The Efficacy of Autologous Platelet Gel in Pain Control and Blood Loss in Total Knee Arthroplasty

An Analysis of Hemoglobin, Narcotic Requirements, and Range of Motion

Pekka A. Mooar, MD;
Michael J. Gardner, BA; and
Paul R. Klepchick, BA;

Department of Orthopaedic Surgery
Medical College of Pennsylvania and Hahnemann University
School of Medicine

Please address all correspondences to:

Pekka A. Mooar, M.D.
Department of Orthopaedics
Medical College of Pennsylvania Hospital
3300 Henry Avenue
Philadelphia, PA 19129
(215) 842-7710

ABSTRACT

Background: Total knee arthroplasty is a procedure that may be complicated by postoperative pain and persistent wound drainage. Autologous platelet gel, prepared perioperatively by extracting the platelet rich plasma centrifuged from the patient's blood, is applied to exposed tissues, synovium, and the lining of the wound at closure. Platelet-derived proteins, particularly platelet-derived growth factor, have been shown to have profound effects on inflammation and tissue repair. Concentrating and applying these factors directly to the wound leads to more complete hemostasis, reduction in perioperative blood loss, accelerated tissue repair, and decreased postoperative pain.

Methods: Ninety-eight unilateral total knee arthroplasties were evaluated retrospectively for clinical benefits of platelet gel administration. Categories analyzed were postoperative hemoglobin loss, intravenous and oral narcotic requirements, range of motion on discharge, and total hospital days stayed.

Results: Patients receiving APG had less blood loss, as measured by difference in preoperative and postoperative day 3 hemoglobin (2.68 g/dl vs. 3.16 g/dl); required less IV (17.0 mg/day vs. 36.3 mg/day) and oral (1.84 pills/day vs. 2.75 pills/day) narcotics; achieved higher functional ROM (78.2° vs. 71.9°); and were discharged an average of 1 day earlier than their control counterparts when evaluated with a one-tailed T-Test.

Conclusions: Autologous platelet gel is clinically beneficial following total knee arthroplasty. The results of this study indicate that application of autologous platelet gel leads to improved hemostasis, better pain control, and a decreased hospital stay.

Keywords: Autologous platelet gel, total knee arthroplasty, pain management, blood loss, wound healing, platelets, platelet-derived growth factor

Successful outcome in total knee arthroplasty (TKA) depends on achieving satisfactory post-operative range of motion, which depends on many factors including primary soft tissue hemostasis and adequate tissue repair.[2,6] Wound hematoma and seroma formation, arthrofibrosis, and prolonged post-operative pain are responsible for less than optimal outcomes after TKA.[1,3,11,29] The nature of total knee replacement may involve significant post-operative pain and discomfort, and while analgesic medications are highly effective in pain management, they do have side effects. These include sedation, respiratory depression, and constipation, which are potentiated in the elderly population. Perioperative techniques that decrease demand for narcotics are beneficial, leading to less sedation, earlier physical therapy, and a shorter hospital stay.

Treatment with autologous platelet gel (APG) involves direct application of concentrated platelets and their growth factors, specifically platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β), which has many favorable effects.[7,9,12] Both by mechanically sealing the tissues, vessels, and lymphatics, and augmenting the healing cascade,[16] platelet gel used during TKA may decrease both blood loss and pain medication requirements, thereby accelerating recovery of range of motion.

Materials and Methods

Platelet Gel Preparation and Use

Platelet gel is a platelet-based biological clot that utilizes the platelet-rich buffy coat harvested from centrifuged autologous whole blood. One unit (approximately 450 milliliters) of blood is drawn perioperatively into an anti-coagulation bag containing citrate, phosphate, and

dextrose. The blood is centrifuged in the operating room using the Medtronic Sequestra 1000 Autotransfusion System (Medtronic, Inc., Minneapolis, MN). The buffy coat is then suspended in 30-50 milliliters of plasma and separated from the red blood cell mass and the platelet-poor plasma. The platelet concentration in the layer ranges from 500,000 to 1,100,000 per milliliter. When ready for use, 8 ml of the platelet concentrate is mixed with 0.5 ml of calcified thrombin, significantly less than the concentration used in spray thrombin preparations, and rapidly applied to the dried surfaces.[15]

