37.8
Spine surgery	7.1	16.7	11.9
Overall	12.2	45.5	34.1

Figure 4 Percentage of transfused patients by country.

two-sample test). Leukocyte filtered blood was used in only 6% of the transfusions; 94% were buffy coat-depleted blood transfusions.

The Hb values just before transfusion did not differ between the EPO and the BSC patients: 8.6 ± 1.2 g/dl for EPO patients and 8.4 ± 0.9 g/dl for BSC patients; overall 8.5 ± 1.0 g/dl.

Transfusions by country

The percentage and composition of transfusions differed between the participating countries (figure 4). One of the major differences between countries is the use of autologous blood transfusions. Autologous blood donation is standard care in France and Germany, but it is rarely used in the other participating countries.

Pre-transfusion Hb varied by country from 7.8 to 9.1 g/dl. Apart from Germany, all transfusion triggers were above 8.0 g/dl.

Time to ambulation, time to discharge

On average, patients could walk again after 3.3 days (± 2.7 days). Time to ambulation was not different between EPO and BSC, but it was statistically significantly longer in transfused than in not-transfused patients (3.8 ± 4.0 vs. 3.1 ± 2.2 days) ($p=0.004$; Wilcoxon two-sample test). This was found in both the EPO

Figure 5 Time to discharge, by treatment and by transfusions.

group (transfused vs. not-transfused 4.2 ± 3.7 vs. 3.2 ± 2.3 ; $p=0.01$) and the BSC group (transfused vs. not-transfused 3.6 ± 4.1 vs. 2.9 ± 1.7 ; $p=0.07$).

For the homogenous subgroup of Dutch patients who underwent primary hip surgery the number of days to ambulation was not statistically different from that of the total group: 3.5 ± 2.0 for EPO and 3.4 ± 1.9 for BSC (EPO vs. BSC: $p=0.354$), but also in this group time to ambulation was significantly longer in transfused patients: 4.2 ± 3.1 vs. 3.3 ± 1.6 ($p=0.038$; Wilcoxon two-sample test). In this group only 24 of 293 (8.2%) EPO patients received transfusions, versus 63 of 148 (42.6%) BSC patients.

Patients were discharged from hospital after an average stay of 10.8 days (± 5.5). Again, this parameter was not different between the EPO and BSC groups, but transfused patients stayed significantly longer in hospital than not-transfused patients: 12.9 ± 6.4 vs. 10.2 ± 5.0 days, respectively ($p<0.001$; Wilcoxon two-sample test) (figure 5).

This was found in both the EPO group (transfused vs. not-transfused 15.5 ± 7.2 vs. 10.4 ± 5.3 ; $p<0.001$) and the BSC group (transfused vs. not-transfused 11.5 ± 5.4 vs. 9.4 ± 3.8 ; $p<0.001$).

Dutch primary hip patients stayed on average in the hospital for 9.8 ± 5.0 days. There was no difference between EPO and BSC, but time to discharge was 11.4 ± 6.1 in transfused patients vs. 9.4 ± 4.6 in not-transfused patients ($p < 0.001$; Wilcoxon two-sample test). In the EPO group the difference in time to discharge between transfused and not-transfused patients was 5.5 days (15.1 in transfused patients and 9.7 in not-transfused patients), whereas this difference was 1.5 days in the BSC group.

Infections

In total 9.8% of the patients had one or more postoperative infections, 5.5% were confirmed by a positive culture. Most patients had the first infection in the hospital: 7.2%, versus 2.6% after discharge (with positive culture: 4.3% and 1.2%). Urinary tract infections were the most common in-hospital infections (4.3%; 2.9% with positive culture), followed by wound infections (2.5%; 1.3% with positive culture).

The total percentage of infections was not different between EPO (9.4%) and BSC (10.6%).

In transfused patients infection rate was 12.9%; in not-transfused patients 8.9% ($p = 0.130$; NS; Fisher's Exact test). However, it was significantly different in the more homogenous Dutch primary hip patients: 13.8 in transfused vs. 6.8% in not-transfused patients ($p = 0.032$; Pearson Chi-square test).

There was no statistically significant difference in the infection rate between patients receiving allogeneic or autologous transfusions, with infections in 12.9% of patients receiving only allogeneic transfusions versus 10.0% in those given only autologous transfusions (NS; Fisher's Exact test).

Of all patients 13.5% took antibiotics for therapeutic use (EPO: 14.0%; BSC: 12.6%; transfused patients: 16.9%; not-transfused patients: 13.3%).

Adverse events

No differences were observed in the adverse events frequency between EPO and BSC treatments. Three thrombotic events occurred in the population: two in the EPO group and one in the BSC group.

DISCUSSION

This study addresses several important questions about blood management in hip and knee arthroplasty. First it studied the effect of preoperative epoetin alpha on perioperative Hb values and on transfusion requirements in daily hospital care. Secondly the implications of this treatment and of transfusions on postoperative recovery time and postoperative infection rate were evaluated.

The observation that preoperative epoetin alpha treatment enhanced perioperative and postoperative Hb values and reduced transfusion requirements confirms earlier results. Furthermore, the observation that iron administration in the BSC group (taken by 77%) did not increase the Hb values confirms previous observations.

EPO treatment was associated with a lower transfusion rate and transfusion was associated with a significant extension of time to ambulation and time to discharge both within the EPO and the BSC treatment groups. However, no differences in time to discharge and infection rate were observed between EPO and BSC treated patients. Possible explanations are that daily life setting in this study may have produced a more heterogeneous population, as patients with several types of surgery, with and without rheumatoid arthritis and from several countries were enrolled. Concerning infection rate, this is very low in orthopaedic surgery, especially for clinical relevant infections.

The results might also have been confounded by a higher complication rate in the group of EPO patients who received transfusions, as seen by the outcomes (longer time to ambulation, longer hospital stays and the highest number of antibiotic use). The severe drop in haemoglobin level might be explained by surgical complications, causing major bleedings. In EPO-treated patients with high pre-operative Hb values severe blood loss is needed before a transfusion is given. A surgical complication might explain this heavy blood loss and the consecutive bad outcome. Unfortunately this assumption can not be confirmed. This effect is intensified by the very low number of transfused patients in the EPO group (56 patients, 12%).

The finding that infection rate and hospitalisation time are influenced by complications (and thus by transfusions) rather than by anaemia was also observed in unpublished data of 410 primary hip revision patients at the Sint Maartens-

kliniek, Nijmegen, the Netherlands, in whom hospital procedures regarding surgery techniques, discharge policy and so on were kept similar. Allogeneic transfusions appeared to have the highest prospective value for longer hospitalisation, followed by wound problems, age and operation time. Other factors such as sex, length, weight, BSE, CRP, preoperative albumen, perioperative blood loss and use of gentamycin cement were no confounding factors.

Several studies have been performed to evaluate the impact of blood transfusions on hospitalisation time, recovery and infection rate. These studies all confirm a relation between allogeneic blood transfusions and increased risk of infections and/or time to discharge, but the absolute data differ considerably between studies. This might be caused by differences in definitions of infection and length of stay. Some studies in surgery only consider wound infections, whereas this study tried to document all infections. Length of hospitalisation is a complex parameter, as it is not merely determined by clinical factors. In this study it has been noticed that decisions to discharge were often based on reimbursement issues, availability of home nurses, private family issues, etc.

Nowadays so-called accelerated stay programs may influence hospitalisation times more than transfusions or complications. In many countries hip and knee surgery are performed in such programs, which include hospitalisation times limited to less than a week. But epoetin alpha treatment may be very important in such programs, as extensive rehabilitation starts already on the first day after surgery with low haemoglobin levels. Energy expenditure in patients is doubled after surgery (unpublished data Maasland Hospital, Sittard, the Netherlands) and exercise capacity is reduced by 20–25% on the fourth postoperative day (unpublished data Maasland Hospital, Sittard, the Netherlands). Buick et al. found a reduced VO_2 max after phlebotomy and a distinct increase in VO_2 max following induced erythrocythaemia. They suggest that oxygen transport limits maximal aerobic capacity. These findings suggest that the postoperative higher haemoglobin levels might become more and more important as rehabilitation becomes more strenuous due to reduction in hospitalisation. Preoperative epoetin alpha administration will thus become more important, especially in the more compromised patients, as they suffer more from the changes in rehabilitation and lower accepted haemoglobin levels.

This study leads to the conclusion that in routine daily setting of major orthopaedic surgery epoetin alpha treatment is an efficient method to decrease perio-

perative transfusion requirements and to increase perioperative haemoglobin levels. As hospitalisation time is severely reduced by new rehabilitation procedures, this might be an even more important action.

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CHAPTER 9

OPTIMAL USE OF EPOETIN ALFA IN
ORTHOPAEDIC SURGERY
CALCULATION OF FACTOR 10^{-4}

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Submitted.

ABSTRACT

Background. The treatment protocol of epoetin alpha prior to orthopaedic surgery consists usually of a fixed weekly dose. Although easy to use, it has its limitations. In some patients the dose is too low to produce an adequate increase in serum haemoglobin level. This study was developed to determinate a more appropriate dosage method for the individual patient.

Study design and results. 334 patients with a preoperative haemoglobin level of 100–130 g/l scheduled for major orthopaedic surgery participated in the study. Patients were treated following a fixed protocol with three subsequent subcutaneous injections of 40,000 IU epoetin alpha at day 21, 14 and 7 before surgery. The increase of haemoglobin level was measured. Simple formula calculates the amount of haemoglobin in grams. This erythropoietin output (=EO-40,000) was 34 gram haemoglobin (SD±17).

Conclusion. Factor EO-40,000 can be used as an aid to predict the increase in the serum haemoglobin level in the individual patient. Also the number of epoetin alpha injections (40,000 IU) needed to reach the desired serum haemoglobin level can be calculated for the individual patient. With this knowledge, patients can be better prepared for surgery and homologous blood transfusions can be avoided as far as possible.

