Lasers in Surgery and Medicine 52:503–508 (2020)

Photodynamic Therapy for the Treatment of Complex Anal Fistula

Antonio Arroyo, MD, PhD,[1] Luis Sánchez-Guillén, MD,[1*] Pedro Antonio Parra, MD, EBSQ-c,[2] Luis García-Catalá, MD,[1] Emilio Peña-Ros, MD, PhD, EBSQ-c,[2] Manuel Ferrer-Márquez, MD, PhD, EBSQ-c,[3] Carmen Nofuentes Riera, MD,[4] Xavier Barber-Valles, PhD,[5] and Manuel Romero-Simó, MD, PhD[6]

[1]*Colorectal Unit, Department of General Surgery, Elche University Hospital, Miguel Hernández University, Carrer Almazara, 11, Elche, Alicante, 03203, Spain*

[2]*Colorectal Unit, Department of General Surgery, Reina Sofía University Hospital, UCAM Universidad Católica de Murcia, Av. Intendente Jorge Palacios, 1, Murcia, 30003, Spain*

[3]*Colorectal Unit, Department of General Surgery, Torrecardenas University Hospital, Calle Hermandad de Donantes de Sangre, s/n, Almería, 04009, Spain*

[4]*Colorectal Unit, Department of General Surgery, San Juan University Hospital, Miguel Hernandez University, Ctra. Nnal. 332, s/n, 03550 Sant Joan d'Alacant, Elche, Alicante, Spain*

[5]*Center of Operations Research, Miguel Hernandez University, Avinguda de la Universitat d'Elx, s/n, Elche, Alicante, 03202, Spain*

[6]*Colorectal Unit, Department of General Surgery, Alicante University General Hospital, Miguel Hernandez University, Pintor Baeza, 11, Elche, Alicante, 03010, Spain*

Background and Objectives: To validate and analyze the results of intralesional photodynamic therapy in the treatment of complex anal fistula.

Study Design/Materials and Methods: This prospective multicentric observational study enrolled patients treated for complex anal fistula who underwent intralesional photodynamic therapy (i-PDT). The included patients were treated from January 2016 to December 2018 with a minimum follow-up of 1 year to evaluate recurrence, continence and postoperative morbidity. Intralesional 5-aminolevulinic acid (ALA) gel (2%) was injected directly into the fistula. The internal and external orifices were closed. After an incubation period of 2 hours, the fistula was irradiated using an optical fiber connected to a red laser (Multidiode 630 PDT) operating at 1 W/cm for 3 minutes (180 J).

Results: In total, 49 patients were included (61.2% male). The mean age was 48 years, and the mean duration of fistula was 13 months. Of the fistulas included, 75.5% were medium transphincteric, and 24.5% were high transphincteric. The median fistula length was $4 \pm 1{,}14$ cm (range: 3–5). A total of 41 patients (83.7%) had a previous history of fistula surgery. Preoperatively, some degree of anal incontinence was found in 5 patients (10.2%). No center reported any other procedure-related complications intraoperatively. Phototoxicity was found in one patient. In the first 48 hours after the procedure, fever was reported in 2 patients (4%). At the end of follow-up, total healing was observed in 32/49 patients (65.3%). No patient reported new incontinence postoperatively.

Conclusion: i-PDT could be considered a good choice in patients with complex anal fistulas to avoid surgery and its complications. Lasers Surg. Med. © 2019 Wiley Periodicals, Inc.

Key words: complex anal fistula; surgery; photodynamic therapy; incontinence; proctology

INTRODUCTION

Cryptoglandular anal fistula is a complex disorder for patients and colorectal surgeons. It is diagnosed on the basis of clinical features, physical examination, and radiological tests [1,2] and has a substantial impact on the physical health, social functioning, and quality of life of patients.

Complex anal fistula management still represents a therapeutic challenge for colorectal surgeons. Successful healing must restore a fragile balance between perianal sepsis control while preserving sphincteric apparatus and the mechanism of continence [3].

