

Tension-free Primary Closure with Autologous Platelet Gel versus Vivostat™ for the Definitive Treatment of Chronic Sacrococcygeal Pilonidal Disease

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Abstract. *Objective:* A randomized clinical trial was performed in patients with chronic or recurrent pilonidal sinus (PS) comparing primary closure coupled with random application of in house autologous platelet gel or produced by means of Vivostat™ in order to assess whether a standardized product had an impact on the wound healing process. *Patients and Methods:* Between June 2006 and June 2009, 100 patients (82 males, 18 females: median age 30 years; range, 16-51 years) underwent wide excision of the pilonidal area with midline tension-free closure and were randomly given either the in house autologous platelet gel (Group 1) or the Vivostat™ gel (Group 2). *Results:* Group 2 patients had shorter wound healing time (8 vs. 10 days; $p < 0.0001$), time to return to full activity (11 vs. 16 days; $p < 0.0001$), less uncomplicated fluid collections (120 vs. 190 ml: $p < 0.0001$), and fewer postoperative wound complications (1/50=2% vs. 5/50=10%, $p < 0.001$). After a median follow-up of 21 months (range: 4-40 months), two recurrences were detected in Group 1. *Conclusion:* The standardized production of platelet gel by means of the Vivostat™ system guarantees the reproducibility of the procedure and its use was correlated with an improved outcome, with a high degree of patient satisfaction and better cosmetic results.

Pilonidal sinus (PS) is a rather common disease that arises in the hair follicles of the natal cleft of the sacrococcygeal area; it primarily affects young adults and teenagers, with a 70-80% male predominance (1, 2). Although PS cannot be regarded as a life-threatening condition, it may be a serious cause of morbidity, with postoperative pain, time lost from

school or work, even for some months. Patients with uncomplicated disease, such as those with asymptomatic pits, do not require any treatment (2). Half of all patients present with an abscess and adequate surgical drainage is required, unless spontaneous drainage has already occurred (2, 3). For the majority of these patients, abscess drainage provides a definitive treatment but if the disease persists beyond two or three months, additional surgery should be considered (3, 4). The treatment of chronic or recurrent pilonidal sinus is much more controversial: basically, treatment requires eradication of the sinus tract, complete healing of the overlying skin, and prevention of recurrence. After excision of the pilonidal area the surgical wound may be left open, with healing by secondary intention. The supporters of this open method suggest that it reduces wound tension, and wound infection, as well as recurrent disease. However, it requires an aggressive management by both the patient and the surgeon in order to keep the wound clean, with longer healing time, resumption of normal activities, and less than optimal cosmetic results (1). Conversely, primary closure has the potential to achieve early wound healing if infection does not develop, with less morbidity and earlier return to full activity. Several techniques have been proposed in order to reduce wound tension, with midline as opposed to off-midline closures and flap repairs (1, 5). Recently, attention has been directed toward the use of biological materials aimed at improving the wound healing process, with special emphasis on fibrin glue, due to its sealant properties (4, 6-7).

In our former experience, a consecutive clinical study was performed in 30 patients with complex chronic or recurrent PS, and an improved outcome was observed in patients undergoing an original technique of midline tension-free closure as compared to the traditional open method. In a subsequent set of 15 patients, this tension-free surgical technique was coupled with the application of an autologous platelet gel that remarkably improved tissue repair, thus avoiding any wound dehiscence or recurrence (8). This effect was specifically related to the biological properties of the platelet gel, which couples the sealant properties of fibrin

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Key Words: Pilonidal sinus, platelet gel, surgical technique.

Table I. Patient characteristics.

	Age (years)		Gender		BMI			Duration of symptoms		Type of disease months	
	<25 n (%)	>25 n (%)	M n (%)	F n (%)	<25 n (%)	25-30 n (%)	>30 n (%)	<12	>12	Primary	Recurrent
Group 1 (n=50)	24 (48)	26 (52)	42 (84)	8 (16)	23 (46)	25 (50)	2 (4)	18 (36)	32 (64)	46 (92)	4 (8)
Group 2 (n=50)	23 (46)	27 (54)	40 (80)	10 (20)	20 (40)	27 (54)	3 (6)	22 (44)	28 (56)	43 (86)	7 (14)
Total (n=50)	47	53	82	18	43	52	5	40	60	89	11

BMI: Body mass index.

