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Original Article

The effects of allogeneic and autologous blood transfusion on immune function in patients receiving total hip replacement

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Abstract: Objective: To evaluate the effects of allogeneic and autologous blood transfusion on immune function and postoperative inflammation in patients after total hip replacement. Methods: In this retrospective study, the clinical data of 60 patients undergoing total hip arthroplasty through a posterolateral approach were analyzed. The patients were grouped into an autologous blood transfusion group (allo group) (n = 30) and an autologous blood transfusion group (auto-group) (n = 30) according to the treatment they received. All patients did not receive preoperative and intraoperative blood transfusion. The blood collected in the operation area was transfused to the patients in the auto-group with the autotransfusion device and the allogeneic blood was transfused to the patients in the allo-group after the operation. The average amount of blood transfusion was 400 ml. The immune function after blood transfusion was mainly evaluated by natural killer cell cytotoxicity (NKCC) and interleukin-2 (IL-2) using ELISA kits, meanwhile the changes of cellular immune factor levels (differentiation cluster of differentiation, CD) (CD3+, CD4+) and humoral immune factor levels (Immunoglobulin E, IgE) after blood transfusion were determined by flow cytometry. The secondary outcome was postoperative inflammatory response measured by white blood cell (WBC) count, neutrophil percentage (NP) and C-reactive protein (CRP). Results: The parameters of both groups of patients were comparable. The auto-group significantly outperformed the Allo-group in the following laboratory parameters: NKCC (%, E:T = 10:1) at day 2 [26.1 (Auto) vs 19.3 (Allo); $P = 0.0025$], NKCC (%, E:T = 5:1) at day 2 [20.0 (Auto) vs 17.3 (Allo); $P = 0.0094$], CD3+ (%) at day 2 [50.5 (Auto) vs 40.8 (Allo); $P = 0.0233$], CD4+ (%) at day 2 [41.2 (Auto) vs 26.3 (Allo); $P = 0.0122$], IgE (U/mL) at day 2 [157.8 (Auto) vs 319.8 (Allo); $P = 0.0064$]. Conclusion: Autotransfusion can safely replace allogeneic blood transfusion and reduce the damage of postoperative immune function after total hip arthroplasty.

Keywords: Allogeneic and autologous blood transfusion, immune function, postoperative inflammation, total hip replacement

Introduction

Osteoarthritis (OA) is a common disease and the number of joint replacement surgeries will continue to increase due to the aging population and the rising obesity rate [1]. It is estimated that by 2030, total hip replacements will be twice the current number according to research in the United States [2]. Total hip replacement is the most common surgical intervention for the treatment of hip OA, which can improve pathological pain, function and quality of life [3]. There are many different surgical approaches for total hip replacement, primarily including direct lateral approach (Hardinge), posterior approach and direct anterior approach. The posterolateral approach was used for total hip replacement in our study.

Blood transfusion plays a significant role in the development of modern medicine and surgical practice. However, the side effects and risks involved have been well documented over the years. Moreover, compared with autotransfusion, allogeneic blood transfusion is associated with more side effects, including allergic shock

and transfusion related acute lung injury. Furthermore, the case of allogeneic blood transfusion can lead to virus infections, such as hepatitis and human immunodeficiency virus (HIV) or graft-versus-host disease [4]. The increasing number of allogeneic blood transfusion is also a predictor of post-traumatic sepsis [5]. Consequently, autotransfusion is supposed to be safer than allogeneic transfusion.

Studies have shown that improving immune function in the perioperative period has a major impact on the prognosis of patients [6-8]. For example, low-dose Naloxone can improve immune function, alleviate pain intensity and has low opioid-related side effects in patients undergoing thoracoscopic excision of lung cancer [6]. Pre-postoperative nutritional conditioning for patients with malignant obstructive jaundice of cholangiocarcinoma can lead to a better prognosis and improve clinical results and immune function [7]. Appropriate preoperative enteral nutrition for patients with gastric cancer can improve their postoperative immune function, reduce inflammatory reaction, and is more conducive to the rehabilitation of patients [8].

