Platelet-rich plasma prevents blood loss and pain and enhances early functional outcome after total knee arthroplasty: a prospective randomised controlled study

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Abstract

Purpose The purpose of this study was to determine whether platelet-rich plasma (PRP) might prevent blood loss and postoperative pain and expedite wound healing following total knee arthroplasty (TKA).

Methods Forty consecutive patients with knee arthritis who were matched for age, sex and body mass index (BMI) were randomly allocated to either receive or not receive PRP application over the wound, including capsule, medial and lateral recesses, during TKA. Postoperative haemoglobin, blood loss, blood transfusion, visual analogue scale (VAS) score, wound score, Knee Society Score (KSS) and Western Ontario and McMaster Osteoarthritis Index (WOMAC) score were recorded and evaluated.

Results The platelet-rich plasma and control groups comprised 17 and 23 patients, respectively. The PRP group recorded significantly less reduction in haemoglobin and need for blood transfusion ($p=0.00$ and $p=0.001$, respectively), experienced less pain ($p=0.00$) and required fewer narcotics than the control ($p=0.00$). There was significant difference in range of motion (ROM) at three months ($p=0.01$), no significant difference in wound scores ($p=0.311$) and significant difference in KSS and WOMAC scores at 12 weeks ($p=0.00$, 0.00). However no significant difference was found at six months.

Conclusions PRP has significant effect in preventing blood loss, postoperative pain and need for narcotics after TKA and has a positive effect on short-term clinical outcome.

Keywords Osteoarthritis · Total knee arthroplasty · Autologous platelet-rich plasma · Blood loss · Pain · Functional outcome

Introduction

Total knee arthroplasty (TKA) is performed to reduce pain, correct deformity and restore function in the arthritic knee [1]. Patients demand a speedy recovery, earlier hospital discharge and reduced hospital cost after TKA [2]. Consequently, there is greater motivation to ensure rapid postoperative recovery. Despite technical improvements in implant materials, surgical approaches and the use of navigation systems, concern remains with regard to blood loss, pain and wound healing postoperatively. A significant amount of postoperative blood loss occurs following TKA, which contributes to impaired outcome due to the development of wound haematoma, postoperative pain, seroma formation and arthrofibrosis [3]. Many strategies, such as the use of tranexamic acid, have been used to reduce postoperative blood loss and the subsequent need of allogenic blood transfusion [4, 5]. Recently, platelet-rich plasma (PRP) has been reported to be useful in improving the biological milieu at the repair site of the wound [6]. Autologous platelet gel (APG) is a biological delivery system of a complex mixture of bioactive proteins essential to natural repair. Scanty literature is available on the use of PRP during TKA [7, 8]. Gardner et al. [7], in a retrospective study, reported the efficacy of PRP on blood loss and pain after TKA. To the best of our knowledge, prospective randomised controlled studies on the effect of PRP in TKA are not available in the literature. Hence, this study was designed to

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evaluate the efficacy of leucocyte-free autologous PRP on blood loss, pain, wound healing and functional outcome after TKA. We postulated that application of PRP would help reduce blood loss and postoperative pain and expedite wound healing, providing better short-term functional outcome following TKA.

Patients and methods

In a prospective randomised controlled double-blind clinical trial from January 2010 to June 2011, 40 consecutive patients with knee arthritis who had similar deformity and preoperative range of motion (ROM), matched for age, sex and body mass index (BMI), were recruited. The study was approved by the institutional ethics committee and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All patients provided written informed consent prior to their inclusion in the study. The study was registered in the ClinicalTrials.gov registry (NCT01563380). Post hoc power analysis was conducted to define the smallest difference detectable, i.e. reduction of blood loss by at least 1.0 g/dl after use of platelet concentrate during TKA, keeping the study power $\geq 80\%$ (type II error < 0.20) and bilateral alpha 0.05. Based on power analysis, a minimum of 15 patients was required in each group to show a significant difference ($\alpha = 0.05$, $\beta = 0.8$, $2n = 30$). Inclusion criteria were patient of either sex who underwent primary unilateral or bilateral surgery or the first surgery of a staged bilateral total knee replacement (TKR) where the second stage was at least six weeks later, and those willing and able to return for follow-up over at least a six-month postoperative period. Patients with preoperative haemoglobin below 10 g/dl and with bleeding disorder were excluded from the study. Patient demographic data was recorded. All routine investigations were carried out and the results noted. Preoperative haemoglobin, ROM, Western Ontario and McMaster Osteoarthritis Index (WOMAC) scores [9] and Knee Society Scores (KSS) [10] were noted. Patients were randomly allocated to the platelet gel group or the control group using opaque envelopes opened on the day of surgery. The intervention group comprised 17 patients; 23 patients served as controls. All operations were performed by the same surgeon (AKA).