Table II. Outcome measures in the three groups of patients.

Outcome measure	Group 1	Group 2	P-value
Operative time (minutes)	40 (range: 35-48)	42 (range: 38-47)	0.5437
Oral analgesic needed (no. of tablets)	6 (range: 4-9)	4 (range: 2-5)	<0.0001
Serous drainage (ml)			
Suction drainage	80 (range: 60-100)	50 (range: 40-60)	<0.0001
Needle aspiration	110 (range: 90-130)	70 (range: 60-80)	<0.0001
Total	190 (range: 150-230)	120 (range: 100-140)	<0.0001
Wound healing time (days)	10 (range: 8-13)	8 (range: 7-9)	<0.0001
Time to return to full activity (days)	16 (range: 12-28)	11 (range: 8-18)	<0.0001
VAS			
Preoperative	4	4	0.4529
Postoperative	7	9	<0.0001
Postoperative complications			
Bleeding	1 (2%)	0	<0.0001
Wound dehiscence	3 (6%)	1 (2%)	0.6173
Wound infection	1 (2%)	0	<0.0001
Total	5 (10%)	1 (2%)	<0.0001
Recurrence	2 (4%)	0	0.4949

VAS: Visual analogue scale.

with the promoting activities of tissue repair due to the release of growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), insulin growth factor-I (IGF-I) and IGF-II, which are stored within platelet α-granules (9-12). However, because of the variability of platelet concentration of the patient's starting material, method of collection, modalities and time of preparation, there is no real standardization of the final product (13, 14). Such standardization seems to be guaranteed by the Vivostat™ system (Vivostat A/S, DK-3450, Allerød, Denmark) which prepares autologous platelets with growth factors in a fibrin sealant matrix (15).

On these grounds, a randomized clinical trial was performed in patients with chronic or recurrent PS comparing our original midline tension-free technique of wound reconstruction coupled with a in-house autologous

platelet gel, or prepared by means of Vivostat™ system in order to assess whether the standardized product might improve the wound healing process, as well as speed up and guarantee the reproducibility of the procedure.

Patients and Methods

Between June 2006 and June 2009, 100 patients with chronic or recurrent PS were recruited in a randomized clinical trial that was performed at the Department of General Surgery, Colo-Rectal Unit of San Martino University Hospital in Genoa, Italy. Institutional Ethic Committee approval and written informed consent was obtained. Patients underwent a complete medical history and full clinical examination. The following data were collected: age, gender, body mass index, duration of the symptoms, type of disease (primary or recurrent). Patient characteristics are shown in Table I. The operation was always performed as a one-day surgical

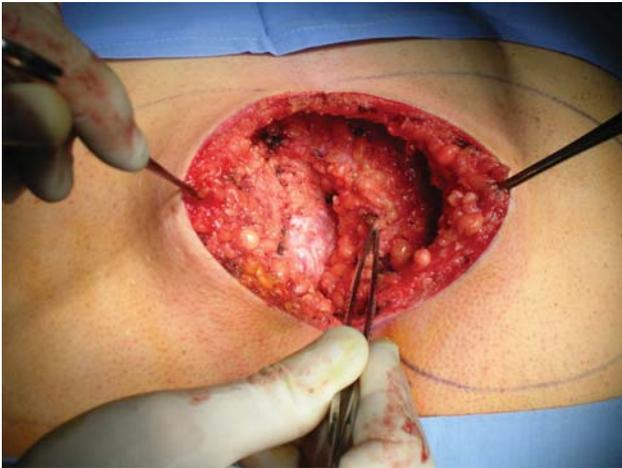


Figure 1. Following the complete excision of the pilonidal area, a thick fibroadipose flap is prepared on both sides; the flap on the right of the operative field can be seen.



Figure 3. The stitches on the midline have been tied and a second dose of in-house autologous platelet gel is applied to the more superficial space underlying the subcutaneous tissue.



Figure 2. Once the first row of stitches on the midline has been performed, the in house autologous platelet gel is applied to the bottom of the operative field, to fill the deep space overlying the postsacral fascia.