INTRODUCTION

Transfusions of allogeneic red blood cells can have risks and complications for the individual patient. This problem still exists despite increased care in the preparation of homologous red blood cells in Europe. Especially for orthopaedic surgery a causal relationship has been established between homologous red blood cell transfusions and an immunosuppressive response in the individual patient. The immunosuppressive response results in an increased risk of postoperative infections, problems with wound healing, and a longer hospital stay (1,2,3,4,5).

One of the most elegant measures to avoid homologous red blood cell transfusions in patients with a lowered haemoglobin level (10–13 g/dl) is erythropoietin. The current treatment protocol of erythropoietin consists of a fixed dose in all patients, according to Goldberg (6). Although easy to use, it has its limita-

tions. In some patients the dose is too low to produce an adequate increase in serum erythropoietin level. In other cases a lower treatment dose will suffice.

A total of 334 patients scheduled for major orthopaedic surgery were treated for decreased serum haemoglobin levels. Erythropoietin and iron were used three weeks prior to surgery to increase the level of serum haemoglobin. Afterwards we calculated the exact erythropoiesis output in grams of haemoglobin. These calculated data can be used to determine a more appropriate dosage method for the individual patient.

MATERIALS AND METHODS

Altogether, 334 patients scheduled for major orthopaedic surgery were asked to participate in the study. The ethics committee approved the study and written informed consent was obtained from all patients. The inclusion criteria consisted of major orthopaedic surgery such as total hip replacement, revised total hip replacement, spinal fusion surgery and total knee replacement surgery. Further, a preoperative haemoglobin level of 10–13 g/dl was required at the preoperative screening three weeks before surgery. All in- and exclusion criteria are summarised in table 1.

Patients were treated following a fixed protocol with three subsequent subcutaneous injections of 40,000 IU epoetin alpha at day 21, 14 and 7 before surgery. Elementary iron 200 mg a day was given orally from day 21 before surgery until discharge after surgery.

The haemoglobin level was measured at day 21 before surgery and thus prior to epoetin alpha administration, and on the day of surgery. If surgery was postponed for more than nine days after the last dose of epoetin alpha, patients were excluded from further calculations.

The following formula was used to calculate the amount of haemoglobin (Hb) in grams after the above treatment with epoetin alpha and iron.

1. $EBV = \text{patient's estimated blood volume in litres} = \text{body weight in kg} \times 0,07 \text{ l/kg}$

Table 1 Inclusion and exclusion criteria.*Inclusion criteria*

Major orthopedic surgery

Hemoglobin level between 100–130 g/l

Over 18 years of age

Exclusion criteria

Infection of any body system at preoperative screening or by elevated sedimentation rate or by elevated C-reactive protein.

Patients with autologous blood donation

Any homologous blood transfusion in the past 6 weeks

Any surgery in the past 6 weeks

Presence of clinically significant disease/dysfunction of the hepatic, pulmonary, hematological, neurological, endocrine, gastrointestinal or genitourinary systems

Clinical or laboratory evidence of untreated iron, folate or vitamin B12 deficiency

Presence of concomitant malignancy

Uncontrolled hypertension (diastolic blood pressure >100 mmHg)

History of seizures

Administration of medication known to suppress erythropoiesis (e.g. cytotoxic agents, immunosuppressants) within one month prior to enrolment. Low-dose steroids were permitted

Pregnancy or lactation

Known hypersensitivity to epoetin alpha or one of its components

2. $EO-120,000 = \text{erythropoiesis output in grams after three subsequent injections of } 40,000 \text{ IU epoetin alpha} = EBV \times (\text{Hb (in g/l) day of surgery} - \text{Hb (in g/l) prior to administration of epoetin alpha})$
3. $EO-40,000 = \text{calculated erythropoiesis output in grams after } 40,000 \text{ IU epoetin alpha} = EO-120,000/3.$

When it is known how many grams of haemoglobin are produced after a single subcutaneous injection of 40,000 IU epoetin alpha, the number of epoetin alpha injections needed to reach the desired serum haemoglobin level can be calculated. The formula is:

Number of epoetin alpha (40,000 IU) injections:

$$\frac{\text{EBV} \times (\text{desired serum Hb (g/l) level} - \text{serum Hb (g/l) level prior to epoetin})}{\text{EO} - 40,000}$$

RESULTS

Of all the patients (n=334), 30 did not receive three doses of epoetin alpha. In another five patients the haemoglobin level was not measured prior to surgery. This left data from 299 patients (19 males, 280 females) which were used for further calculations. All these patients received three epoetin alpha subcutaneous injections (40,000 IU) at day 21, 14, and 7 before surgery and iron therapy (200 mg elementary iron a day) was also used in this same period. At day 21 before surgery and thus before the first epoetin alpha injection, the mean serum haemoglobin was 123 g/l, while on the day of surgery the mean haemoglobin had increased to 143 g/l. The mean EO-120,000 was 102 g and the EO-40,000 was 34 g (table 2). The increase in haemoglobin according to body weight is shown in figure 1.

Using this factor EO-40,000 together with the individual body weight and individual serum haemoglobin level, the number of epoetin alpha injections needed to reach a preoperative haemoglobin level of 150 g/l can be calculated (see table 3).

There was no significant difference for EO-40,000 between males (mean 30 g/l; SD 20) and females (mean 33 g/l; SD 17).

To calculate the number of epoetin alpha doses (40,000 IU) the following formula was used:

$$\frac{\text{EBV} \times (\text{desired serum Hb (g/l) level} - \text{serum Hb (g/l) level prior to epoetin})}{\text{EO} - 40,000}$$

Table 2 Results and EO-40,000. EBV= estimated blood volume; data are presented as mean values, standard deviation between brackets. For further explanation see text.

	Outcome
Number of patients (n)	334
Patients with incomplete data	35
Male / female (%)	6.3 / 93.7
Mean body weight (kg)	73
Mean EBV (liter)	5.11
Hb prior to epoetin alpha administration (gram)	123 (7)
Hb day of surgery (gram)	143 (12)
EO-120,000 (gram)	120 (52)
EO-40,000 (gram)	34 (17)

Table 3 Number of preoperative epoetin alpha injections (40,000 IU) needed to reach a hemoglobin level of 150 g/l prior to surgery, according to preoperative hemoglobin levels and body weight.

Body weight in kg	40	50	60	70
Preoperative hemoglobin 100 g/l	4	5	6	7
Preoperative hemoglobin 110 g/l	3	4	5	6
Preoperative hemoglobin 120 g/l	2	3	4	4

Figure 1 Hemoglobin poduction.

Table 4 Prices of different sources of hemoglobin Prices are according to Dutch price levels. Assumption: the use of non-COX-2 selective NSAIDs increases blood loss by 15%; mean low vacuum drainage is 350 ml with a mean hemoglobin level of 12.0 g/dl.

	Total amount in gram hemoglobin	Price in Euros per gram hemoglobin
1 patient (70 kg, Hb 128 g/l)	640	Price-less
1 unit homologous packed cells	53	32
1 unit autologous packed cells	53	36
1 EO-40,000	34	136
Postoperative low vacuum cell saving (Bellovac ABT)	43	12
Non-COX-2 selective NSAIDs	75	

DISCUSSION

Factor EO-40,000 was calculated precisely to 34 gram in 299 healthy patients prior to elective orthopaedic surgery. Factor EO-40,000 can be used as an aid to predict the increase in the serum haemoglobin level in the individual patient. Also the number of epoetin alpha injections (40,000 IU) needed to reach the desired serum haemoglobin level can be calculated for the individual patient. As depicted in table 2, more than the usual three epoetin alpha injections are needed to reach the desired serum haemoglobin (150 g/l) level prior to surgery. With this knowledge, patients can be better prepared for surgery and homologous blood transfusions can be avoided as far as possible.

A second important use of factor EO-40,000 is for making a financial comparison. As we know the price of one injection of epoetin alpha (40,000 IU), we can work out the price of 1 gram of haemoglobin. It is now easy to compare this with other sources of haemoglobin (homologous blood, autologous blood donation, cell-saving procedures, etcetera). For instance, one homologous or autologous red blood cell transfusion consists of 300 ml red blood cells with a haemoglobin level of 180 g/l, 54 gram in total. Again the price can be calculated accurately per gram or mmol (see table 4). Prices are shown in table 4 according to the initial expense. Costs related to laboratory (cross match, irregular antibodies, storage), adverse effects or complications of disposables, transfusions or epoetin alpha are not included.

In all, the calculated factor EO-40,000 can help to target treatment better to the individual patient to reach the optimum preoperative haemoglobin level prior to surgery. In cases where the haemoglobin level is low prior to surgery, epoetin alpha treatment can be used more precisely before major orthopaedic surgery.

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CHAPTER 10

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SUMMARY

In orthopaedic surgery blood loss is often compensated for by homologous blood transfusion (HBT). However, HBT might have deleterious effects because of transfusion-related immunomodulatory effects. In an effort to reduce HBT we evaluated the efficacy of an auto transfusion system for shed blood. We performed a prospective observational quality assessment study in 135 consecutive patients scheduled for elective total knee arthroplasty (TKA) or total hip arthroplasty (THA). The control group consisted of a historic group of 96 patients. Autotransfusion reduced the percentage of patients receiving HBT from 35% to 22% ($p<0.001$). The reduction was more pronounced in TKA (18% to 6%, $p<0.001$) compared with THA (47% to 34%, $p<0.05$). In TKA, transfused packed red cells per operation decreased from 0.45 HBT/operation to 0.11 HBT/operation ($p<0.001$), a reduction of 0.34 HBT (75%) in every TKA. These results indicate that autotransfusion may be a useful method to reduce HBT during major orthopaedic surgery.

INTRODUCTION

Preventing homologous transfusion after hip and knee arthroplasty can decrease transfusion-related complications and duration of hospital stay (1). Several techniques can reduce the need or perioperative transfusion: the use of erythropoietin to increase preoperative haemoglobin concentration, preoperative blood donation, and surgical methods to prevent blood loss.

