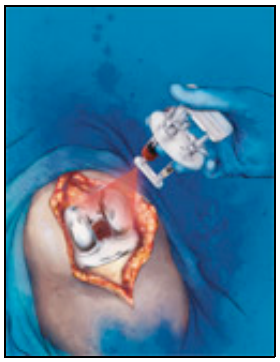
Platelet-Rich Plasma Application During Closure Following Total Knee Arthroplasty

By William J. Berghoff, MD; William S. Pietrzak, PhD; Richard D. Rhodes, MD
ORTHOPEDICS 2006; 29:590

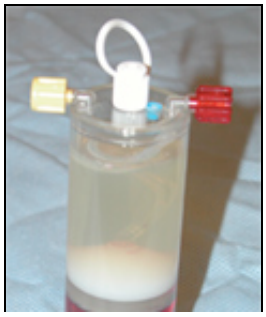
July 2006

Platelet treatment appears to improve several short-term outcomes following total knee arthroplasty.



Total knee arthroplasty (TKA) is one of the most common orthopedic procedures performed, restoring function and reducing pain in the arthritic knee.[1] In general, results are excellent with reported survival rates as high as 90%-95% at 10-15 year follow-up.[2] Complications are infrequent, with reoperations occurring in approximately 1% of patients per year.[3] With an aging population, elective TKA rates are steadily increasing. In addition, there is a trend toward earlier hospital discharge during a more acute phase of recovery in an effort to reduce hospital costs.[4,5] Consequently, there is great motivation for ensuring expedient postoperative recovery.

Postoperative wound healing is mediated by signaling proteins such as growth factors and cytokines. These messengers direct cellular chemotaxis, proliferation, and differentiation, resulting in the formation of extracellular matrix and the establishment of the appropriate environment for site-specific tissue regeneration, eg, skin, cartilage, fibrous tissue, bone, etc.[6,7] Platelets play a fundamental role in the process through their participation in hemostasis as well as their secretion, on activation, of various growth factors and cytokines that set the pace of wound healing.[8-12] Anticoagulated autologous blood drawn preoperatively may be processed to yield platelet-rich plasma, containing a platelet concentration in excess of baseline.[10,13-16] Platelet-rich plasma, activated to a gel with thrombin and calcium chloride, may be placed at the wound site to enhance healing and also act as a hemostatic agent.[9,11,12,17-21] A byproduct of platelet-rich plasma production is platelet-poor plasma, which, when activated in a similar manner as platelet-rich plasma, can be used as a hemostatic agent.[22] Several commercial systems are available that collectively use from one unit of blood to as little as ≤45-60 mL, producing approximately 10% by volume of platelet-rich plasma with a platelet concentration ratio of 2-8x above baseline.[10,11,13] Clinical use of platelet-rich plasma is most commonly reported in the periodontal and oral surgery literature,[20,21,23-29] but other areas of application include maxillofacial,[29] cosmetic and plastic surgery,[9,19,30] spinal fusion,[31-33] heart bypass,[17] and the treatment of chronic skin and soft-tissue ulcers.[34,35]



Use of platelet-rich plasma and fibrin sealant during TKA procedures has been reported. Mooar et al[36] performed a controlled study of platelet-rich plasma use in TKA, finding that the group receiving platelet-rich plasma required significantly less narcotics, achieved a higher functional range of motion (ROM) two days earlier, and had a lower postoperative decrease in hemoglobin than the control population.

Levy et al[37] studied the effects of a commercially available fibrin sealant used prior to closure following TKA on the need for blood transfusion afterward. The treatment group had less hemoglobin decrease and required less transfused blood than the control group. While these studies demonstrated benefit of the use of platelet-rich plasma and/or fibrin sealants in the immediate postoperative period, the outcomes reported were limited

in scope and follow-up was limited to a few days.

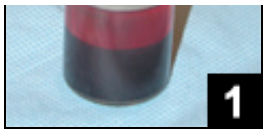


Figure 1: Gravitational Platelet System tube with blood after centrifugation, showing stratification of platelet-poor plasma (top), platelet-rich plasma (middle), and packed red blood cells (bottom).

Despite widespread clinical use and the general consensus by most investigators that platelet-rich plasma application enhances healing, conclusive evidence of a positive effect has been hampered by at least two issues.[10,11,19,25,27,31,38-40] First, many clinical studies lack controls. Therefore, despite excellent outcomes, it is difficult to reach a conclusion regarding platelet-rich plasma influence. Second, platelet product characteristics such as count, premature activation, and maintenance of viability during processing, all of which can influence the biological effect of platelet-rich plasma, often are unknown.[22] One platelet concentration system that has been well characterized is the GPS Gravitational Platelet System (Biomet Biologics, Warsaw, Ind).[10,15] The platelet concentration in the platelet-rich plasma produced by this system was approximately eightfold greater than baseline, which is in the upper range of fold-increase cited by others.[10,11,13] Also, with this system platelets remained intact and were not prematurely activated during processing. On activation, growth factors released included transforming growth factor- 1 (TGF- 1), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and endothelial growth factor (EGF).[10]

We hypothesized that application of autologous platelet-rich and platelet-poor plasma, produced from a well-characterized system, would result in a significant enhancement of short-term (6-week) outcomes following TKA.

