Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2020;9(4):970-7

A common but not well-known cause in anal fissure development and treatment failure: Isotretinoin treatment for acne vulgaris

Pelin Basim[1], Mavise Yuksel[2]

[1]*Medipol University, Faculty of Medical, Department of General Surgery, Istanbul, Turkey*
[2]*Medipol University , Faculty of Medical, Department of Dermatology, Istanbul, Turkey*

Received 20 July 2020; Accepted 06 August 2020
Available online 22.10.2020 with doi: 10.5455/medscience.2020.07.141

Abstract
To investigate the underrecognized effects of isotretinoin as a cause of anal fissures (AF) and compare AF patients undergoing systemic isotretinoin treatment (SIT) and those not receiving this treatment. This study was conducted with 118 patients with newly diagnosed AF, 54 undergoing SIT (Group 1) and 64 not undergoing SIT (Group 2). The same clinical treatment modalities including first-line conservative and medical treatments during the first eight weeks, followed by interventional methods (botulinum injection or sphincterotomy) for unresponsive/recurrent cases were used for all patients. A comparative analysis was also performed. Age and body mass index (BMI) were statistically low in group 1 ($p=0.003$; $p=0.032$). Similarly, the VAS pain and Wexner constipation scores and the duration of symptoms were lower in group 1 than Group 2 ($p=0.003$, $p<0.001$, and $p<0.001$, respectively). Atypical fissure localization was clearly associated with group 1 ($p=0.012$), and although SIT did not increase the surgery rate, atypical fissures and longer symptom duration constituted the most important factors determining requirement of surgical. SIT, a very successful treatment for nodulocystic acne disease, can facilitate AF development in younger individuals with a low BMI even without significant constipation.

Keywords: Anal fissure, isotretinoin, acne vulgaris, retinoids, surgical treatment

Introduction

Anal fissures (AFs) are painful longitudinal tears in the anal canal starting from below the dentate line and extending through the epidermal lining of the anus. Since they were first described by Lockhart-Mummary in 1934, many theories have been proposed about their etiopathogenesis and treatment options through multiple clinical series [1]. AFs can be classified as acute or chronic but there is no other grading or staging system for this most common cause of anal pain. Acute fissures present with sharp pain and a shallow tear in the anoderm, lasting no more than six to eight weeks whereas chronic fissures are long-term conditions accompanied by a triad of a fissure base with sphincter fibers, hypertrophied anal papilla, and a skin tag in the anoderm [2]. They are typically seen in younger to middle-aged adults, and most cases are self-limited; therefore, the true epidemiology in a given population cannot be estimated [3].

Although the exact cause of AFs is not entirely clear, it is assumed that the triggering event for the development of a fissure is trauma to the anal canal, including hard or large caliber stool, local irritation caused by chronic diarrhea, anorectal surgery, or anal intercourse [4]. Sphincter spasm and hypertonicity may be both a result and a cause of the process, leading to an ongoing relative ischemia and ulceration [5,6].

Regardless of the underlying etiology and type of fissure, all first-line treatments are conservative based on life-style changes and medical management methods [3]. Several guidelines have been published following clinical trials but their impact on clinical practice remains unclear [7-11]. Higher body mass index (BMI), longer duration of symptoms, chronic type AFs, and higher Wexner constipation scores were found to be factors related to the increased likelihood of non-response to medical therapy [12]. When conservative management fails, the botulinum toxin injection may be an alternative method with acceptable side effects and a considerable rate of success. In selected cases in which no other treatment modality works, lateral internal sphincterotomy; i.e., division of four-fifths of the internal anal sphincter under direct vision using the open or closed technique is the gold standard surgical method [2].

Isotretinoin, a synthetic vitamin A derivative, is a well-known and frequently prescribed medication for the treatment of a wide variety of dermatologic conditions [13]. Although it is the most effective treatment for nodulocystic acne vulgaris, systemic isotretinoin treatment (SIT) has many side effects, including dryness and fragility of skin and mucous membranes. To the

***Coresponding Author:** Pelin Basim, Medipol University, Faculty of Medical, Department of General Surgery, Istanbul, Turkey. E-mail: pelinakbaba@gmail.com

best of our knowledge, there are only a limited number of case reports in the literature referring to the relationship of SIT and AF and rectal bleeding [14-16]. In this study, we aimed to investigate the underrecognized effects of isotretinoin as a cause of AF development and compare the demographic and clinical characteristics, treatment modalities and outcomes between the AF patients receiving SIT and those not ongoing this treatment.