Natural killer cells (NK cells) are important immune cells in the body and the main "soldiers" in the body responsible for killing abnormal cells such as senescent cells, virus-infected cells and tumor cells [9]. Interleukin-2 (IL-2) is a member of the chemokine family that plays an important role in the immune response and antiviral infection of the body. It can stimulate the proliferation of T cells that have been activated by specific antigens or mitogenic factors; and it can stimulate NK cell proliferation, enhance NK killing activity, produce cytokines, and induce LAK cell production [10]. Therefore, natural killer cell cytotoxicity (NKCC) and IL-2 can serve as a pair of indicators for monitoring immune function.

So far, Dan Steinitz and colleagues [11] reported that patients who underwent hip replacement surgery and received allogeneic blood transfusion during the perioperative period had an increased risk of postoperative infection compared to those who received autologous blood transfusion. Murphy and colleagues [12] reported that the infection rate of allogeneic blood transfusions was significantly higher than that of autologous blood transfusions in hip replacement surgery (P = 0.0029). Fernandez and colleagues [13] studied 376 patients but found no significant difference in infection rates between patients who received blood transfusions and those who didn't. However, their research only focused on postoperative infection rates but did not address immune function at the molecular level, and the results were inconsistent. Therefore, in this study, we mainly evaluated the immune function after blood transfusion by detecting NKCC and IL-2 and compared the changes of cellular immune factor (CIF) levels (differentiation cluster of differentiation, CD) (CD3+, CD4+) and humoral immune factor (HIF) (Immunoglobulin E, IgE). The secondary outcome was postoperative inflammatory response measured by white blood cell (WBC) count, neutrophil percentage (NP) and C-reactive protein (CRP).

Methods

Patients

In this retrospective study, we analyzed the medical records of 60 patients who underwent total hip replacement surgery at Hanchuan People's Hospital from 2018 to 2020. Inclusion criteria: (1) patients who had not received preoperative or intraoperative blood transfusions; (2) patients who had relevant immune indicators measured during the perioperative period; (3) patients who had not received surgical treatment within the previous year; (4) patients without cancer, other orthopedic diseases, or other serious chronic diseases; (5) patients who had not undergone total hip replacement surgery before. The research plan was developed based on the *Helsinki Declaration* and approved by the Ethics Committee of Hanchuan People's Hospital. Due to the nature of a retrospective study design, informed consent was waived.

Intervention

All the patients received the surgery with a posterolateral approach. The patients were placed in a lateral position with the affected side on top. Midazolam (Item No.: 200544, purchased from Shandong Jinyuan Chemical Co., Ltd.) (0.05-0.1 mg/kg), sufentanil (Item No.: 200825, purchased from Humanwell Pharmaceutical Group Co., Ltd.) (1.0-2.0 μg/kg) were used for intravenous general anesthesia;

propofol (Item No.: 191123, purchased from Sinopharm Chemical Reagents Co., Ltd.) (2-2.5 mg/kg), rocuronium (Item No.: 201233, purchased from North China Pharmaceutical Co., Ltd.) (0.6-1.2 mg/kg) and remifentanil (Item No.: 200714, purchased from Sinopharm Chemical Reagents Co., Ltd.) (0.2-0.25 μg/kg/min) were injected to maintain anesthesia. Afterwards, a skin incision was made after sterilization to expose the damaged femoral head and acetabulum; the hip prosthesis, of which the size and figure were pre-designed using X-ray imaging, was carefully fixed. At last, the skin incision was sutured.

The Auto-group received salvage autologous blood transfusion. Intraoperative bleeding was collected by using a negative pressure absorption device of the blood recovery machine, and mixed with an appropriate amount of anticoagulant. The collected blood was filtered through multiple layers, and then separated using a high-speed centrifugal blood recovery tank. The waste liquid, broken cells, and harmful components were then shunted into the waste liquid bag; The blood cells were then washed with physiological saline, purified, and concentrated before being transfused back into the patients immediately after surgery. For patients in the allo-group, blood of the same blood type as the patients was prepared and transfused. The average blood transfusion volume of both groups was approximately 400 mL.

In terms of analgesia, ultrasound-guided bilateral superior inguinal fascial block was used for intraoperative and postoperative analgesia. In cases where required, morphine and non-steroidal anti-inflammatory drugs were administered for pain relief during the perioperative period.