Materials and Methods

Study Design

This was a retrospective study, with data gathered through chart review. Patients were included if they had a primary diagnosis of osteoarthritis and no prior history of TKA. Both the control population (66 patients, 72 knees) and the treatment population (71 patients, 81 knees) received unilateral or bilateral TKA, the latter group also receiving platelet-rich and platelet-poor plasma during wound closure. Outcome data was gathered for six postoperative weeks, and the results obtained from the two groups were compared.

Procedural Details

Preoperatively, patients were counseled on the risks and benefits of TKA and platelet-rich/platelet-poor plasma application. Following spinal or general anesthesia, patients received unilateral or bilateral cemented, non-constrained, cruciate-retaining, primary knee prostheses (Richards Genesis II; Smith & Nephew, Memphis, Tenn), (Biomet Maxim; Biomet, Warsaw, Ind), or (Zimmer NexGen; Zimmer, Warsaw, Ind) through a medial parapatellar approach using intramedullary guides to make the osteotomies. All procedures were performed with use of a tourniquet to minimize bleeding. Patients in the treatment group received platelet-rich plasma and platelet-poor plasma during wound closure, while those in the control group did not. All surgeries were performed by the senior author (W.J.B.).

There were 71 patients (81 knees) in the treatment group and 66 patients (72 knees) in the control group. The surgery dates for control patients ranged from March 2002 to December 2002 while the dates for platelet-treated patients ranged from January 2003 to October 2003. Preoperative comparisons of these populations included age, gender, body mass index, preoperative ROM, and the presence of comorbidities (particularly rheumatoid arthritis, diabetes mellitus, kidney failure, and cardiovascular disease).

For patients in the treatment group, 55 mL of venous blood was drawn preoperatively and mixed with 5 mL of acid-citrate-dextrose-A (ACD-A) anticoagulant in a 60-mL syringe. The syringe contents were then transferred to the processing tube of the GPS Gravitational Platelet System. Following the manufacturer's instructions, the tube, appropriately counterbalanced, was placed in the GPS centrifuge and spun at 3200 RPM for 15 minutes. The system operates on the principle that plasma, the buffy coat (that contains platelets and leukocytes), and red blood cells have different densities (increasing in that order). As these layers stratify, a pair of buoys move to a neutral density position, effectively trapping the buffy coat within a contained volume of approximately 6 mL of plasma (Figure 1). The tube was then vigorously shaken to suspend the platelets within this small plasma volume. The balance of the plasma (~30 mL), contained within a separate compartment in the tube, was deficient in platelets, ie, platelet-poor plasma. Ports connected to the platelet-rich plasma and platelet-poor plasma chambers allowed their respective contents to be drawn into separate syringes.

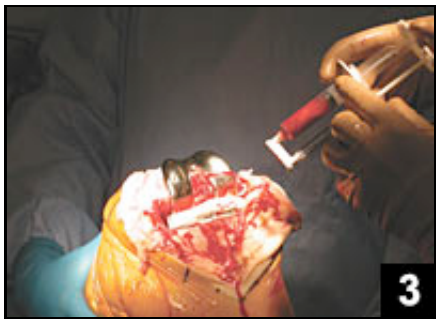


Figure 2: Left: dual spray apparatus showing both the platelet-rich plasma treatment syringe (large) and activation syringe (small) connected in tandem. Right: corresponding arrangement for platelet-poor plasma treatment. **Figure 3:** Administration of activated platelet-rich plasma to surgical bed with dual sprayer.

Activation solution was prepared by mixing 1000 units of topical bovine thrombin (Jones Pharma, St Louis, Mo) per milliliter of 10% $CaCl_2$ solution. The thrombin directly activates platelets and participants in the coagulation cascade. The $CaCl_2$ replenishes the ACD-A-bound calcium ion, also a critical element in the coagulation cascade. Activation solution was drawn into two 1-mL syringes. The treatments, ie, platelet-rich and platelet-poor plasma, were drawn into two 10-mL syringes, respectively. A treatment syringe (platelet-rich plasma or platelet-poor plasma) and an activation syringe were connected, in tandem, to a dual spray apparatus (Micromedics, St Paul, Minn) (Figure 2). This allowed both syringe plungers to be advanced in unison, mixing the two sprays in a 1:10 (activation:treatment) volume ratio. In this way, the treatments (platelet-rich plasma or platelet-poor plasma) were activated prior to reaching the wound bed. During closure, activated platelet-rich plasma was sprayed onto the cut bone surfaces, synovia, tendons, and the joint capsule (Figure 3). The activated platelet-poor plasma was then applied to the subcuticular surface prior to closure. Closure was performed using Vicryl (Johnson & Johnson, New Brunswick, NJ) sutures on the extensor mechanism and subcutaneous tissues, and staples for the skin. Postoperative drains were placed in the lateral gutter of the knees in both patient groups. Drainage was collected into an autosuction collection system (Stryker Kalamazoo, Mich). Drainage from the canister was filtered and reinfused during the first six postoperative hours. A complete blood count was performed each morning during the hospital stay. Patients with a hemoglobin concentration <10 g/dL received a transfusion of packed red blood cells. Immediately after surgery, patients were allowed weight bearing as tolerated. During hospitalizition, patients underwent continuous passive motion and physical therapist-supervised ROM exercises and gait training. Afterwards, physical therapy consisted of three weeks of outpatient strength and ROM exercises, for three sessions per week.