A medial parapatellar approach to the knee was used and the patella was everted. A cruciate-sacrificing prosthesis was used, intramedullary femoral alignment and extramedullary tibial alignment was employed, and both components were cemented. A tourniquet was used, and after cementing it was deflated, hemostasis was obtained with electrocautery, and the wound was dried. Platelet gel was then initially applied to the posterior recess, the gutters, and the exposed surfaces of the femur and tibia. The wound was closed in layers without the placement of any drains, and the remaining platelet gel was placed on the repaired extensor mechanism and prepatellar fat.

The activated gel forms a temporary watertight seal if wound coverage was complete, and concentrates platelets and growth factors at the wound site. Postoperatively, the knee was immobilized in bulky dressings for 24 hours and then CPM was started at 0 to 40° and advanced as tolerated. Lateral retinacular releases, while not specifically quantified, were performed very infrequently.

Study Parameters

A retrospective analysis of ninety-eight consecutive patients, who underwent unilateral TKA by the senior author (PAM) between 1995 and 1999, was performed. The "study group" was comprised of the sixty-one patients in whom APG was used during TKA, and the "control group" consisted of the remaining thirty-seven patients who underwent TKA without APG. Data collected from patient charts includes the following: patient age, date of surgery, discharge date, pre-operative hemoglobin concentration, postoperative day three hemoglobin concentration, pre-operative range of motion (ROM), ROM on post-operative days one through three, ROM at discharge, patient-controlled anesthesia (PCA) pump intravenous morphine requirement, and oral oxycodone (5 milligrams) and acetaminophen (325 milligrams) requirement.

A one tailed t-test was used to evaluate study patients versus control patients based on five different parameters. The change in the patient's hemoglobin was evaluated, calculated as the difference between the preoperative value and the postoperative day three value. The number of milligrams of intravenous morphine required, as well as the number of oxycodone pills required in the post-operative course were tabulated, as milligrams per day, and pills per day, respectively. Lastly, both discharge ROM in degrees of flexion, and length of hospital stay from date of surgery to discharge date were analyzed. All patients were evaluated post-operatively by the same physiotherapy team and placed on similar mobilization regimens, and all patients were entered into the same algorithm for a target discharge of 4 days.

The patients analyzed as the "study group," having received APG, averaged 73.3 years old, and the control group averaged 72.9 years old. The sexes of the subjects in the study group were 73% female and 27% male (45 females and 17 males), and in the control group, 77% were female and 23% were male (34 females and 10 males). All had end-stage osteoarthritis.

An important caveat to the study is the discrepancy in the number of subjects among the groups. There are several reasons for this. Some patients were treated with different post-operative pain-control regimens, such as intrathecal morphine, due to allergies, intolerance, or patient preference. Because of the inherent difficulties in standardizing different medications based on efficacy, only those patients who received the common protocol of intravenous morphine and oral oxycodone/acetaminophen were evaluated for pain medication requirements. Five patients in the study group and two patients in the control group were not discharged in a timely fashion due to difficulty with placement into a rehabilitation program, and were thus excluded from the "days stayed" analysis. In addition, three patients in each group had an impaired cardiovascular status and were transfused with a much lower threshold, regardless of the post-operative hemoglobin, and were removed from the analysis.

Results

Patients receiving APG had a smaller decrease in postoperative hemoglobin (2.68 g/dl vs. 3.16 g/dl) [see Figure 1], as compared to the controls. This a statistically significant difference, with a p-value of 0.026 [see Table 1.]

The study group required less intravenous (17.0 mg/day vs. 36.3 mg/day) and oral (1.84 pills/day vs. 2.75 pills/day) narcotics [see Figures 2 and 3] than the control group. The p-values were 0.024 and 0.063, respectively.

Functional ROM achieved by discharge was greater in the APG-treated TKA's (78.2° vs. 71.9°) [see Figure 4] relative to the control TKA's, with a p-value 0.052.

