

Phase I/II prospective trial of autologous platelet tissue graft in gynecologic surgery

James Fanning, DO, Luis Murrain, DO, Robert Flora, MD, Timothy Hutchings, DO, Jil M. Johnson, DO, and Bradford W. Fenton, MD, PhD

From the Department of Obstetrics and Gynecology, Summa Health System, Northeastern Ohio Universities College of Medicine, Akron, Ohio (all authors).

KEYWORDS:

Autologous platelet tissue graft;
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Pain

Abstract

STUDY OBJECTIVE: To perform the original phase I/II trial of autologous platelet tissue graft in gynecologic surgery to evaluate toxicity and efficacy on decreasing pain.

DESIGN: Prospective nonrandomized trial (Canadian Task Force classification II-A).

SETTING: Teaching hospital.

PATIENTS: Fifty-five consecutive patients undergoing major gynecologic surgery were entered into this prospective phase I/II trial and were matched with 55 patients from the previous 6 months.

INTERVENTION: After anesthesia was induced, peripheral venous blood (55 mL) was obtained from the patient producing, autologous platelet tissue graft (20 mL). At completion of surgery, autologous platelet tissue graft was directly applied to the surgical site.

MEASUREMENTS AND MAIN RESULTS: Median pain on the day of surgery was 2.7 (mild) in the autologous platelet tissue graft group vs 6.7 (severe) in the control group, $p < .001$. Likewise, pain on postoperative day 1 was 2.1 (mild) in the autologous platelet tissue graft group vs 5.5 (moderate) in the control group, $p \leq .001$. Median of morphine per hospital stay for the autologous platelet tissue graft group was 17 mg (range 1–98 mg) vs 26 mg (range 3–90 mg) in the control group, which was statistically significant at $p = .02$. There were no adverse effects associated with autologous platelet tissue graft.

CONCLUSIONS: In the original phase I/II prospective trial of autologous platelet tissue graft in gynecologic surgery, there were no apparent adverse effects, and pain was significantly reduced.

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More than 350 000 women undergo major gynecologic surgery in the United States each year. Major morbidity associated with gynecologic surgery includes pain, bleed-

ing, infection, hernia, and wound dehiscence. Reduction in the incidence of these morbidities would improve patient care and decrease medical expense.

Recently, several autologous platelet-rich plasma preparations, including autologous platelet tissue graft (BioMet Biologics, Warsaw, IN), have been used clinically to enhance hemostasis and wound healing.^{1,2} Application of autologous platelet tissue graft to the operative site has a 3-fold effect (Figure 1). First, the concentrated platelets form a fibrin clot that aids in hemostasis. Second, the platelets degranulate and release numerous chemotactic and mitogenic growth factors (including platelet-derived growth

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Corresponding author: James Fanning, DO, Department of Obstetrics and Gynecology, Summa Health System, Northeastern Ohio Universities College of Medicine, 525 E. Market Street, Medical II, Akron, OH 44309.
E-mail: fanning@summa-health.org

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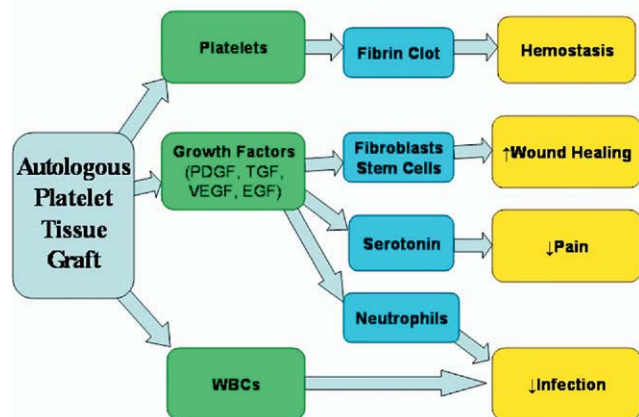


Figure 1 Autologous platelet tissue graft: mechanism of action. EGF = epidermal growth factor; PDGF = platelet-derived growth factor; TGF = transforming growth factor; VEGF = vascular endothelial growth factor; WBC = white blood cells.

factor, transforming growth factor, vascular endothelial growth factor, and epidermal growth factor), which aid in wound healing and decrease infection and pain. Third, increased white blood cell (WBC) concentration also aids in decreasing infection. Recent studies have shown that autologous platelet tissue graft produced by the Gravitational Platelet Separation system (BioMet Biologics) contains an 8-fold increase in platelet count, 5-fold increase in white blood cell count, a 4- to 6-fold increase in growth factors, and a 7-fold increase in serotonin^{3,4} compared with serum levels.

