Autologous Predeposit: To Leukocyte Deplete Or Not to Leukocyte Deplete?

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Key Words

Autologous transfusion · Allogenic transfusion · Hip arthroplasty · Immunomodulation · Humoral immune system · Cellular immune system · Postoperative infection

Summary

In five studies comparing different forms of storage of autologous blood the allogenic transfusion rate, humoral and cellular immune parameters and the postoperative infection rate were investigated. In a prospective, randomized study 21 volunteers donated one unit of blood. Retransfusion of stored autologous whole blood, but not of autologous packed red cells and fresh frozen plasma, induced a limited response of the immune system. Four prospective, randomized, partially or totally blinded studies investigating autologous donation in primary hip arthroplasty were carried out: In the first study including 94 patients, in which autologous blood was stored as whole blood, leukocyte-depleted whole blood or as blood components, the allogenic transfusion rates were compared. The type of storage of autologous blood did not influence homologous transfusion requirements. In a second study dealing with humoral immune factors, 97 patients were allocated at random to two groups. In one group, the autologous donation was stored as whole blood, in the other group the donation was separated into blood components before storage. With respect to the parameters studied, there were no significant differences between patients transfused with whole blood and those transfused with blood components. Moreover, these values also did not differ from those of patients not transfused. In a third study, the phagocytosis and respiratory burst activity of neutrophil granulocytes and of monocytes was measured in 58 patients who were randomly allocated to two groups as in the previous study. Neither the time course of phagocytosis nor that of respiratory burst activity showed a significant difference between both groups. In a fourth multicenter study, 953 patients were allocated to either of two groups. The first group of patients received autologous blood stored as whole blood, in the second group leukocyte depletion was done before storage. When comparing the outcomes of both groups, it could be shown that leukocyte depletion of autologous whole blood did not reduce the number of postoperative infections in primary hip surgery. It is therefore concluded that neither leukocyte depletion nor blood component separation is mandatory when using autologous predeposit in primary hip arthroplasty.

Schlüsselwörter

Autologe Transfusion · Allogene Transfusion · Hüftgelenkendoprothetik · Immunomodulation · Humorales Immunsystem · Zelluläres Immunsystem · Postoperative Infektion

Zusammenfassung

In fünf Studien wurden die allogene Transfusionsrate, humorale und zelluläre Immunfaktoren und die postoperative Infektionsrate bei verschiedenen Formen der Lagerung autologen Bluts verglichen: In einer prospektiven, randomisierten Studie spendeten 21 Freiwillige eine Einheit autologes Blut. Die Retransfusion von gelagertem autologem Vollblut – nicht jedoch die von autologen Erythrozytenkonzentraten und tiefgefrorenem Frischplasma – induzierte eine begrenzte Immunantwort bei den Probanden. In der primären Hüftgelenkendoprothetik wurden vier prospektive, randomisierte, teilweise oder ganz verblindete Studien durchgeführt: In der ersten Studie mit 94 Patienten wurde das autologe Blut als Vollblut, als leukozytendepletiertes Vollblut oder in Blutkomponenten separiert gelagert und die sich in den verschiedenen Gruppen ergebende allogene Transfusionsrate verglichen. Die Art der Lagerung des autologen Bluts beeinflusste die allogene Transfusionsrate nicht. In einer zweiten Studie, die humorale Immunfaktoren untersuchte, wurden 97 Patienten einer von zwei Gruppen zugeteilt. In der einen Gruppe wurde das autologe Blut als Vollblut, in der anderen in Komponenten separiert gelagert. Hinsichtlich der untersuchten Parameter fanden sich keine Unterschiede zwischen der Gruppe von Patienten, die mit Vollblut, der Gruppe die mit Komponenten und den Patienten, die nicht transfundiert wurden. In einer dritten Studie, die 58 Patienten einschloss, wurden die Phagozytose und der «respiratory burst» von neutrophilen Granulozyten und von Monozyten untersucht. Es im zeitlichen Verlauf der Parameter bestand zwischen den Untersuchungsgruppen kein signifikanter Unterschied. In einer vierten Multicenter-Studie wurden 953 Patienten zwei Gruppen zugeordnet. In der ersten Gruppe wurde das autologe Blut als Vollblut, in der zweiten als leukozytendepletiertes Vollblut gelagert. Die Leukozytendepletion verringerte die Zahl der postoperativen Infektionen nicht. Die Ergebnisse dieser Studien sprechen nicht für die Forderung, autologes Blut für die primäre Hüftgelenkendoprothetik einer Separierung oder einer Leukozytendepletion zu unterziehen.