Finally, this occurred in the study group an average of one day earlier than their control counterparts, as the patients treated with APG averaged one less hospital day (4.04 days vs. 5.29 days) [see Figure 5], with a p-value of 0.002.

Discussion

APG has been shown to have short-term benefits in the post-operative course in TKA. We hypothesize that the beneficial effects seen are based on the growth factors and cytokines present in the platelet-rich plasma concentrate.

Growth Factors

Primary wound healing occurs by the activation of acute inflammation, which initiates a biochemical cascade at the site of repair. Several studies have shown that two growth factors, PDGF and TGF-β, are key mediators in many different phases of the inflammation and tissue healing process[4,8,13,14,17,20].

PDGF is a glycoprotein that weighs approximately thirty kilodaltons. It has traditionally been known to originate from the alpha granules of platelets, but more recently has been shown to exist in both endothelial cells and the monocyte cell line as well[24]. PDGF has multiple effects in augmenting tissue repair, and early in the process, the protein plays a dual role in augmenting healing. First, PDGF acts as a potent chemoattractant molecule factor for monocytes and fibroblasts[26]. Assays that have measured numbers of inflammatory cells in wounds both treated and untreated with recombinant PDGF have supported this[5,19,25]. Secondly, and equally as important, PDGF *activates* these cells. Studies have shown the presence of receptors for PDGF

on both monocytes/macrophages and fibroblasts. When stimulated, these receptors cause both a mitotic proliferation and upregulation of macrophage and fibroblast activity and secretion[5]. PDGF potentiates macrophages' scavenging and debridement of the wound site, and also increases production of growth factors, including PDGF, TGF-β, interleukin-1, and others. The importance of this is that PDGF has a long-lasting effect in repairing the wound, longer than the life of the original platelets, due to autocrine and paracrine effects[27].

Following the chemotaxis and activation of inflammatory cells, angiogenesis, deposition of a provisional extracellular matrix, and formation of mature collagen are all crucial to wound healing[21]. PDGF is a major factor in the later phases of wound healing as well. Through its interactions with fibroblasts, PDGF enhances synthesis of fibronectin, glycosaminoglycan, and hyaluronic acid. The increased concentrations of these raw materials of the procollagen scaffold lead to faster formation of new tissue and a more rapid gain of wound strength[9].

TGF-β is a superfamily of growth factors, of which TGF-β1 and TGF-β2 are the most prominent. Each protein weighs approximately twenty-five kilodaltons, and, like PDGF, is released from platelets, macrophages, and fibroblasts. Several trials have demonstrated the strong chemotactic effect of TGF-β on inflammatory cells using both *in vitro* and *in vivo* assays[23,28]. Aside from causing increased influx of inflammatory mediators, TGF-β has a profound direct effect on fibroblasts. Similarly to PDGF, TGF-β increases synthesis of procollagen, fibronectin, thrombospondin, and other proteins necessary for matrix deposition, as well as more TGF-β, propagating the cascade of tissue repair by a positive feedback loop mechanism[10,22]. Animal and human models have been used to evaluate the consequences of treatment with exogenous TGF-β and PDGF on wound healing *in vivo*[18]. Increased granulation

tissue production, accelerated extracellular matrix deposition, and stimulation of local collagen synthesis all lead to earlier wound closure and faster gain of wound tensile strength[16,17,19,20].

Other studies have confirmed efficacy of concentrating platelets by centrifugation of whole blood and harvestation of the platelet-rich plasma layer. Marx et al. conducted platelet counts on patients' whole blood, and compared them to the platelet counts of the platelet rich plasma. Patients in the study averaged platelet counts of 232,000 per milliliter (range of 111,000 to 523,000), and their buffy-coat counts averaged 785,000 per milliliter (range of 595,000 to 1,100,000), which was an average increase of 338%[15].

In addition to the growth factors present in platelet-rich plasma, other proteins elicited from platelets include thromboxane A2, thrombin, and adenosine diphosphate. These attract additional platelets to the wound site, potentiating the activity of the original applied platelets in forming a platelet plug, augmenting the inflammation cascade, and allowing for earlier hemostasis and repair. The buffy-coat, which is sequestered in the process, also contains concentrated leukocytes, which may add an anti-bacterial component to the gel, although this has not been substantiated[7,12].