Figure 4. Autologous cryoplatelet gel is sprayed into the wound when the Vivostat™ system is used.

procedure; all patients were operated on under spinal anaesthesia. Antibiotic prophylaxis was performed with amoxicillin-clavulanic acid, starting with 1.2 g intravenously at induction of anaesthesia, and 1.2 g after 12 h on the operative day, followed postoperatively by 1 g orally given twice daily for five days. A wide excision of the pilonidal area down to the postsacral fascia with complete removal of the raphe was always performed; a midline tension-free technique of wound reconstruction was adopted in all patients (Figures 1-4), as described elsewhere (8). Moreover, an autologous platelet gel produced in house (Group 1) or by means of Vivostat™ system (Group 2) was randomly applied before wound closure into both the deep and subcutaneous space. Patients were always discharged from hospital with suction drainage in place, and it was always removed after five days. Needle-aspiration of the wound was routinely performed during outpatient visits in order to empty any fluid

collection, even if clinically undetectable. Patients were requested to register the total number of tablets (ketorolac, 10 mg) they had consumed in the postoperative period for an indirect quantification of pain; moreover, a visual analogue scale (VAS) of 0-10 score was preoperatively obtained as baseline disease-related index of satisfaction, with a re-assessment one month after surgery.

Primary outcomes included: a) time to wound healing, defined as full epithelization over the wound (days); b) uncomplicated serous collection within the wound (ml); c) postoperative wound complications (infection, dehiscence, bleeding), and d) recurrence. Secondary outcomes included: a) postoperative pain assessment (overall consumption of ketorolac tablets); b) time to return to full activity (days); and patient satisfaction (pre- vs. post-operative VAS, 0-10). Follow-up examinations were conducted at 3, 6, 12 and 18 months after surgery.

Technique for in-house preparation of platelet gel. Patients undergoing platelet gel application were accepted two days before the operation at the Immunohematology Service where 450 ml±10% of whole blood were collected in a standard quadruple blood bag. The blood was immediately centrifuged to obtain packed red blood cells (PRBCs) and platelet-rich plasma (PRP). PRBC were reinfused to the patient. PRP was centrifuged to obtain platelet-poor plasma (PPP) and platelet-concentrate (PC). PPP was immediately frozen at -80°C in a mechanical refrigerator in order to obtain fresh frozen plasma. The frozen plasma (FFP) was then kept at 4°C for 18 h for spontaneous thawing. Cryodepleted plasma was removed and the cryoprecipitate was suspended in 30 ml of cryodepleted plasma. The cryoprecipitate was again stored at -30°C, while PC was kept at 22°C under continuous agitation.

As regards the quality control of the product, PC had a total platelet count of $0.6 \times 10^{11} \pm 10\%$, residual leukocytes of 0.2×10^9 , and volume of $40 \text{ ml} \pm 10\%$. The cryoprecipitate had factor VIII >70 UI×100 ml, fibrinogen ≥140 mg/unit, and a volume of $30 \pm 2 \text{ ml}$.

Technique for preparation of autologous thrombin. For the preparation of autologous thrombin, 27 ml of blood were collected in three sterile tubes at the moment of blood donation, with 1 ml in full ACD-A solution. The tubes were centrifuged at 3,000 rpm for 10 min. The plasma was transferred, under sterile conditions, to a second sterile tube and 1 ml of sterile CaCl was added to 5 ml of plasma. The tubes were incubated for 30 min at 37°C. The clotted plasma was then centrifuged for a second time for 10 min at 3,000 rpm. The supernatant is serum rich in thrombin and must be stored at -30°C until used.

Preparation of in-house platelet gel. The preparation of the platelet gel was as follows: $10 \pm 2 \text{ ml}$ of PC were mixed with $10 \pm 2 \text{ ml}$ of cryoprecipitate in a sterile plastic Petri-dish of 10 cm diameter. For each 10 ml of PC and cryoprecipitate solution, 1 ml of autologous thrombin and 1 ml of calcium gluconate were added, then the contents of the Petri-dish were mixed. After 10 to 15 minutes of incubation at room temperature, a gel-like material was obtained. The platelet gel so obtained, kept at room temperature, must be used within 8 hours.