Patients were followed for six weeks postoperatively, documenting a variety of outcomes, ie, days to discharge, discharge location (home or rehabilitation), active ROM, number of units of transfused packed red blood cells used, hemoglobin level, pain (1-10 point scale with greater scores indicating greater pain), patient-controlled analgesia, and cellulitus.

Statistical Analysis

Treatment and control means were statistically compared using the two-tailed *t* test. Nominal data was compared using the Chi-square or two-tailed Fischer exact test. Ordinal data was compared using the Mann-Whitney rank sum test. Differences between means were considered to be significant for $P<05$.

Results

The preoperative comparison of the control and treatment populations is summarized in Table 1. The only significant preoperative difference between the two groups was that there were significantly more women in the control population.

Table 1

Preoperative Patient Comparisons

Parameter	Control	Treatment	*P* value
No. patients	66	71	N/A
No. knees	72	81	N/A
Age	68.2±9.8	65.0±10.0	.061
Percent female	81.8	64.8	.040*
Percent unilateral	90.9	85.9	.520
BMI (kg/m^2)	34.6±8.86	33.6±6.18	.583
Preoperative ROM	112.7°±14.6°	110.9°±12.2°	.421
Diabetes mellitus	13	11	.673
Rheumatoid arthritis	5	6	.899
Kidney failure	2	0	.230
Cardiovascular disease	0	4	.121

Abbreviations: BMI=body mass index, Hb=hemoglobin, and ROM=range of motion.
**Denotes significance at* P<.05.

For both populations, morphine was the sole postoperative patient-controlled analgesia used by approximately 90% of the patients. During inpatient stay, the balance received a combination of morphine, meperidine, nalbuphine, and/or hydromorphone. In one case, no patient-controlled analgesia was required. For comparison purposes, the amounts of these analgesics were expressed in "morphine equivalents" based on the relative doses required. For instance, it was estimated that 1 mg of meperidine, nalbuphine, and hydromorphone were roughly equivalent (in effect) to 0.1 mg, 1 mg, and 5 mg of morphine, respectively.[41-43]

Table 2 summarizes the postoperative parameters collected for the two groups of patients.

Table 2

Postoperative Patient Comparisons

Parameter	Control group	Treatment group	*P* value
Hospital stay (days)	3.97±1.14	3.53±0.907	.015†
Discharge (home/rehab)	2.00	2.94	.402
Preoperative ROM	112.7°±14.6°	110.9°±12.2°	.421
Day 1 ROM	43.0°±16.4°	51.4°±14.4°	<.001†
Day 2 ROM	66.1°±13.5°	72.9°±13.4°	.002†
Day 3 ROM	75.4°±11.7°	79.2°±11.8°	.066
6 Week ROM	105.3°±12.1°	110.2°±9.77°	.009†
Transfusion (units/patient)	0.70±0.94	0.39±0.57	.035†
Hb baseline (g%)	12.1±1.29	12.1±1.33	.997
Day 1 ΔHb (g%)*	−1.1±0.88	−0.68±0.79	.006†
Day 2 ΔHb (g%)*	−1.8±0.92	−1.37±1.08	.007†
Day 3 ΔHb (g%)*	−2.0±1.1	−1.77±1.01	.294
Pain on Day 1 (1-10 scale)	4.68±1.82	4.14±1.95	.073
PCA (morphine equivalents, mg)	61.5±35.7	52.4±46.2	.207
Cellulitis incidence	5	6	.899

Abbreviations: Hb=hemoglobin, PCA=patient-controlled analgesia, rehab=rehabilitation, and ROM=range of motion.
**Denotes change in hemoglobin level with respect to baseline value.*
†*Denotes significance at* P<.05

Patients receiving the platelet-rich/platelet-poor plasma treatment were discharged from the hospital sooner, had greater postoperative active ROM through six weeks (with the exception of postoperative day 3), received fewer

units of transfused packed red blood cells, and had less hemoglobin decrement compared to baseline on the first two postoperative days than the control patients. There was no influence of platelet treatment on the location to which patients were discharged (home versus rehabilitation) or on the incidence of cellulitis. There were no deep infections in either group over the follow-up period. On average, treated patients had less pain on the first postoperative day and used less patient-controlled analgesia during inpatient stay; however, these averages were not significantly different than those of the control patients. Figure 4 shows the ROM values, Figure 5 shows the change in hemoglobin levels compared to the preoperative baseline, and Figure 6 shows the pain score on the first postoperative day, patient-controlled analgesia through the entire inpatient period in morphine equivalents, length of the inpatient stay, and the number of units of packed red cells used per patient. To fit the data in Figure 6 on the same axes, the values for a given type of measurement were normalized to the average respective control value.

