The Use of Autologous Platelet Concentrate (APC+) Grafting for the Treatment of Recalcitrant Wounds

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Since the earliest hominid began inhabiting the face of our planet, chronic wounds have plagued the species. It has taken more than 3.6 million years for Man to evolve to the point where we recognize him today.[1] The care and treatment of difficult wounds is well documented by the Egyptians possibly as early as 3000 BC, where they were the first to adopt the use of the adhesive bandage, among other modalities like the use of honey as a medicament.[2] Since these crude early attempts, there has been a plethora of advancements, especially within the last several years, for the treatment of chronic wounds. One of the more notable advancements is the use of autologous platelet-derived growth factors. This technology is now becoming recognized as an important modality to accelerate healing not only in the treatment of chronic wounds, but in other surgical procedures in specialties such as orthopedics, maxillofacial, and plastic surgery.[3,4,5] Human epidermal growth factor (EGF) has been shown to enhance wound healing in diabetic ulcers.[6] The use of autologous derived platelet growth factors can be found in the literature under several different names: APC+ (autologous platelet concentrate), PRP (platelet rich plasma), PC (platelet concentrate), and PG (platelet gel). Although these terms are often interchanged in the literature, they are not necessarily clinically and biologically equivalent.

Basic Science of Wound Healing:

When a wound occurs, the complex biological mechanism of human wound healing begins. In the 21'st Century, this mechanism is still not completely understood. Ongoing research continues to investigate the role growth factors play in wound healing. This research effort is identifying and beginning to explain more growth factors, their cellular mechanisms, and ways they interact with other proteins to effect the healing of both hard and soft tissue types. There are four phases involved in the wound healing process: 1) the Hemostatic phase, 2) Inflammatory phase, 3) Regenerative phase, and 4) tissue remodeling phase. The hemostatic phase begins immediately following tissue injury. Platelets migrate and bind to the wound site, reducing/stopping blood flow. Fibrinogen is converted to fibrin by thrombin and a complex platelet/fibrin structure is formed. Growth factors released from platelets trapped in this structure initiate the wound healing process. The inflammatory phase can last up to 7 days and is the infiltration of white cells into the wound site with the purpose of removing foreign material and to release additional growth factors. The proliferative phase, which is also known as the fibroblastic phase begins after the inflammatory phase, and involves tissue regeneration, angiogenesis, matrix formation, and epithelialization.[8] The final phase of wound healing, remodeling, can last up to 24 months after the proliferative phase. In this phase of wound healing, excess tissue matrix is proteolytically removed by complexes of enzymes, while there is a continual process of collagen synthesis and breakdown.[9] It is important to note that these phases of wound healing overlap each other, and are not separately identifiable chronological events.

Human platelets play an important role in controlling bleeding. They interact with the fibrin network and create a platelet/fibrin "plug" that achieves hemostasis. Perhaps more importantly, alpha granules on the surface of human platelets store most of the growth factors needed to start the healing process. These growth factors are immediately released from platelets activated by the clotting process occurring in the wound. These growth factors are involved in every phase of wound healing, and are critical for any wound to heal.[8] There have been a number of growth factors identified, including: PDGF (platelet- derived growth factor), EGF (epidermal growth factor), TGF-ß (transforming growth factor-beta), VEGF (vascular endothelial growth factor) as well as IGF-I (insulin growth factor-I). Platelet-derived growth factors effect chemotaxis and migration (recruiting stem cells to the wound site). They also attach to cell receptors and control the genetic expression of stem cells via modulation of signal transduction pathways of secondary proteins, resulting in cellular division and differentiation. They promote angiogenesis and start the tissue regeneration and remodeling process.[8]