Data acquisition

Baseline characteristics, including age, sex, and body mass index (BMI) were recorded at admission. In this study, the immune function was evaluated through determining NKCC, IL-2, and the changes of CIF levels (CD3+, CD4+) and HIF levels (IgE). The postoperative inflammatory response was measured by WBC, NP and CRP. The indexes were assessed before operation, 1 day and 2 days after blood transfusion.

NKCC assay

The blood was mixed with the same volume of Roswell Park Memorial Institute (RPMI) 1640 medium (Gibco, Invitrogen, CO), placed in a Histipaque-1077 (Sigma, CA) and centrifuged (2000 revolutions per minute for 20 min at 10°C). After that, a layer of peripheral blood mononuclear cells was collected and washed twice with RPMI 1640 and placed in RPMI 1640 containing streptomycin.

NKCC was determined by CytoTox 96 Non-Radioactive Cytotoxicity Assay (Promega Co., WI). LDH was quantitatively determined by this colorimetric method. Peripheral blood mononuclear cells (effector cell, E) and K562 cells (2×10^4 cells/well; targeted cell, T) were mixed at different E:T proportions (10:1 and 5:1) in a 96-well and incubated at 37°C with 5% CO_2 overnight in accordance with the manufacturer's instructions [9]. The NKCC of effector cells was measured with multilabel reader (Victor X5, PerkinElmer) at 490 nm and the calculation method is as follows: NK cell cytotoxicity (%) = (EET-ELDH-TLDH)/(TMAX-TLDH)*100% (EET = experimental LDH release of cocultured effector and target cells, ELDH and TLDH = the spontaneous released LDH of the effector and target cells alone, TMAX = the maximum LDH release of target cells).

IL-2 detection

The absorbance was read at 450 nm using a commercial ELISA Kit (quantikine human IL-2 ELISA kit; R&D System Inc.) and a spectrum Max 190 microplate reader (molecular devices, Sunnyvale, California).

Statistical analysis

The collected data were statistically analyzed by SPSS 20.0 software. All data were displayed as mean ± SD. Furthermore, the normally distributed data were compared by independent sample *t*-test, and the data with skewed distribution were analyzed by Mann Whitney *U*-test. $P < 0.05$ was considered as a statistical difference.

Results

Patients

A total of 60 eligible cases were included as the research subjects. Among them, 30 who

Table 1. Baseline data of patients

	Allo-Group (n = 30)	Auto-Group (n = 30)	*t* value	*P* value
Male	52.3%	56.6%	1.5871	0.2331
Age (yr)	56.2 (6.2)	53.6 (6.4)	1.3788	0.4333
BMI	25.3 (3.5)	25.0 (3.1)	1.1356	0.7825
Daily smoking (N%)	5 (6.67)	8 (5.28)	1.3899	0.4313
Operation time (h)	3.0 (0.3)	3.1 (0.3)	1.2735	0.6735
Blood loss (mL)	1068 (342)	1206 (398)	1.5344	0.2344
Blood transfusion volume (mL)	400 (10)	400 (10)	0.7845	0.9923
Knee-extension strength (nm/kg)	1.2 (0.6)	1.2 (0.5)	0.8956	0.9902
Knee pain during walking (mm)	38 (8.3)	32 (7.6)	1.5012	0.2554
Fluid intake (mL)	1400 (390)	1382 (352)	0.7045	0.9926

Note: Unless otherwise specified, the data provided is the mean (SD). BMI: Body mass index.