Discussion

There are several reasons for the current clinical interest in using platelet concentrates to enhance wound healing. First, the immediate natural response of the body to tissue damage is the accumulation of large numbers of activated platelets at the injury site.[22] These platelets, activated by contact with biomolecules (eg, collagen) that become exposed on tissue damage, become sticky and form a platelet plug. For small vascular breaches, this may be sufficient to effect hemostasis. For large vascular defects, however, a clot is required. The activated platelets interact at several levels within the coagulation cascade, quickly forming a clot comprised of a fibrin mesh with entrapped platelets and red and white blood cells.[22] Consequently, administration of a supraphysiological dose of platelets would be expected to improve hemostasis. Second, on activation, the -granules contained within the platelets fuse with the platelet plasma membrane and release their contents, a cocktail of over 30 bioactive proteins (growth factors, cytokines, and chemokines), outside of the cell.[8,9,11,22,27,39,40] These proteins, which include PDGF- , - , and - , as well as TGF- 1 and - 2, collectively set the stage for tissue healing by attracting macrophages, mesenchymal stem cells, osteoblasts, and other cells that are responsible for the removal of necrotic tissue and regeneration of site-specific tissue. The bioactive proteins released by platelets act as chemotactic agents, morphogens, and mitogens. Secretion of presynthesized proteins occurs within 10 minutes of platelet activation; >95% are secreted within the first hour.[22] The platelets then continue to synthesize and secrete these proteins for the balance of their 5-10 day lifespan. Thus, as with hemostasis, a supraphysiological dose of activated platelets might theoretically increase the rate of healing. Third, technology has become available that makes it convenient for the surgeon to remove a small amount (55-60 mL) of venous blood from the patient for processing to platelet-rich and platelet-poor plasma.[10,11,22] Due to the small volume removed, the residual packed red blood cells do not require infusion back into the patient.

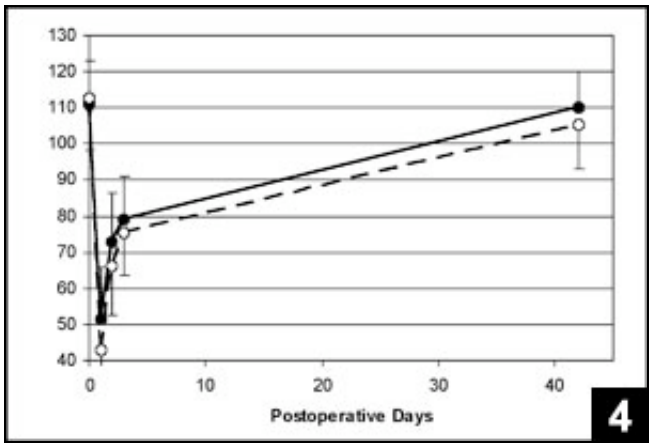


Figure 4: Range of motion (ROM) data for treatment (filled-in dot) and control (open dot) patients. Time zero represents the preoperative ROM. Average±SD.

Several lines of evidence support the use of platelets in this manner. In vitro studies have shown that there is a dose-response relationship between platelet concentration and the proliferation of adult mesenchymal stem cells, the proliferation of fibroblasts, and the production of type I collagen.[44,45] Controlled animal studies have demonstrated a positive effect of platelet-rich plasma on both hard- and soft-tissue healing.[46,47] A limited number

of controlled human clinical studies have shown an enhancement of wound healing. For example, Marx[39] performed histomorphometry on core biopsies taken from the mandibles of 44 patients following bone augmentation for dental implants. He reported that there was a significant improvement in graft maturation and trabecular bone area after six months compared to grafts in which platelets were not used. Margolis et al[35] performed a meta-analysis of >25,000 cases of neuropathic diabetic foot ulcers treated with or without platelet therapy. Ulcers treated with platelets were 14%-59% more likely to heal than those treated without. Pietrzak and Eppley[22] summarized several other controlled, clinical studies that support the use of platelet-rich plasma.

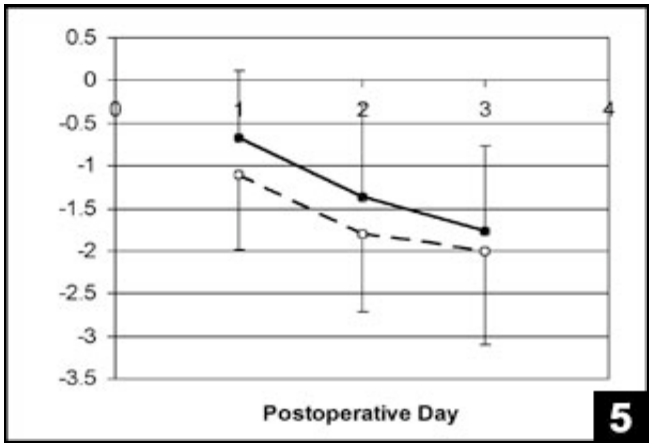


Figure 5: Change in hemoglobin concentration on the first three postoperative days (compared to baseline prior to surgery) for treatment (filled-in dot) and control (open dot) patients. Average±SD.