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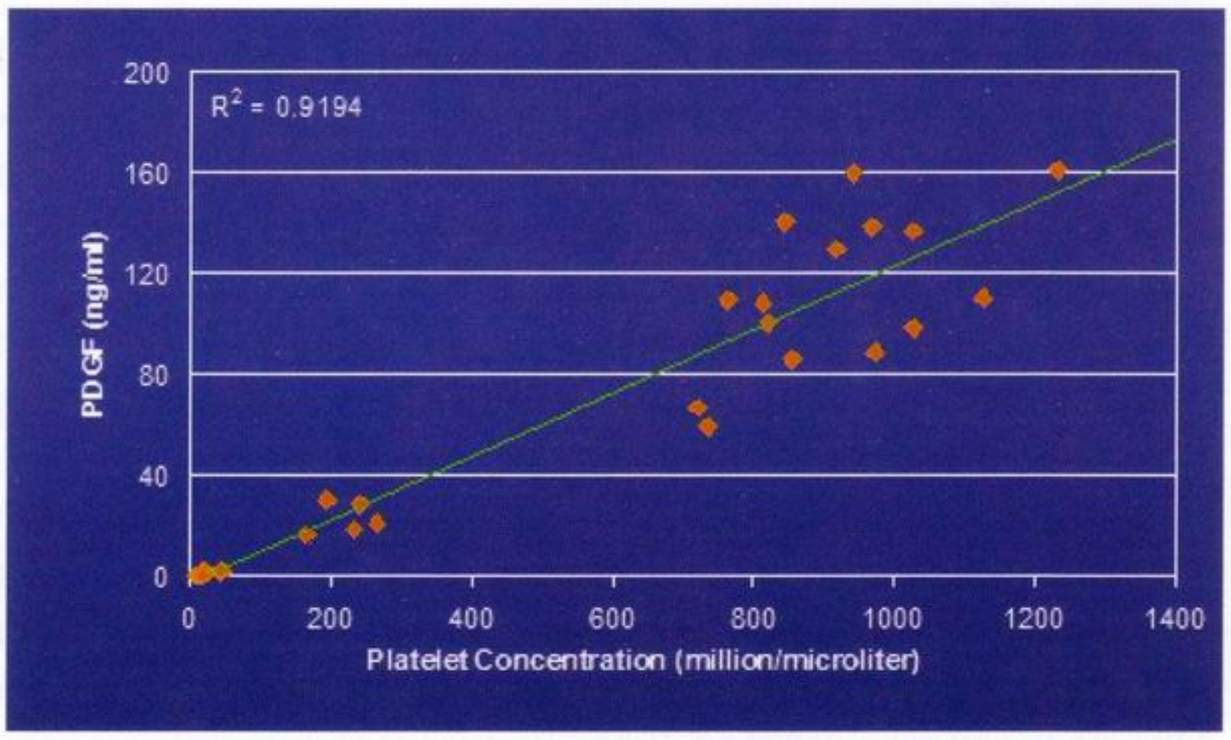
Autologous Platelet Concentrate:

Some of the complex interaction and function of platelet-derived growth factors has been reported in the literature. Enhancement of osseous repair of bone grafts has been effected by the use of platelet concentrates.[4] Degranulation (release of growth factors from the alpha granules) of the platelet at the wound site is known to initiate and enhance the healing cascade.

Diagram 1:



By processing the patient's own blood, to derive a platelet concentrate, the surgeon can then use this auto graft in the treatment of both hard and soft tissue wounds. Autologous platelet concentrate has been applied to an osteotomy site, or in combination with a bone graft to fill a large defect, and to accelerate and enhance soft tissue wound healing. Kevy and Jacobson, from the Center for Blood Research Laboratories have shown that platelets concentrated using Harvest Technologies' SmartPReP® system maintain normal functionality and are not activated or damaged during the separation process.[10] They also reported that as platelet concentration increases, so does the concentration of growth factors released from those platelets (see Diagram 1). Autologous platelet concentrate prepared with the SmartPReP® resulted in 4 to 6 times greater concentration of platelets than normal baseline platelet levels.

Table 1

Protocol[14]	Centrifuge Spins/time (min) g force	Whole Blood Volume Processed (ml)	Sterile Barrier Entries	Technologist Time (min)	Process Time (min)	Total Time (min)
SmartPReP® Automated	Automated	50	5	2	13	15
PVP[15] Double Spin	IEC, CENTRA CL2 1 1900g 3min 2 2100g 12min	43	33	15	15	30
LA[15] Single Spin	Sorval RT 6000B 1 200g 10min 2 200g 10min	52	28	10	20	30
AN[15] Single Spin	Sorval RT 6000B 1 160g 6min	54	26	6	6	12
SDS[15] Single Spin	Cliniseal 1 715g 12min	27	12	5	12	17

Table 2

Device	Baseline Platelet Concentration X $10^3/\mu l$	Platelet Concentrate Volume (ml)	Platelet Concentration X $10^3/\mu l$	Increase Above Baseline Platelet Concentration
University of Miami, Jackson Memorial Hospital, Miami - 7 ml PC target volume				
SmartPReP® Automated	269	7.4	1086	404%
Cliniseal Single Spin	269	7.6	401	150%
PVP Double Spin	269	7.8	493	180%
Center for Blood Research, Boston - 10ml PC target volume				
SmartPReP® Automated	228	11.3	738	324%
Anitua Single Spin	228	9.5	433	190%
Landesberg Double Spin	228	10.6	336	150%

Table 3

Device	PRP				
	Product Vol (ml)	Plt Conc X $10^3/\mu l$	Plt Yield %	PDGF-AB ng/ml	TGF-ß1 ng/ml
University of Miami, Jackson Memorial Hospital, Miami - 7 ml PC target volume					
SmartPReP® Automated	7.4 ± 0.5	1086 ± 227	62 ± 4.4	133 ± 29.2	170 ± 42.3
Cliniseal Single Spin	7.6 ± 1.5	401 ± 267	39 ± 16.3	46 ± 15.3	55 ± 18.7
PVP Double Spin	7.8 ± 0.6	493 ± 245	33 ± 14.2	35 ± 17.2	43 ± 17.9
Center for Blood Research, Boston - 10ml PC target volume					
SmartPReP® Automated	11.3 ± 1.7	738 ± 54	78 ± 15.8	97 ± 22.9	130 ± 37.2
Anitua Single Spin	9.5 ± 4.1	433 ± 129	35 ± 16.8	35 ± 11.3	52 ± 7.6
Landesberg Double Spin	10.6 ± 2.4	336 ± 141	30 ± 10.3	26 ± 13.7	50 ± 10.8