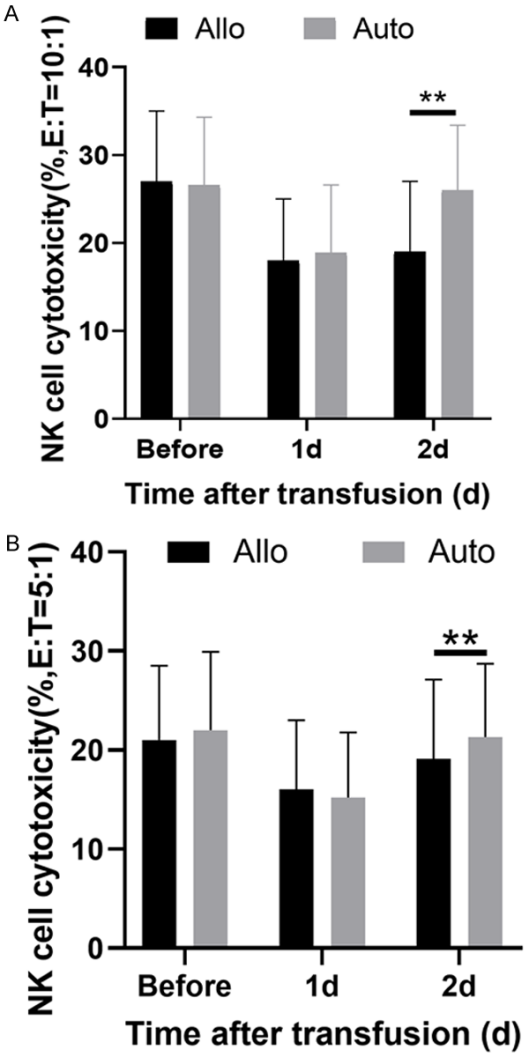

Figure 1. Changes of NKCC before and after blood transfusion (mean ± SD). A. The NKCC (E:T = 10:1) of patients of total hip replacement was detected by ELISA. B. The NKCC (E:T = 5:1) of patients of total hip replacement was detected by ELISA. $P < 0.01$ (**). E: effector cell; T: target cell; NKCC: natural killer cell cytotoxicity.

received allogeneic blood transfusions were included into the allo-group, and the other 30 who received autologous blood transfusions were classified into the auto-group. The baseline data of two groups of patients showed that there was no noteworthy discrepancy between the two groups in terms of gender, age, BMI, length of operation, blood transfusion and blood loss volume (**Table 1**) (all $P > 0.05$).

Immune function assessed by NKCC and IL-2

NKCC in both groups decreased on day 1 after transfusion and partially recovered on day 2 after operation compared to preoperative counts (**Figure 1A**, **1B**). The difference in the changes in NKCC between the two groups on the first day after blood transfusion was not significant ($P > 0.05$), but there was a noteworthy discrepancy on the second day ($P < 0.01$) (**Figure 1A**, **1B**). The level of IL-2 in both groups increased remarkably after blood transfusion and partially recovered but were both higher than the preoperative counts. The differences in changes in IL-2 between the two groups during the perioperative period was not significant ($P > 0.05$) (**Table 2**).

Immune function assessed by CD3+, CD4+ and IgE

We observed that after blood transfusion, CD3+ and CD4+ levels decreased first and then increased and were all lower than preoperative counts (both $P < 0.05$) (**Figure 2A**, **2B**); IgE level first increased and then decreased and were all higher than preoperative counts ($P < 0.05$) (**Figure 2C**). The numerical changes between the two groups on the first day after blood transfusion were not significant. CD3+

Table 2. NKCC and IL-2 level

		Allogeneic (n = 30)	Autologous (n = 30)	*t* value	*P* value
IL-2 (pg/mL)	Preoperative	1.88 (2.13)	1.92 (2.45)	0.8421	0.9912
	1 d after transfusion	3.14 (2.58)*	2.81 (2.11)*	1.1892	0.0718
	2 d after transfusion	3.12 (1.87)*	2.75 (2.23)*	1.2894	0.0626
NKCC (%, E:T = 10:1)	Preoperative	27.4 (8.0)	26.6 (7.9)	0.5869	0.9941
	1 d after transfusion	18.2 (7.1)	18.9 (7.2)	0.7560	0.9922
	2 d after transfusion	19.3 (8.2)	26.1 (7.5)	2.8947	0.0025
NKCC (%, E:T = 5:1)	Preoperative	21.0 (7.5)	22.1 (7.9)	1.3421	0.4591
	1 d after transfusion	16.2 (6.8)	15.3 (6.6)	1.6213	0.1892
	2 d after transfusion	17.3 (7.8)	20.0 (7.4)	2.6211	0.0094

Note: $P < 0.05$ (*), compared with preoperative level. Values are mean (SD). IL-2: Interleukin-2; NKCC: natural killer cell cytotoxicity.