Materials and Methods

Study Design

This retrospective study was conducted with 118 patients aged 18 to 44 years, who presented to the general surgery outpatient clinics of our university Medical Faculty between January 2016 and January 2018. Eighty-four of the patients were female and 34 were male. To form the first group, 872 patients [mean age: 27.9 ± 6.9 (18-50)], who were planned to start SIT in the dermatology clinic for nodulocystic acne vulgaris and referred for anal pathology examination to the general surgeon conducting the study, were screened. Of the 377 patients without history or already present AF, 60 presented to or were referred by the dermatologist to the same general surgeon with the complaint of an anal fissure during ongoing SIT, but only 54 completed the follow-up (Group 1). Group 2 consisted of 64 patients, who had not used any SIT and presented to the same general surgery clinic with the same symptomatology during the same period without previous history of AF. All patients in Group 1 were treated with the same dosage of isotretinoin, 1 mg/kg/d taken in a single morning dose for four to six months. We reviewed the electronic medical charts of all patients and analyzed the demographic and disease-related data according to the treatment methodology and outcomes. Pregnant women, patients with inflammatory bowel diseases, tuberculosis, human immunodeficiency virus, syphilis or any type of cancer, and those that were lost to follow-up were excluded from the study considering the possibility of recurrence after any treatment. The minimum and maximum follow-up times of the patients after the final treatment session were six and 12 months, respectively. The study was approved by the ethics committee of university (10840098-604.01.01-E.4560 Decision number: 35) and conducted in accordance with the principles of the Declaration of Helsinki.

Data Collection

The demographic data, including age, gender, education level, marital status, and BMI of 118 consecutive cases of AF diagnosed clinically based on the digital examination findings were recorded. Pain related to AF was scored using the Visual Analog Scale (VAS), and constipation using the Wexner constipation score (WCS). The other disease-related data were the duration of symptoms, accompanying bleeding, diarrhea, type (acute or chronic) and localization (typical or atypical) of fissures, presence of skin tag, hypertrophic papilla, anal stenosis, perianal fistula, irritable bowel syndrome, and previous perianal surgery. The persistence of symptoms after SIT, treatment methods, and reasons for surgical operations were also compared between the two groups.

Treatment Algorithm

All patients presenting with either acute or chronic AF were treated with conservative measures and medical therapy in the first step, comprising changes in lifestyle and eating habits, sitz bath, stool softeners, and topical ointments; including local anesthetic and topical nitroglycerin agents. The patients were followed up at the first, second, fourth and ultimately eight weeks after the first given treatment. The cases that never responded to treatment (no pain relief or a persistent fissure in the anorectal examination) or recurrence after at least six months following the eight-week treatment were accepted as candidates for advanced treatment with either botulinum injection or surgical operation, namely lateral internal sphincterotomy (LIS) with the open technique. Those who were treated by interventional methods either with botulinum injection or LIS signed a written informed consent form. However, studies have shown that individuals with developing immunity still have sufficient protection against HBV even if anti-HBs levels are very low (19).

To the best of our knowledge, this is the first clinical research of the 1-18-year age group for HbsAg seroprevalence and anti-Hbs seropositivity in Usak province. When compared with other provinces and Turkey in general, HbsAg seropositivity is relatively low in this study. Despite the fact that three-dose vaccination rate is 97% in Turkey and 98% in Usak (5), the seropositivity in the 1-18-year age group is lower than expected. This study has been preformed to specify HbsAg seroprevalence and efficacy of HBV vaccination. The findings of the present study would help to take precautions for decreasing HbsAg seroprevalence and appoint extra measures for increasing the success rates of vaccination schedules in children and young adults.

Statistical Analysis

The clinical data were compared between the groups. The data were analyzed using SPSS software, version 15.0 (SPSS Inc. Chicago, IL). The descriptive statistics were expressed as number and percentages for categorical variables, and the mean, standard deviation, minimum and maximum values for numerical variables. Since the numerical variables met the normal distribution condition, the Mann-Whitney U test was conducted for the comparison of two independent groups. The percentages of the groups were compared using the chi-square analysis. The significant factors were further evaluated using the logistic regression analysis. The alpha statistical significance level was accepted as $p < 0.05$.