Our study showed that TKA patients treated with platelet-rich and platelet-poor plasma had significantly shorter hospital stay after surgery, had improved ROM for six weeks, required fewer units of transfused packed red cells, and had an improved hemoglobin profile compared to patients receiving no platelet-rich/platelet-poor plasma. All of these improved outcomes can be rationalized by the known mechanisms by which platelets (and platelet-poor plasma) influence hemostasis and wound healing.

Mooar et al[36] performed a similar study in 85 individuals, finding that TKA patients receiving platelet gel experienced a significantly lower reduction in hemoglobin levels (2.68 g/dL versus 3.12 g/dL), demonstrating a hemostatic effect, and achieved a significantly higher ROM (79.7° versus 72.1°) earlier (4.35 days versus 6.38 days) than did patients that did not receive platelet therapy.

Wang et al[48] used a non-autologous fibrin sealant following TKA (22 patients) and compared results with a control cohort (24 patients). The decrease in hemoglobin level on the first postoperative day in fibrin sealant-treated patients was 28.9% less than in the control group (P=.0005).

Levy et al[37] used a commercial fibrin sealant following TKA in a prospective, controlled, randomized clinical study. Fibrin-treated patients required significantly less transfused blood than did the control patients (P<.001) and exhibited less hemoglobin decrease (P<.001). Collectively, these studies corroborate many of our positive findings on the influence of platelet-rich plasma and platelet-poor plasma on outcomes following TKA.

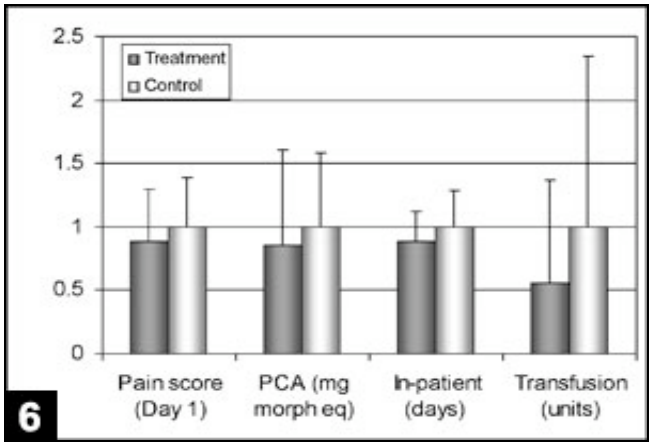


Figure 6: Pain score on the first postoperative day, patient-controlled analgesia in morphine equivalents (morph eq), length of inpatient stay (days), and the number of units of transfused packed red cells. All scores are normalized to respective control values. Average±SD.

These positive findings suggest that the platelet-rich/platelet-poor plasma application can have a beneficial effect on TKA outcome as early as the day of surgery as shown by reduced transfusion requirement, to at least the sixth postoperative week as suggested by improved ROM. Certainly the hemostatic effect would be expected to be achieved quickly, within minutes of application, based on the speed with which the coagulation cascade reacts to form the clot. As stated above, the majority (>95%) of the presynthesized bioactive proteins are released within one hour of clot formation. Conceptually, the additional bolus release provided by the administered platelet-rich plasma could increase the rate of precursor cell migration and proliferation within hours and days. The ability of activated platelets to continue to produce and secrete these protein factors for 5-10 days can provide the opportunity to amplify healing within this period. To the extent that knee ROM is reflective of tissue healing around the implant, this suggests that the state of healing remained more advanced in the patients treated with platelet-rich and platelet-poor plasma at six weeks.

Some of the outcomes of the current study were statistically unaffected by the platelet-rich/platelet-poor plasma treatment. Although average pain on the first postoperative day and overall patient-controlled analgesia use was less for the treated patients than for the control patients, the differences were not significant. Also, there was no significant difference in the incidence of cellulitis between the two groups. Mooar et al[36] reported TKA patients receiving platelet gel required significantly less intravenous and oral narcotics than did control patients. In that study, however, platelet gel was produced from 500 mL of autologous blood. It is possible that a greater amount of platelets were administered compared to our study, and this may account for the significant reduction in analgesia use. Advocates of the use of platelet concentrates believe that such treatment can decrease postoperative infection.[49] Although there is little evidence for this, and this was not demonstrated in the current study, some potential mechanisms can be proposed. The buffy coat is comprised of not only platelets, but leukocytes as well. Thus, leukocytes are concentrated in platelet-rich plasma over baseline values. Their increased number may help to diminish infection. Additionally, platelet-induced migration of neutrophils and macrophages to the wound site might provide additional benefit.