Cell saving techniques are another effective approach to prevent blood transfusion (2). Shed blood may be re-infused after filtration (unprocessed) or after treatment in a cell separator (processed). Transfusion of unprocessed shed blood is a relatively simple and inexpensive method to restore normovolaemia, in contrast to autotransfusion of processed blood, which requires an expensive cell separator and disposables. However, since the first widely applied perioperative (unprocessed) autotransfusion system was applied in clinical practice by Dyer (1966) (3), some authors published severe complications, primarily haemostatic disorders and impairment of renal function. Although the incidence of these symptoms seemed to be very low and were related to large transfusion volumes (4), these reports have hampered further developments of this promising technique.

In the present study, we evaluated a postoperative wound drainage and re-infusion system with filter in patients undergoing total hip or knee replacement. The aim of the study was to determine the effect of re-infusion of shed blood on the requirement for homologous blood transfusion ratio in primary total hip or knee arthroplasty.

MATERIALS AND METHODS

Using a prospective observational quality assessment design, we compared 135 patients scheduled for elective total knee arthroplasty (TKA) or total hip arthroplasty (THA) at the University Hospital Maastricht, the Netherlands, with a historic group of 96 patients who underwent similar surgery at the same institution. In the study group the Bellovac® A.B.T. autotransfusion system (Astra Tech, Gotenburg, Sweden) was used. It consists of a blood collection suction bellows connected to an autotransfusion bag with a 200 µm filter. The bellows inlet and the autotransfusion bag inlet each contain a one-way valve. The autotransfusion bag is connected to a transfusion set with a 40 µm filter. Before closure of the surgical wound a drainage tube is inserted and connected with the suction bellows. By emptying the bellows the drained blood is transported to the transfusion bag. The shed blood is re-transfused either when 500 ml is collected (collection is then resumed with a new transfusion bag) or at most 6 hours after the operation. Blood collected more than 6 hours after the operation is not re-transfused. In the control group, standard suction drains (redondrain Medinorm) were used and the drained blood was discarded. All patients were treated according to standard hospital protocol. All knee operations were done in a bloodless field using pneumatic tourniquets. All patients received nadroparin (2850 IE) s.c. the evening before the operation for prophylaxis of thrombosis. Homologous blood was transfused according to standard protocol (post-operative Hb of less than 9.6 g/dl or clinical symptoms of anaemia). The following data were obtained in both groups: haemoglobin levels (preoperatively, first post-operative day and on the day of discharge), total volume of blood collected in the drain in the study group, volume of blood reinfused in the study group, and number of homologous blood units transfused.

The results were analysed statistically using ANOVA followed by Student's T-test when appropriate and published as mean (SD) or percentage. A p-value of < 0.05 was considered statistically significant.

RESULTS

In the study group 135 patients, and in the historic control group 96 patients were available for analysis. Of the 135 patients, 129 patients received re-transfusion of drained blood. These 129 patients consisted of 41 cementless THA, 35 cemented THA, 10 cementless TKA and 43 cemented TKA.

Haemoglobin levels

We observed no statistical differences between the pre-operative, postoperative, and discharge haemoglobin concentrations in the control and study group (table 1). Haemoglobin concentrations for all subgroups were comparable also. There were no complications or adverse events after re-transfusion of autologous shed blood.

Table 1 Haemoglobin levels g/dl mean (SD) for all groups.

		No BELLOVAC	BELLOVAC drain	p
All	n=231	n=96	n=135	
Hb pre-operative	14.0 (1.22)	14.0 (1.26)	14.1 (1.2)	N.S.
Hb post-operative	10.4 (1.49)	10.4 (1.39)	10.3 (1.55)	N.S.
Hb discharge	10.4 (1.14)	10.4 (1.17)	10.3 (1.12)	N.S.
THA	n=138	n=58	n=80	
Hb pre-operative	14.0 (1.26)	13.9 (1.36)	14.0 (1.22)	N.S.
Hb post-operative	9.9 (1.41)	10.2 (1.41)	9.6 (1.36)	N.S.
Hb discharge	10.2 (1.04)	10.3 (1.04)	10 (1.04)	N.S.
TKA	n=93	n=38	n=55	
Hb pre-operative	14.2 (1.14)	14.2 (1.12)	14.2 (1.18)	N.S.
Hb post-operative	11.0 (1.34)	10.8 (1.33)	11.2 (1.34)	N.S.
Hb discharge	10.7 (1.23)	10.5 (1.36)	10.8 (1.14)	N.S.

n=number; p<0.05 statistically significant; THA=Total Hip arthroplasty; TKA=Total Knee Arthroplasty; Hb=Hemoglobin

Figure 1 Transfusion incidence [%] in relation with type of surgery (* p<0,05, ** p<0,001) .

Table 2 Transfused HBT per operation; THA = Total Hip arthroplasty, TKA = Total Knee Arthroplasty, - = cementless, + = cemented.							
	n	Mean (SD)	No BELLOVAC		BELLOVAC Drain		p
			n	Mean (SD)	n	Mean (SD)	
All	231	0,68 (1,34)	96	0,85 (1,37)	135	0,56 (1,30)	0,059
THA-	72	0,83 (1,18)	29	0,90 (1,14)	43	0,79 (1,22)	0,978
THA+	66	1,14 (1,82)	29	1,34 (1,70)	37	0,97 (1,92)	0,79
TKA-	22	0,09 (0,43)	11	0,18 (0,60)	11	0,00 (0,00)	0,038
TKA+	71	0,30 (0,92)	27	0,56 (1,31)	44	0,14 (0,51)	0,001
All THA	138	0,98 (1,53)	58	1,12 (1,45)	80	0,87 (1,58)	0,717
All TKA	93	0,25 (0,83)	38	0,45 (1,16)	55	0,11 (0,46)	0

Homologous Transfusion Requirements

Autotransfusion reduced the number of patients receiving HBT overall from 35% to 22% (p<0.001, figure 1).

In the THA group there was a statistically significant decrease of blood transfusion requirement from 47% to 34%. There were no statistical differences in transfusion rates between the cemented and non-cemented THA subgroups.

Table 3 Reinfused volume in patients with autotransfusion device in relation with allogenic transfusion Perioperative. THA = Total Hip arthroplasty, TKA = Total Knee Arthroplasty, - = cementless, + = cemented.

	All		No transfusion		Transfusion		p
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	
All	135	516 (352)	105	533 (366)	30	467 (304)	N.S.
THA-	43	417 (271)	29	419 (320)	14	427 (147)	N.S.
THA+	37	378 (308)	24	296 (172)	13	530 (435)	N.S.
TKA-	11	634 (340)	11	634 (340)	—	—	—
TKA+	44	700 (380)	41	723 (383)	3	383 (126)	N.S.
All THA	80	399 (287)	53	362 (267)	27	476 (318)	N.S.
All TKA	55	687 (371)	52	704 (373)	3	383 (126)	N.S.

The homologous transfusion requirement after TKA was decreased from 18% to 6% ($p < 0.001$). In cementless vs. cemented TKA this was 9% to 0% and 22% to 7% respectively ($p < 0.001$). The total number of transfused packed cells in the TKA group was reduced from 0.45 pc/operation to 0.11 pc/operation ($p < 0.001$), a 75% reduction per operation (tabel 2).

DISCUSSION

Re-transfusion of autologously shed blood has been shown to be a safe and effective method to reduce exposure to homologous blood in orthopaedic and cardiovascular surgery (5,6,7,8), although conflicting data have been published concerning the efficacy of the use in cardiac surgery (9). In this study re-transfusion of drained blood using a Bellovac® A.B.T. significant reduced homologous blood transfusion after TKA, whereas we did not observe a statistically significant reduction after THA. This may be related to surgical technique: as in most hospitals, TKA surgery was performed using a bloodless field, so that blood loss occurred only in the post-operative period, in contrast to THA surgery where blood loss occurred during the whole procedure. Re-transfusion of shed blood is most effective if all lost blood can be collected (table 3). This is the case in TKA surgery, but not in THA surgery, where significant blood loss occurs during the operation. In THA we can not recover intra-operative blood loss (and even then visible blood loss is only 50% of total intra-operative blood loss (10)), and so the efficacy or auto-transfusion will be reduced.

Although we observed no complications during re-transfusion, our group may have been too small for a safety assessment. One of the most common side effects is a febrile reaction after autotransfusion of shed blood, and this complication may have been reduced by the presence of the filter in the system used in this study. When blood is shed, the composition changes. The intrinsic and common coagulation pathway are activated, which results in formation of clot and fibrinogen degradation products. Several authors have demonstrated high concentrations of C3a, SC5b-9, TNF- α , IL-1 β , IL-6 and IL-8 in shed blood, but only elevated IL-6 plasma levels after transfusion of filtered shed blood (11,12,13). Handel et al reports a relation between increased interleukin-6 concentrations in shed drainage blood and the occurrence of febrile reactions after re-transfusion of such blood (14). If the collection duration of shed blood is extended, the IL-6 concentrations increase further with a possible increase in febrile reactions (15). Another concern would be the presence of methyl methacrylate monomer (MMM) in re-transfused blood. However, systemic blood showed no evidence of MMM after re-infusion of salvaged blood (16) in cemented TKA surgery. After spine surgery one study showed a tendency of increased blood serum levels of CK, GOT and LDH, if postoperative re-transfusion was used as a blood saving method (8). Therefore, caution should be taken when these serum enzyme levels are used for diagnosis.

A cost-benefit analysis of the system is difficult to make, because of the complex costs involved in blood transfusion (which really should include the cost of complications, increased duration of hospital stay, etc.). In TKA surgery, transfusions were reduced by 0.34 packed red cells per operation. The costs for the Bellovac drain system are approximately € 75.- per operation in the Netherlands. In our hospital a HBT costs approximately € 180.-. Therefore, a reduction of 0.34 reduces the costs by € $(180 * 0.34) = € 61.20$ per operation. Thus, calculated on this basis, the autotransfusion system is still more expensive than HBT. However, this approach is simplistic: the HBT cost does not include handling costs of the hospital of HBT and the possible extended hospitalisation and other immunomodulatory effects due to a homologous blood transfusion (17). Thus, a formal cost-benefit study is required to address this issue.