Results

When the results were examined, the age and BMI of the patients who received SIT (Group 1) were statistically significantly lower than those that did not receive SIT (Group 2) ($p = 0.003$ and $p = 0.032$, respectively). The mean age and BMI were calculated as 24.1 ± 4.4 (18-44) years and 25.3 ± 3.4 (19.3-31.4), respectively for Group 1, and 28.2 ± 7.4 (18-44) years and 26.9 ± 3.8 (20.2-33.5), respectively for Group 2. No statistically significant difference was found in the remaining demographic characteristics (gender, education level, and marital status) of the patients in the two groups (Table 1).

Table 1. Demographic data of the all the participants

		Isotretinoin Use				p
		Absent		Present		
		n	%	n	%	
Gender	Female	42	65.6	42	77.8	0.160
	Male	22	34.4	12	22.2	
Age*,year		28.2 ± 7.4 (18-44)		24.1 ± 4.4 (18-44)		0.003
Education level	Illiterate	0	0.0	2	3.7	0.184
	Primary School	15	23.4	7	13.0	
	High School	28	43.8	29	53.7	
	University	21	32.8	16	29.6	
Marital status	Single	33	51.6	36	66.7	0.097
	Married	31	48.4	18	33.3	
BMI*		26.9 ± 3.8 (20.2-33.5)		25.3 ± 3.4 (19.3-31.4)		0.032

BMI: Body mass index , *Mean ± SD (Min-Max)
¶p value <0.05 considered statistically significant

Table 2 shows the comparative disease characteristics of the two groups. The VAS pain and Wexner constipation scores and the duration of complaints of the patients in Group 1 were statistically significantly lower than those in Group 2 ($p = 0.003$, $p < 0.001$, and $p < 0.001$, respectively). In Group 1, the mean pain VAS score was 5.2 ± 1.4 (2-8) and the Wexner constipation score was 8.3 ± 2.6 (3-14), while in Group 2, these values were 6.2 ± 1.9 (3-9) and 17.1 ± 6.4 (4-29), respectively.

The mean duration of complaints was 7.3 ± 2.2 (3-13) and 12.2 ± 6.2 (2-24) in Groups 1 and 2, respectively. The frequency of atypical local anal fissures was statistically significantly higher in Group 1 compared to Group 2 ($p = 0.012$). The rates of skin tag, anal stenosis, and inflammatory bowel disease (IBD) were statistically significantly lower in Group 1 ($p = 0.021$ $p = 0.002$, and $p = 0.001$, respectively). Although there was no statistically significant difference between the two groups in terms of fissure types classified as acute and chronic, it was determined that skin tag and anal stenosis, which are defined as the findings of chronic AFs, were less seen in Group 1. Similarly, no statistically significant difference was found between the two groups in terms of rectal bleeding, diarrhea, hypertrophic papilla formation, perianal fistula, and previous perianal surgery (Table 2).

The parameters related to the treatment of the disease in the two groups are given in Table 3. In Group 1, 42.6% (n = 23) of the patients stated that their complaints continued after SIT while 57.4% (n = 31) responded to their ongoing medical treatment for AF following SIT. When Groups 1 and 2 were compared, no statistically significant difference was found in terms of the percentages of applied treatment methods, the rate of and reasons for the decision to have a botulinum injection, and the reasons for moving from medical therapy to surgery. Although the difference was statistically non-significant, it is noteworthy that none of the patients who received botulinum in Group 2 required surgical treatment while three (42.8%) of the seven patients who received botulinum in Group 1 required surgery due to non-response to conservative treatment (Table 3).

When all the patient groups were evaluated together in terms of the treatment methods, the mean duration of complaints, chronic fissure rate, atypical fissure location, presence of anal papilla, and stenosis rate were statistically significantly higher in patients treated by surgery compared to those receiving non-surgical treatments ($p = 0.001$, $p = 0.017$, $p = 0.001$, $p = 0.015$, and $p = 0.037$, respectively). In addition, the VAS pain and Wexner constipation scores, SIT use, bleeding, diarrhea, presence of skin tag, perianal fistula, IBD, and previous perianal surgery did not statistically significantly differ between the patients that underwent surgical and non-surgical treatments (Table 4).