For allogenic blood, the production of components is state of the art. In addition, leukocyte depletion has been introduced for all allogenic components in Germany and in other countries. For autologous blood, the production of components does not seem routinely necessary. Of the documented and possible advantages of leukocyte reduction and leukocyte depletion, only the longer storage time of red cells and a reduced immunomodulation by biologically active substances may be of relevance (table 1). There is no evidence that leukocyte depletion improves the outcome of patients receiving autologous blood. Nevertheless, the German Guidelines for the Production of Blood Products and Hemotherapy from 2005 require autologous blood to be stored either leukocyte-depleted or as components [1]. As a result, the requirements for personal and machine resources have increased. This reduces the cost-effectiveness of autologous donation and may prevent the implementation of preoperative deposit, particularly in smaller hospitals [2].

In five studies the effects of different forms of storage of autologous blood on the allogenic transfusion rate, the humoral and cellular immune system, and the postoperative infection were investigated (table 2) [3–6].

Methods

Essentially, we used two models for investigation:

- In a prospective, randomized study, volunteers donated one unit of autologous blood. The whole blood and the blood components (after removal of the buffy coat) were retransfused after 5 and 7 weeks, respectively.
- Four prospective, randomized, partially or totally blinded studies were carried out in patients undergoing surgery for primary hip arthroplasty. In weekly intervals 2–3 autologous blood units were donated; the deferral hemoglobin concentration was 11 g/dl. Iron was substituted orally. The autologous blood was stored as whole blood (non-leukocyte-depleted), as leukocyte-depleted whole blood or as components (after removal of the buffy coat).

Statistical analysis included parametric and nonparametric tests. For the parameters measured over time, the area under the curve was integrated for comparison. The α -value was set at 5 %.

Studies

Hip Arthroplasty: The Allogenic Transfusion Rate

In a randomized study on 94 patients, the storage of autologous blood as whole blood, as leukocyte-depleted whole blood or as blood components (after removal of the buffy coat) was compared [5]. In the respective groups surgery was carried out in weeks 5, 6 and 7 after first autologous donation.

Fig. 1. Volunteer Study: Postoperative course of IL-6 (median, 1st and 3rd quartiles).

t₀ = Before transfusion, t₁ = immediately after transfusion, t₂ = 3 h after transfusion, t₃ = 9 h after transfusion, t₄ = 24 h after transfusion, t₅ = 48 h after transfusion, t₆ = 7 days after transfusion. $p < 0.05$. From [3] with permission of Blackwell Publishing, Ames, IA, USA.

● whole blood, □ PRC/FFP.

The total blood loss and the number of transfused autologous units were comparable in the three groups. Postoperative hemoglobin concentration was almost identical. Allogenic transfusion was required in 2 patients each in groups one and two and in 1 patient in group 3 (table 3). This difference is not significant.

Conclusion

These data does not indicate that homologous transfusion requirements in primary hip arthroplasty are influenced by the type of storage of autologous blood.

Volunteer Study: Immunological Parameters

In 21 male volunteers aged between 30 and 38 years it was investigated whether the storage type of autologous blood donations (non-leukocyte-depleted whole blood or blood components) has different effects on the immunological markers IL-6, TNF- α (as pro-inflammatory cytokines), C3a, SC5b-9 (as indicators of complement activation) and neopterin (as a measure for acquired immunity) as well as on phagocytosis and respiratory burst activity of neutrophil granulocytes and monocytes [3]. Re-transfusion was carried out 5 (whole blood) and 7 weeks (blood components) after the donation.

Some – but not all – parameters showed a moderate increase of short duration after transfusion of whole blood as shown for IL-6 in figure 1. This effect was not observed after the transfusion of blood components.