While there are other methods to process a patient's blood in order to make a platelet concentrate, Kevy and Jacobson have shown that the SmartPReP® system results in a greater platelet yield, greater platelet concentration and increased growth factor levels (see Tables 1-3) than these other devices.[10]

Some clinicians involved in wound care have made the erroneous conclusion that the use of autologous platelet concentrate is similar to using Procuren®, or that it is like a recombinant growth factor preparation like Regranex®. However, unlike a single growth factor recombinant preparation, autologous platelet concentrate results in a multiplicity of growth factors released into the wound site, synergistically working together to enhance the wound healing event. It is not limited to a single regeneration pathway, but provides a more complete biologic event which is able to effect the entire healing cascade.

Procuren® is a manufactured pharmaceutical material of extracted wound healing proteins suspended and diluted in a biological carrier. The product is devoid of all cellular components and their receptor site. Although blood is drawn from the patient to produce Procuren®, and it is processed at a remote laboratory, there is no similarity between autologous platelet concentrate and Procuren® or other recombinant single growth factor preparations.

Preparation of Autologous Platelet Concentrate:

Harvest Technologies has made the integration of this advanced technology simple for office based practices. Their SmartPReP® system is small, simple to use, and very time efficient, (see Photo 1). Prior to wound debridement, 20ccs of blood is drawn from the patient. Other systems require large amounts of blood to be taken from the patient ranging from 60-300ccs. This can be very problematic for the patient and clinician, and is avoided with the small amount of blood required for use with the SmartPReP® system. The drawn blood is introduced into the sterile centrifuge container, and then placed into the machine. It takes about 14 minutes to process the autologous platelet concentrate (APC+). (See Photos 2 and 3.) The platelet concentrate is re-suspended in a small amount of platelet poor plasma. The recovered autologous platelet concentrate can then be used at any time over the next 6-8 hours, since it is not activated until placement onto the wound. Using the Harvest double syringe applicator, the gel is formed, via activation with calcium chloride/thrombin mixture at the time of application to the wound. (Refer to Photo 4.)

Clinical Study—Objectives:

Initially, 16 patients, comprising 17 chronic wounds were enrolled into an office based study for treatment of their wounds with autologous platelet concentrate (APC+) grafting, using the Harvest Technologies' SmartPReP® system, in addition to standard wound care protocols for debridement, offloading, and topical applications of hydrocolloids. Patients were not included into this study until they had failed to have any reduction in wound size after four weeks of standard modalities of wound care. Wounds that were included in this patient mix were diabetic ulcers, decubitus ulcers, venous stasis ulcers, and complicated surgical wound dehiscence. After initial patient assessment, including patient history and physical examination, the wounds were measured, and digitally photographed. Patients were not included into the study if they had an infected wound. After thorough and complete debridement of the wound, an autologous platelet gel graft was placed onto the wound bed. Several seconds were allowed for the gel to set, and then petrolatum impregnated gauze was placed onto the graft. Several layers of gauze dressing were then used to cover this area. Patients were instructed to leave this dressing undisturbed for a minimum of 5 days, and preferably one week. The dressings were then removed, and the wounds were evaluated, and photographed. Patients were then instructed to apply a topical hydrocolloid daily to keep the wound moist, followed by another gauze dressing. They would then return between the 10th and 14th day after the initial autologous platelet graft for additional treatments with platelet concentrates, if needed. This protocol was continued until complete epithelialization was achieved. No patient was deemed to have reached the endpoint until complete wound closure was achieved. 16 of the 17 wounds treated resulted in successful wound closure. There was a 94% success of epithelialization. One of the patients had a recurrence of a sub first metatarsal head ulceration due to non-compliance. The number of autologous platelet concentrate applications ranged from 1 to 5. In addition to the results table (see Table 4 below), three case studies are included for illustration of results normally seen with the use of autologous platelet grafting.

Table 4: Patient Data Compilation

Pt.	Duration of Wound before Tx	# of PRP Tx's	Dates of PRP Tx':	Status:
L.B.	2 months	1	10-05-02	Closed 11-5-03
R.F.	4 months	3	10-15, 19-02 11-11-02	Closed
N.W. (1) upper	4 months	5	10-31-02 11-11, 26-02 12-17-02 01-20-03	Closed 2-3-03
N.W. (2) lower	2 months	4	10-31-02 11-11, 26-02 12-17-02	Closed 12-23-02
M.I.	2.5 months	4	05-02, 26-03 12-17, 30-02	Closed/Reopened Non compliant
P.K.	4.5 weeks	1	11-05-02	Closed 11-20-02
J.L.	1 month	2	11-20-02 12-04-02	Closed 12-16-03
J.S.	8 or more months	3	12-05-02 01-9, 24-03	Closed 01-6-03
B.R.	2 months & 2 days	2	02-18-03 02-28-03	Closed 3-11-03
J.S.	2 months	3	12-5-02 01–9, 24-03	Hosp. for other
I.G.	2 months & 14 days	2	03-17, 31-03	Closed 5-20-03
E.W.	3 months	1	04-7-03	Closed 6-10-03
W.P.	2 months	2	01-13, 21-03	Closed 2-28-03
D.L.	2 months	2	01-21-03 02-4-03	Closed 2-20-03
J.C.	2 months	2	02-21, 28-03	Closed 4-1-03
B.P.	2 months	2	02-26-03 03-11-03	Closed 4-4-03
R.C.	1 month	2	05-9, 19-03	Closed 6-1-03