According to the multivariate logistic regression analysis model constructed based on disease characteristics and SIT use to identify the factors that predicted the requirement of surgical treatment, the fissure location being atypical and the duration of complaints were found to be the most significant factors ($p = 0.05$ and $p = 0.027$, respectively for the enter method, and $p = 0.005$ and $p = 0.002$, respectively for the backward method) (Table 5).

Table 2. Patient characteristics

		Isotretinoin Use				
		Absent		Present		P
		Mean ± SD (Min-Max)		Mean ± SD (Min-Max)		
VAS pain score		6.2 ± 1.9 (3-9)		5.2 ± 1.4 (2-8)		*0.003
Wexner constipation score		17.1 ± 6.4 (4-29)		8.3 ± 2.6 (3-14)		*<0.001
Duration of complaints		12.2 ± 6.2 (2-24)		7.3 ± 2.2 (3-13)		*<0.001
		n	**%**	**n**	**%**	**P**
Bleeding		48	75.0	43	79.6	0.551
Diarrhea		13	20.3	8	14.8	0.437
Fissure type	Acute	30	46.9	26	48.1	0.890
	Chronic	34	53.1	28	51.9	
Fissure location	Typical	56	87.5	37	68.5	*0.012
	Atypical	8	12.5	17	31.5	
Skin tag		42	65.6	24	44.4	*0.021
Papilla		26	40.6	14	25.9	0.093
Stenosis		17	26.6	3	5.6	*0.002
Fistula		3	4.7	2	3.7	1.000
IBD		20	31.3	4	7.4	*0.001
Previous anal surgery		6	9.4	5	9.3	0.983

VAS: Visual Analog Scale; IBD: Inflammatory bowel disease
Mann Whitney-U test, Chi square test, *p value <0.05 considered statistically significant
P<0.05 considered statistically significant

Table 3. Treatment characteristics

		Isotretinoin Use				p
		Absent		Present		
		n	**%**	**n**	**%**	
Continued after treatment	No			23	42.6	
	Yes			31	57.4	
Treatment	Medical	40	62.5	33	61.1	
	Surgery	17	26.6	14	25.9	0.944
	Botulin	7	10.9	7	13.0	
Rate of and reason for surgery after botulin injection	No surgery	7	100.0	3	50.0	0.064
	No response to treatment	0	0.0	3	50.0	
Rate of and reason for moving to surgery	No surgery	46	71.9	37	68.5	
	No response to treatment	12	18.8	11	20.4	0.917
	Recurrence	6	9.4	6	11.1	

Chi square test, *p value <0.05 considered statistically significant

Table 4. Patient characteristics according to treatment modalities

		Treatment				p
		Surgical		Non-surgical		
		Mean ± SD (Min-Max)		Mean ± SD (Min-Max)		
VAS pain score		6.2 ± 2.0 (3-9)		5.6 ± 1.6 (2-9)		0.100
Wexner constipation score		14.9 ± 8.0 (5-27)		12.5 ± 6.1 (3-29)		0.279
Duration of complaints		12.9 ± 6.0 (5-24)		8.9 ± 4.7 (2-22)		*0.001
		n	**%**	**n**	**%**	**p**
Isotretinoin Use		14	45.2	40	46.0	0.938
Bleeding		24	77.4	67	77.0	0.963
Diarrhea		4	12.9	17	19.5	0.407
Fissure type	Acute	9	29.0	47	54.0	*0.017
	Chronic	22	71.0	40	46.0	
Fissure location	Typical	18	58.1	75	86.2	*0.001
	Atypical	13	41.9	12	13.8	
Skin tag		20	64.5	46	52.9	0.262
Papilla		16	51.6	24	27.6	*0.015
Stenosis		9	29.0	11	12.6	*0.037
Fistula		0	0.0	5	5.7	0.324
IBD		8	25.8	16	18.4	0.378
Previous anal surgery		3	9.7	8	9.2	0.937

VAS: Visual Analog Scale; IBD: Inflammatory bowel disease
Mann Whitney-U test, Chi square test, *p value <0.05 considered statistically significant

Table 5. Results of the multivariable logistic regression analysis of the factors that determine surgical treatment