Several different therapeutic approaches to this pathology currently exist, reflecting the complexity of anal fistulas. Most of them have a high rate of complications, including recurrence (30–40%) or fecal incontinence (0–45%) [4,5].

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

*Correspondence to: Luis Sánchez-Guillén, MD, Hospital General Universitario de Elche, Carrer Almazara, 11, 03203 Elche, Alicante. E-mail drsanchezguillen@gmail.com

Accepted 2 September 2019
Published online 19 September 2019 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/lsm.23162

In the quest for safer and simpler procedures, some sphincter-preserving techniques have been developed in recent years, including anal collagen plugs [6], video-assisted anal fistula treatment [7], ligation of interesphincteric fistula tract (LIFT) [8,9] and fistula laser closure (FILAC) [10,11]. Although they showed minor or no detrimental effects on continence, high recurrence rates have been reported (30–60%). Thus, none have been universally accepted as the gold-standard surgical approach [12].

Recently in dermatology, photodynamic therapy (PDT) has been increasingly used for the treatment of chronic inflammatory skin disorders such as Hidrosadenitis suppurativa. This therapy has shown to have promising results, with healing rates of up to 76.3% [13] and a negligible associated morbidity. These results suggest that this may be a new, safe, and reproductible tool to consider.

Our group pioneered a pilot study using PDT for complex anal fistula. In our sample of 10 patients, this therapy resulted in an initial healing rate up to 80%, with a median follow-up duration of 14.9 months [14]

The present study aimed to validate and analyze the results of this technique performed in several hospitals among a larger number of patients.

METHODS

This prospective, observational study enrolled patients treated for complex anal fistula who underwent PDT in the coloproctology units of the General Hospital of Elche, Reina Sofia Hospital of Murcia, General Hospital of Alicante, Torrecardenas Hospital of Almeria, and San Juan Hospital of Alicante. Included patients were treated from January 2016 to December 2018 with a minimum follow-up of 1 year. The study was approved by the Clinical Research Ethics Committee of the hospital (ID: TFD-ALA) and registered at ClinicalTrials.gov (NCT03864718). All participants were informed and signed consent.

Patients were diagnosed by physical examination, proctoscopy, and preoperative ultrasound.

Complex anal fistulas were included in the analysis according to Parks classification [1] and were divided into high fistulas or high tracks (suprasphincteric [SS] and high transphincteric [HT]) and non-high fistula or non-high tracks (medium transphincteric). An SS fistula was defined as a track that crossed the intersphincteric space between the external sphincter and the puborectal muscle and then returned to the perianal skin. A transphincteric fistula was defined as a fistula that crossed both sphincters. According to the sphincter percentage involved below the track, we defined a fistula as high transphincteric when it involved more than 50% of the external sphincter and as a medium transphincteric fistula when it affected less than 50%.

Patients with non-cryptoglandular fistulas, acute sepsis, inflammatory bowel diseases and simple fistulas (defined as subcutaneous, intersphincteric and low transphincteric fistula) were excluded from the study, as were those who were pregnant, classified as ASA IV, aged younger than 18 years, immunocompromized (e.g., HIV) or refused to give their consent.

PDT was performed by two colorectal surgeons according to a defined and reproducible procedure. Data were collected following a protocol designed for this study. Anal incontinence was evaluated by the Wexner scale, ranging from 0 (full continence) to 20 (total incontinence).

Surgical Technique

A preoperative prophylactic dose of antibiotic (metronidazole 1.5 g/intravenous + tobramycin 250 mg/intravenous) and no mechanical bowel preparation was prescribed to all patients. Regional anesthesia (a spinal or sacral block) is preferred since the probing of fistula and track is painful and often fails. Intrathecal hyperbaric anesthetic, bupivacaine 10 mg, was administered in a sitting position for 5 minutes, thereby producing anesthesia in the desired area during the time required to perform the two procedures. The surgical site was chosen, and the patient was placed in the lithotomy position.