Because autologous platelet tissue graft is obtained in the operating room and immediately directly applied to the patient's own operative site, adverse effects should be minimal or nonexistent. Because of the small risk of adverse effects and encouraging initial empiric results, the use of autologous platelet tissue graft is increasing.^{1,2} However, the clinical effectiveness and safety in gynecologic surgery have not been proven. In general, there are 3 phases of clinical testing of new therapeutic agents.⁵ Phase I trials are designed to evaluate toxicity. Phase II trials determine efficacy. If phase I/II trials show safety and efficacy, a phase III trial is performed to determine whether the new treatment is more effective or safer than standard therapy. Therefore our purpose was to perform the original phase I/II trial of autologous platelet tissue graft in gynecologic surgery to evaluate toxicity and efficacy on pain.

Materials and methods

Eligibility

Patients undergoing major gynecologic surgery (laparoscopic-assisted vaginal hysterectomy, laparoscopic-assisted vaginal hysterectomy with laparoscopic lymphadenectomy, abdominal hysterectomy, advanced laparoscopic proce-

dures, and advanced urogynecologic procedures requiring multiple repairs), aged 18 years or older, nonpregnant, and able to give informed consent comprised the study group. Institutional review board approval was granted, and written informed consent was obtained from all patients.

Patient characteristics

From August 5, 2005, through February 6, 2006, 55 consecutive patients were entered into this phase I/II trial, and none were excluded. Two patients declined to enter the trial. Patients were recruited from 3 physician offices—1 private gynecology group, 1 academic urogynecologist, and 1 academic gynecologic oncologist. Patient characteristics are presented in Table 1. Median age was 55 years old (24–84 years old), median weight was 167 lbs (112–260 lbs), and 78% had medical comorbidities. Twenty-five percent of surgical procedures were laparoscopic-assisted vaginal hysterectomy, 20% were extended urogynecologic procedures, and 22% were laparoscopic gynecologic oncology procedures.

Comparison group

Fifty-five patients from the previous 6 months were matched by surgeon and surgical procedure. As can be seen from patient characteristics in Table 1, there was no difference between the groups in age, weight, race, medical comorbidities, or types of surgery. We believed this comparison group was justified because both groups had the same prospective pain evaluation by the same nursing staff who were blinded to the study's objectives. Also, the same pre-printed postoperative pain management protocol was used for both groups.

Table 1 Patient characteristics

	APTG	Control	p
Age (yrs)	55 (24–84)	49 (27–76)	.06
Weight (lbs)	167 (112–260)	160 (67–250)	.13
Race			.90
White	87%	80%	
Black	13%	20%	
Comorbidity	78%	63%	.10
Procedure (No., %)			.10
LAVH	14 (25)	14 (25)	
LAVH nodes	12 (22)	10 (18)	
Scope	4 (7)	4 (7)	
TAH	14 (25)	12 (22)	
Urogyn	11 (20)	15 (27)	

APTG = autologous platelet tissue graft; LAVH = laparoscopic-assisted vaginal hysterectomy; LAVH nodes = LAVH with lymphadenectomy; Scope = advanced laparoscopic procedure; TAH = abdominal hysterectomy; Urogyn = advanced urogynecologic procedure.

Technique of autologous platelet tissue graft (BioMet Biologics)

After induction of general anesthesia, peripheral venous blood (55 mL) was obtained from the patient and mixed with acid-citrate-dextrose-A 5 mL, an anticoagulant, in a 60-mL syringe. The syringe contents were transferred to the Gravitational Platelet Separation system disposable separation tube (GPSII; BioMet Biologics) (Figure 2) and spun in a BioMet centrifuge for 15 minutes at 3200 rpm. After centrifugation, 2 aliquots of 7 mL of platelet-poor plasma and 3 mL of platelet concentrate (platelets and WBCs) were obtained and transferred to two 10-mL syringes. An activation solution was prepared by mixing 1000 units of topical bovine thrombin (Jones Pharma, St. Louis, MO) per milliliter of 10% CaCl₂ solution. The thrombin directly activates platelets, and the CaCl₂ deactivates the acid-citrate-dextrose-A anticoagulant. The activation solution was drawn into two 1-mL syringes. The 10-mL platelet-poor plasma/platelet concentrate syringe and the 1-mL activation syringe were connected, in tandem, to the BioMet Malleable Dual Cannula Tip, a dual-spray apparatus (Figure 3). This allows both syringe plungers to be advanced in unison, mixing the 2 sprays, which allows activation before reaching the wound bed. At completion of the surgical procedure and after ensuring adequate hemostasis, the autologous platelet tissue graft was directly applied to the surgical site (including the vaginal cuff, parametrium, and fascia). Depending on the surgical procedure, autologous platelet tissue graft was applied vaginally, laparoscopically, or transabdominally (Figure 4). Surgical application takes approximately 1 minute.