		P	OR	95% CI	
Enter method	VAS pain score	0.878	0.972	0.678	1.394
	Bleeding	0.786	0.846	0.254	2.823
	Wexner constipation score	0.604	1.033	0.913	1.169
	Diarrhea	0.602	0.696	0.179	2.714
	Fissure type (acute)	0.438	0.513	0.095	2.772
	Fissure location (atypical)	*0.050	3.165	0.998	10.035
	Skin tag	0.292	0.407	0.076	2.169
	Papilla	0.497	1.594	0.415	6.125
	Stenosis	0.542	1.604	0.352	7.312
	Fistula	0.999	0.000	0.000	.
	IBD	0.816	1.177	0.299	4.632
	Previous anal surgery	0.304	0.353	0.049	2.570
	Duration of complaints	*0.027	1.166	1.017	1.337
	Isotretinoin use	0.221	3.071	0.510	18.500
Backward Method	Fissure location (atypical)	*0.005	4.179	1.530	11.414
	Duration of complaints	*0.002	1.141	1.050	1.240

VAS: Visual Analog Scale; OR: odds ratio; CI: confidence interval; IBD: inflammatory bowel disease,
*p value <0.05 considered statistically significant

Discussion

Among the most common theories about the etiopathogenesis of AF, a cycle of the tear and wear of the anal mucosa is currently widely accepted and considered to prevent wound healing and result in increased internal anal sphincter tone complicated with decreased blood flow, especially to the posterior midline [3,17]. There is a positive correlation between fissures and hypertonic sphincters demonstrated manometrically, as well as an association between hypertonic sphincter and decreased anodermal blood flow [3]. Hard stool, diarrhea, and other conditions causing harm to the anal mucosa may be the triggering factors during the disease process [2,4]. Eliminating these triggering factors may be helpful in the conservative management of AF. For both acute and chronic types, the first treatment option of AF is conservative management, including a high-fiber diet program, increased intake of fluid, sitz baths, stool softeners, and locally applied pharmacological preparations consisting of local anesthetics, topical nitrates, and calcium channel blockers [2-5]. There are many studies in the literature conducted with topical use of nitrates and calcium channel blockers in chronic AF, associated with 50% and 65-90% complete healing rates, respectively [19,20].

For persistent or recurrent cases, botulinum toxin injection may be a secondary option before a surgical procedure. The action mechanism of botulinum toxin is irreversible binding to presynaptic nerve terminals, preventing acetylcholine release and breaking up ordinary neural transmission. However, since it is an expensive treatment modality, it is mostly suitable for the patients unresponsive to topical treatments considering the consensus of the guidelines on the equal efficacy of topical nitrates and botulinum injection in terms of relieving AF symptoms. Another important point is that the technique, dose and site of injection do not affect the rate of healing and the success of treatment [7,8,10,11].

Among surgical procedures, lateral internal sphincterotomy is attributed to be the standard treatment for patients that are either unresponsive to treatment or experiencing frequent recurrences [18]. In the literature, not only chronic type AF but also some other factors, such as higher BMI, longer duration of symptoms, and higher Wexner constipation scores were found to be related to the increased incidence of surgical treatment [12]. Gupta et al. [21] reported higher patient satisfaction rates with LIS if the removal of hypertrophied anal papillae and fibrous anal polyps was added to the standard procedure. Multiple randomized trials have consistently confirmed the superiority of the surgical technique compared with other modalities, with excessively higher healing rates varying between 88 and 100% depending on the case series [7]. Generally reserved for patients that either do not comply with medical treatment or have a higher rate of persistent symptoms following non-operative management, LIS results in significant improvement in the quality of life within a short period after the procedure [22]. However, despite its superiority in treatment success, surgeons may be reluctant to perform LIS because of the probability of either gas or fecal incontinence. Brady et al. specifically referred to the susceptibility of women of childbearing age to incontinence after the procedure, which was not limited to the short-term postoperative period but also affected these patients all their lives due to their anatomic differences and changes associated with pregnancy and delivery [1].

The literature on the treatment of fissures has been consistently concerned about recurrences and complication rates of different treatment types. The real issue in this case is whether the selection of patients for treatment type is appropriate in all cases [22]. Fissures in selected patient groups are proven to be difficult to manage, and thus require more insistent effort, focusing on the treatment of the underlying medical condition. Fissures related to Crohn's disease and sexually transmitted diseases, such as HIV and anogenital herpes infections are more prone to recurrence after treatment. These patients are primarily treated with conservative approaches, including the medical treatment of the underlying disease [23,24].