The fistula track and internal opening were identified by injecting hydrogen peroxide through the external opening. Then, the internal opening was closed using a simple polyglactin 3-0 suture, and 2 ml of 2% 5-ALA in saline was directly injected with an intramuscular needle around and at the depth of the internal opening.

The fistula track was filled with 2% ALA through the external opening using a plastic 14F catheter with catheter marks in centimeters in the fistula track. A volume of 2 ml of ALA was used per centimeter to obliterate the entire fistula. The external opening was closed using a simple polyglactin 3-0 suture to keep the solution in the fistula track during the incubation period of 2 hours.

In a second stage of the procedure after 2 hours in the recovery room, a guide wire and a plastic 14F catheter marked in centimeters was inserted into the fistula track after removing the external opening suture. The laser fiber is introduced into the centimeter catheter with its tip at the internal opening. Beginning from the internal opening and progressively withdrawn the fiber at 1 cm (Fig. 1), the fistula was irradiated by a continuous wave of 630-nm light from the optical fiber, which was connected to a red laser (Multidode 630 PDT; INTERmedic, Barcelona, Spain) operating at 1 W/cm for 3 min (180 J).

Laser device is a single-use fiberoptic silica/fluoropolymer with 600 μm diameter and 0.37 NA. The fiber is flat cut with no diffuser at the end. An internal photodiode and an external test verify the correct light irradiated.

2% 5-ALA is a magistral preparation formulated in the Pharmacy Hospital Service.

Postoperative Stage

All patients were discharged from the hospital the same day of the operation with normal diet, oral antibiotics (metronidazole, 500 mg every 8 hours for 7 days) and an analgesic (lornoxicam, 8 mg every 12 hours for 5 days).

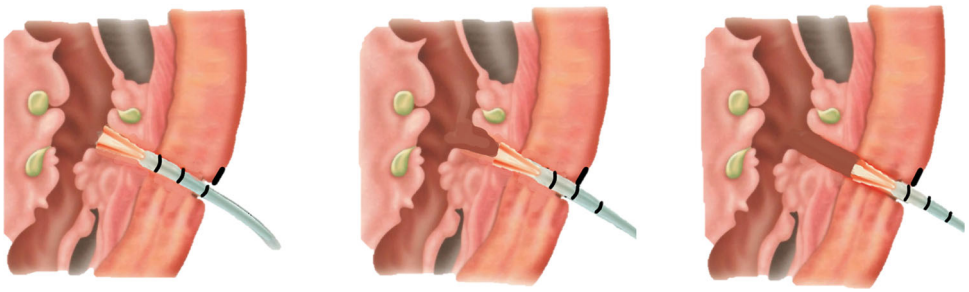

Fig. 1. Laser fiber irradiating fistula track from the internal opening and progressively withdrawing the fiber at 1 cm until the external fistula opening.

Follow-up

The patients were examined on a regular basis in the outpatient clinic at the first, third, sixth, and twelfth postoperative months. Physical examination and a proctoscopy were conducted at every visit. Continence was assessed at every visit according to the Wexner continence grading scale. Pain was evaluated using a visual analog pain scale score (0 = no pain, 10 = extreme pain) at three time points (during the first day, during the first week and after 30 days). Adverse effects (swelling, pain, erythema, and other side effects) were also assessed.

Fistula healing was considered when patients had no purulent drainage through the fistula track and when the external and internal openings had healed or closed with no symptoms.

The primary outcome was recurrence and was defined as the presence of purulent drainage or any openings 3 months after surgery. In addition, we considered recurrence as the new opening of a fistula after initial healing.

Statistical Analysis

The descriptive statistics were calculated depending on whether the variable was continuous (mean and standard deviation) or discrete (percentage). The following tests were used: Fisher's exact test for categorical variables, Mann–Whitney *U* or Kruskal–Wallis tests for ordinal variables, and non-parametric ANOVA for continuous variables by applying of rank transformation on the dependent variable.