Technique for the preparation of cryoplatelet gel with Vivostat™. The Vivostat™ system is a medical device for the preparation and application of patient-derived platelet-rich fibrin (PRF). The system is fully automated, microprocessor controlled, and made up of three components: i) a processor unit; ii) an applicator unit, and iii) a disposable single-patient-use kit that includes a preparation set and a spray-pen applicator. On the day of surgery, citrate is added to a preparation bowl; 120 ml of the patient's own blood is drawn into the same unit. The preparation unit is placed into the processor unit. After only 23 minutes, a syringe of $6 \pm 1 \text{ ml}$ autologous PRF solution is ready for use. The PRF solution is loaded into an applicator unit and is applied by a unique spray-pen. Due to the instant polymerization of the fibrin, the PRF solution remains where it is applied to the surgical field.

The quality control of the product was as follows: the concentration of platelets was approximately 10 times the base level of the donor's blood; the concentration of fibrin was approximately 7 times the base level of the donor blood.

Statistical analysis. Quantitative variables were fitted with the use of parametric tests (Gaussian distribution and homoscedastic variance).

Data were expressed as mean±standard deviation (SD) and percentages. The differences between groups were tested for significance by independent sample *t*-test. The level of significance was considered as $\alpha \leq 0.05$. Univariate analysis of variance was compared by ANOVA test and was used to assess the variation of VAS scores.

Results

There were 82 male and 18 female patients, with a median age of 30 years (range 16-51 years). In all patients, histopathology confirmed the clinical diagnosis of PS, with detection of hair tufts in the cavities of PS. Patient characteristics were similar in the two groups of patients (Table I). With regards to the quantitative and qualitative assessment of in house platelet gel (Group 1), patients were given 22 g, with a thickness of platelet gel ranging from 1 to 2 mm, and a mean platelet total count of $0.15 \times 10^{11} \pm 56\%$. Patients in Group 2 received a median volume of 5 ml, with a mean platelet total count of $0.12 \times 10^{11} \pm 17\%$.

The analysis of outcome measures is reported in Table I. Patients in Group 1 had a higher consumption of analgesic tablets in the postoperative period (6 vs. 4: $p < 0.0001$). Group 2 patients had a shorter wound healing time (8 vs. 10 days: $p < 0.0001$) and an earlier return to full activity (11 vs. 16 days: $p < 0.0001$). The mean total amount of uncomplicated fluid collected in the wound (suction drainage plus needle-aspiration after drainage removal) was higher in Group 1 (190 vs. 120 ml: $p < 0.0001$). The overall wound complication rate was higher in Group 1 (10% vs. 2%: $p < 0.001$), with bleeding ($n=1$), wound dehiscence ($n=3$), and wound infection ($n=1$) in Group 1 as compared to wound dehiscence ($n=1$) in Group 2. Moreover, in 4 patients (8%) receiving the in house platelet gel, an overgrowth of regenerative tissue from the midline wound occurred, and it was treated with repeated topical application of silver nitrate stick. There were two recurrences (4%) in Group 1 as compared with no recurrence in Group 2.

A significant increase in the patient satisfaction index was observed in Group 2 as compared to Group 1, comparing pre- and postoperative VAS scores ($p < 0.0001$). In both groups, however, patients were generally satisfied with the operation, mainly because wound healing was rather quick without the need for frequent and painful dressing, even for months, contrary to the lay people belief derived from the experience of patients undergoing healing by granulation of open wounds. Moreover, the cosmetic result of the midline wound was greatly appreciated. The duration of follow-up ranged from 4 to 40 months (median: 21 months), no patients being lost at follow-up; two recurrences were detected in Group 1 patients.

Discussion

From the clinical standpoint, two categories of PS can be differentiated. First, that of acute pilonidal abscess which is usually treated merely by drainage with local anaesthesia, in

compliant patients. In the clinical experience of Jensen and Harling (16), this policy achieved healing in 58% of patients and only 27% required definitive treatment of the underlying PS. Second, that of chronic or recurrent PS, managed by many methods, such as sinus extraction (Lord-Bascom procedure), excision and healing by granulation, excision and marsupialization, excision and primary closure, or excision and flap closure (17). The ideal operation should be simple, require a short hospitalization time with minimal postoperative pain, disability and a low risk of complications, such as recurrence or persistence of the sinus or ongoing infection (18).