As described above, patients treated with platelet-rich and platelet-poor plasma exhibited a significantly lower drop in hemoglobin levels during the first two postoperative days, suggesting a hemostatic effect of this treatment. Another method by which hemostasis might have been demonstrated is comparison of the collected wound drainage between the treatment and control cohorts. An attempt was made to perform such a comparison in this study until it was determined that errors incurred in the reporting of this data made the analysis unreliable. Prior studies have shown that collected wound drainage is significantly less following fibrin sealant-treatment in TKA patients. For example, Wang et al[48] measured the collected drainage volume using wound drains. They found that within 12 hours postoperatively, patients treated with a commercial fibrin sealant (no platelet-rich plasma) yielded about half the volume of collected drainage as the control population (185.5 mL versus 408.3 mL), a significant difference. Levy et al[37] also used drains and calculated blood loss through direct measurement, as well as by a calculation that uses the maximum postoperative decrease in hemoglobin adjusted for the height and weight of the

patient to account for extravasation of blood into the tissues. Mean measured postoperative blood losses were 360 mL for the fibrin sealant-treated patients and 878 mL for the control group ($P<.001$). Calculated means were 1063 mL and 1768 mL ($P<.001$), respectively.

There were several limitations to this study. First, its retrospective nature limited the comparisons that could be made between the two groups since the study design was not optimized prior to its performance. For instance, many factors may affect postoperative ROM, including preoperative, operative, and postoperative factors.[50] Preoperative factors include gender, which was not equivalent between the two groups, with the control population having a significantly greater proportion of females. Operative factors include implant design. While a variety of implants were used, all shared many features in common (cemented, non-constrained, cruciate-retaining, primary knee prosthesis). In a similar study, Levy et al[37] also used a variety of total knee prostheses in their comparison of the effects of fibrin sealant on outcomes following TKA. Second, patients were followed only to the sixth postoperative week. From a healing standpoint, six weeks was felt to be sufficient for both cohorts to demonstrate substantial healing and return of function, as was seen. However, wound remodeling will continue for months and years after surgery, and longer follow-up, perhaps to 12 months or beyond, would be required to determine whether the ROM of the control patients would eventually become equivalent to that of the platelet-rich/platelet-poor plasma–treated patients.[3] Third, more complete patient assessments, such as the Knee Society clinical rating system, SF-36, or Western Ontario and McMaster Osteoarthritis Index may have enabled a more critical comparison of outcomes between the two groups.[51,52] Despite these limitations, several beneficial effects of platelet-rich and platelet-poor plasma on outcomes following TKA were demonstrated, and corroborated and extended results from prior studies.

The optimal use of platelet-rich and platelet-poor plasma is likely procedure- and site-specific and may be also specific to the equipment used in its production. Future work should include a prospective, randomized, blinded clinical study with follow-up to at least one year, to more fully determine the benefit of platelet-rich and platelet-poor plasma in TKA.

Conclusion

In this retrospective 6-week study, TKA patients treated with platelet-rich and platelet-poor plasma during wound closure demonstrated shortened hospital stay, improved ROM, improved hemoglobin profile, and reduced need for blood transfusion compared to control patients who received no platelet-rich or platelet-poor plasma treatment. On average, treated patients had reduced pain and used less narcotics than untreated control patients, but these differences were not significant. There was no difference in the incidence of cellulitis between the two groups.

References

1. Masri BA, Laskin RS, Windsor RE, Haas SB. Knee closure in total knee replacement: a randomized prospective trial. *Clin Orthop*. 1996; 331:81-86.
2. Peters C, Erickson J, Kloepper R, Mohr RA. Revision total knee arthroplasty with modular components inserted with metaphyseal cement and stems without cement. *J Arthroplasty*. 2005; 29:302-308.
3. Heck DA, Robinson RL, Partridge CM, Lubitz RM, Freund DA. Patient outcomes after knee replacement. *Clin Orthop*. 1998; 356:93-110.
4. Jones CA, Voaklander DC, Suarez-Alma ME. Determinants of function after total knee arthroplasty. *Phys Ther*. 2003; 83:696-706.
5. Kumar PJ, McPherson EJ, Dorr LD, Wan Z, Baldwin K. Rehabilitation after total knee arthroplasty: a comparison of 2 rehabilitation techniques. *Clin Orthop*. 1996; 331:93-101.
6. Anderson JM. The cellular cascades of wound healing. In: Davies JE, ed. *Bone Engineering*. Toronto, Canada:em squared inc; 2000:81-93.
7. Buckwalter JA, Einhorn TA, Bolander ME, Cruess RL. Healing of musculoskeletal tissues. In: Rockwood CA Jr, Bucholz RW, Green DP, Heckman JD, eds. *Fractures in Adults*. Philadelphia, Pa: Lippincott-Raven; 1996:261-304.
8. Anitua E, Andia I, Ardanza B, Nurden P, Nurden AT. Autologous platelets as a source of proteins for healing and tissue regeneration. *Thromb Haemost*. 2004; 91:4-15.
9. Bhanot S, Alex JC. Current applications of platelet gels in facial plastic surgery. *Facial Plastic Surgery*. 2002; 18:27-33.
10. Eppley BL, Woodell JE, Higgins J. Platelet quantification and growth factor analysis from platelet-rich plasma: implications for wound healing. *Plast Reconstr Surg*. 2004; 114:1502-1508.
11. Marx RE. Platelet-rich plasma: evidence to support its use. *J Oral Maxillofac Surg*. 2004; 62:489-496.