Logistic regression models were used to identify potential predictors and to estimate risks (odds ratios [OR]) and 95% confidence intervals (95% CI) of response Wexner score at the end of the study. Variables with a P value ≤ 0.2 on univariate testing were selected for the multivariate analysis.

All tests of significance were two-tailed. Statistical significance was set at $P < 0.05$. Analysis was performed using R software 3.5.1 (R Core Team, 2018).

RESULTS

In total, 49 patients were included in this study: 30 male (61.2%) and 19 female. The mean age was 51 ± 14.01 years (IC range: 18–65). The median BMI was 29 ± 6 (ranging from 25.75 to 33.72). Most of the patients had an ASA score grade of I and II (98%), and 14.3% had diabetes mellitus. Among female patients, one-third (32.4%) had had at least one vaginal childbirth.

Of the fistulas analyzed, 75.5% were medium transphincteric, and 24.5% were high transphincteric. In all, 46.9% of fistulas were anterior location and the median fistula length of all the group was 4 ± 1.14 cm (IC range: 3–5).

Moreover, 41 patients (83.7%) had a previous fistula surgery, including cutting setons, advancement flaps and other techniques; of these, 17 patients (34.7%) had undergone more than one procedure.

The median duration of symptoms in the current episode was 13 ± 15.5 months (IC range: 8–20).

Preoperatively, 5 patients (10.2%) reported some degree of anal incontinence according to Wexner score: one patient reported minor incontinence (Wexner < 3), and four patients had a score of Wexner > 3 (range: 6–12). Sphincteric defect was preoperatively detected in two patients by ultrasound.

Intraoperative PDT

The median incubation time was 120 ± 9.2 minutes (IC range: 120–120).

The median energy was 938 ± 333.8 J (IC range: 704–1114).

The median total time was 722 ± 188.5 seconds (IC range: 541–902).

The median number of cycles was 4 ± 1 (IC range: 3–5). (Each cycle corresponds to a laser emission of 180 J [1 W emission during 180 seconds]).

Complications

Any intraoperatively procedure-related complication was reported by the center. During the follow-up, only one patient exhibited phototoxicity, and five patients reported local skin soreness, which was efficiently treated with oral NSAIDs.

In the first 48 hours after the procedure, fever was reported in 2 patients (4%).

Primary Healing and Recurrence

Of the 49 studied fistulas, 6 healed primarily during the first month, 9 healed during the third month, 9 healed during the sixth month, and 10 healed 1 year after surgery. Two patients with primary healing suffered a recurrence of suppuration during the follow-up period.

Therefore, 32/49 (65.3%) patients exhibited total healing by the end of the follow-up period.

Of the 17 patients with recurrence, 4 patients had a loose seton placed, and 2 patients underwent the LIFT procedure. A mucosal flap advancement was performed in 2 patients. One patient underwent fistulotomy, and fistulectomy with primary sphincteroplasty was performed in another patient. Fistulectomy was carried out in 2 patients. Information was not available in 5 patients.

In the subgroup analysis of 13 female patients with anterior fistula, 9 patients (69.2%) were healed at the 1-year follow-up.

The variables associated with fistula healing in the univariate analysis are shown in Table 1. Only the presence of early complications was found as a risk factor for healing.

Incontinence

Any patient increased the preoperative incontinence scores. Patients with fecal incontinence improved their Wexner score. Only one patient had a Wexner score of 3 at 6 months; all patients had a Wexner score of 0 after 1 year of follow-up.

DISCUSSION

To our knowledge, this is the first multicentric study on using PDT to treat anal fistula. Previously, our group reported a pilot study of 10 patients with anal fistula treated with PDT, with excellent results [14]. Here, we present our results in a larger cohort of patients after a mean of 12 months of follow-up, analyzing recurrence and continence. The high rate of healing (65.3%) was found with i-PDT compared with the best reported sphincter-preserving techniques—including LIFT, FiLaC®, PDT, fibrin glue, fistula plug, and others—which generally yield high recurrence rates (30–60%) [6–12]. In addition, these initial results showed that all types of fistulas could be initially considered for i-PDT, especially for female patients with anterior fistula where 69.2% healed at 1-year follow-up.