CLINICAL CASES

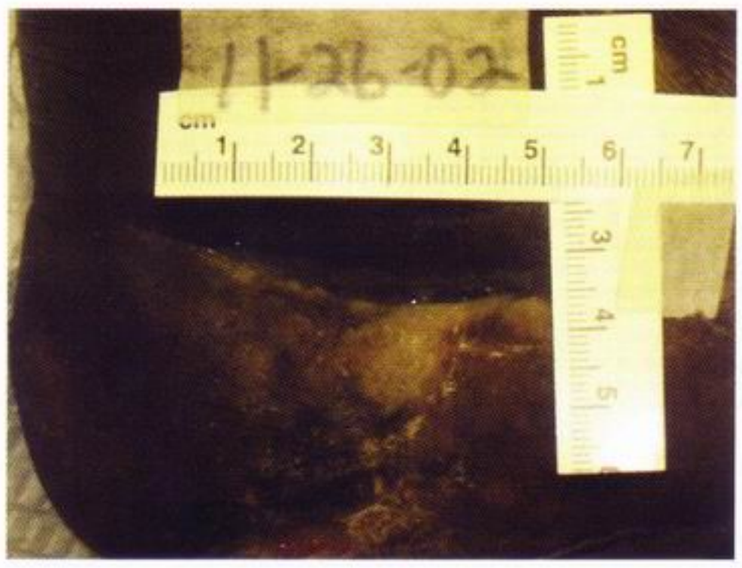
Case #1

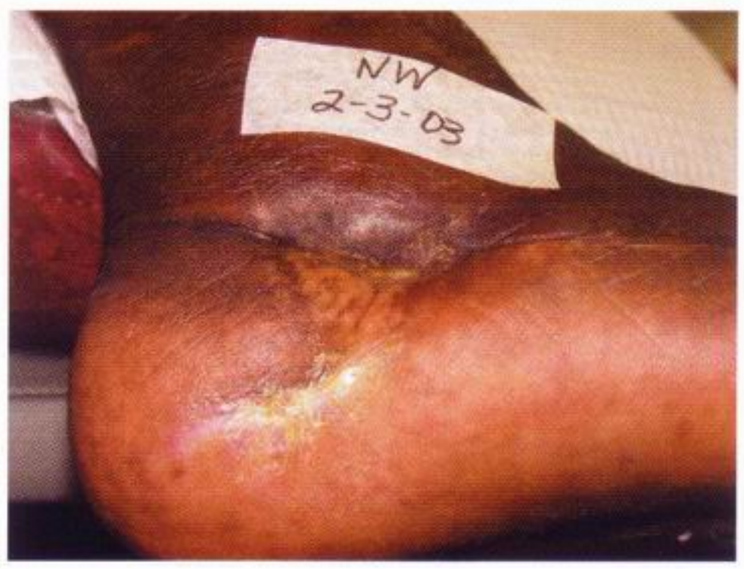
N.W. This 72 year old black male initially presented to the clinic on 10/31/2002, with two large, non-infected chronic wounds on the heel of the right foot, and the lateral aspect of the right heel. The patient was well controlled, with a recent blood sugar of 111g/dl, and appeared well nourished, and oriented.

History of Present Illness: The patient described an episode of stepping on a small object when he went out to get his newspaper. He believes it was a small pebble or stone that was inside of his shoe. Because of his diabetic peripheral neuropathy he was unable to feel its presence, and consequently developed ulceration on the plantar lateral aspect of his right heel. He describes this as happening approximately 90 days prior to his initial visit at our facility. He initially treated himself with hydrogen peroxide, but ended up in the hospital several weeks later with osteomyelitis of the right calcaneus, in addition to cellulitis. He remained hospitalized for 45 days, during which time he had a partial calcanectomy with extensive debridement to treat the osteomyelitis. The incision used to perform the calcanectomy also dehisced, and became a chronic wound in addition to the original ulceration. In addition to standard wound care protocol, he had 40 hyperbaric oxygen treatments, and VAC therapy.

Physical Examination: There were trace palpable dorsalis pedis, and posterior tibial pulses. Two large, mildly draining wounds were present. The plantar lateral heel ulceration measured 31mm x 9mm, with a depth of 5mm. This wound had a granular wound base and was not infected. The second wound, on the lateral aspect of the right heel had dimensions of 50mm x 11mm, with a depth of 16mm. This wound was deep, with skin edges that were involuted, and exposed bone.