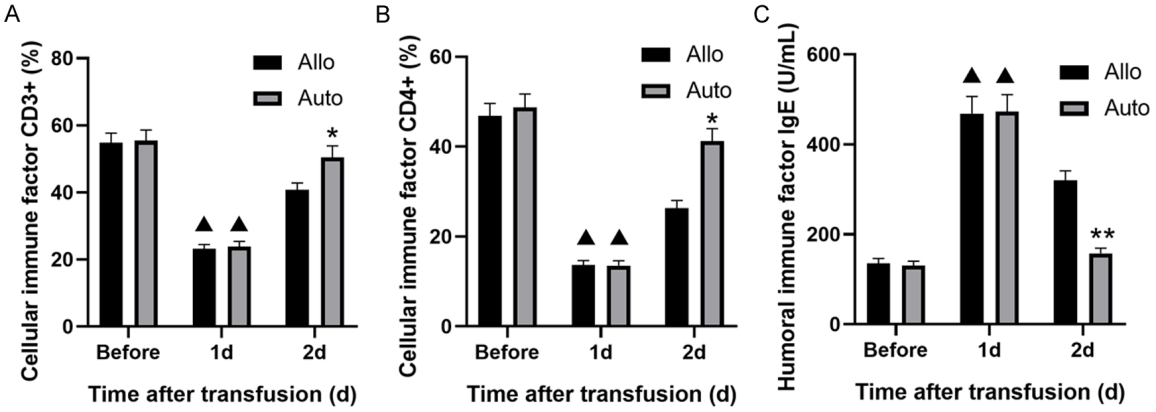

Figure 2. CD3+, CD4+ and IgE levels. A. Cellular immune factor CD3+ of patients after total hip replacement was detected by flow cytometry. B. Cellular immune factor CD4+ of patients after total hip replacement was detected by flow cytometry. C. IgE of patients after total hip replacement was detected by flow cytometry. ▲Compared with preoperative level, $P < 0.05$; $P < 0.05$ (*), $P < 0.01$ (**), compared with allo-group. IgE: Immunoglobulin E.

and CD4+ levels in the auto-group were remarkably higher than those in the allo-group on day 2 after blood transfusion (both $P < 0.05$) (**Figure 2A**, **2B**; **Table 3**), and the levels of IgE on day 2 after blood transfusion were remarkably lower than those in the allo-group ($P < 0.05$) (**Figure 2C**; **Table 3**).

Postoperative inflammatory reaction

WBC, NP and CRP in each group increased compared with the preoperative value. However, there was no noteworthy discrepancy in postoperative inflammatory response assessed by WBC, NP and CRP between the two groups (**Figure 3**; **Table 4**).

Discussion

Osteoarthritis (OA) affects 30% of the population over 65 years old [14]. In sub-Saharan Africa, the prevalence may reach 33% in people over 35 years old [15]. The symptoms of pain, local joint swelling, stiffness and difficulty in activities of daily living seriously affect the quality of life of patients [16]. Studies have reported a high complication rate of OA and hyperuricemia [17-19]. Uric acid may activate the innate immune response of OA and contribute to the progress of the disease [20, 21]. Total hip replacement is the most common surgical intervention for the treatment of hip OA, which has a certain clinical effect. However, the pathological mechanisms of post-operative allograft transfusion induced immune regulation are complex and its application in the perioperative period is controversial [22, 23]. Our results show that autologous blood transfusion is better than allogeneic blood transfusion on the immune function of patients after total hip replacement. There were significant differenc-

Table 3. CD3+, CD4+ and IgE levels

	Allogeneic (n = 30)			Autologous (n = 30)			*t* value	*P* value
	Preoperative	1 d After	2 d After	Preoperative	1 d After	2 d After	2 d After	2 d After
CD3+ (%)	54.8 (2.9)	23.2 (1.3)▲	40.8 (2.0)	55.4 (3.2)	23.8 (1.6)▲	50.5 (3.4)	2.1025	0.0233
CD4+ (%)	46.9 (2.7)	13.7 (1.0)▲	26.3 (1.7)	48.7 (3.0)	13.5 (1.0)▲	41.2 (2.8)	2.2311	0.0122
IgE (U/mL)	135.7 (10.5)	468.9 (37.9)▲	319.8 (21.4)	130.5 (9.8)	473.2 (37.6)▲	157.8 (11.5)	2.7491	0.0064

Note: ▲Compared with preoperative, $P < 0.05$; the *P* value in table indicates the comparison with allo-group at day 2. IgE: Immunoglobulin E.