The etiology of anal fistulas is assumed to occur due to an infection of the anal glands, located in the Morgagni crypts of the anal canal at the level of the pectineal line, and its prevalence is high in the population. According to this hypothesis, the infection of these glands by enteric germs leads to the formation of an abscess that can diffuse through different spaces of the anal canal, resulting in external orifice of the fistulas after the abscess is drained or opens spontaneously [15]. Usually, anal fistulas are classified as simple or complex. Complex fistulas are those that cross a large part of the sphincter apparatus of the anus; recurrent fistulas are those that have secondary trajectories, and even patients at risk of preoperative incontinence, although anatomically the fistula is simple. The usual and traditional treatment of fistulas is surgical, with the primary objective to destroy all the fistulous tissue [2].

The treatment of complex anal fistulas is controversial since different surgical techniques used have high rates of fecal incontinence and recurrence with a great alteration in the quality of life of the operated patient and a considerable cost. In addition, many of these patients require several surgeries, elevating the risk of incontinence [16]. Although the use of substances such as fibrin, collagen, and stem cells have been proposed as

TABLE 1. Association of Variables Related to the Patient, the Surgery and the Fistula Tract With Healing at Univariate Analysis (χ^2 Test)

Variable		Healed by 1 month	*P*	Healed by 3 months	*P*	Healed by 6 months	*P*	Healed by 12 months	*P*
Gender	Male	2	0.304	8	0.978	12	0.386	18	0.327
	Female	3		5		10		14	
Loose seton	No	4	0.363	10	0.175	15	0.367	21	0.386
	Yes	1		3		7		11	
Previous surgery	No	1	0.815	3	0.442	4	0.751	7	0.149
	Yes	4		10		18		25	
Fistula location	Anterior	3	0.537	7	0.560	11	0.698	15	0.990
	Posterior	2		6		11		17	
Type of fistula	Transphincteric medium	4	0.805	10	0.890	16	0.683	23	0.417
	Transphincteric high	1		3		6		9	
Sphincteric defect	No	5	0.626	13	0.386	22	0.192	31	0.642
	Yes	0		0		0		1	
Length <3 cm	No	1	0.143	4	0.088	8	0.064	14	0.162
	Yes	4		9		14		18	
Internal closed	No	0	0.297	4	0.100	5	0.274	5	0.855
	Yes	5		9		17		27	
Early complications	No	5	0.626	13	0.386	22	0.192	32	0.048
	Yes	0		0		0		0	

alternatives to surgery to avoid continence disorders, they have very low cure rates [12].

PDT is a therapeutic treatment based on the photooxidation of biological materials induced by a photosensitizer, which is selectively localized in inflammatory cells or tumor tissues to be illuminated with a light of adequate length and insufficient dose, said cells are selectively destroyed [17,18].

It can be said that PDT is ideal in the treatment of skin lesions because the accessibility of the skin makes lighting techniques relatively simple, with few risks and excellent results, especially compared with surgery or cryotherapy in oncological and dermatological pathology. Its local effect, simplicity and efficacy have led to a greater number of therapeutic indications in recent years [19,20]. PDT is also being used safely and without side effects in the area of skin and anal mucosa in the treatment of anal intraepithelial neoplasia and skin tumors and anal margin [21].

However, one of the main limitations of topical PDT is the poor penetration inside the tissue. Recently, ALA was manufactured in lyophilized solution or gel and can be applied by injecting it "intralesional" (i-PDT) directly into the lesion with the selective destruction of the deeper inflammatory tissue for healing without damage of the surrounding tissues. For this procedure, a high initial cure rate of 100% has been reported, with the maintenance of response of 93.75% in a long follow-up period in nodular BCC [22] and a rate of complete response (76.3%) in patients with hidradenitis suppurativa [23,24] treated with i-PDT.