PRP was prepared from 50 ml of the patient's blood, centrifuged for 15 minutes at 1,500 rpm on a table-top centrifuge, extracted, passed through a leucocyte filter (Imugard III-PL, Terumo Penpol Co) and 8 ml of PRP was used in each knee. The entire procedure was done under complete aseptic precautions. The calcium chloride required for activation was given in a separate syringe in a ratio of 4:1. To confirm sterility, PRP culture and sensitivity was performed.

All the operations were performed under regional spinal/epidural anaesthesia. The patient was placed in a supine

position. A pneumatic tourniquet was applied. A medial parapatellar approach to the knee was used, and the patella was everted. A cruciate-sacrificing cemented prosthesis was used. After prosthesis cementing, the tourniquet was deflated, lavage was given with saline and the wound was dried. Tranexamic acid was not used. PRP and calcium chloride were injected into the posterior recess, gutters and capsule in a ratio of 4:1. No suction drain was used. The remaining platelet gel was infiltrated into the repaired extensor mechanism and prepatellar fat. In bilateral TKA cases, both knees received PRP. Postoperatively, the knee was immobilised in bulky dressings for 24 hours. Blood transfusion was given if necessary due to intraoperative blood loss, which was assessed by measuring haematocrit or if postoperative haemoglobin was below 8 g/dl.

The standard postoperative treatment protocol was followed in both APG and control groups. All patients were given two intravenously administered antibiotics: cefoperazone 1.5 g 12 hourly and amikacin 1 g 24 hourly. The antibiotics were started 12 hours prior to surgery and given for three days. Antithrombotic prophylaxis with aspirin administered orally (150 mg one day before surgery and 150 mg daily through the tenth postoperative day) was provided. Analgesia protocol consisted of fixed dosage of 75 mg diclofenac injections given twice daily for three days and narcotic analgesic in the form of pentazocine injections given on demand. Pain was measured daily using the visual analogue scale (VAS), which consisted of markings from 1 to 10. The number of narcotic (pentazocine) injections given was also noted. Haemoglobin was measured on the day of surgery and postoperative day three by a Sysmex automated analyser. The number of blood units transfused was also recorded. Postoperative wound dressing was done on day three, or earlier in the case of soakage. The wound was assessed using a wound-score form. Similar physiotherapy was advised for both groups. All patients were advised to begin isometric quadriceps and ankle pumping exercises on postoperative day 0 (POD0). Patients with less pain did the exercises on POD0 only and then began ROM exercises and straight-leg raising on POD1. Patients with decreased pain and who were comfortable were ambulating with the help of a walker on POD2. ROM was recorded five days, six weeks, 12 weeks and six months postoperatively by an independent observer (SVS). Similarly, WOMAC scores and KSS were noted, as shown in the outcome evaluation. Unilateral and bilateral TKR cases were grouped separately and analysed.