We conclude that the Bellovac® A.B.T. device reduced homologous blood transfusions in TKA. The use of the system is less complicated and less expensive compared to auto re-transfusion using a cell separator. This method of auto re-transfusion should therefore be considered in TKA surgery.

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CHAPTER 11

AN ALGORITHM TO REDUCE HOMOLOGOUS RED BLOOD CELL TRANSFUSIONS FOR MAJOR ORTHOPAEDIC SURGERY

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ABSTRACT

Introduction. In an earlier prospective study we have corroborated that transfusion-related immunosuppression favours postoperative infections, perturbs postoperative wound healing and thereby results in protracted hospital stay. This adds to the well known risks such as transmission of infectious illness or transfusion reactions, and urged us to redefine transfusion guidelines. Goal: to redefine a comprehensive scheme that allows for relevant reduction of homologous red cell transfusions in orthopaedic surgery.

Method. A relational database with data on 28.861 orthopaedic surgery patients was used to identify where and how to improve these guidelines for transfusions.

Results. The survey disclosed the issues related to a high incidence of homologous red cell infusion: negligence of guidelines, the preoperative use of non-selective NSAID's, low preoperative Hb level, non-retrieved blood loss, and high cut-off values for homologous red cell transfusion. The first step was the restriction that the Hb level should be assessed prior to red cell infusion to ensure compliance with pre-defined cut-off values. Subsequent measures included: confinement to COX-2-selective NSAID in the perioperative period; erythropoietin and iron therapy at the Hb level below 13 g/dl; consequent cell salvage during and after surgery; administration of aprotinine in cases with expected high blood loss. The type of anaesthetic procedure was found to be not relevant for blood-sparing effect.

Discussion. The steps do not involve a medical novelty. Rather, we show that strict rules with the appropriate steps and in sequence resulted in an 80% reduction of use of homologous red blood cells. Noteworthy, the yield of sparing blood goes beyond financial saving. The incidence of deep wound infections decreased by 40%.

Conclusions. The outcome is described in an algorithmic format summarising steps in a comprehensive perioperative blood management scheme.

INTRODUCTION

Inherent risks in homologous transfusions persist despite all efforts to minimise and exclude as many of these as possible. In addition to well-known risks such as transmission of infectious illness or transfusion reactions, concern is raised - espe-

Table 1 Incidence of postoperative infection, perturbed postoperative wound healing, and duration of hospital stay in relation to presence or absence of allogenic red blood cell infusion (n=975).			
blood transfusion /number of patients	Incidence of infection	Incidence of perturbed wound healing	Duration of Hospital stay (days)
0 / n=867	3.8%	16%	8.3
+ / n=108	6.3%	31%	11.7
0=no blood transfusion, + 1 or more blood transfusions, n=number of patients			

cially for orthopaedic surgery - over the issue of a causal relationship between homologous red blood cell transfusions and immunomodulation. The transfusion related immunosuppression is considered to favour postoperative infections, perturb postoperative wound healing and thereby to result in protracted hospital (1,2,3,4,5). In our prospective study - that included 975 major orthopaedic surgical procedures such as total hip arthroplasty and knee replacement surgery, fusion surgery of the lumbar, thoracic or cervical spine - we corroborate this notion (table 1).

These data on the consequences of infusion of homologous red blood cells warrant guidelines for proper use of red cell transfusion. Below we summarise how we developed our guidelines and the quantitative contribution of each step added to our guidelines. At present we have attained an 80% reduction of the incidence of red cell infusion.

Relational database underlying the development of transfusion guidelines

A mainstay in redefining the guidelines for red cell infusion was the inventory of detailed clinical data gathered in the past. Starting in 1991, all details regarding all orthopaedic surgical procedures in our clinic were fed into a relational database. We registered for each patient: date of surgery, date of birth, hospital registration number, surgeon, anaesthesiologist, type of surgery, diagnose, duration of surgery, volume of blood loss during surgery, and the anaesthetic procedure. This database is coupled to the database of the financial department that contains for example the details on hospital stay and that of our laboratory with the data on red cell transfusions, infections, etc. We analysed these data for 28.861 patients in order to identify the most relevant issues for improved guidelines in our clinic.

Table 2 Outcome of analysis for relevant issues in limiting need for allogenic red blood cell transfusions.

Period	Relevant issues
Preoperative	Hb, Ht, MCV
	Drugs that perturb clotting cascade
During surgery	Cut-off values for transfusion (transfusion trigger)
	Measures to activate clotting cascade
	Cell saving
	Normothermia
Postoperative	Cut-off values for transfusion (transfusion trigger)
	Blood loss
	Cell saving

Table 2 outlines the outcome of the analysis of our database that taught us where to focus for improved management.

Relevant issues and restrictive strategies to minimise transfusion of homologous red blood cells

We recognise that the steps added to our general intent not to transfuse homologous red cells unless considered necessary, bears no involve medical novelties. Rather, this review shows how a well-chosen algorithm effected an 80% reduction of use of homologous red blood cell transfusions. We will describe the steps for minimising the need to transfuse homologous red blood cells in a fore ward progression, and show how the gain from each step sums with the prior one. The algorithmic format summarises these steps in a comprehensive perioperative blood management scheme (figure 1).

Preoperative assessment

In our clinic, the anaesthesiologist is part of the team that evaluates each of the 4,500 patients per year scheduled for orthopaedic surgery. Preoperative assessment is performed at least 3 to 4 weeks before surgery. The preoperative evaluation at this stage and involving anaesthesiologists allows for the appropriate clinical evaluations in preparation for delivery of the anaesthetic, and management of special requirements to the surgical procedure. Part is the definition of the indi-

Figure 1 Blood management in elective orthopedic surgery in adult patients.

Table 3 Peroperative blood loss in first elective total hip surgery patients for coxarthrosis.			
Year	1994	1997	2000
Number of procedures	226	362	420
NSAID	Diclofenac	Diclofenac/Meloxicam	Meloxicam
Average blood loss per procedure	701	562	515
Duration of surgery	65	71	63

visualised guideline for blood management. Analysis of the relational database learned that two items were of special interest: preoperative NSAID's medication that can perturb coagulation of the blood during surgery, and preoperative laboratory studies for CBC to identify the need for erythropoietin administration. Noteworthy, other factors had been controlled and the most relevant ones are included in the algorithm presented in figure 1 and table 2.

NSAID's

Non steroidal anti-inflammatory drugs (= NSAID's) used in the perioperative period for analgesia and reduction of oedema in the surgical field have well known unwanted side effects, including COX-1 related effects that leads to impaired platelet aggregation. These data were produced in laboratory studies, and - in order to corroborate the relevance of this data in the clinic - we evaluated blood loss for 1 specific surgical procedure (coxarthrosis: first hip replacement) for the period that we switched from non-specific to COX-2 selective NSAID's. The data show that total blood loss declined with 26%, with other factors (e.g. duration of surgery), anti thrombosis prophylaxis unchanged (see table 3).

These data and the above considerations made us decide to evaluate the effect of the NSAID's on blood loss in clinical studies.

In the first double blind randomised study, blood loss of 50 patients during and after total hip surgery was compared for the conditions of two-week preoperative use of ibuprofen or placebo (6). We showed that ibuprofen pre-treatment was associated with a 45% higher perioperative blood loss than after placebo (ibuprofen 1161 ml (SD 472 ml) versus placebo 796 ml (SD 337 ml); $p < 0.001$). In a subsequent double blind randomised study we included 169 total hip surgery patients, wherein we compared blood loss after prescription of the NSAID's indomethacin 50 mg ($n=83$) and meloxicam 15 mg ($n=86$) given orally one hour before surgery. We assessed that when indomethacin was used preoperatively the mean volume of perioperative blood loss was 623 ml (SD 243 ml) and postoperative blood loss 410 ml (SD 340 mL), after meloxicam 524 (SD 304 ml) and 357 mL (SD 272 ml). The latter blood loss is 17.1% ($p=0.0095$) less than that after the indomethacin. We conclude that these in vivo findings are consistent with the in vitro results and showed that avoiding the use of non-selective NSAID's will spare 17% of blood loss.

Recombinant human erythropoietin

Recombinant human erythropoietin has been approved for use in patients undergoing major orthopaedic surgery in the Netherlands. The cut-off value for including a patient for this treatment is 10–13 g/dl. This value was chosen when the analysis of our relational database had shown that 50% of all allogenic red cell transfusions had occurred in this group of patients. The standard treatment consists of 4 administrations of 40,000 IE erythropoietin at weekly intervals, independent of age and gender (7). This treatment is started strictly 3 weeks before surgery, with the final dose administered directly post-operatively if haemoglobin is below 15 g/dl. The variability of the response to erythropoietin relates to iron-restricted erythropoiesis, the iron consumption due to enhanced erythropoiesis should be covered with iatrogenic iron depletion to be avoided. Therefore, we co-medicate with 200 mg elemental iron per day. We assessed in 127 patients the gain, and showed an average gain of 1.9 g/dl (SD 0.48) in Hb content in the blood.

*During surgery**Intra-operative blood salvage*

Intra-operative blood salvage is presently common practice is hospitals involved in major surgery. In our clinic two cell savers 5 (Haemonetics) are used when the blood loss is expected to be over 1.5 litre, e.g. during revision hip and spinal surgery.

Intersurgeon variations in blood loss.

Relevantly, we keep tract of the blood loss for each surgeon. The data are presented to the group anonymously, and each individual surgeon is informed on his / hers performance. Thereby, meticulous techniques and appropriate salvage are sustained.

*Medicaments to reduce bleeding**Aprotinine*

A naturally occurring serine protease inhibitor—modifies the haemostatic system and reduces bleeding. We introduced the drug for infusion when the estimated blood loss exceeds 2 litre (8). In our clinic, major spinal fusion surgery of the lumbothoracic spine (scoliosis, M. Bechterew) or major revision hip surgery result in such losses. The dose regiment is: test dose; after the induction of anaesthesia

Table 4 The introduction of aprotinine in major spinal surgery (scoliosis).