Isotretinoin, a synthetic vitamin A derivative, has a mechanism of action in which it is transformed into trans-retinoic acid forms in vivo, binding to cellular retinol-binding proteins or retinoic acid nuclear receptors. First used in 1982 to treat severe nodulocystic acne disease resistant to standard therapy, isotretinoin is now prescribed to many patients worldwide and accepted as a revolution in the treatment of acne and its variants [13].

The results of the isotretinoin use for nodulocystic acne disease was first described by Shalita et al. [25] in a large case series in 1983. This study revealed that SIT had an impact on cell-cycle progression, cellular differentiation, cell survival, and apoptosis, which constitute all the principle etiological factors implicated in the development of acne, and resulted in a significant reduction in sebum production, comedogenesis, and anti-inflammatory action. A direct anti-microbial effect is not considered as a factor in the mechanism of action of SIT but since it alters surface microenvironment, microbial colonization, especially that of Propionibacterium acnes is prevented, leading to the suppression of microbial count much greater than achieved by oral or topical antimicrobials [26].

The most important target of SIT for nodulocystic acne disease is complete healing with minimal side effects. At the time the drug is discontinued, at least 80% of complete healing is intended since a remarkable clinical improvement is also achieved after its termination. Shalita et al. reported that duration of treatment was directly related to the overall success and maintenance of therapy, and recommended at least four to six months uninterrupted therapy, particularly in severe and intractable cases [25].

Clinicians who follow-up patients under SIT encounter a variety of side effects in large numbers related to drug usage [13-16,25,26]. Rare occurrences of some central nervous system disorders (e.g., pseudotumor cerebri and seizures), hepatic side effects, sacroiliitis, and psychosis are all presumed to be related to hypervitaminosis A syndrome. SIT is almost completely discontinued in all these patient groups immediately after the diagnosis is made until the real underlying pathology is defined and SIT is confirmed to be not responsible. On the other hand, some mild side effects involving the skin and mucous membranes can be expected to happen in almost 94-100% of patients, and this predictable outcome is known to be completely reversible following the discontinuation of therapy [25,26].

Although not definitely proven, the mucocutaneous side effects of SIT are most probably a result of the effect of hypervitaminosis A on the barrier function of the stratum corneum layer of the epithelium. Only in a few days after treatment, patients present with cheilitis, facial dermatitis, xerosis, pruritus, and desquamation, and

all these discomforting symptoms persist throughout the treatment period even under suitable preventive measures. Eye irritation due to dryness, as well as dryness of vaginal mucosa and even the urethral meatus, dry lips, and nose bleeds occur fairly frequently, and different types of preventive or therapeutic measures have been defined in the literature [25-27].

Skin fragility was also described by Holmes et al. [28] in 1995 and traumatic abrasions and erosions were proposed as a precursor of secondary diseases and bacterial superinfections. In 1997, Goldfarb [28,29] recommended avoiding dermabrasions for at least six months after the completion of SIT to prevent delayed wound healing, keloid formation, and development of pyogenic granuloma-like lesions and irreversible significant mucocutaneous side effects.

Although the use of SIT in severe recalcitrant acne has been proven to be effective, due to its long list of frequent side effects, it should be used with caution, and patients should be informed of all possible side effects and preventive measures. Nevertheless, some side-effects that are not well known in dermatological practice seem to be unrelated to treatment and underestimated in most cases. An association between SIT and AF, rectal bleeding, and proctitis were previously described as potential side effects in certain case reports, especially in the gastroenterology field. Although research undertaken in recent years revealed skin fragility during SIT, to date, no study has examined the effects of isotretinoin treatment on the development, ongoing course, convalescence and recurrence of AF. During our literature search, we encountered four case reports describing a total of seven patients with SIT-induced AF and rectal bleeding. Of these patients, five were female and two were male, presenting with typical acute AF symptoms intensified by defecation. The disease seems to be self-limited since all patients were advised to discontinue SIT, and the patients' condition started to subside gradually within the following two weeks and achieved complete healing in approximately four weeks. This suggests that AF is probably a consequence of the laceration of the already xerotic and fissured anal mucosa following forceful defecation [14-16,30].