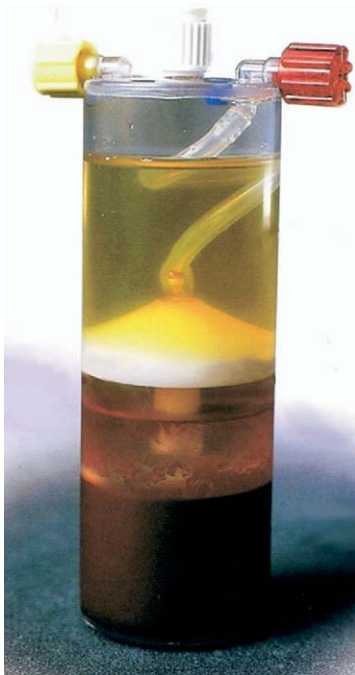


Figure 2 Gravitational Platelet Separation (GPSII) tube.



Figure 3 BioMet Malleable Dual Cannula Tip.

Data collection

All hospital data were collected prospectively before discharge. Patients were followed up for 28 days with outpatient checkups scheduled for the seventh and twenty-eighth postoperative day. Pain was evaluated with the visual analog scoring system⁶: 0 = no pain, 2 = mild, 5 = moderate, 7 = severe, 10 = excruciating. At Summa, visual analog scoring is prospectively performed and recorded every 4 hours by the nursing staff. The highest visual analog score on postoperative day 0 and postoperative day 1 was used. Preprinted postoperative pain management protocol was the same for both groups: ketorolac 30 mg intravenously every 6 hours for 4 doses, morphine 2 to 5 mg intravenously every 2 hours as needed, and oxycodone/acetaminophen 5/325 mg 1 to 2 tablets orally every 6 hours as needed. For the few patients that required meperi-

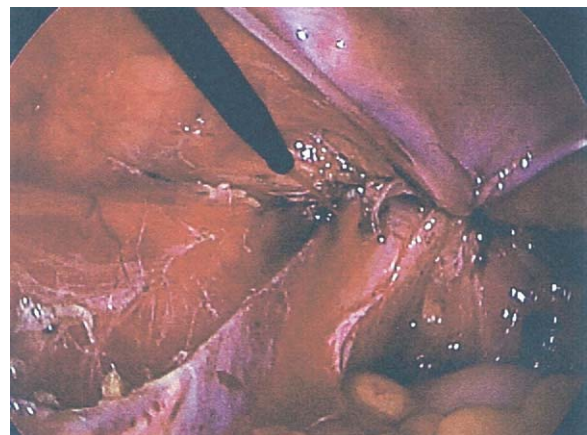


Figure 4 Laparoscopic application of autologous platelet tissue graft.

dine, a conversion of meperidine 75 mg to morphine 10 mg was used. The oxycodone/acetaminophen to morphine conversion was 2 tablets to 4 mg of morphine. For the comparison group, hospital data were collected, as well as outpatient follow-up for 28 days. Because the control group was not prospectively evaluated after hospital discharge, accurate visual analog scores for pain on postoperative day 7 and 28 are not available.

Statistics

Discrete variables were compared by use of χ^2 or Fisher's exact test, and continuous variables were compared by *t* testing. A power analysis was performed with a *p* value = .05, power of .80 and a 25% difference in pain as being medically significant. Sample size calculation estimated a required sample size of 35 patients per group.

Results

Results are shown in Table 2. Median blood loss was 270 mL (10–500 mL), and median operative time was 163 minutes (75–330 minutes). Median change of postoperative hemoglobin was 1.8 g, and median length of stay was 1.3 days. Comparing these results with the 55 matched control subjects (Table 2); there was no statistically significant difference in blood loss, operative time, median change in hemoglobin, or length of stay.

