Lateral Internal sphincterotomy is still crucial to heal hypertonic chronic anal fissure and normalize the internal anal sphincter tone? Is V-en Y plastic a valuable alternative?



Ann. Ital. Chir., 2021 92, 5: 554-559 pii: S0003469X21035090

Beatrice D'Orazio*/**, Sebastiano Bonventre*, Carmelo Sciumé*, Bianca Cudia*, Gloria Terranova*/**, Gaetano Di Vita*, Girolamo Geraci*

*General Surgery Unit - Department of Surgical, Oncological and Stomatological Sciences, University of Palermo, Palermo, Italy **Postgraduate Medical School in General Surgery, University of Palermo, Palermo, Italy

Lateral Internal sphincterotomy is still crucial to heal hypertonic chronic anal fissure and normalize the internal anal sphincter tone? Is V-en Y plastic a valuable alternative?

INTRODUCTION: The role of augmented internal anal sphincter (IAS) tone in the genesis of chronic anal fissure (CAF) is still unclear. Lateral internal sphincterotomy (LIS) is the most employed surgical procedure, aiming to reduce the IAS tone leaving a permanent anatomical alteration and it is burdened by high risk post-operative anal incontinence (AI). The aim of this work was to evaluate if the pre-operative manometric alterations of CAFs with hypertonic IAS would normalize after sphincter preserving surgical procedure. METHODS: We enrolled 108 consecutive patients affected by idiopathic and non-recurrent CAF undergone fissurectomy

METHODS: We enrolled 108 consecutive patients affected by idiopathic and non-recurrent CAF undergone fissurectomy and anoplasty with V-Y cutaneous flap advancement and pharmacological sphincterotomy, matched with 54 healthy subject in a 1 to 2 ratio, and followed up for at least for 2 years. The goals were patient's complete healing, the evaluation of AI, recurrence rate and manometry parameters.

RESULTS: All wounds healed within 40 days after surgery. We recorded 7 cases of recurrences healed with medical therapy. We recorded 3 "de novo" post-operative cases of AI all temporary and low grade. Pre-operative values of maximum resting pressure (MRP) and detection of ultraslow wave activity (USWA) were significantly higher than in the healthy control group, but both come back to be similar to those recorded in healthy subject after 24 months from the surgery.

CONCLUSION: The high healing rate without post-operative "de novo" AI cases with the normalization of manometric parameters suggest that fissurectomy and anoplasty with V-Y cutaneous advancement flap and pharmacological sphinc-terotomy is an adequate procedure for the treatment of CAF with IAS hypertonia.

KEY WORDS: Anal fissure, Anoplasty, Fissurectomy, Proctology, Sphincterotomy

Introduction

Chronic anal fissures (CAF) are small, painful ulcers located at the transition cutaneous-mucosal zone of the

anal canal; they are the most frequent proctological disease. In the US 342.000 new cases are reported each year ¹, in England the rate of hospitalisation from 2005 to 2006 was 1,56 case on 10,000 people 2; in Italy they account for the second most frequent proctological disease ³.

At present their etiopathonegesis is not completely understood, CAFs have been associated with increased internal anal sphincter (IAS) tone for many years, while during the last decade various series demonstrated that an increased IAS tone is detected only in the 60-70% of CAFs ⁴⁻⁸. Nevertheless, in the event of CAFs, which are refractory to dietary and pharmacological therapy, later-

Pervenuto in Redazione Ottobre 2020. Accettato per la pubblicazione Novembre 2020

Correspondence to: Gaetano Di Vita, General Surgery Unit, Department of Surgical, Oncological and Stomatological Sciences, University of Palermo. Via Liborio Giuffrè 5, 90127 Palermo, Italy. (e-mail: divitagaetano@libero.it)

al internal sphincterotomy (LIS) is still the treatment of choice regardless from IAS tone. In fact this latter surgical procedure is characterised by a low rate of post-operative complications and a high healing rate, while its main disadvantage is the high rate of anal incontinence (AI), which can occur up to the 14% of cases ⁹. AI has a strong impact on patients' quality of life and could be more disabling than CAF itself ¹⁰; various risk factors are involved in the development of AI ^{11,12}, IAS tone contributes for the 70-85% of resting sphincter pressure and it is chiefly responsible for anal continence at rest ¹³⁻¹⁴.