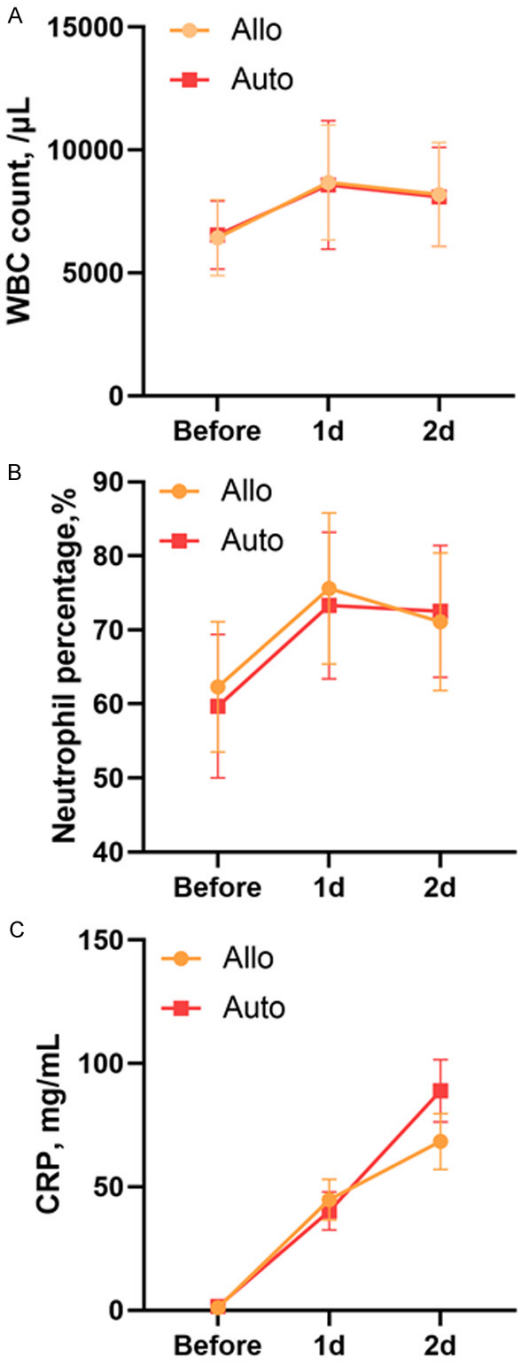

Figure 3. Changes of WBC, NP and CRP before and after blood transfusion. WBC: White blood cell; NP: neutrophil percentage; CRP: C-reactive protein.

es in the expression levels of NKCC, CD3+, CD4+ and IgE between the two blood transfusion methods two days after operation.

Natural killer (NK) cells are crucial immune cells in the human body. They are not only associated with anti-tumor, anti-virus infection and immune regulation but also involved in allergy and autoimmune diseases in some cases and can discern target cells and killing media. Different from T and B cells, NK cells are a sort of lymphocyte that can nonspecifically kill tumor cells and virus-infected cells without pre-sensitization [24-27]. In addition, NK cell responses are not static, but adapt to their environment. Recent studies have revealed that NK cells can also install an antigen-specific immune memory. Therefore, NK cells play complex biological functions that are properties of innate and adaptive immunity [28, 29]. The immune system of patients undergoing surgery is affected by anesthesia and surgical trauma. After using volatile anesthetics and opioids, immune response changes including NK cell activity can be discovered [30, 31]. IL-2 can positively regulate the activation and differentiation of NK cells. The addition of these cytokines can remarkably enhance the killing activity of NK cells *in vitro*. NK cells have affinity receptors for IL-2 on the surface. Furthermore, IL-2 can promote NK killing activity [32-34]. A study [35] by So Yeon Kim and colleagues showed that there was no difference in postoperative levels of NKCC and IL-2 between the opioid and ON-Q groups when their pain control effects were similar. The incidence of postoperative complications and recurrence or metastasis within 1 year after surgery was comparable between the two groups. The postoperative inflammatory reactions were also similar between the two groups. A study [36] by Jin Sun Cho and colleagues showed that compared to sevoflurane anesthesia and postoperative fentanyl analgesia, propofol anesthesia combined with ketorolac postoperative analgesia had a favorable effect on the immune function of can-