Comparing patients treated with autologous platelet tissue graft to matched controls, postoperative pain was significantly reduced. Median pain on the day of surgery was 2.7 (mild) in the autologous platelet tissue graft group vs 6.7 (severe) in the control group, *p* < .001. Likewise, pain on postoperative day 1 was 2.1 (mild) in the autologous platelet tissue graft group versus 5.5 (moderate) in the control group, *p* ≤ .001. Median pain in the autologous platelet tissue graft group was 0.3 on postoperative day 7 and 0 on postoperative day 28. The median dose of morphine per hospital stay for the autologous platelet tissue graft group was 17 mg (1–98 mg) vs 26 mg (3–90 mg) in the control group, which was statistically significant at *p* = .02.

Table 2 Surgical characteristics

	APTG	Control	<i>p</i>
Blood loss	270 (100–1500)	272 (50–1000)	.48
OR Time (min)	163 (75–330)	143 (40–360)	.06
Δ Hgb (g/dL)	1.8	2.0	.16
LOS (days)	1.3 (1–4)	1.4 (1–5)	.17
Pain day 0	2.7 (0–7)	6.8 (1–10)	<.001
Pain day 1	2.1 (0–6)	5.6 (1–10)	<.001
Pain day 7	0.3 (0–3)		
Pain day 28	0		
Morphine (mg)	17 (1–98)	26 (3–90)	.02

APTG = Autologous platelet tissue graft; Δ Hgb = change in hemoglobin level; LOS = length of hospital stay.

No patient treated with autologous platelet tissue graft had a surgical site infection or postoperative dehiscence develop. Because the control group was not prospectively followed up, data on infection and dehiscence was not available. Autologous platelet tissue graft was not associated with any apparent adverse effects.

Discussion

Autologous platelet tissue graft is being used clinically to enhance hemostasis and wound healing after surgery.^{1,2} Concentrated platelets obtained from the patient's own blood are applied directly to the operative site. The 8-fold increase in platelet count forms a fibrin clot, which aids in hemostasis^{3,4} (Figure 1). When the concentrated platelets degranulate they release numerous chemotactic and mitogenic growth factors (including platelet-derived growth factor, transforming growth factor, vascular endothelial growth factor, and epidermal growth factor), which aid in wound healing, decrease infection, and decrease pain^{3,4} (Figure 1). Growth factors have a chemotactic and mitogenic effect on fibroblasts and mesenchymal stem cells, which leads to reepithelialization, angiogenesis, and collagen formation, which accelerates wound healing. The 5-fold increase in white blood cell count along with the chemotactic and mitogenic effect of growth factors on neutrophils may help decrease infection. Also, the growth factor chemotactic effect increases the concentration of serotonin, which helps decrease pain.

Although autologous platelet tissue graft is clinically being used,^{3,4} the clinical effectiveness and safety has not been proven, and thus we performed the original phase I/II trial of autologous platelet tissue graft (BioMet Biologics) in gynecologic surgery. None of the 55 patients treated developed a side effect from autologous platelet tissue graft. This was expected because autologous platelet tissue graft is obtained in the operating room from the patient and immediately directly applied to the patient's own operative site. In the phase II portion, we found a significant reduction in pain. Patients treated with autologous platelet tissue grafting had an approximate two-thirds reduction in pain resulting in mild postoperative pain versus moderate to severe postoperative pain in the control subjects (statistically significant, *p* < .001). Also, morphine use was reduced approximately 50% in the autologous platelet tissue graft group compared with the control subjects, which was statistically significant at *p* = .02. Because this was a phase I/II trial, blinding was not performed, and therefore placebo effect can not be excluded. Although our study did not have enough power to evaluate efficacy on surgical site infection or postoperative dehiscence, no patients treated with autologous platelet tissue graft developed these complications.

Multiple additional investigations of autologous platelet tissue graft are needed. We are presently evaluating postoperative adhesions in a swine model. In the future, we are planning to evaluate the effects of autologous platelet tissue grafting on

postoperative malignant growth. We are also planning to evaluate autologous platelet tissue grafting as a drug delivery system. Finally, because we performed a phase I/II trial, there was no control group. Therefore we are presently performing a phase III prospective randomized controlled trial on autologous platelet tissue graft in cesarean sections.

Conclusion

In the original phase I/II prospective trial of autologous platelet tissue graft in gynecologic surgery, there were no adverse effects, and pain was significantly reduced. We are presently developing a phase III prospective placebo-controlled randomized trial to verify the results of our phase I/II trial, evaluate placebo effect and to evaluate the efficacy of autologous platelet tissue graft on surgical site infection and postoperative dehiscence.

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