	No aprotinine	aprotinine
N	21	22
Duration of surgery (min)	205	221
Average blood loss (ml)	2772	2172
Mean number of units of red cells per patient	1.3	0.4

10^6 KIU/h and, subsequently infuse the drug in the rate of 0.5×10^6 KIU/h. We evaluated the effect in 43 patients for scoliosis surgery by 1 orthopaedic surgeon and found a 20% lower blood loss (table 4).

Factor VIIa

In specific cases in cases of severe bleeding we do use thrombocytes and coagulation factors to treat coagulopathy caused by specific deficiencies. More recently we introduced the use of recombinant blood coagulation factor VIIa (rFVIIa, NovoSeven®). The drug forms a complexes with tissue factor (TF) which is present in the wound bed, and thereby acting as catalyst of local blood coagulation. It proved effective in some patients, but has not been used routinely. Although controlled trials are required to prove the potential benefit in cases of massive blood loss the first case reports and experience is very hopeful for the future (9,10).

Normothermia

Two independent studies claimed the effect of normothermia in total hip surgery(11,12). A decrease in body temperature of 1.5 °Celsius at the end of surgery increased the perioperative blood loss by 500 ml. Although we didn't evaluate the effect of normothermia, the finding was important enough to introduce optimal warm air fields during surgery.

The postoperative period

Transfusion trigger

Restrictive use of cut-off values for homologous red cell infusion in the post-operative period. In Dutch hospitals some 60% of the units of homologous red cells are ordered when relevant blood loss was anticipated (13,14). Noteworthy, the actual infusion of homologous red cells was independent of a low Hb content in 96.2% of the patients. These unrestricted infusions are based on "clinical signs" such as fatigue, paleness, or blood is infused as a matter of "routine". In

Table 5 Transfusion policy – based on the Hb-level as transfusion trigger – incorporates most recent national (Dutch) transfusion guideline.

Within 4 hours of surgery	More than 4 hours after surgery
Hb>6.4 g/dl = 0 packed cells	Hb>6.4 g/dl = 0 packed cells
Hb<6.4 g/dl = 1 packed cells	Hb<6.4 g/dl = 1 packed cells
Hb<4.8 g/dl = 2 packed cells	Hb<5.6 g/dl = 2 packed cells
Within 4 hours of surgery	More than 4 hours after surgery
Hb>7.2 g/dl = 0 packed cells	Hb>8.0 g/dl = 0 packed cells
Hb<7.2 g/dl = 1 packed cells	Hb<8.0 g/dl = 1 packed cells
Hb<6.4 g/dl = 2 packed cells	Hb<7.2 g/dl = 2 packed cells
Within 4 hours of surgery	More than 4 hours after surgery
Hb<8.8 g/dl = 0 packed cells	Hb<8.8 g/dl = 1 packed cells
Hb<8.0 g/dl = 1 packed cells	Hb<8.0 g/dl = 2 packed cells
Hb<7.2 g/dl = 2 packed cells	Hb<7.2 g/dl = 2 packed cells

Table 6 Mean transfusion rate according to three different transfusion guidelines and transfusion triggers.

	Period A	Period B	Period C
Number of surgical procedures	4620	5703	4264
Type of anaesthesia % general/spinal/plexus	38 / 56 / 6	37 / 55 / 17	39 / 56 / 11
Male/female (%)	39 / 61	39 / 61	39 / 61
Average age (years)	40.6	37.1	42.5
Average duration of surgical procedure (min)	48.0	49.1	50.1
Number of allogenic red cell infusions	2218	1882	981

our hospital we made a simple but major step forward by simply forbidding any infusion of homologous red cells when Hb- and the Ht- values are unknown. The trigger value applied was adapted from Dutch national guidelines (15,16), which for that purpose were transformed in a practical format (table 5). For the first 4 hours postoperatively, we took the effect of haemodilution into account and allowed for the lower Hb level (table 5)

These guidelines were introduced in our intensive care unit in May 1996, and several months later the guideline was applied for the hospital.

It was of interest to evaluate the effectiveness of such a simple measure. For that purpose, 3 periods were sampled: period A (no guideline), period B (guideline

Table 7 Number of allogenic red cell infusions in total knee surgery.

Year	1997	2000
Number of procedures	137	153
Number of allogenic red cell infusions	77	0

Table 8 Allogenic red cell infusions in the Sint Maartenskliniek in the period 1995 - 2001.

Year	1995	1996	1997	1998	1999	2000	2001
Number of surgical procedures	3398	4246	4034	4253	4078	4242	4610
Total blood loss (l)	845.3	859.2	825.1	817.4	876	795	780
Average blood loss (ml)	265	209	201	192	210	187	169
Number of allogenic red cell infusions	1172	1022	918	734	867	382	340
Average transfusion rate	0.34	0.24	0.23	0.17	0.21	0.09	0.07

applied in the ICU only) period C (restricted guideline for the hospital). Demographic data and type of surgery were not different for the patients in the three groups. We found that the number of units per procedure diminished from 0.48, to 0.33 and 0.23 in period A, B, and C respectively (16) (see table 6).

Postoperative cell saving (Bellovac® A.B.T)

The Bellovac® A.B.T system (A.B.T. = autologous blood transfusion) concerns a form of postoperative cell saving where blood from the operation wound is collected and filtered and then returned to the patient. This blood salvaging system helped to reduce the number of blood transfusions at our clinic to zero in total knee replacement surgery. Also, the system is used when patients subjected to total hip arthroplasty and revision hip arthroplasty show blood loss of more than 500 ml. Knee replacement surgery is performed using a tourniquet and the benefit of the postoperative salvage drain was marked (table 7).

The effect of blood sparing measures as a function of time.

The sequence of above described measures produced a steady decline in the use of packet red cells (table 8).

DISCUSSION

An overwhelming selection of therapeutic modalities is available to minimise the need for homologous red cell infusions. Rather than simply including measures at random, we choose to rely on our relational database and identified which conditions associate with homologous red cell transfusions. Thereby, a tremendous decline of 80% in the use of red cells was achieved. In the algorithmic format (figure 1) the sequences are presented.

Every day's practice in our hospital was not different from that in any general hospital in the Netherlands. Systematic presentations on "how we did it" resulted in the introduction of the measures in several of the hospitals in the region and a steady 5–7% decline per year in the utilisation of the use of homologous red cell transfusions.

It is of relevance to realise that each blood sparing measure on its own produces but a little decline. The full algorithm plus specific measures for the individual hospital results in a tremendous decline in the use off homologous red cells. Above we stated that a major reason for further efforts to reduce homologous red cell infusion relates to the notion that it is associated with transfusion-related immunosuppression favours postoperative infections, perturbs postoperative wound healing and thereby results in protracted hospital stay. One may expect that have achieved such decline in transfusions shows in these figures as well. Analysis of our database for these data showed a decline of the postoperative infections with 42% (table 9).

Table 9 Infection rate in the Sint Maartenskliniek 1997 – 2001.

Year	1997	1998	1999	2000	2001
Number of surgical procedures	4034	4253	4078	4242	4610
Incidence (%) of postoperative wound infections	2.6	2.1	1.7	1.8	1.5

CONCLUSIONS

Simple inexpensive measures help to reduce the need for homologous red cell transfusions. The savings in health care cost can be used for further improvement, and eventually, such infusions may occur anecdotally.

Based on our above experience and other systematic improvements in the chain of patient care, we recommend:

- Restrictive guidelines for homologous red cell infusion;
- Automated relational databases that allow for feedback on clinical practice;
- Preoperative assessment that involves the anaesthesiologists and allows for pre-operative planning along a comprehensive algorithm.

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CHAPTER 12

GENERAL DISCUSSION AND SUMMARY

The identification of different blood types by Landsteiner at the beginning of the 20th century was the first major improvement of the safety and efficacy of blood transfusion (**Chapter 2**). Later on, developments in storage technology and screening for infectious agents made transfusion of blood even safer (**Chapter 3**). This progress, however, has led to the paradoxical situation that, although transfusions are safer than ever, both doctors and patients are much more aware of its risks, and thus more reluctant to use them. In terms of peri-operative patient management, one of the major challenges to the anaesthetist then has become to avoid blood transfusions. With this guiding principle in mind, this thesis set out to answer two questions: What are the deleterious effects of blood transfusions in elective orthopaedic surgery, and what can the anaesthetist do to minimize these?

Perioperative blood loss is still a major problem in elective orthopaedic surgery. Homologous blood transfusion (HBT) is the standard approach to treat potentially detrimental decreases in haemoglobin (Hb) concentration. However, HBT is associated with various adverse events, including febrile reactions, transmission of infectious diseases, and an immunomodulatory effect, which is hypothesized to increase the frequency of postoperative infections. This issue is far from resolved, as observational cohort studies, randomised controlled studies and a recent meta-analysis on the subject produced conflicting results. Nonetheless, the clinical observation that patients who receive any HBT after major orthopaedic surgery do stay in the hospital significantly longer is undisputed. As postoperative infections are relatively rare (1–3%), and as the role of HBT herein is not yet established, other factors are likely to be responsible for the prolonged hospital stay. To address this issue we undertook a prospective observational study (**Chapter 4**). In 444 patients who underwent elective total hip arthroplasty, we studied (among other parameters) the frequency of HBT, wound disturbances, superficial and deep wound infections, and length of hospital admission.

In this prospective observational study we found that HBT is associated with prolonged hospital admission. We found that this prolonged admission is not a straightforward consequence of an increased postoperative infection rate. However, HBT was the sole significant predictor of the development of wound healing disturbances, and together these two factors were the main predictors of prolongation of hospitalisation. No significant influence on wound disturbance and hospitalisation was found, either by univariate or multivariate analysis, of age, sex, length, weight, operation duration, blood loss or the use of gentamicin cement.

Although we did not study the mechanism underlying of wound disturbances, the more pragmatic conclusion we reach from our study is that prevention of HBT may be of relevance in limiting duration of admission after elective orthopaedic surgery. If this is indeed the case, measures to prevent perioperative blood loss, cell saving techniques and methods to enhance preoperative Hb (such as EPO) might be attractive treatment options.