Statistical analysis

Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA, version 15.0) was used to analyse data. All quantitative variables were estimated using measures of central location (mean, median) and dispersion [standard deviation

Table 1 Preoperative demographic data in bilateral and unilateral total knee arthroplasty (TKA) with statistical analysis

Description	Bilateral TKA		<i>P</i> value	Unilateral TKA		<i>P</i> value
	APG (<i>n</i> =10)	Control (<i>n</i> =9)		APG (<i>n</i> =7)	Control (<i>n</i> =14)	
Age	57.10±10.04	62.89.10±7.88	0.184	56.43±7.59	53.79±9.75	0.539
BMI	27.02±2.11	27.23±2.40	0.840	27.47±2.15	26.52±2.99	0.465
Hb	11.88±1.23	11.86±0.53	0.976	12.06±1.46	12.84±1.47	0.265
Mean VAS	6.55±1.36	7.39±1.09	0.044	6.43±1.13	7.36±1.28	0.120
ROM	76.3±8.7	76.9±7.3	0.793	85.7±13.0	76.8±9.7	0.092
KSS	80.05±8.83	82.11±9.42	0.491	89.71±12.23	80.14±12.93	0.120
WOMAC	71.30±4.75	71.50±6.21	0.911	69.00±6.27	68.50±7.90	0.886
Platelet count (PRP in millions)	334.00±129.58	—		257.71±104.11	—	

BMI body mass index, *Hb* haemoglobin, *VAS* visual analogue scale, *ROM* range of motion, *KSS* Knee Society Score, *WOMAC* Western Ontario and McMaster Osteoarthritis Index, *PRP* platelet-rich plasma, *APG* autologous platelet gel

(SD) and standard error (SE)]. Normality of data was checked by measures of skewness and Kolmogorov–Smirnov tests. For normally distributed data, means were compared using Student's *t* test for two groups. For more than two groups, analysis of variance (ANOVA) was applied. For skewed data, Mann–Whitney *U* test was applied. All statistical tests were two sided and performed at a significance level of $\alpha=0.05$. The interobserver reliability and intraobserver reproducibility were analysed by Kappa (κ) coefficient.

Results

Various observations and results are presented in Tables 1 and 2. Among 40 patients (59 knees), 17 (27) were included in the APG group and 23 (32) served as controls. Ten patients in the APG group and nine in the control group underwent bilateral TKA (*P* 0.218); seven patients in the APG group and 14 in the control group had unilateral TKA.

Table 2 Comparative results of various primary and secondary outcome measures in bilateral and unilateral total knee arthroplasty (TKA) with statistical analysis

Description	Bilateral TKA		<i>P</i> value	Unilateral TKA		<i>P</i> value
	APG (<i>n</i> =10)	Control (<i>n</i> =9)		APG (<i>n</i> =7)	Control (<i>n</i> =14)	
POD0 Hb	9.60±1.57	8.68±1.04	0.153	11.03±1.43	11.51±1.50	0.493
POD3 Hb	9.62±0.97	7.60±0.42	0.00	10.49±1.42	9.72±1.35	0.024
Blood units transfused	1.00±0.67	2.22±0.44	0.00	0.00±0.00	0.93±0.26	0.00
VAS 6 weeks	2.70±0.57	4.06±0.94	0.00	2.57±0.54	3.57±1.09	0.01
VAS 12 weeks	1.60±0.59	2.33±0.49	0.00	1.57±0.54	2.29±0.91	0.03
Narcotics	14.90±2.03	22.44±3.39	0.00	15.71±2.69	22.79±3.07	0.00
ROM POD5	79.3±3.4	72.2±3.5	0.00	80.0±4.1	76.8±5.0	0.00
ROM 6 weeks	95.5±3.9	85.0±4.5	0.00	97.9±2.7	89.6±4.9	0.00
ROM 12 weeks	97.3±2.5	92.8±4.3	0.01	98.6±2.4	95.4±4.1	0.01
Wound score	30.0±12.1	36.3±12.5	0.121	33.7±12.7	33.1±12.9	0.915
KSS 6 weeks	158.90±3.09	149.17±7.52	0.00	159.14±3.24	148.79±9.23	0.00
KSS 3 months	167.00±2.84	161.33±5.18	0.00	167.00±1.73	161.85±5.87	0.01
KSS 6 months	178.25±2.45	177.28±3.70	0.340	178.57±1.81	177.36±5.26	0.447
WOMAC 6 weeks	17.20±2.31	22.61±3.47	0.00	17.57±2.23	23.21±4.49	0.00
WOMAC 3 months	11.05±1.43	14.61±2.73	0.00	10.14±1.22	14.21±3.02	0.00
WOMAC 6 months	7.70±0.98	8.17±1.65	0.291	7.14±0.69	7.86±1.23	0.173