Table 4. Changes of WBC count, NP and CRP before and after blood transfusion

		Allogeneic (n = 30)	Autologous (n = 30)	*t* value	*P* value
WBC (/μL)	Preoperative	6433 (1544)	6544 (1387)	0.7212	0.9924
	1 d After	8681 (2341)*	8577 (2611)*	0.6147	0.9934
	2 d After	8189 (2115)*	8091 (2013)*	0.8425	0.9911
Neutrophil percentage (%)	Preoperative	62.3 (8.8)	59.7 (9.7)	0.1213	0.9998
	1 d After	75.6 (10.2)*	73.3 (9.9)*	0.4165	0.9956
	2 d After	71.1 (9.3)*	72.5 (8.9)*	0.5837	0.9943
CRP (mg/L)	Preoperative	1.1 (0.23)	1.5 (0.30)	0.2892	0.9972
	1 d After	44.8 (8.21)*	40.2 (7.68)*	0.1042	0.9994
	2 d After	68.4 (11.3)*	88.9 (12.6)*	0.8956	0.9902

Note: $P < 0.05$ (*), compared with preoperative level. Values are mean (SD). WBC: White blood cell; NP: neutrophil percentage; CRP: C-reactive protein.

cer surgery patients by preserving NKCC. In our study, NKCC decreased while IL-2 increased remarkably in both groups after operation. Moreover, there were remarkable differences in NKCC between the two groups two days after transfusion, suggesting that allogeneic transfusion can cause short-term cell-mediated immunosuppression and induce various immune cells and cytokines to participate in complications compared with autotransfusion.

Effective immune response depends largely on the activation of T lymphocytes and B lymphocytes. Various cytokines secreted by activated T lymphocytes participate in immune regulation. The decrease in CD3+ and CD4+ T lymphocyte subpopulations observed after allogeneic blood transfusion may be mediated by leukocyte antigens and plasma components [37, 38]. Patients who reported cancer recurrence and metastasis had lower T cell counts than other study subjects [39, 40]. Therefore, we believe that a decrease in the CD3+ and CD4+ T cells may have adverse effects on immune function. We checked the serum concentration of perioperative T lymphocyte subsets (CD3+, CD4+) and investigated the level of humoral immune factor (Immunoglobulin E, IgE) to further evaluate the effect of autologous and allogeneic blood transfusion on the immune status of patients. Our study showed that the levels of CD3+ and CD4+ cells in the allo-group were remarkably lower than auto-group, and the level of IgE was remarkably higher than auto-group two days after transfusion. This further indicates that compared with allogeneic blood transfusion, autologous blood transfusion can better improve the immune status of patients and improve their quality of life.

This research has some limitations. Above all, we only analyzed the short-term data. The patients were not followed up within half a year after the transfusion. Although there was no dramatic difference in short-term postoperative inflammatory response between the two groups, further studies to evaluate long-term outcomes are needed. Secondly, we cannot rule out the possibility of the impact of postoperative personal care on immune response, because their sleep, diet and psychological status were not strictly controlled within two days after transfusion.

Generally speaking, our study shows that autologous blood transfusion is superior to allogeneic blood transfusion on the immune function of patients after total hip replacement. Contrary to the expectation is that the short-term postoperative inflammatory response was similar for both modalities.

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Disclosure of conflict of interest

None.

Abbreviations

OA, Osteoarthritis; NKCC, natural killer cell cytotoxicity; CD, differentiation cluster of differentiation; IgE, Immunoglobulin E; IL-2, interleukin-2; WBC, white blood cell; CRP, C-reactive protein; CO_2, carbon dioxide; LDH, lactate dehydrogenase; Allo-group, allogeneic transfusion group; Auto-group, autotransfusion group; CIF,

cellular immune factor; HIF, humoral immune factor; NP, neutrophil percentage.

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