One of the simplest and cheapest ways to optimise the use of blood transfusions would theoretically be the development of a transfusion protocol. Indeed, in the light of the risks described above and the fact that blood supply in The Netherlands is not infinite, a nationwide consensus on guidelines for packed red blood cells (PRBC) transfusions in the perioperative period was reached in 1997. This nationwide consensus resulted in a transfusion protocol for our hospital in which the haemoglobin concentration was the sole indication for homologous blood transfusion (HBT). We investigated the HBT ratio before and after the introduction of the new protocol in our hospital (**Chapter 5**). Over a 33-month period 14587 patients were included in the study. We found a 50% decrease in PRBC transfusions after implementation of the guidelines.

Of course is it not possible to maintain constant all confounding factors that can affect perioperative blood loss during a period of evaluation as long as our study. Several important factors changed in our hospital during the evaluation period. Changes occurred in the surgical staff, and the percentage of loco-regional anaesthesia increased. Also, during the evaluation period the introduction of more COX-2 selective NSAID's took place. Undoubtedly, these factors were, to some extent, responsible for the decreased blood loss and thus for decreased perioperative transfusion requirements. Still, our study clearly shows the benefits of employing strict perioperative transfusion guidelines, as a 50% decrease in PRBC transfusions was seen during the observation period compared to the 25% decrease in blood loss during the same periods. Perioperative transfusions are responsible for 60% of all transfusions in the Netherlands. According to a representative survey, the indications were poorly specified for 40% of these: blood loss, routine practice, cardiovascular changes, weakness or fatigue were cited. Current guidelines, which our study corroborates, indicate that in the peri-operative period a patient should only be transfused if the haemoglobin concentration is known.

Apart from adherence to a strict protocol, there are more specific methods with the potential to minimise the use of blood transfusions. Among these is the use of the new generation non-steroidal anti-inflammatory drugs (NSAID's), the COX-2 antagonists with less influence on blood coagulation. Moreover, sophisticated technology now enables the anaesthetist to retrieve RBC's peri- and post-operatively. Finally, the hormone EPO may be used to boost the number and contents of the RBC's pre-operatively. We studied all these potential blood sparing methods sequentially.

NSAID's are used in the perioperative period for analgesia and reduction of oedema in the surgical field. Beside these benefits there are unwanted side effects: reduction of renal blood flow, gastric complaints and increase of blood loss during surgery by influencing the coagulation cascade. Ibuprofen is a commonly used NSAID in the Netherlands, and we wished to assess its effects on perioperative blood loss in patients undergoing hip arthroplasty in a randomised double-blinded placebo controlled study in 50 patients (Chapter 6).

In this study preoperative (2 weeks) pre-treatment with ibuprofen showed an increase in blood loss of 46% intra-operatively and during the first 24 hours after total hip replacement surgery. Confounding factors in our study were the use of prophylaxis against thromboembolism by acenocoumarol, and the technique of measuring blood loss. The study was also not designed to prove that an increase in blood loss resulted in increased transfusion requirements or perioperative morbidity/ mortality. However, although we thus did not prove that the increased blood loss was clinically relevant, the fact remains that compared to a placebo, ibuprofen caused more blood loss perioperatively.

To tackle this problem there are two options: discontinue NSAID's far ahead of scheduled major orthopaedic surgery, or change NSAID's three days before surgery into COX-2 selective agents, with a potentially better safety profile with regard to perioperative blood loss.

The anti-inflammatory, analgesic and antipyretic action of NSAID's are mediated through inhibition of prostaglandin synthesis by inhibiting cyclo-oxygenase (COX), which is now known to exist in at least two isoforms known as COX-1 and COX-2. COX-1 is important in "housekeeping" functions at the gastro-intestinal mucosa, kidneys and vasculature. In contrast, the inducible isoform COX-2, mainly contributes to the pathophysiological process of inflammation.

From this one could reason that selective COX-2 inhibiting NSAID's have fewer side effects.

We have taken this idea further and designed a prospective randomised study to test the hypothesis that use of more cyclooxygenase-2 (COX-2)-selective NSAID's can reduce perioperative blood loss compared with non-selective NSAID's. We studied 200 patients who underwent total hip replacement (Chapter 7). Two NSAID's were compared: conventional NSAID indomethacin (3 x 50 mg daily) and the COX-2 selective meloxicam (1x 15 mg daily). Total perioperative blood loss after meloxicam was 17% ($p < 0.05$) less than that observed after indomethacin. However, whether this is of clinical significance and influences patient outcome remains to be determined. In addition, the potential beneficial effects of these compounds on blood loss should be weighed against potential detrimental effects (such as a potentially increased risk for cardiovascular events) before routine use can be recommended.

One of the more elegant measures to avoid red blood cell transfusions in patients with a lowered haemoglobin level (10–13 g/dl) is epoetin alpha (EPO). To study the effects of EPO on the number of perioperative BTs we undertook a multi-centre randomised controlled trial (RCT) (Chapter 8). In this RCT the effects of preoperative administration EPO and best standard of care (BSC) in 695 orthopaedic surgery patients were compared in normal clinical routine in six countries. EPO-treated patients had higher Hb values from the day of surgery until endpoint and lower transfusion rates (12% vs. 46%). EPO treatment delivered no significant effect on postoperative recovery (time to ambulation, time to discharge, infection rate). Time to ambulation and time to discharge were, however, longer in transfused than in not-transfused patients. Side effects in both groups were comparable. EPO increased perioperative Hb in mild-moderate anaemic patients and reduced transfusion requirements. Patients receiving blood transfusions required a longer hospitalisation than not-transfused patients.

Apart from the above EPO probably also plays an important role in post-operative rehabilitation. In many countries hip and knee surgery are performed in accelerated rehab programs, which limit hospitalisation times to less than a week. Thus postoperative higher haemoglobin levels might become more important as rehabilitation becomes more strenuous due to reduction in hospitalisation. Pre-operative EPO administration will thus become more important, especially in the more compromised patients, as they suffer more from the changes in rehabili-

tation and lower accepted haemoglobin levels. This study leads to the conclusion that in routine daily setting of major orthopaedic surgery EPO treatment is an efficient method to decrease perioperative transfusion requirements and to increase perioperative haemoglobin levels. As hospitalisation time is severely reduced by new rehabilitation procedures, this will become even more important.

The current treatment protocol of EPO consists of a fixed dose in all patients, according to Goldberg. Although easy to use, it has its limitations, since the inter-patient variability in response is considerable. In a prospective study we investigated whether pre-operative EPO dosing can be specifically tailored to the individual patient's needs (**Chapter 9**). A total of 334 patients scheduled for major orthopaedic surgery were treated for decreased serum haemoglobin levels. EPO and iron were used three weeks prior to surgery to increase the level of serum haemoglobin. Afterwards we calculated the erythropoiesis output in grams of haemoglobin after one injection of 40,000 IU of EPO (i.e. Factor EO-40,000). In our study factor EO-40,000 was 34 grams. Factor EO-40,000 can be used to predict the increase in the serum haemoglobin level in the individual patient, as the number of EPO injections (40,000 IU) needed to reach the desired serum haemoglobin level can now be calculated. With this knowledge, patients can be better prepared for surgery and homologous blood transfusions can be avoided as far as possible.

As stated above another method to reduce perioperative blood transfusions is the use of an autotransfusion system for shed blood. Cell saving techniques are an effective approach to prevent blood transfusion. Shed blood may be re-infused after filtration (unprocessed) or after treatment in a cell separator (processed). Transfusion of unprocessed shed blood is a relatively simple and inexpensive method to restore normovolaemia, in contrast to autotransfusion of processed blood, which requires an expensive cell separator and disposables. We performed a prospective observational quality assessment study of the Bellovac® post-operative wound drainage and reinfusion system in 135 consecutive patients scheduled for elective total knee arthroplasty or total hip arthroplasty (**Chapter 10**). The control group consisted of a historic group of 96 patients. Autotransfusion reduced the percentage of patients receiving HBT from 35% -22%). The reduction was more pronounced in the knee surgery patients (18% to 6%) compared with the hip surgery patients (47% to 34%). In the knee patients, transfused packed red cells per operation decreased from 0.45 HBT/operation to 0.11

HBT/operation, a reduction of 0.34 HBT (75%) in every total knee arthroplasty. This was also found in the hip surgery patients, although this did not reach statistical significance. This may be related to surgical technique: as in most hospitals, knee arthroplasty surgery was performed using a tourniquet, so that blood loss occurred only in the post-operative period, in contrast to the hip surgery where blood loss occurred during the whole procedure. Re-transfusion of shed blood is of course most effective if all lost blood can be collected, as is the case in knee surgery, but not in hip surgery, where significant blood loss occurs during the operation.

Although we observed no complications during re-transfusion, our patient group may have been too small for a safety assessment. One of the most common side effects is a febrile reaction after autotransfusion of shed blood, which we did not see. Another concern would be the presence of methyl methacrylate monomer (MMM) in re-transfused blood. However, systemic blood showed no evidence of MMM after re-infusion of salvaged blood in cemented knee arthroplasty surgery.

A cost-benefit analysis of the system is difficult to make, because of the complex costs involved in blood transfusion. At first glance autotransfusion is more expensive, but a future formal cost-benefit study should also take into account possible extended hospitalisation and immunomodulatory effects due to a homologous blood transfusion. We conclude that the Bellovac® A.B.T. device reduced homologous blood transfusions in TKA. The use of the system is less complicated and less expensive than auto re-transfusion using a cell separator. This method of auto re-transfusion should therefore be considered in knee surgery.