POD postoperative day, Hb haemoglobin, VAS visual analogue scale, *BMI* body mass index, *Hb* haemoglobin, *ROM* range of motion, *KSS* Knee Society Score, *WOMAC* Western Ontario and McMaster Osteoarthritis Index, *APG* autologous platelet gel

Fig. 1 **a** Greater decrease in haemoglobin (Hb) postoperatively following unilateral total knee replacement (TKR) in the autologous platelet gel (APG) and control groups; this difference was statistically significant ($p=0.00$). **b** Greater decrease in Hb postoperatively following bilateral TKR in APG and control groups; this difference was statistically significant ($p=0.00$)

Postoperative decrease in Hb, amount of blood transfused, reduction in pain, number of narcotics required, wound scores, ROM, KSS and WOMAC scores are shown in Tables 1 and 2 and Figs. 1, 2, 3, 4 and 5. Hospital stay in the APG/control groups was between four and eight (mean 5.2)/six to 11 (mean 7.9) days.

Discussion

TKA is associated with significant intraoperative and postoperative blood loss [11–13]. The important complications

that lead to significant perioperative morbidity are blood loss, pain, infection, wound complications, stiffness and deep vein thrombosis [11, 12]. Most surgeons are accustomed to using a tourniquet intraoperatively to achieve a bloodless surgical field. This practice increases the hidden blood loss by extravasation of blood into the tissues, residual blood left in the joint space and blood loss due to haemolysis [11, 14]. Thus, patients frequently have lower postoperative haemoglobin, which delays functional recovery after arthroplasty [15]. Postoperative blood transfusion is fraught with risks of serious complications [15]. A few

Fig. 2 Number of blood units transfusion in autologous platelet gel (APG) and control groups; this difference was statistically significant ($p=0.00$)

studies have found tranexamic acid useful in TKR when used intravenously or intra-articularly [4, 5].

Recently, PRP has been used to reduce blood loss in TKA. Few studies have been reported on the use of autologous platelet gel in TKA [7, 8, 14, 16, 17]. PRP releases thromboxane A2, thrombin, adenosine diphosphate and several growth factors, which in turn attract more platelets to the wound site. These large numbers of platelets form a platelet plug, augment the inflammatory cascade and result in haemostasis [7, 8, 14, 16–19]. In our study, APG group patients had a lesser decrease in Hb and a lower rate of blood transfusion compared with the control group. The difference in pre-operative and postoperative day three Hb between the APG and control groups, respectively, was 1.97 and 3.56. There was a 12.15 % lesser decrease in Hb in cases than controls, which was statistically significant ($p=0.00$). Bilateral TKA resulted in a smaller decrease in Hb (preoperative POD3) compared with the control group (2.26/4.27), which was statistically significant ($p=0.00$). Unilateral TKA also had a smaller decrease in Hb (preoperative POD3) compared with the control group, which was statistically significant ($p=0.00$). Though there was a greater decrease of Hb in bilateral compared with unilateral TKR, similarly matched controls demonstrated greater reduction in Hb compared with the APG group, which was statistically significant. These results are similar to those reported by Gardner et al. [7], Berghoff et al. [8] and Everts et al. [14]. However, Horstmann et al. [17] and Peerbooms et al. [16] found no statistically significant difference in the decrease in Hb. APG group patients (0.59 U) required 58.74 % less blood transfusion than controls (1.43 U) ($p=0.00$). In bilateral cases, the comparative amount of blood transfused (control/APG) was 2.22 U/1.00 U ($p=0.00$), whereas in unilateral cases, the comparative amount of blood transfused (control/APG) was 0.93 U/0.00 U ($p=0.00$) (Table 2). There was a statistically significant difference in the amount of blood transfused in APG versus control groups. These results were similar to those reported by Berghoff et al.