Treatment: The patient underwent 5 autologous platelet concentrate (APC+) tissue grafts using the Harvest Technologies' SmartPReP® system. The wound beds, and margins were extensively debrided to assure removal of all necrotic tissue, and develop a freely bleeding surface. The APC+ was then applied, covered with a non-adherent dressing, with a gauze outer layer. This patient required 5 autologous platelet grafts on: 10/31/2002, 11/11/2002, 11/26/2002, 12/17/2002, and1/20/2003. The wound on the plantar aspect of the heel was completely epithelialized, and healed on 12/23/2002, therefore not requiring any application of the PRP on the last date.





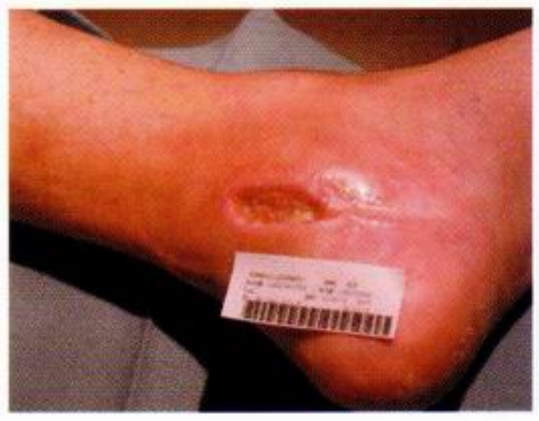
Treatment Results:

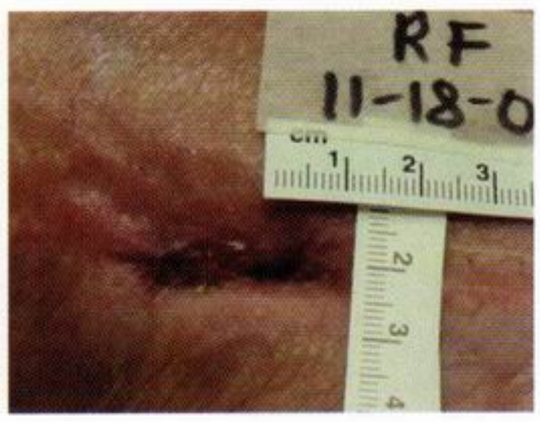
DATE OF WOUND	WOUND 1	WOUND 2
10/31/2002*	50mm x 11mm x 16mm	31mm x 9mm x 5mm
11/04/2002	39mm x 6mm x 10mm	23mm x 6mm x 2.5mm
11/11/2002*	31mm x 5mm x 7mm	15mm x 3mm x 2mm
11/26/2002*	34mm x 3mm x 7mm	9mm x 4mm x 1mm
12/17/2002*	25mm x 2mm x 4mm	epithelialized/closed
1/20/2003*	21mm x 3mm x 2mm	—
2/03/2003	epithelialized/closed	—

* *APG with PRP treatment*

Case #2

History of Present Illness: R.F. is a 64 year old male, in good health, who developed a wound dehiscence after tarsal tunnel decompression surgery on the left ankle. The patient is not diabetic, nor immunocompromised. He was referred to a hospital based wound care center, and had 54 hyperbaric treatments in addition to standard wound care protocols and treatments. The wound had failed to heal with that treatment.





Physical Examination: Initial evaluation revealed the presence of a wound 35mm x 14mm x 3mm, with surrounding redness, and pain with palpation. A deep tissue culture was taken, and Klebsiella pneumoniae was grown out. Appropriate antibiosis cleared the infection in one week. The wound bed was fibrinous, and poorly granulated, which was the result of heavy colonization.

Treatment: Once the infection had resolved, the patient presented to the clinic for extensive wound debridement, which required local anesthetization, followed by application of an autologous platelet graft (APC+) from the Harvest Technologies' SmartPReP® system. He was grafted 3 times as delineated in the table below.

Treatment Results:

DATE:	10/15/02*	10/29/02*	11/11/02*	11/20/02
Wound Size:	35mm x 14mm x 3mm	24mm x 5mm x 1.5mm	18mm x 3mm x 2mm	CLOSED

* *APG with PRP treatment*

Summary: This patient's wound was completely closed in 35 days, with 3 autologous grafts using APC+. It is also important to note that not only was the clinical result excellent, but as can be seen from the copy of his bill from the wound care center, this treatment was also economically beneficial.

ST DAVID'S HOSPITAL [redacted]

STATEMENT DATE PAGE 3 OF 4

ACCOUNT NUMBER	PATIENT NAME	STATEMENT PERIOD	AMOUNT DUE
70[redacted]	[redacted] RICHARD [redacted]		

MAIL PAYMENT TO

TO VIEW/PAY YOUR ACCOUNT VIA THE INTERNET SEE THE WEB ADDRESS BELOW
TO RECEIVE PROPER CREDIT, PLEASE RETURN THIS PORTION WITH YOUR PAYMENT
NOTE: SHOULD YOU WISH TO PAY BY CREDIT CARD, SEE AUTHORIZATION NOTICE ON THE BACK.