12. Tischler M. Platelet rich plasma. The use of autologous growth factors to enhance bone and soft tissue grafts. *N Y State Dent J*. 2002; 68:22-24.
13. Arm DM. Autologous platelet-based therapies for orthopaedic tissue regeneration. 2004. In: Telecki G, ed. *Wiley Encyclopedia of Biomedical Engineering*. New York, NY: John Wiley & Sons Inc. In Press.
14. Hannon TJ, et al. Determination of platelet yields from platelet rich plasma for five autotransfusion machines. *Anesth Analg*. 1996; 88:SCA104.
15. Marlovits S, Mousavi M, Gabler C, Erdos J, Vecsei V. A new simplified technique for producing platelet-rich plasma: a short technical note. *Eur Spine J*. 2004; 13:s102-s106.
16. Weibrich G, Kleis WK, Hafner G. Growth factor levels in the platelet-rich plasma produced by 2 different methods: curasan-type PRP kit versus PCCS PRP system. *Int J Oral Maxillofac Implants*. 2002; 17:184-190.
17. DelRossi AJ, Cernaianu AC, Vertrees RA, et al. Platelet-rich plasma reduces postoperative blood loss after cardiopulmonary bypass. *J Thorac Cardiovasc Surg*. 1990; 100:281-286.
18. Ghandi A, Van Gelderen J, Berberian WS, O'Connor JP, Parsons JR, Lin SS. Platelet releaseate enhances healing in patients with a non-union. Transactions of the 49th Annual Meeting of the Orthopaedic Reseach Society. New Orleans, LA; February 2-5, 2003. Poster no. 492.
19. Man D, Plosker H, Winland-Brown JE. The use of autologous platelet-rich plasma and autologous platelet-poor plasma in cosmetic surgery. *Plast Reconstr Surg*. 2001; 107:229-236.
20. Petrungaro PS. Using platelet-rich plasma to accelerate soft tissue maturation in esthetic periodontal surgery. *Compend Contin Educ Dent*. 2001; 22:729-746.
21. Soffer E, Ouhayoun JP, Anagnostou F. Fibrin sealants and platelet preparations in bone and periodontal healing. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2003; 95:521-528.
22. Pietrzak WS, Eppley BL. Platelet rich plasma: biology and new technology. *J Craniofac Surg*. 2005; 16:1043-1054.
23. Anitua E. Plasma rich in growth factors: preliminary results of use in the preparation of future sites for implants. *J Oral Implantol*. 1999; 14:529-535.
24. Della VA, Sammartino G, Marenzi G, et al. Prevention of postoperative bleeding in anticoagulated patients undergoing oral surgery: use of platelet-rich plasma gel. *J Oral Maxillofac Surg*. 2003; 61:1275-1278.
25. Froum SJ, Wallace SS, Tarnow DP, Cho SC. Effect of platelet-rich plasma on bone growth and osseointegration in human maxullary sinus grafts: three bilateral case reports. *J Periodontol*. 2002; 22:45-53.
26. Kassolis JD, Rosen PS, Reynolds MA. Alveolar ridge and sinus augmentation utilizing platelet-rich plasma in combination with freeze-dried bone allograft: case series. *J Periodontol*. 2000; 71:1654-1661.
27. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma: growth factor enhancement for bone grafts. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1998; 85:638-646.
28. Robiony M, Polini F, Costa F, Politi M. Osteogenesis distraction and platelet-rich plasma for bone restoration of the severely atrophic mandible: preliminary results. *J Oral Maxillofac Surg*. 2002; 60:630-635.
29. Whitman DH, Berry RL, Green DM. Platelet gel: an autologous alternative to fibrin glue with applications in oral and maxillofacial surgery. *J Oral Maxillofac Surg*. 1997; 1294-1299.
30. Welsh W. Autologous platelet gel-clinical function and usage in plastic surgery. *Cosmetic Derm*. 2000; 13:13-18.
31. Bose B, Balzarini MA. Bone graft gel: autologous growth factors used with autograft bone for lumbar spine fusions. *Adv Ther*. 2002; 19:170-175.
32. Hee HT, Majd ME, Holt RT, Myers L . Do autologous growth factors enhance transforaminal lumbar interbody fusion? *Eur Spine J*. 2003; 12:400-407.
33. Lowery GL, Kulkarni S, Pennisi AE. Use of autologous growth factors in lumbar spinal fusion. *Bone*. 1999; 25:47s-50s.
34. Knighton DR, Ciresi K, Fiegel VD, Schumerth S, Butler E, Cerra F. Stimulation of repair in chronic, nonhealing, cutaneous ulcers using platelet-derived wound healing formula. *Surg Gynecol Obstet*. 1990; 170:56-60.
35. Margolis DJ, Kantor J, Santanna J, Strom BL, Berlin JA. Effectiveness of platelet releasate for the treatment of diabetic neuropathic foot ulcers. *Diabetes Care*. 2001; 24:483-488.
36. Mooar PA, Gardner MJ, Klepchick PR, et al. The efficacy of autologous platelet gel in total knee arthroplasty: an analysis of range of motion, hemoblobin,and narcotic requirements. American Academy of Orthopedic Surgeons, 67th Annual Meeting. American Academy of Orthopaedic Surgeons; 2000:PE148.
37. Levy O, Martinowitz U, Oran A, Tauber C, Horoszowski H. The use of fibrin tissue adhesive to reduce blood loss and the need for blood transfusion after total knee arthroplasty. A prospective, randomized, multicenter study. *J Bone Joint Surg Am*. 1999; 81:1580-1588.
38. Gonshor A. Technique for producing platelet-rich plasma and platelet concentrate: background and process. *Int J Periodontics Restorative Dent*. 2002; 22:547-557.
39. Marx RE. Platelet concentrate: a strategy for accelerating and improving bone regeneration. In: Davies JE,