[8] (0.39/0.7; $p=0.03$) and Everts et al. [14] (0.17/0.52; $p=0.001$). Gardner et al. [7] and Peerbooms et al. [16], however, did not mention the amount of blood transfusion required. In the study by Horstmann et al. [17], allogenic blood transfusions were not given in either group. In our study, no suction drains were used, as they might have drained platelets and growth factors released from the PRP gel.

APG group patients experienced less pain (11.65 %, 30.47 %, and 30.3 %) than controls in the immediate postoperative period, at six weeks and at three months, respectively. Horstmann et al. [17] observed significantly less pain at rest in the APG group on the third postoperative day ($p=0.04$), but pain scores during exercise were not statistically significant between groups. Peerbooms et al. [16] found no significant difference in pain scores. In our study, APG group patients used fewer narcotics (15.24) compared with control group patients (22.65). This difference was statistically significant ($p=0.00$). In bilateral cases, comparative use of narcotics (APG/control) was 14.90/22.44 ($p=0.00$); in unilateral cases, comparative use (APG/control) was 15.71/22.79 ($p=0.00$) (Fig. 3a, b). Berghoff et al. [8] and Peerbooms et al. [16] found no significant difference ($p=0.2$ and 0.9, respectively) in the use of pain medication between control and intervention groups. APG provides pain relief possibly by accelerating haemostasis, augmenting the healing cascade and resulting in lesser haemarthroses [7, 8, 14, 16–19]. It decreases the need for postoperative narcotic use and reduces the incidence of side effects caused by such narcotic use [7, 8, 14, 16–19].

Reports of infection rates after TKA vary from 0.5 to 12 % [20]. Wound complications after TKA increase the cost and length of hospitalisation, readmission rates, additional surgeries and risk of deep infection [12, 20]. Platelets accelerate wound repair by releasing locally acting growth factors, such as platelet-derived growth factor, transforming growth factor- β , platelet factor-4, interleukin-1, platelet-derived angiogenesis factor,

Fig. 3 a Significantly reduced numbers of narcotic doses during hospital stay following unilateral total knee replacement (TKR) in autologous platelet gel (APG) versus control groups. **b** Significantly reduced numbers of narcotic doses during hospital stay following bilateral TKR in APG versus control groups

vascular endothelial growth factor and epidermal growth factor via α -granule degranulation. In our study, wound healing was assessed using the wound score form [16]. Though the APG group had lower wound scores (30.96/34.91), there was no significant difference between groups ($p=0.227$). Except for one patient in the control group, none of the patients had deep infection. Even Peerbooms et al. [16] and Horstmann et al. [17] observed similar results and found no difference in wound healing between groups ($p=0.4$, $p>0.05$, respectively).

Stiffness and limited ROM is a disabling complication [21]. We observed that APG group patients had earlier increased ROM than the control group on POD5 and at six and 12 weeks. This difference was statistically significant ($p=0.00$, 0.00 , 0.00 , respectively). There was no significant intraobserver and interobserver variability ($p>0.05$). APG group patients had 7.03 %, 10.43 % and 3.94 % more ROM than controls on POD5 and at six and 12 weeks, respectively. Berghoff et al. [8] found no significant difference in ROM on POD3, but the APG group had higher ROM at six weeks

Fig. 4 Mean Knee Society Score (KSS) and trend of autologous platelet gel (APG) and control groups at subsequent follow-ups. There was significant difference between groups at 6 weeks and 3 months ($p=0.00$, 0.00) but it was insignificant at 6 months ($p=0.285$)

compared with controls ($p=0.009$). Peerbooms et al. [16] and Horstmann et al. [17] found no significant difference in ROM between groups ($p=0.9$, $p>0.05$). Hence, this may explain the absence of any difference between groups (Table 3).

Patients in the APG group had earlier improvement in physical function and quality of life. There was a significant difference in functional outcome as assessed by KSS scores at six and 12 weeks ($p=0.00$, $p=0.00$), respectively. There was no difference in KSS scores between groups at six months ($p=0.285$). To our knowledge, such results have not been reported in the literature.