Conclusion

These data indicates that re-transfusion of stored autologous whole blood induces a limited response of the immune system. This response is not evident if autologous packed red cells and fresh frozen plasma are transfused.

Fig. 2. Hip arthroplasty: Postoperative course of IL-6.
 t_1 = Before anaesthesia, t_2 = before transfusion t_3 = after transfusion of the first autologous unit; t_4 = 6 h after surgery, t_5 = 1 day after surgery, t_6 = 7 days after surgery. n.s. From [6] with permission of Blackwell Publishing, Ames, IA, USA.
 ○ whole blood, ● blood components, □ not transfused.

Fig. 3. Hip arthroplasty: Phagocytic activity of monocytes (median, 1st and 3rd quartiles).
 t_0 = Prior to skin incision, t_1 = 2 h after skin incision, t_2 = 6 h after skin incision, t_3 = 12 h after skin incision, t_4 = 24 h after skin incision, t_5 = 2 days after skin incision, t_6 = 7 days after skin incision. n.s. From [4] with permission of Blackwell Publishing, Ames, IA, USA.
 ● whole blood, □ blood components, Δ not transfused.

Hip Arthroplasty: Humoral Immune Parameters

The same humoral parameters as in the volunteers study were investigated perioperatively up to postoperative day 7 [6]. 97 patients were allocated at random into two groups. In one group, autologous donations were stored as whole blood (non-leukocyte-depleted); in the other group autologous donations were stored as components. Perioperatively, 30 patients received autologous whole blood, 40 patients received packed red cells, and 27 patients were not transfused. None of the patients was transfused with allogenic blood.

The parameters studied did not show significant differences between the three groups. Data for IL-6 are given in figure 2.

Conclusion

The data indicates that the transfusion of the autologous buffy coat is not of relevance compared to the effects of surgery.

Hip Arthroplasty: Cellular Immune System

Phagocytosis and respiratory burst activity of neutrophil granulocytes and monocytes were studied in 58 patients who were allocated at random into two groups [4] as in the previous study. 25 patients were transfused with whole blood, 24 patients were transfused with blood components, and 9 patients were not transfused. None of the patients was transfused with allogenic blood. There was no significant difference in the time courses of the measured parameters between the three groups (fig. 3).

Conclusion

In the perioperative situation, a specific cellular immune reaction after autologous transfusion cannot be shown, irrespective of whether autologous blood is stored as whole blood or as components.

Hip Arthroplasty: Postoperative Infection

Several previous investigations demonstrated a positive effect of autologous vs. allogenic transfusion with regard to postoperative infection in hip arthroplasty (table 4). However, to our knowledge there is no study comparing different storage methods used for autologous predonation with respect to the postoperative infection rate.

In a prospective, double-blind, multicenter study patients were allocated into either of two groups. In one group of patients (WB) autologous blood was stored as whole blood (non-leukocyte-depleted), in the other (ldWB) the predeposit was stored as leukocyte-depleted whole blood. Two or three autologous units were donated in weekly intervals, and surgery was scheduled for the 5th week after the first donation. No other autologous methods were implemented. Leukocyte-depleted packed red cells were used for allogenic transfusion. Peri- and postoperative infection monitoring included clinical investigation, urine analysis, wound inspection (modified ASESPPSIS wound score), blood culture (if fever with temperatures above 39 °C occurred after postoperative day 2), and X-ray for suspected pneumonia. The study was concluded with a 3-month follow-up after surgery. The primary purpose of the follow-up was to determine if there was any infection in the postoperative course. The sizes of the study groups were selected to yield a statistic power of 80%.

Of the 1,085 patients originally included in the study, 139 were excluded because of violations of the protocol. General data and calculated blood volume in the two groups were comparable. 357 patients donated three autologous units, 561 two

Table 1. Advantages of leukocyte reduction or depletion

	Leukocyte reduction (removal of the buffy coat)	Leukocyte depletion (inline filtration prior to storage)
Proven advantages	longer storage time of erythrocytes* preserved coagulation factors in FFP** nonhemolytic transfusion reactions less frequent immunization against HLA-antigens reduced	transmission of CMV, EBV, HTLV-1 reduced transfusion associated lung insufficiency (TRALI) less frequent graft-versus-host disease in predisposed patients rare
Possible advantages		reduced immunomodulation through biologically active substances* reduced immunomodulation through persistence of donor leukocytes in the recipient (mixed chimerism) reduced transmission of other leukotropic viruses hypothetically: infection with new variant Creutzfeld-Jakob disease reduced

*Possibly of relevance for autologous predeposit.