The findings of this clinical study support previous case reports in terms of the easy development of medically resistant AF under SIT. However, none of these papers reported prespecified outcomes nor the comparison of specific AF patient groups with and without ongoing SIT. In the current study, we concluded that the patients that developed AF under SIT were at younger ages and their BMI was relatively lower compared to the normal population. The use of SIT in relatively younger age groups would indicate a bias, but when we compared all 872 patients using SIT with Group 2 in terms of age, there was no statistically significant difference [27.9 ± 6.9 (18-50) and 28.2 ± 7.4 (18-44) years, respectively]. Although skin fragility is a recognized important effect of oral retinoid treatment, our research suggests that younger age and lower BMI constitute higher risk in all SIT users compared to the normal population [28, 30].

It was also notable that AF patients under SIT (Group 1) had lower baseline VAS pain and Wexner constipation scores and shorter duration of symptoms. These patients seemed to be more prone to developing fissures with atypical localization. All these differences of Group 1 compared to Group 2 can be attributed to increased mucocutaneus fragility, especially dry lips and cheilitis associated with SIT, resulting in skin crackles causing secondary infections [27,31,32]. These basic findings are consistent with previous research showing that some degree of cheilitis is an indication of sufficient drug bioavailability. However, it should also be noted that only approximately half of the patients responded well to medical therapy even just after two weeks following the termination of SIT, contrary to previous studies stating that mucocutaneous symptoms resolved within two weeks after treatment [26,27]. In the light of these findings, a higher rate of surgical treatment would be expected in SIT-induced AF, but surprisingly only 25.9% of these patients required surgical treatment at the end of eight-week medical treatment, which was statistically very similar to Group 2. Our study also demonstrated that SIT did not change the ordinary course of chronicity development in AF nor the requirement of surgical treatment.

Our study revealed significant evidence that hypertrophic papilla and stenosis indicated the chronicity and atypical localization of AFs, and this chronicity coupled with longer symptom duration significantly increased the rate of surgical treatment rate. For patients using SIT, atypical fissure localization and longer symptom duration were the two significant parameters that determined the treatment option being surgical or non-surgical.

To the best of our knowledge, this is the first article concerning the relationship between SIT and its clinical consequence, AF; however, this study had certain limitations, including its retrospective feature and lack of a relatively long follow-up of the patients to exclude the long-term recurrence of AF. Despite these limitations, surprisingly, a considerable percentage of our participants were compliant, strictly following treatment recommendations and attending all follow-up sessions.

Conclusion

We conclude that SIT can be an accepted as a risk factor for AF development at younger ages even in patients with a low BMI and Wexner constipation scores, and the risks and benefits should be well considered before making this treatment decision. In clinical practice, we recommend a gradual precautionary approach for the prevention of AF in patients who are planned to use SIT. Lifestyle changes, including the modification of dietary and sportive habits may be an alternative for this age group, and hydrating and emollient products can also be investigated in terms of their efficacy in preventing AF associated with SIT. Larger, longer-term observational or prospective studies are warranted to determine the patient group predisposed to AF during optimal SIT, identify the optimal adjunctive treatment for AF, achieve clinical resolution, and prevent recurrence.

Conflict of interests

The authors declare that they have no conflict of interest related to the publication of this manuscript.

Financial Disclosure

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

The study was approved by the ethics committee of Medipol University (08.01.2020-10840098-604.01.01-E.4560 Decision number: 35) and conducted in accordance with the principles of the Declaration of Helsinki.