Healing by granulation of open wounds has been traditionally matched with healing by primary healing of closed wounds. Data from a recent meta-analysis suggest: firstly, more rapid healing after primary closure, with a time ranging from 41 to 91 days for open wounds as compared to 14 to 27 days for closed wounds; secondly, although the general consensus in the surgical literature would confirm that healing by secondary intention results in a lower infection rate, this was not supported by the review (risk ratio=1.2: 0.55-2.63, 95% CI); thirdly, early return to work, which is a function of several variables including time to wound healing, pain, wound complications and wound dehiscence, represents an important outcome in the management of a disease that predominantly affects younger people, and a clear benefit was found in patients undergoing primary closure, with a mean difference of 10.48 days (5.75-15.21 days, 95% CI); fourthly, the recurrence rate was lower for open *versus* closed wounds, with an overall risk ratio of 0.42 (0.26-0.66, 95% CI) but the difference was not significant for off-midline procedures (1).

Most drawbacks of closed wounds regarding wound complications and recurrence are related to the type of midline closure, because simple closure in the midline after wide excision of the pilonidal area is usually performed under tension and this may lead to ischemia of the wound edges, with higher risk of local infection. On the other hand, should the surgeon hesitate to perform a wide excision with clear margins for fear of closure problems, the risk of wound contamination or residual disease is increased further. In fact, infection rates after midline closure are quite variable, ranging from 0 to 35.9%, wound dehiscence is excess of 7%, and recurrence ranges from 1.4 to 21.2%; conversely, infection rates after off-midline closure range from 1.8 to 8.5%, wound dehiscence is low at 1.8%, and recurrence ranges from 0.9 to 4.4% (5). These data are explained by the pathogenesis of the disease which is now widely accepted to be an acquired phenomenon. According to Karydakis, hair insertion at the depth of the natal cleft, the raphe, is the true cause of PS. Three main factors contributing to the hair insertion process were identified: i) the invader, consisting of loose hair; ii) the force (the depth and narrowness of the

natal cleft together with friction movements between its sides), which causes hair insertion; and iii) the vulnerability of the raphe (19). Surgical treatment can modify at least two of these factors, namely the force and the vulnerability of the raphe. Karydakis's original operation increased local defences against hair insertion by removing the vulnerable raphe, replacing it with healthy skin and avoiding any midline wound scar at the depth of the natal cleft. In his experience on 5,876 patients, a remarkable 8.5% wound infection rate and 0.9% recurrence rate were reported (19). In a recent modification of this technique, the base of the flap is sutured directly to the lateral edge of the wound: postoperative complication rate was 7.3% and no recurrence after a mean follow-up of 20±6.8 months (20).

Our surgical approach pursued these same objectives, that is the complete removal of the vulnerable raphe down to the level of the tip of the coccyx and flattening of the natal cleft, due to the specific type of wound reconstruction, in order to prevent the development of future sinuses. The use of two thick fibroadipose flaps, which were prepared by undermining just superficial of the gluteus muscle fascia and sutured on the midline to create the first deep suture line, flattened the natal cleft. Moreover, they proved effective in preventing wound dehiscence by reducing suture line tension, according to a basic tension-free principle in surgery. However, this type of reconstruction was hampered by an increased amount of serous discharge, which might predispose to wound infection and dehiscence (8). Although suction drainage may be helpful in preventing fluid collection into the wound it cannot be regarded *per se* as the optimal solution, unless the complete obliteration of the cavity with regenerated tissue can be rapidly obtained. Hence, the true biological innovation was represented by the use of an autologous platelet gel, which couples the sealant properties of fibrin gel to the regenerative potential of growth factors (PDGF, TGF- β , IGF-I and IGF-II) released by platelet α -granules, which promote the process of tissue repair (9-12). Thanks to regenerative surgery, we demonstrated that complete wound healing was accomplished in a short time with minimal postoperative disability and no recurrence, short follow-up notwithstanding (8).