ed. *Bone Engineering*. Toronto, Canada:University of Toronto; 2000:447-453.
40. Marx RE. Platelet-rich plasma (PRP): what is PRP and what is not PRP? *Implant Dent*. 2001; 10:225-228.
41. Chan WH, Lin CJ, Sun WZ, Tsai SP, Tsai SK, Hsieh CY. Comparison of subcutaneous hydromorphone with intramuscular meperidine for immediate postoperative analgesia. *Kaohsiung J Med Sci*. 1999; 15:419-427.
42. Ho ST, Wang JJ, Liu HS, Hu OY, Tzeng JI, Liaw WJ. Comparison of PCA nalbuphine and morphine in Chinese gynecologic patients. *Acta Anaesthesiol Sin*. 1998; 36:65-70.
43. Sinatra RS, Lodge K, Sibert K, et al. A comparison of morphine, meperidine, and oxymorphone as utilized in patient-controlled analgesia following cesarean delivery. *Anesthesiology*. 1989; 70:585-590.
44. Haynesworth SE, Kadiyala S, Liang L, Bruder SP. Mitogenic stimulation of human mesenchymal stem cells by platelet releasate suggest a mechanism for enhancement of bone repair by platelet concentrates. 48th Annual Meeting of the Orthopaedic Research Society. February 10-13, 2002, Dallas, Tex, poster no. 462.
45. Liu Y, Kalen A, Risto O, Wahlstrom O. Fibroblast proliferation due to exposure to a platelet concentrate in vitro is pH dependent. *Wound Repair Regen*. 2002; 10:336-340.
46. Carter CA, Jolly DG, Worden CE, Sr, Hendren DG, Cane CJ. Platelet-rich plasma gel promotes differentiation and regeneration during equine wound healing. *Exp Mol Pathol*. 2003; 74:244-255.
47. Fennis JPM, Stoelinga PJW, Jansen JA. Mandibular Reconstruction: A clinical and radiographic animal study on the use of autogenous scaffolds and platelet-rich plasma. *J Oral Maxillofac Surg*. 2002; 31:281-286.
48. Wang GJ, Hungerford DS, Savory CG, et al. Use of fibrin sealant to reduce blood drainage and hemoglobin loss after total knee arthroplasty: a brief note on a randomized prospective trial. *J Bone Joint Surg Am*. 2001; 83:1503-1505.
49. Waters JH, Roberts KC. Database review of possible factors influencing point-of-care platelet gel manufacture. *J Extra Corpor Technol*. 2004; 36:250-254.
50. Ryu J, Saito S, Yamamoto K, Sano S. Factors influencing the postoperative range of motion in total knee arthroplasty. *Bull Hosp Jt Dis*. 2005; 53:35-40.
51. Hawker G, Melfi C, Paul J, Green R, Bombardier C. Comparison of a generic (SF-36) and a disease specific (WOMAC) (Western Ontario and McMaster Universities osteoarthritis index) instrument in the measurement of outcomes after knee replacement surgery. *J Rheumatol*. 1995; 22:1193-1196.
52. Insall JN, Dorr LD, Scott RD, Scott WN. Rationale of the knee society clinical rating system. *Clin Orthop*. 1989; 248:13-14.

Authors

Dr Berghoff is from Orthopedics Northeast, Fort Wayne, Ind; Dr Pietrzak is from the Department of Bioengineering, University of Illinois, Chicago, Ill; and Dr Rhodes is from the Fort Wayne Medical Education Program, Fort Wayne, Ind.

Dr Berghoff is a consultant and Dr Pietrzak is an employee of Biomet.

Reprint requests: Richard D. Rhodes, MD, 6 MDOS/6 GOSO, 8415 S Bayshore Blvd, MacDill AFB, FL 33621-1607.