There was a significant difference in WOMAC scores at six and 12 weeks ($p=0.00$, $p=0.00$), respectively. The APG group had 24.39 % and 24.79 % lower WOMAC scores than the control group at six and 12 weeks, respectively, indicating early functional recovery. There was no difference in WOMAC scores between groups at six months ($p=0.193$). Only Peerbooms et al. [16] reported no significant difference in WOMAC scores ($p=0.7$).

Of the five studies published, two were retrospective. In the Horstmann et al. [17] study, sample size and follow-up time were small, and the authors used a postoperative drain, which would have drained platelets, thus affecting the results. Peerbooms et al. [16] had incomplete data for their patients. We used a leucocyte filter to procure leucocyte-free PRP, with the average number of platelets injected being three billion. The presence of leukocytes in PRP increases inflammation and pain after PRP injection [18, 19, 22]. None of the authors of the other five studies used leucocyte-free PRP. APG contains high levels of platelets (four to seven times baseline), the full complement of clotting factors, secretory proteins and growth factor. Due to the increased concentration and release of these factors, APG enhances recruitment and proliferation of tenocytes, stem cells and endothelial cells.

The strengths of our study are as follows: we compared results in 40 consecutive patients (59 knees) operated upon by a single surgeon in a single institute in a placebo-controlled study, which minimised confounding factors; patients were randomly allocated to one of the two groups; the process of

Fig. 5 Mean Western Ontario and McMaster Osteoarthritis Index (WOMAC) scores and trend of autologous platelet gel (APG) and control groups at follow-ups. There was significant difference between groups at 6 weeks and 3 months ($p=0.00$, 0.00) but it was insignificant at 6 months ($p=0.193$)

Table 3 Comparison of various studies

Study	Decrease in Hb (control/case)	No. of blood units transfused	Pain at 6 weeks	No. of narcotic doses	ROM at 6 weeks	KSS (control/case)		WOMAC (control/case)	
						6 weeks	12 weeks	6 weeks	12 weeks
Gardner et al. [5]	3.16/2.68 (day 3) ($p=0.026$)	NA	NA	36.3/17.0 $p=0.063$	ROM at discharge 71.9/78.2 ($p=0.05$)	NA	NA	NA	NA
Berghoff et al. [6]	1.8/1.37 (day 2) ($p=0.007$)	0.7/0.39 ($p=0.03$)	NA	61.5/52.4 $p=0.207$	105/110 $p=0.000$	NA	NA	NA	NA
Everts et al. [12] (PG + fibrin sealant)	5.2/2.5 ($p=0.001$)	0.52/0.17	NA	NA	66.1/82.4 ($p=0.001$)	NA	NA	NA	NA
Peerbooms et al. [14]	1.58/1.75 ($p=0.2$)	NA	2/2 ($p=0.08$)	2/2 ($p=0.5$)	100/99 ($p=0.9$)	NA	NA	24/26 ($p=0.7$)	21/25 ($p=0.4$)
Horstmann et al. [15]	2.5/2.4 ($p>0.05$)	NA	NA	NA	NA	NA	NA	NA	NA
Our study	3.56/1.97 ($p=0.00$)	1.43/0.59 ($p=0.00$)	3.8/2.6 ($p=0.00$)	22.65/15.24 ($p=0.00$)	87.1/96.1 ($p=0.00$)	149/159 $p=0.00$	161/167 ($p=0.00$)	23/17.3 $p=0.00$	14.4/10.8 ($p=0.00$)

NA not available, PG platelet gel, ROM range of motion, KSS Knee Society Score, WOMAC Western Ontario and McMaster Osteoarthritis Index

randomisation was concealed; patients, examiners and analysers all were blinded throughout the study period; no patients were lost to follow-up. We used leucocyte-free PRP, for which there was no extra cost involved. The only limitation was a relatively small sample size.

Conclusion

We found significant reduction in blood loss, postoperative pain and need for narcotic use after application of APG in patients undergoing TKA, but wound healing was statistically insignificant. Achievement of earlier and greater ROM and quicker and better functional outcome were observed in the APG group. However, at six months and later follow-up, both groups had similar functional scores. We recommend local application of PRP during TKA to reduce blood loss and pain.

Conflict of interest None.

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