However, a methodological bias was represented by the variable composition of the in house autologous platelet gel which is related to platelet concentration in the patient's starting material, method of collection, modalities and time of preparation, and concentration of growth factors, so that there is no real standardization of the final product, thus reducing the reproducibility of the procedure (13, 14). Moreover, in house product is prepared by an open method which may increase the risk of platelet gel contamination. Standardization seems to be guaranteed by the Vivostat™ system which allows, on the same day of surgery, just a

couple of hours before the scheduled operation, a gel with a sufficient quantity of growth factors to be obtained using a completely sterile and standardized technology, with less variability of total platelet count.

Our findings suggest that the combined use of a midline tension-free closure coupled with the traditional application of in house autologous platelet gel achieved early wound healing and recovery of full activity, and an appreciable cosmetic result coupled with a low recurrence rate (4%), thus confirming the results of our preliminary experience. The use of a standardized gel produced with the Vivostat™ system proved even more effective in promoting the wound healing process, it required a single visit to the hospital on the day of the scheduled operation, and it was available in a sterile set easily applied. The Vivostat™ technology provides sustained release and protection against proteolytic degradation of endogenous fibrogenic factors, which may be relevant for wound healing (15). Of note, this sustained and progressive growth factor release from platelets, which is a specific feature of the Vivostat™ system as compared to the massive release of growth factors of in house thrombin-activated PC, may explain the occurrence of an overgrowth of regenerative tissue arising from the wound observed in a few patients (8%) receiving the in house gel. In this clinical setting, what is actually needed is a regulation of the wound healing process more than a maximal stimulation of tissue regeneration as is required in other patients, *i.e.* those with chronic ulcers whose tissues have completely lost any regenerative property. There was also a close correlation between an earlier return to full activity with an increased index of patient satisfaction due to reduced postoperative pain, lower request for analgesic drugs, less fluid collection and painless wound dressing.

The regenerative properties of the autologous cryoplatelet gel and the flattening of the natal cleft obtained with this type of midline tension-free wound reconstruction played a synergistic role in avoiding recurrent disease. The possibility of achieving a rapid and safe wound closure makes the surgeon more comfortable in performing wide excision of the pilonidal area and the raphe, which is the mainstay for the prevention of disease recurrence. From the surgical standpoint, there is a substantial difference with the combined approach proposed by Seleem and Al-Hashemy (4), because their tension-free technique consisted of the removal of a minimal amount of skin and subcutaneous tissue. A rather limited excision was also reported by Greenberg *et al.* (6), who used a skin flap with removal of the pilonidal cysts and sinuses without skin excision, and used fibrin glue as a sealant, in order to fill the dead space under it. Only Altinli *et al.* (7) performed a wide excision of the pilonidal area down to the postsacral fascia and laterally to the fascia of the gluteus maximus muscle; the operation was completed with a standard Limberg flap technique alone or with fibrin sealant

application before drain insertion. Interestingly, only fibrin glue was used as a sealant in these studies, and it is produced from a large pool of blood donation with higher risk of transfusion-transmitted disease. Our regenerative approach was substantially different: firstly, only autologous platelet gel was given to the patients, thus avoiding any side-effects due to allogenic blood product transfusion; secondly, this gel combines the sealant properties of fibrin with the promoting activities of tissue repair due to the release of growth factors not included in commercial fibrin glue (9-12). The production of this gel by means of the Vivostat™ system allows the determination of both the volume of gel actually delivered into the wound and its concentration of growth factors, using a completely sterile and standardized technology, thus ensuring the reproducibility of the procedure.

Conclusion

The standardized production of autologous platelet gel by means of the Vivostat™ system guarantees the reproducibility of the procedure due to the defined volume of platelet gel that can be delivered into the wound and concentration of growth factors. This was translated into an improved outcome of patients undergoing surgical excision of chronic or recurrent PS with midline tension-free closure, as suggested by the short wound-healing time, time to return to full activity, high degree of patient satisfaction, better cosmetic results, and absence of recurrence, so that it may be regarded as a viable treatment option in the management of such patients.

Conflict of Interest

In regard to the use of Vivostat™, no conflict of interest exists.

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Received December 23, 2009

Revised April 21, 2010

Accepted April 28, 2010