Having defined several methods to decrease perioperative blood transfusion, we subsequently implemented these improvements in our daily clinical routine. The first step was the restriction that the Hb level should be assessed prior to red cell infusion to ensure compliance with pre-defined cut-off values. Subsequent measures included: confinement to COX-2 selective NSAID in the perioperative period; EPO and iron therapy at the Hb level between 10 and 13 g/dl; consequent cell salvage during and after surgery; administration of aprotinine in cases with expected high blood loss (> 1.5 l). We then studied the effect of these alterations in our clinical routine. To this end we surveyed a relational database with data on 28.861 orthopaedic surgery patients in our clinic before and after implementation (Chapter 11). The survey disclosed the following issues related to a high incidence of homologous red cell infusion: negligence of guidelines, the pre-

operative use of non-selective NSAID's, low preoperative Hb level, non-retrieved blood loss, and high cut-off values for homologous red cell transfusion. The type of anaesthetic technique was found to be not relevant for blood-sparing effect.

The steps mentioned above do not involve a medical novelty. Rather, we show that strict rules with the appropriate steps and in sequence resulted in an 80% reduction of use of homologous red blood cells. Of note is that the incidence of deep wound infections decreased by 40% over the same time, but whether this is related solely to our blood-saving measures remains to be seen.

Daily clinical practice in our hospital was not different from that in any general hospital in the Netherlands. Systematic presentations on “how we did it” resulted in the introduction of the measures in several of the hospitals in the region and a steady 5–7% decline per year in the utilisation of the use of homologous red cell transfusions.

One needs to keep in mind that each blood sparing measure on its own produces but a little decline. However the combination of all measures for the individual hospital results in a tremendous decline in the use of homologous red cells. Does this decline in HBT also result in a decrease in postoperative infections, as one would expect from the literature? Analysis of our database for these data showed a decline of the postoperative infections with 42%, but whether this temporal relation is also a causal one is unsure.

Based on our above experience and other systematic improvements in the chain of patient care, we recommend:

- Restrictive guidelines for homologous red cell infusion.
- Automated relational databases enabling feedback on clinical practice
- Preoperative assessment that involves the anaesthesiologists and allows for pre-operative planning along a comprehensive algorithm (Chapter 11)

HOOFDSTUK 13

ALGEMENE BESCHOUWINGEN

SAMENVATTING

De identificatie van de verschillende bloedtypes door Landsteiner in het begin van de 20e eeuw was één van de eerste grote verbeteringen op het gebied van veiligheid en gebruik van bloedtransfusies (**Hoofdstuk 2**). De latere ontwikkelingen in opslag en het testen op infectieuze agentia hebben de veiligheid van bloedtransfusies verder verbeterd (**Hoofdstuk 3**). Deze vooruitgang heeft echter tot de paradoxale situatie geleid dat alhoewel bloedtransfusies veiliger zijn dan ooit, zowel de dokter als de patiënt zich meer bewust zijn van de eventuele risico's en daarom minder genegen zijn een bloedtransfusie te accepteren. Maar zonder negatieve gevolgen zal een bloedtransfusie wellicht nooit worden. In termen van perioperatief patiëntenbeleid, blijft het voorkomen van een bloedtransfusie een van de uitdagingen voor de anesthesioloog.

Met deze principes in gedachten proberen we in dit proefschrift twee vragen te beantwoorden: wat zijn de schadelijke effecten van een bloedtransfusie bij electieve orthopedische chirurgie, en wat kan de anesthesioloog doen om een bloedtransfusie te verminderen?

Perioperatief bloedverlies is een van de problemen bij electieve orthopedische chirurgie. Een homologe bloedtransfusie (HBT) is de standaard benadering om de potentieel schadelijke effecten van een te lage hemoglobine concentratie (Hb) te voorkomen. Echter een HBT wordt geassocieerd met verschillende schadelijke bijwerkingen, koortsreacties, verspreiding van infectieuze ziekten en immuun modulerende effecten. Door deze immuun modulerende effecten verdenkt men dat een HBT mogelijk een toename kan geven van postoperatieve infecties. Deze hypothese is echter nog lang niet opgelost. Observationale cohort onderzoeken, gerandomiseerde gecontroleerde onderzoeken en een recente meta-analyse hebben tegenstrijdige resultaten opgeleverd. Maar de klinische observatie dat patiënten die een HBT krijgen na grote orthopedische chirurgie langer in het ziekenhuis blijven is onweerlegbaar. Omdat postoperatieve infecties relatief zeldzaam (1–3%) zijn en de rol van een HBT hierin nog niet bewezen, zijn mogelijk andere factoren verantwoordelijk voor de verlengde ziekenhuisopname. Om dit nader te onderzoeken hebben we een prospectief observationeel onderzoek gedaan (**Hoofdstuk 4**). Bij 444 patiënten die een electieve totale heupoperatie ondergingen hebben we “behoudens andere parameters” de frequentie van HBT, wondrandstoornissen, oppervlakkige en diep wondinfecties en de opnameduur onderzocht. In dit prospectief observationeel onderzoek hebben we gevonden dat een HBT geassocieerd is met een verlengde opnameduur. We vonden dat het verlengde opnameduur niet direct het gevolg was van een verhoogde postoperatieve

infectie ratio. Een HBT was de enige significante voorspeller voor de ontwikkeling van wondrandstoornissen, en deze factoren samen waren voorspellers voor de verlenging van het ziekenhuisverblijf. Er werd geen significante invloed op wondrandstoornissen en ziekenhuisopname duur gevonden bij univariaat en multivariaat analyse van leeftijd, geslacht, lengte, gewicht, operatieduur, bloedverlies, of het gebruik van gentamycine cement. Alhoewel we niet het mechanisme van de wondrandstoornissen hebben onderzocht kunnen we de meer pragmatische conclusie uit ons onderzoek stellen dat het voorkomen van een HBT mogelijk relevant is in het beperken van de opnameduur na electieve orthopedische chirurgie. Als dit inderdaad het geval is kunnen maatregelen om het perioperatief bloedverlies te verminderen goede behandelingsopties zijn. Een van de meest simpele en goedkoopste manieren om het gebruik van bloedtransfusies te optimaliseren is in principe het ontwikkelen van een transfusieprotocol. Inderdaad is in het licht van de hierboven beschreven risico's en het feit dat de bloedvoorraad in Nederland niet oneindig is een nationale consensus over transfusies opgesteld in 1997. Deze consensus resulteerde in een aangepast transfusieprotocol voor de St. Maartenskliniek waarin de hemoglobine concentratie de enige indicatie voor een HBT was. Retrospectief hebben we de HBT ratio voor en na introductie van het nieuwe protocol in de St. Maartenskliniek onderzocht (Hoofdstuk 5). Gedurende 33 maanden werden 14.587 patiënten geïncludeerd in het onderzoek. We vonden een 50% reductie in "packed cells" gebruik na implementatie van de strak geprotocolleerde richtlijnen. Natuurlijk is het niet mogelijk om alle medebepalende factoren die peri-operatief bloedverlies gedurende deze lange periode van het onderzoek beïnvloeden, constant te houden. Enkele belangrijke factoren veranderden gedurende deze evaluatie periode in de St. Maartenskliniek. Er vonden mutaties plaats in de chirurgische staf en het percentage locoregionale anesthesie nam toe. Tevens vond gedurende deze periode de introductie van de meer COX-2 selectieve NSAID's als standaard NSAID plaats. Natuurlijk zijn deze factoren medebepalend (tot een bepaalde hoogte) voor het verminderde bloedverlies en dus ook van het perioperatief transfusiegebruik. Echter ons onderzoek laat duidelijk de voordelen van strikte perioperatieve transfusie richtlijnen zien; een 50% reductie in "packed cells" gebruik bij een 25% reductie in bloedverlies.

Perioperatieve transfusies zijn verantwoordelijk voor 60% van alle transfusies in Nederland. Volgens een onderzoek is de indicatie bij 40% slecht gespecificeerd; bloedverlies routine, cardiovasculaire veranderingen, zwakte en vermoeidheid werden genoemd. Ons onderzoek laat zien dat in de perioperatieve periode een

patiënt alleen een transfusie mag krijgen indien de hemoglobine concentratie bekend is.

Anders dan een strikt transfusieprotocol zijn er nog andere methoden om het aantal perioperatieve bloedtransfusies te verminderen. Onder deze andere methoden is het gebruik van de nieuwe generatie niet steroïdale anti-inflammatoire geneesmiddelen (NSAID's), de meer COX-2 specifieke remmers met minder invloed op de bloedstolling. Buiten dit zijn er nieuwe technieken ter beschikking gekomen die het mogelijk maken om in de perioperatieve fase verloren gegane erythrocyten te hergebruiken. Ook is het nu mogelijk om met behulp van het hormoon erythropoietine (epo) het aantal erythrocyten preoperatief te verhogen. We hebben al deze methoden afzonderlijk onderzocht.

NSAID's worden in de perioperatieve periode gebruikt in verband met analgesie en vermindering van oedeem in het chirurgisch veld. Behoudens deze voordelen zijn er ook nadelige bijwerkingen: verminderde nier doorbloeding, maagklachten en toename van het chirurgisch bloedverlies door invloed op de stollingscascade.

Ibuprofen is een veelgebruikt specifiek NSAID in Nederland en we hebben de effecten op het perioperatief bloedverlies onderzocht in een gerandomiseerde dubbelblinde placebo gecontroleerd onderzoek bij 50 patiënten die geopereerd werden aan een totale heupvervangende prothese (Hoofdstuk 6). In dit onderzoek hadden patiënten die 2 weken voorbehandeld met ibuprofen 46% meer bloedverlies in de eerste 24 uur na een totale heupvervangende prothese. In dit onderzoek hebben we alleen gekeken naar bloedverlies en niet naar verminderde transfusiebehoefte. Alhoewel we niet onderzocht hebben of het verminderd bloedverlies dus klinisch relevant is, laat ibuprofen een duidelijk hoger perioperatief bloedverlies zien. Om dit probleem te ondervangen zijn er 2 mogelijkheden: het staken van NSAID's ver voor de operatie of het NSAID eventueel omzetten in een meer COX-2 specifiek NSAID.