The Value of Autologous Platelet Gel

Blood Loss

Numerous strategies for decreasing postoperative blood loss have been employed for major orthopedic procedures such as TKA. In our study, hemoglobin drop from preoperative level to postoperative day three level was used as an estimate of blood loss. This was based on the assumption that significant hemodilution occurred during this period, so that hemoglobin concentration accurately mirrored blood loss. Patients who were not treated with APG had a

significantly greater drop in hemoglobin concentration (3.16 g/dl) compared to those who were treated with APG (2.68). This difference in blood loss is statistically significant ($p = 0.026$).

Pain Management

Relief of postoperative pain is an important criterion in overall success of a TKA, and many of the possible post-operative complications may be manifested by excessive pain. We have shown in our study that patients who received treatment with APG required lower doses of intravenous morphine than patients who did not receive platelet gel. This is likely secondary to accelerated hemostasis and wound repair, and has many positive consequences. All patients were started on a standard post-operative PCA protocol with a set demand-dose and lockout interval. Patients who require fewer narcotics are likely to be less lethargic, start active rehabilitation sooner and more productively, gain earlier. mobility, and avoid pulmonary complications associated with excess narcotic sedation.

Oral pain medication requirement in study subjects was also decreased. As with intravenous narcotics, this decreased requirement may attributable to PDGF at the wound site accelerating tissue healing and controlling extracellular fluid accumulation. Early conversion to oral analgesics may be one of the factors significantly contributing to the shorter length of hospital stay for patients in the study group. No patients who were taking narcotic pain medication, intravenously or orally, were concurrently taking non-steroidal anti-inflammatory therapy.

Functional Outcome

Assessment of post-surgical outcome is generally quite subjective, but realization of functional ROM is one of the few ways to quantify the success of TKA. Patients who receive

APG achieve an increased range of motion despite a length of stay that is one day shorter than controls. Final functional ROM was measured on the day of discharge, allowing controls a longer recovery time, and an additional day of physical therapy.

Prolonged hospitalization is associated with exposure to virulent infectious agents, patient depression, and increased cost to society. Methods that lead to shortened hospital stay are beneficial to the patient and physician, as well as to the hospital and health care field. Use of APG leads to shortened length of hospital stay when compared to controls that did not receive the treatment. The aforementioned parameters of decreased blood loss, decreased narcotic requirement, and improved functional ROM support earlier discharge.

The process of perioperative donation eliminates clerical errors in the blood bank. Additionally, because the red blood cell mass may be returned to the patient, those who are unable to donate a unit of blood to the blood bank may still undergo platelet gel treatment. The materials cost approximately $180 per use, requires less than one hour of technician time, and the procedure adds only about ten minutes to the total operating room time.

Application of platelet-rich plasma is a safe and simple procedure used perioperatively in total knee replacement. Platelet gel applied directly to the operative site after TKA seals the tissues and delivers platelets directly to the wound, often in concentrations in excess of 1,000,000 per milliliter. With the platelets come their growth factors and other proteins, especially PDGF and TGF-β, which have been shown to attract other inflammatory cells, increase collagen matrix deposition, accelerate wound closure, and augment gain of tensile wound strength.

This study illustrates the clinical benefits of application of APG during TKA. Research of platelets and their proteins indicates a physiologic basis for this effect, which has positive effects on pain medication requirement, hemoglobin loss, range of motion, and length of stay.

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Table 1

Clinical Outcomes

	ΔHgb (g/dl)	IV mg/day	Oral pills/day	Max ROM (°)	Days
Platelet Gels	**2.68 (n=54)**	**17.0 (n=52)**	**1.84 (n=50)**	**78.2 (n=55)**	**4.04 (n=57)**
Std. Dev.	1.14	16.4	1.68	15.7	1.04
Controls	**3.16 (n=34)**	**36.3 (n=24)**	**2.75 (n=25)**	**71.9 (n=32)**	**5.29 (n=35)**
Std. Dev.	1.07	43.1	2.56	17.7	2.24
p value	*0.026*	*0.024*	*0.063*	*0.052*	*0.002*