**Relevant for autologous donors if perioperative blood loss exceeds two thirds of the blood volume of the patient.

Table 2. Studies on effects of autologous blood donation

Reference	Aim	Protocol	Patients (hip arthroplasty) / volunteers	Comparison
Lorentz et al., 2001 [5]	allogenic transfusion rate	prospective, randomized, stratified by sex, blinded for major aim of study	patients	whole blood leukocyte depleted whole blood PRC/FFP
Frietsch et al., 2001 [3]	humoral and cellular immune system	prospective, randomized	healthy male volunteers	whole blood PRC/FFP
Tolksdorf et al., 2001 [6]	humoral immune system	prospective, randomized, stratified by sex	patients	whole blood PRC/FFP
Frietsch et al., 2001 [4]	cellular immune system	prospective, randomized, stratified by sex	patients	whole blood PRC/FFP
Multicenter study	postoperative rate of infection	prospective, randomized, stratified by sex, double blind	patients	whole blood leukocyte depleted whole blood

Table 3. Study 'Allogenic Transfusion Rate':
Blood loss and transfusion [from 5]

	Study group		
	WB (n = 32)	ldWB (n = 29)	PRC/FFP (n = 33)
Total blood loss, ml*			
Median	2,270	1,850	1,680
Range	970–3,760	930–3,680	480–3,390
Autologous transfusion			
Transfused/donated units	52/95	44/87	50/99
Allogenic transfusion*			
Transfused patients	2	2	1
Units/patient	2.1	2.1	1

WB = Whole blood; ldWB = leukocyte-depleted whole blood; PRC/FFP = packed red cells / fresh frozen plasma.
*Not significant.

Table 4. Positive effect of autologous vs. allogenic blood in hip arthroplasty (TEP)

Reference	Study	Number of patients	Outcome parameters
Borghi and Casati, 2000 [7]	prospective observational study	2,216	wound infection, wound hematoma, cardiovascular complications, pneumonia, pulmonary embolism
Qualitätsicherung im Krankenhaus, Arbeitsgruppe Orthopädie 2004 (unpublished data)	retrospective uncontrolled cohort study	29,967	cardiovascular complications, wound hematoma, wound infection, pneumonia, pulmonary embolism
Innerhofer et al., 2005 [8]	prospective observational study	308	infection
Weber et al., 2005 [9]	prospective observational study	444	wound healing, hospital stay

Table 5. Infections

	Study group		p value
	WB (n = 465)	ldWB (n = 486)	
Urinary tract infection	66	69	n.s.
Wound infection	10	8	n.s.
Fungal infection (local)	1	5	n.s.
Respiratory infection (acute purulent bronchitis, pneumonia)	2	4	n.s.
Other infections	5	3	n.s.
Number of patients with one or more infections	82	86	n.s.

WB = Whole blood; ldWB = leukocyte-depleted whole blood; n.s. = not significant.

units, and 28 one unit. The perioperative data of the two groups were comparable. Calculated total median blood loss was 1,740 ml for group WB and 1,660 ml for group ldWB. 248 patients vs. 255 patients were transfused with autologous blood. In addition 25 vs. 14 patients received allogenic blood units. 42 vs. 55 patients developed fever with temperatures above 39 °C after postoperative day 2. The median wound score was 5 (range 0–53) vs. 6 (0–51). The time of hospital stay was comparable. 82 patients in group WB vs. 86 patients in group ldWB developed one or more infections (Tab. 5). This difference between the two groups was not significant.

Conclusion

Leukocyte depletion of autologous whole blood does not reduce the number of postoperative infections in primary hip surgery.

General Conclusion

The data of the studies presented here do not support the concept of requiring leukocyte depletion for autologous predeposit in primary hip arthroplasty.

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