SUMMARY OF ACCOUNT

[redacted]

STATEMENT DATE 11/28/02

STATEMENT PERIOD	PATIENT NAME	ACCOUNT NUMBER
09/13/02 TO 11/25/02	[redacted]	70[redacted]

THE INSURANCE CLAIMS OUTSTANDING REPRESENTS OUR ESTIMATE OF INSURANCE LIABILITY BASED ON OUR BEST INFORMATION

ACCOUNT BALANCE LAST STATEMENT	NEW CHARGES OR ADJUSTMENTS	NEW PAYMENTS OR CREDITS	NEW ACCOUNT ADJUSTMENTS	INSURANCE CLAIMS OUTSTANDING	AMOUNT DUE
0.00	68863.73	0.00	0.00	68,863.73	$0.00

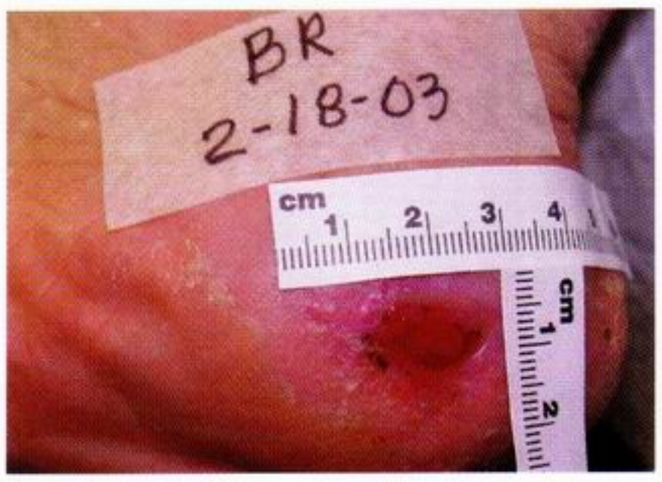
DATE	DESCRIPTION	UNITS	AMOUNT	DATE	DESCRIPTION	UNITS	AMOUNT
*10/22/02	REM DEVITALIZED TISS NS	1	480.42	*10/23/02	KERLIX ROLL	1	13.90
*10/23/02	KLING,4 INCH	1	9.81	*10/23/02	OPTIPORE SPONGE	1	8.18
*10/23/02	OPTIPORE SPONGE	1	8.18	*10/23/02	OPTIPORE SPONGE	1	8.18
*10/23/02	SPONGE, 4X4,GAUZE	1	9.54	*10/23/02	SPONGE, 4X4,GAUZE	1	9.54
*10/23/02	ADAPTIC GAUZE 3X8	1	19.35	*10/23/02	DRESSING, TRIAD WOUND	1	80.39
*10/23/02	HBO THERAPY,PER 30MN SES	4	1,188.12	*10/23/02	REM DEVITALIZED TISS NS	1	480.42
*10/24/02	HBO THERAPY,PER 30MN SES	4	1,188.12	*10/24/02	REM DEVITALIZED TISS NS	1	480.42
*10/26/02	KERLIX ROLL	1	15.50	*10/26/02	OPTIPORE SPONGE	1	9.00
*10/26/02	DRESSING, TRIAD WOUND	1	88.50	*10/26/02	HBO THERAPY,PER 30MN SES	4	1,308.00
*10/26/02	REM DEVITALIZED TISS NS	1	528.50	*10/28/02	SPONGE, 4X4,GAUZE	1	10.50
*10/28/02	DRESSING, TRIAD WOUND	1	88.50	*10/28/02	HBO THERAPY,PER 30MN SES	4	1,308.00
*10/28/02	REM DEVITALIZED TISS NS	1	528.50	*10/29/02	COLLAGENASE OINT 30GM	1	193.75
*10/30/02	HBO THERAPY,PER 30MN SES	4	1,308.00	*10/30/02	REM DEVITALIZED TISS NS	1	528.50
*10/31/02	HBO THERAPY,PER 30MN SES	4	1,308.00	*10/31/02	REM DEVITALIZED TISS NS	1	528.50
*11/01/02	HBO THERAPY,PER 30MN SES	4	1,308.00	*11/01/02	REM DEVITALIZED TISS NS	1	528.50
*11/02/02	HBO THERAPY,PER 30MN SES	4	1,308.00	*11/05/02	HBO THERAPY,PER 30MN SES	4	1,308.00
*11/05/02	REM DEVITALIZED TISS NS	1	528.50	*11/06/02	INTRASITE GEL DSG	1	34.50
*11/06/02	KERLIX FLUFF	1	16.00	*11/06/02	TELFA	1	5.50
*11/06/02	SODIUM CHLORIDE,250	1	39.00	*11/06/02	CLEANSING BOTTLE	1	7.00
*11/06/02	DRESSING, SKINTEMP COLLA	1	43.50	*11/06/02	HBO THERAPY,PER 30MN SES	4	1,308.00
*11/06/02	REM DEVITALIZED TISS NS	1	528.50	*11/07/02	HYPAFIX DRESSING 4"	1	34.00
*11/07/02	SPONGE, 4X4,GAUZE	1	10.50	*11/07/02	HBO THERAPY,PER 30MN SES	4	1,308.00
*11/07/02	REM DEVITALIZED TISS NS	1	528.50	*11/08/02	HBO THERAPY,PER 30MN SES	4	1,308.00
*11/08/02	REM DEVITALIZED TISS NS	1	528.50	*11/20/02	REM DEVITALIZED TISS NS	1	528.50
					TOTAL CHARGES		68,863.73
					ACCOUNT BALANCE		68,863.73
					ESTIMATED INSURANCE		68,863.73