References

1. Brady JT, Althans AR, Neupane R, et al. Treatment for anal fissure: Is there a safe option? Am J Surg. 2017;214:623-8.
2. Beaty JS, Shashidharan M. Anal fissure. Clin Colon Rectal Surg. 2016;29:30-7.
3. Steinhagen E. Anal fissure. Dis Colon Rectum. 2018;61:293-7.
4. Lund JN, Scholefield JH. Aetiology and treatment of anal fissure. Br J Surg. 1996;83:1335-44.
5. Gibbons CP, Read NW. Anal hypertonia in fissures: cause or effect? Br J Surg. 1986;73:443-5.
6. Keck JO, Stauniunas RJ, Coller JA, et al. Computer-generated profiles of the anal canal in patients with anal fissure. Dis Colon Rectum. 1995;38:72-9.
7. Stewart DB Sr, Gaertner W, Glasgow S, et al. Clinical practice guideline for the management of anal fissures. Dis Colon Rectum. 2017;60:7-14.
8. Cross KL, Massey EJ, Fowler AL, et al. The management of anal fissure: ACPGBI position statement. Colorectal Dis. 2008;10:1-7.
9. Altomare DF, Binda GA, Canuti S, et al. The management of patients with primary chronic anal fissure: a position paper. Tech Coloproctol. 2011;15:135-41.
10. Nelson R. Non surgical therapy for anal fissure. Cochrane Database Syst Rev. 2003.
11. Wald A, Bharucha AE, Cosman BC, et al. ACG clinical guideline: management of benign anorectal disorders. Am J Gastroenterol. 2014;109:1141-57.
12. Emile SH, Elgendy H, Elfeki H, et al. Does the duration of symptoms of anal fissure impact its response to conservative treatment? A prospective cohort study. Int J Surg. 2017;44:64-70.
13. Karadağ ŞG, Sönmez HE, Tanatar A, et al. Isotretinoin-induced sacroiliitis: Case series of four patients and a systematic review of the literature. Pediatr Dermatol. 2019;37:171-5.
14. Güngör S, Gökdemir G. Anal fissure and rectal bleeding as a complication of systemic isotretinoin therapy: dermatologists know this side-effect, what about proctologists? Colorectal Dis. 2013;15:1187-8.
15. Erpolat S, Gorpelioglu C, Sarifakioglu E. Isotretinoin associated anal fissure and rectal bleeding: a rare complication. Int J Dermatol. 2012;51:358-9.
16. Radmanesh M. Anal fissure, rectal bleeding and proctitis as complications of systemic isotretinoin therapy: report of two cases. J Eur Acad Dermatol Venereol. 2006;20:1394.
17. Sinha R, Kaiser AM. Efficacy of management algorithm for reducing need for sphincterotomy in chronic anal fissures. Colorectal Dis. 2012;14:760-4.
18. Acar T, Acar N, Gungor F, et al. Treatment of chronic anal fissure: Is open lateral internal sphincterotomy (LIS) a safe and adequate option? Asian J Surg. 2019;42:628-33.
19. Berry SM, Barish CF, Bhandari R, et al. Nitroglycerin 0.4% ointment vs placebo in the treatment of pain resulting from chronic anal fissure: a randomized, double-blind, placebo controlled study. BMC Gastroenterol. 2013;13:106.
20. Sanei B, Mahmoodieh M, Masoudpour H. Comparison of topical glyceryl trinitrate with diltiazem ointment for the treatment of chronic anal fissure: a randomized clinical trial. Ann Ital Chir. 2009;80:379-83.
21. Gupta PJ, Kalaskar S. Removal of hypertrophied anal papillae and fibrous anal polyps increases patient satisfaction after anal fissure surgery. Tech Coloproctol. 2003;7:155-8.
22. Nelson RL, Chattopadhyay A, Brooks W, et al. Operative procedures for fissure in ano. Cochrane Database Syst Rev. 2011.
23. Sweeney JL, Ritchie JK, Nicholls RJ. Anal fissure in Crohn's disease. Br J Surg. 1988;75:56-7.
24. Viamonte M, Dailey TH, Gottesman L. Ulcerative Disease of the anorectum in the HIV+ patient. Dis Colon Rectum. 1993;36:801-5.
25. Shalita AR, Cunningham WJ, Leyden LL, et al. Isotretinoin treatment of acne and related disorders. J Am Acad Dermatol. 1983;9:629-38.
26. Layton A. The use of isotretinoin in acne. Dermatoendocrin. 2009;1:162-9.
27. Brzezinski P, Borowska K, Chirlac A, et al. Adverse effects of isotretinoin: A large, retrospective review. Dermatol Ther. 2017.
28. Holmes SC, Thomson J. Isotretinoin and skin fragility. Br J Dermatol. 1995;132:165.
29. Golfarb MT. The uses of retinoids in dermatology. Curr Opin Dermatol. 1997;4:236-40.
30. Martin P, Manley PN, Depew WT, et al. Isotretinoin-associated proctosigmoiditis. Gastroenterology. 1987;93:606-9.
31. Rademaker M. Adverse effects of isotretinoin: A retrospective review of 1743 patients started on isotretinoin. Australas J Dermatol. 2010;51:248-53.
32. Mobacken H, Sundström A, Vahlquist A. 30 years with isotretinoin. "Miracle Medicine" against acne with many side effects. Lakartidningen. 2014;111:93-6.