On the other hand, Suárez-Valladares et al. studied the role of the immune system in PDT. They achieved an increase in some cytokine levels; so, it would be important to identify a subsequent immune response and some specific activated cells involved in this process [25]. Likewise, recent studies on fistulous tracts in cryptoglandular fistulas reveal higher levels of proinflammatory cytokines (IL-8 and IL-B) and lower levels of E-cadherins in lavish tissues with respect to control tissues. This confirms the fundamental role of these agents in the formation of anal fistulas [26,27].

Therefore, the application of i-PDT in anal fistulas could have three advantages. First, it allows for a deeper application inside a perianal fistula. Second, the selectivity of inflammatory cells allows for the destruction of fistulous tissue without damage of the muscular sphincter apparatus that is crossed by the fistula. Then, it produces the healing of the fistula without affecting fecal continence. Third, its anti-inflammatory, antimicrobial, and immunomodulatory properties would allow healing later than expected. This would explain the increased healing rate over time in our series, from 44.8% at 6 months to 65.3% at the 1-year follow-up.

The main limitation of our study was its small sample size, which made conducting a multivariate analysis by fistula type and indicated therapy difficult. In addition, a blind technique was difficult to implement to ensure that it reached correctly at a deeper level and treated secondary tracks, causing recurrence of the fistula. The development or implementation of an adapted fistuloscope could correct this problem. Finally, the i-PDT is a technique that costs more than the classic techniques. However, economic costs of the procedure should include the savings from treating patients with postoperative fecal incontinence, as well as losses in quality of life, after classical surgical techniques.

The application of other light sources, different concentrations or more powerful photosensitizers, a shorter incubation time, and retreats in patients with initial failure of the therapy should be explored.

Randomized trials comparing i-PDT with classic surgical techniques are necessary to evaluate the true role of this promising therapy to treat complex anal fistula.

In conclusion, i-PDT could be considered a good choice in patients with complex anal fistulas to avoid surgery and its complications.

REFERENCES

1. Parks AG, Gordon PH, Hardcastle JD. A classification of fistula-in-ano. Br J Surg 1976;63(1):1–12.
2. Malik AI, Nelson RL. Surgical management of anal fistulae: A systematic review. Colorectal Disease 2008;10(5): 420–430.
3. Limura E, Giordano P. Modern management of anal fistula. World J Gastroenterol 2015;21(1):12–20.
4. Cadeddu F, Salis F, Lisi G, Ciangola I, Milito G. Complex anal fistula remains a challenge for colorectal surgeon. Int J Colorectal Dis 2015;30(5):595–603.
5. Arroyo A, Pérez-Legaz J, Moya P, et al. Fistulotomy and sphincter reconstruction in the treatment of complex fistula-in-ano: Long-term clinical and manometric results. Ann Surg 2012;255(5):935–939.
6. O'Riordan JM, Datta I, Johnston C, Baxter NN. A systematic review of the anal fistula plug for patients with Crohn's and non-Crohn's related fistula-in-ano. Dis Colon Rectum 2012;55(3):351–358.
7. Meinero P, Mori L, Gasloli G. Video-assisted anal fistula treatment. Dis Colon Rectum 2014;57(3):354–359.
8. Rojanasakul A, Pattanaarun J, Sahakitrungruang C, Tantiphlachiva K. Total anal sphincter saving technique for fistula-in-ano; the ligation of intersphincteric fistula tract. J Med Assoc Thai 2007;90(3):581–586.
9. Hong KD, Kang S, Kalaskar S, Wexner SD. Ligation of intersphincteric fistula tract (LIFT) to treat anal fistula: systematic review and meta-analysis. Tech Coloproctol 2014;18(8):685–691.
10. Wilhelm A, Fiebig A, Krawczak M. Five years of experience with the FiLaC™ laser for fistula-in-ano management: Long-term follow-up from a single institution. Tech Coloproctol 2017;21:269–276.
11. Terzi MC, Agalar C, Habip S, Canda AE, Arslan NC, Obuz F. Closing perianal fistulas using a laser: Long-term results in 103 patients. Dis Colon Rectum 2018;61(5):599–603.
12. Adegbola SO, Sahnan K, Pellino G, et al. Short-term efficacy and safety of three novel sphincter-sparing techniques for anal fistulae: a systematic review. Tech Coloproctol 2017;21(10):775–782.
13. Suárez Valladares MJ, Eiris Salvado N, Rodríguez Prieto MA. Treatment of hidradenitis suppurativa with intralesional photodynamic therapy with 5-aminolevulinic acid and 630nm laser beam. J Dermatol Sci 2017;85(3):241–246.
14. Arroyo A, Moya P, Rodríguez-Prieto MA, et al. Photodynamic therapy for the treatment of complex anal fistula. Tech Coloproctol 2017;21(2):149–153.
15. Schubert MC, Sridhar S, Schade RR, Wexner SD. What every gastroenterologist needs to know about common anorectal disorders. World J Gastroenterol 2009;15(26):3201–3209.