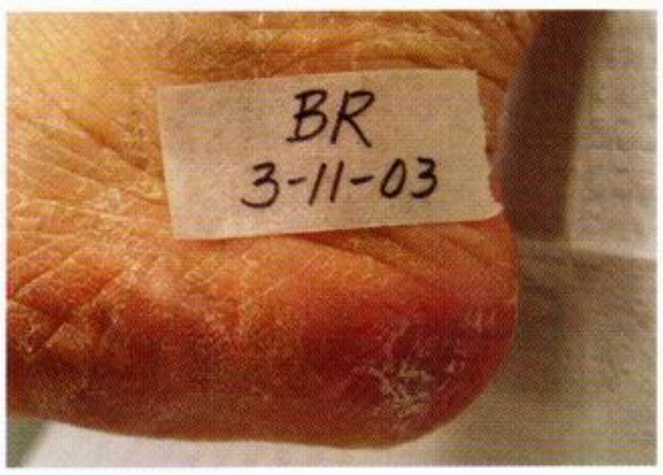
11/28/02 UNITED HEALTHCARE PPO BILLED
* INDICATES NEW ITEMS SINCE LAST STATEMENT

TO VIEW/PAY YOUR ACCT VIA WEB: WWW.STDAVIDSMC.COM/BILL.ASP
IF YOU HAVE QUESTIONS REGARDING YOUR ACCOUNT, PLEASE CALL: 800-627-2130

THANK YOU FOR CHOOSING ST. DAVID'S MEDICAL CENTER.
YOUR INSURANCE HAS BEEN BILLED IF IT WAS PRESENTED AT TIME OF SERVICE

This is a copy of the billing from the wound care center for failed hyperbaric treatment, prior to his inclusion into the APC+ study.





Case #3

History of Present Illness: B.R. This patient had an original complaint of a Diabetic ulcer on the left heel. She had been bed ridden, and was not properly padded to avoid pressure on her heels.

Physical Examination: The wound presented initially at 3.1cm x 1.3cm x 2mm. Pulses were not palpable; however the wound was not infected, and had only mild drainage.

Treatment: The wound beds, and margins were extensively debrided to assure removal of all necrotic tissue, and develop a freely bleeding surface. The APC+ was then applied, covered with a non-adherent dressing, with a gauze outer layer.

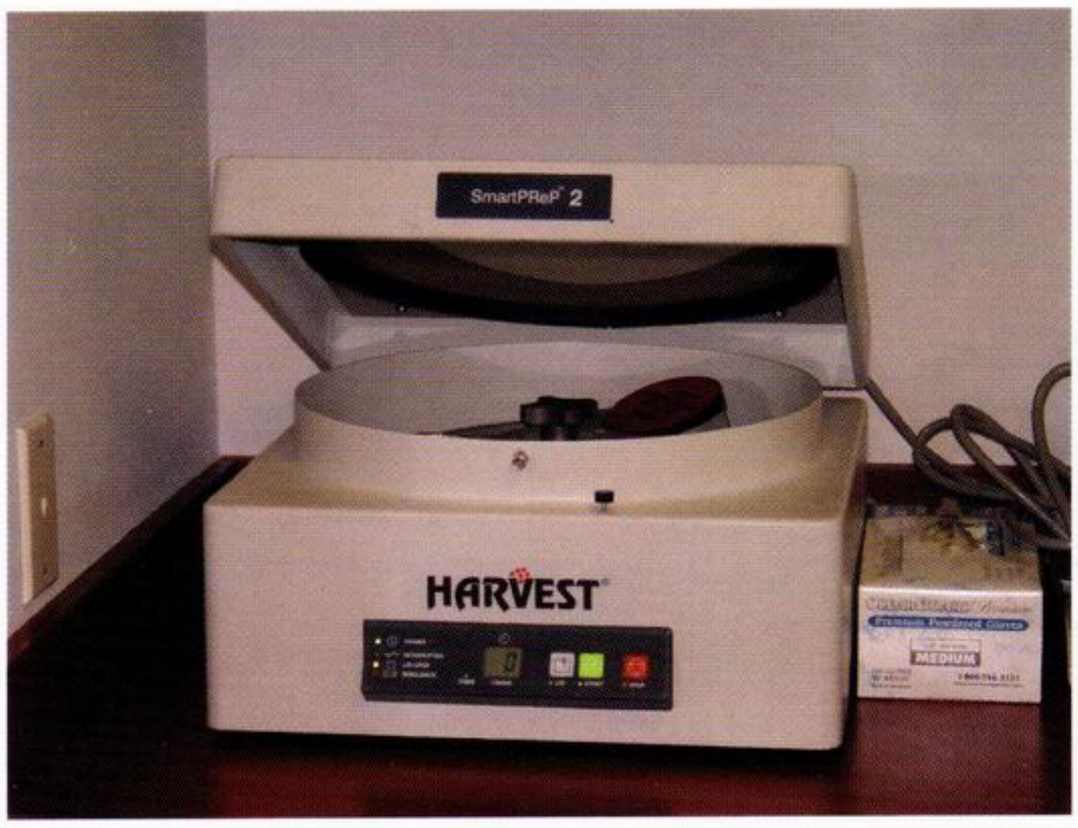
Summary: This wound was successfully closed with 2 treatments of autologous platelet concentrate in 21 days.