We hebben dit dan ook onderzocht in een prospectief gerandomiseerd onderzoek of de hypothese dat het gebruik van meer COX-2 specifieke NSAID's perioperatief bloedverlies kan verminderen in vergelijking met niet specifieke NSAID's (Hoofdstuk 7). In dit onderzoek waarbij 200 patiënten werden geopereerd aan een totale heupoperatie hebben we 2 NSAID's vergeleken: het niet specifieke NSAID indomethacine (3 x daags 50 mg.) en het meer COX-2 specifieke NSAID meloxicam (1 x daags 15 mg.). Het totale perioperatieve bloedverlies was

bij meloxicam gebruik 17% minder dan bij indomethacine. Of dit verschil klinisch relevant is en een betere resultaat voor de patiënt heeft, valt nog te bezien. Wat betreft het perioperatieve bloedverlies is het staken van klassieke NSAID's zeker zinvol voorafgaand aan een electieve operatieve ingreep, vergelijkbaar met anticoagulantia en aspirine. Een van de meer elegante maatregelen om een HBT bij patiënten met een verlaagd hemoglobine gehalte (10–13 gram/dl) te voorkomen is EPO (**Hoofdstuk 8**). Om het effect van EPO op het aantal perioperatieve bloedtransfusies te onderzoeken hebben we een multi-centrum gerandomiseerde gecontroleerde studie gedaan. In dit onderzoek is het effect van preoperatieve toediening van EPO bij 695 orthopedisch chirurgische patiënten vergeleken met “standaard zorg” in 6 verschillende landen. De met EPO behandelde patiënten hadden een hoger Hb gehalte van de dag vanaf operatie tot het eind van de opname en een verminderde transfusieratio (12% versus 46%). EPO behandeling had geen significant effect op postoperatief herstel (bedrust, opnameduur en infectieratio). De bedrust en opnameduur waren bij patiënten die een transfusie hadden gehad langer. De bijwerkingen in beide groepen waren vergelijkbaar. Behalve bovenstaande speelt EPO mogelijk ook een belangrijke rol in de postoperatieve revalidatie. In veel landen worden heup- en kniechirurgie vaak verricht in een versneld revalidatieprogramma waarbij de ziekenhuisopnameduur verminderd is tot minder dan 1 week. Deze verkorte revalidatie vraagt meer inspanning van de patiënt; reden waarom een hoger Hb belangrijk kan zijn. Preoperatief EPO kan dus eventueel belangrijk zijn, speciaal bij meer gecompromitteerde patiënten die mogelijk meer last hebben van een laag Hb gehalte bij deze meer inspannende revalidatie. Dit onderzoek leidt tot de conclusie dat in een routinematige grote orthopedische chirurgie EPO behandeling een efficiënte methode is om het perioperatieve transfusiebehoeft te verminderen en het perioperatief Hb te verhogen, zonder het optreden van ernstige bijwerkingen.

Het huidige behandelingsprotocol met EPO bestaat uit een vaste dosering bij alle patiënten volgens Goldberg (1996). Alhoewel makkelijk in gebruik heeft het zijn beperkingen, daar de interpatiënt variabiliteit aanzienlijk is. In een prospectief onderzoek hebben we onderzocht of de EPO dosering bij de individuele patiënten behoefte kan worden aangemeten (**Hoofdstuk 9**). Bij 334 patiënten die op de wachtlijst stonden voor grote orthopedische chirurgie werden behandeld wegens een lichte anemie. EPO en ijzer werden 3 weken voor operatie toegediend. Naderhand hebben we het erythropoietische effect in grammen hemoglobine na 1 injectie van 40.000 eenheden EPO (factor EO-40.000) berekend. In onze studie was de factor EO-40.000 34 gram. Factor EO-40.000 kan gebruikt worden

om de toename in serumhemoglobine van de individuele patiënt te voorspellen als het aantal injecties EPO om het gewenste serumhemoglobine te bereiken. Met deze kennis kan de patiënt beter voorbereid worden voor de chirurgie en een HBT zoveel mogelijk voorkomen worden.

Een andere methode om het aantal perioperatieve bloedtransfusies te verminderen is het gebruik van autotransfusie systeem voor verloren gegaan bloed. "Cell-saving" technieken zijn een effectieve benadering ter voorkoming van een HBT.

Verloren gegaan bloed kan gereïnfundeerd worden na filtratie (= onbehandeld) of na behandeling in een cellseparator (=behandeld) met behulp van cell-saver. Transfusie van onbehandeld verloren gegaan bloed is een relatief simpele en een goedkope manier om normovolemie te herstellen, in vergelijking met autotransfusie van behandeld bloed dat een dure cellseparator (cell-saver) en disposables verlangt. We hebben een prospectief observationeel kwaliteitsonderzoek gedaan met de Bellovac postoperatief wonddrainage en re-infusiesysteem bij 135 achtereenvolgende patiënten voor electieve heup- en knie vervanging (**Hoofdstuk 10**). De controlegroep bestond uit een historische groep van 96 patiënten. Autotransfusie verminderde het percentage patiënten die een HBT ontvingen van 35% naar 22%. De vermindering was meer uitgesproken bij patiënten die een knie vervanging kregen (18% naar 6%) in vergelijking met patiënten die een heup vervanging kregen (47% naar 34%). Bij patiënten die een knie vervanging kregen verminderde het aantal transfusies van 0,45 HBT/operatie naar 0,11 HBT/operatie, een reductie van 0,34 HBT (75%) bij elke knieoperatie. Een vermindering werd ook gezien bij heupvervanging maar bereikte niet de statistische significantie.

Waarschijnlijk is dit tengevolge van de chirurgische techniek. Een totale knie vervanging wordt voornamelijk verricht tijdens bloedleegte zodat het bloedverlies alleen optreedt in de postoperatieve fase. In tegenstelling tot heupvervanging waarbij het bloedverlies tijdens de gehele procedure plaatsvindt. Retransfusie van verloren gegaan bloed is uiteraard het meest effectief als alle bloed verzameld kan worden zoals het geval bij knie vervangende operaties.

Alhoewel we geen complicaties tijdens retransfusie hebben gezien, is onze patientengroep mogelijk te klein om iets over veiligheidsaspecten te zeggen. Een van de meest voorkomende bijwerkingen is rillen na autotransfusie hetgeen wij echter niet gezien hebben. Een andere zorg zou mogelijk de aanwezigheid van methyl metha-

crylaat (MMM=cement) in transfusiebloed zijn. Echter systemisch bloed liet geen aanwezig MMM zien na reinfusie bij gecementeerde totale knie vervanging.

Een kostenbaten analyse van het systeem in vergelijking met een HBT is moeilijk te maken in verband met de complexe kosten die gepaard gaan met een bloedtransfusie. Op het eerste gezicht is autotransfusie duurder maar een toekomstige kostenbaten onderzoek zou ook rekening moeten houden met de verlengde opnameduur en immuunmodulerende effecten ten gevolge van een HBT. We concluderen dat het Bellovac systeem het aantal HBT's bij totale knie vervangingen reduceert. Het gebruik van het systeem is minder gecompliceerd en goedkoper dan autotransfusie met behulp van een cell separator. De autotransfusie met behulp van het Bellovac systeem zou dan ook overwogen moeten worden bij totale knie vervanging.

Al met al hebben we enkele methoden gedefinieerd ter vermindering van een aantal perioperatieve bloedtransfusies en deze hebben we achtereenvolgens geïmplementeerd in de Sint Maartenskliniek. De eerste stap was de restrictie dat het Hb gehalte bekend moest zijn en voldoen aan een gedefinieerde waarde voordat overgegaan mocht worden tot een transfusie. Andere maatregelen waren het gebruik van COX-2 specifieke NSAID's in de perioperatieve fase; epo en ijzer therapie preoperatief bij een Hb lager dan 13 gram/dl.; consequente cellsaving gedurende en na operatie; toediening van aprotinine bij gevallen met een verwacht hoog bloedverlies. We hebben de effecten van deze veranderingen onderzocht in onze kliniek. Om deze effecten te bestuderen hebben we een relationele database met gegevens van 28.861 orthopedische chirurgische patiënten in de St. Maartenskliniek nagekeken voor en na implementatie (**Hoofdstuk 11**). Oorzaken die voor implementatie van de veranderingen een hoge incidentie van een HBT gaven waren: het niet opvolgen van de richtlijnen, het preoperatief gebruik van non-selectieve NSAID's, een laag preoperatief Hb en bloedverlies dat niet gereïnfundeerd kon worden. De anesthesietechniek bleek geen invloed te hebben op bloedbesparing.

De voornoemde stappen zijn geen medische nouveautés. Echter, het strikt navolgen van de opeenvolgende stappen resulteerden in een 80% reductie van het aantal HBT's. Vermeldenswaard is in hetzelfde tijdsinterval het aantal diepe wondinfecties 40% daalde. Of dit echter alleen toe te schrijven is aan de bloedbesparende technieken valt moeilijk te bewijzen.

De dagelijkse praktijk in de St. Maartenskliniek is niet anders dan in welk ander ziekenhuis in Nederland. De presentatie van “how we did it” resulteerde in maatregelen in enkele ziekenhuizen in de regio met een vermindering van het HBT gebruik van 5–7% per jaar. Men moet in gedachten houden dat een enkele bloedbesparende maatregel op zichzelf weinig effect heeft, echter dat een combinatie van maatregelen een enorm verschil kan geven. En geeft deze vermindering in HBT ook een vermindering in postoperatieve infecties zoals men mag verwachten uit de literatuur? Analyse van de database laat een 42% vermindering zien van de postoperatieve infecties. Of dit echter een causaal effect is, is onduidelijk.

Gebaseerd op onze bovenstaande ervaring en andere systematische verbeteringen in de keten van patiëntenzorg kunnen we aanbevelen:

- Restrictieve richtlijnen voor homologe bloedtransfusies, gekoppeld aan een hemoglobine gehalte.
- Het gebruik van een geautomatiseerde relationele database voor terugkoppeling van de klinische praktijk
- Preoperatief beleid met behulp van de anesthesioloog voor de implementatie van het algoritme zoals beschreven in hoofdstuk 11.

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