16. Alavi K, Chan S, Wise P, Kaiser AM, Sudan R, Bordeianou L. Fecal incontinence: Etiology, diagnosis, and management. J Gastrointest Surg 2015;19(10):1910–1921.
17. Kwiatkowski S, Knap B, Przystupski D, et al. Photodynamic therapy—Mechanisms, photosensitizers and combinations. Biomed Pharmacother 2018;106(10):1098–1107.
18. Grandi V, Sessa M, Pisano L, et al. Photodynamic therapy with topical photosensitizers in mucosal and semimucosal areas: Review from a dermatologic perspective. Photodiagnosis Photodyn Ther 2018;23(9):119–131.
19. Babilas P, Schreml S, Landthaler M, Szeimies RM. Photodynamic therapy in dermatology: state-of-the-art. Photodermatol Photoimmunol Photomed 2010;26(3):118–132.
20. Lee Y, Baron ED. Photodynamic therapy: Current evidence and applications in dermatology. Semin Cutan Med Surg 2011;30(4):199–209.
21. Abbasakoor F, Woodhams J, Farooqui N, et al. Safe ablation of the anal mucosa and perianal skin in rats using photodynamic therapy a promising approach for treating anal intraepithelial neoplasia. Photodiagn Photodyn Ther 2013;10(4):566–574.
22. Suárez Valladares MJ, Pérez Paredes MG, González Sixto B, Rodríguez Prieto MÁ. Long-term follow-up of patients with basal cell carcinoma after successful treatment with intralesional photodynamic therapy. J Am Acad Dermatol 2016; 75(6):e247.
23. Suárez Valladares MJ, Eiris Salvado N, Rodríguez Prieto MA. Treatment of hidradenitis suppurativa with intralesional photodynamic therapy with 5-aminolevulinic acid and 630nm laser beam. J Dermatol Sci 2017;85(3):241–246.
24. Mordon S. Treating hidradenitis suppurativa with photodynamic therapy. J Cosmet Laser Ther 2018;20(4):223–228.
25. Suárez-Valladares MJ, Calleja-Antolín SM, García Ruíz de Morales JM, Rodríguez Prieto MA, Vega-Gutierrez J. Inflammatory response and cytokine levels induced by intralesional photodynamic therapy and 630-nm laser in a case series of basal cell carcinoma. J Am Acad Dermatol 2018;79(3):580–582.
26. Ratto C, Litta F, Lucchetti D, et al. Immunopathological characterization of cryptoglandular anal fistula: A pilot study investigating its pathogenesis. Colorectal Dis 2016;18(12):O436–O444.
27. van Onkelen RS, Gosselink MP, van Meurs M, Melief MJ, Schouten WR, Laman JD. Pro-inflammatory cytokines in cryptoglandular anal fistulas. Tech Coloproctol 2016;20(9): 619–625.