Results and Discussion:

Clinically, the results attained with the use of autologous platelet concentrate have been impressive. A 94% success rate was achieved in this series of chronic wounds. Criteria for success were complete epithelialization. Not only has this technology repeatedly proved itself with closure and epithelialization in different types of wounds, and in the most difficult refractory cases, there is certain economic benefit as well. While this technology is simple to use, and is effective in the office based setting, huge savings of the healthcare dollar can be anticipated once this technology becomes more available. In addition to further implementation of this technology into the wound care arena, it is the author's opinion that widespread use of this technology will become commonplace in other aspects of podiatric surgery. APC+ will effect enhancement and acceleration of bone healing in osteotomies, for example common procedures like bunionectomies, and augment bone grafting techniques. It is also very likely to prove useful in myriad other podiatric situations. Investigation has begun on the use of growth factors in tendonopaties, and degenerative processes in joints. This technology may greatly change the way podiatric surgeons view, and manage many different clinical pathologies.

PHOTOS AND LEGENDS:

PHOTO 1



This is the SmartPReP® system, which is compact and small enough to be transported to the operating room.

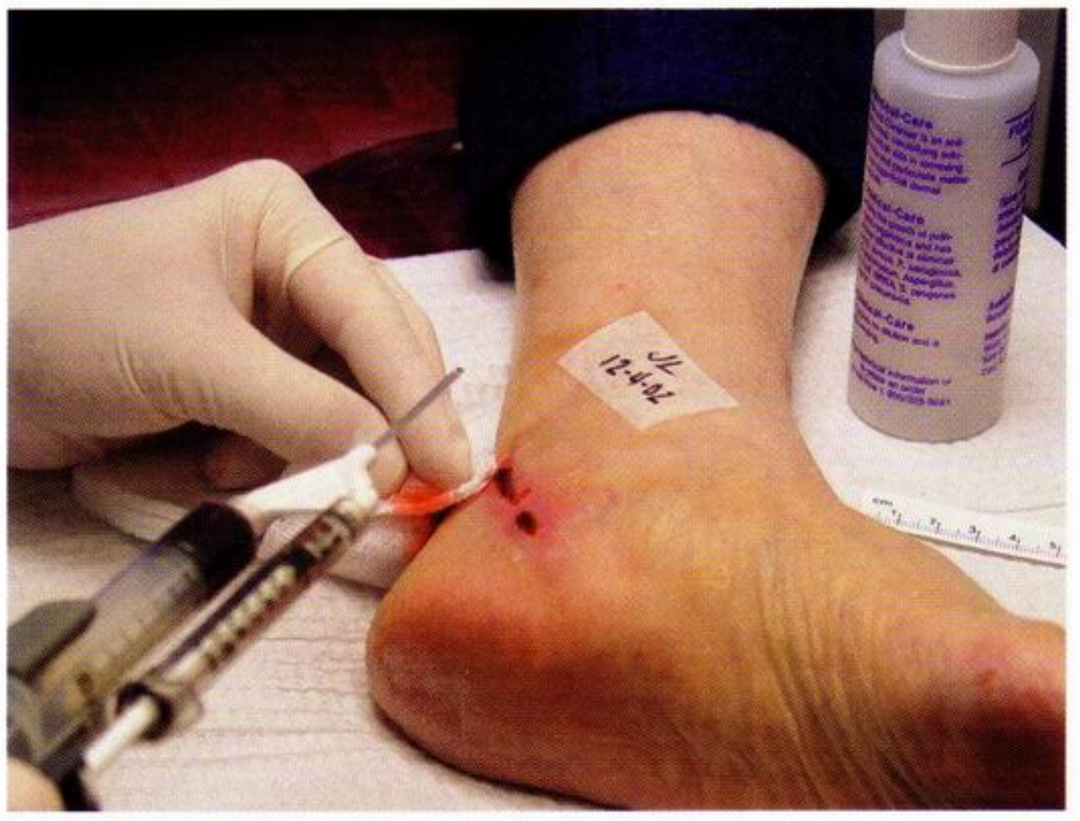
PHOTO 2

After 14 minutes of processing, the platelet concentrate can be seen in the bottom of the sterile container. The amber fluid is the platelet poor plasma, and is pulled off the platelet pellet as seen here.

PHOTO 3

Once the platelet poor plasma (PPP) has been pulled out of the container, the platelet concentrate can then be re-suspended in a small amount of PPP.

PHOTO 4



The double syringe applicator allows for the delivery, activation and application of the autologous platelet concentrate (APC+). The small clear syringe contains the calcium chloride/thrombin solution, while the larger syringe stores the APC+.

References:

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