Available work on sphincter system function after LIS are few ¹⁵⁻¹⁸ and the longer period of post-operative follow up which they took into consideration is 12 months and, all of them highlight a notable reduction of IAS tone, first of all after the first months from the surgery. Rammn et al. ¹⁵ in their series of 50 patients with IAS hypertonia, observed a reduction of maximum resting pressure (MRP) after 12 months from LIS higher than 35 mmHg in the 36% of patients, while in the 6% of them it reached 80 mmHg.

In order to preserve anatomical and functional integrity of the sphincterial system as well as reduce the AI occurrence, the most frequently surgical procedures adopted for the treatment of CAFs are fissurectomy associated with pharmacological sphincterotomy and, sometimes with cutaneous or mucous advancement flap.

Available literature on sphincterial function after this latter procedure is lacking, moreover all the accessible work took into consideration small samples of patients.

The first goal of the present work was to evaluate if the pre-operative manometric modifications would normalize after sphincter saving surgical procedure for CAF with IAS hypertonia; secondly we had the purpose of estimate AI, healing and recurrence rate in a consecutive series of patients affected by CAF with IAS hypertonia underwent fissurectomy and anoplasty with pharmacological sphincterotomy.

Materials and Methods

This study involves 108 patients, all affected by idiopathic and non-recurrent CAF with hypertonic IAS, who underwent fissurectomy and anoplasty with V-Y cutaneous flap advancement from January 2012 to January 2018. Exclusion criteria for the study were: the presence of multiple fissures, fistulas in ano, syphilis, inflammatory bowel disease, anal abscess, malignant disease and previous anorectal surgery. All patients were followed up for at least 2 years after the surgical procedure. The patients' outcome data were retrieved from a prospectively monitored database.

We conduct this study in compliance with the principles of declaration of Helsinki, the protocol for this study has been submitted to the Ethical Committee of our institution, which did not consider necessary to approve it. Written informed consent was obtained from all the study participants.

Preoperative manometric evaluation was performed after a reasonable period of suspension of all medical therapy influencing IAS tone. The manometric evaluation was carried out by a manometric sensor (2.1 mm external diameter) with four circle orifices and a latex microbaloon at its extremity (Marquat C87; Boissy, St-Leger, France) ¹⁹. The machine was connected to a polygraph (Narco; Byosystem MMS 200, Houston TX) using the station pull-through method with perfusion of normal saline and the patient lying in the right lateral position. At manometric evaluation, maximum resting pressure (MRP) and maximum squeeze pressure (MSP) were defined as the maximum pressure detected respectively, on resting and after voluntary contraction. Ultraslow wave activity (USWA) was defined as pressure's waves with frequency of less than 2/min and an amplitude greater than 25 cm H₂O.

The healthy control group included 54 subjects matched by age and gender and in a 1 to 2 ratio with the patients subject to study; in this latter group values of MRP and MSP were respectively 69,8 \pm 11,8 mmHg and 115 \pm 34,5 mmHg; USWA was detected in the 11,1% of healthy subjects. In accordance to Jones et al. ²⁰ the range values of MRP were 45-85 mmHg, so that CAF with hypertonic IAS were defined as those with MRP values > 85mmHg and CAF with hypotonic IAS those with MRP< 45 mmHg. Manometric follow up was performed at 6, 12 and 24 months after the surgery.

All patients underwent fissurectomy and anoplasty with V-Y skin flap advancement lying in a gynecological position under spinal or general anesthesia. In order to expose the anal canal we used four Kocher pliers placed at 3,6,9 and 12 hours to avoid employing anal retractors; an Eisenhammer retractor have been gently introduced just in case of necessity.

After injection of 5 ml of local anesthetic solution (100mg cloridrate mepivacaine and 0,025 ml L-adrenaline), the fibrotic edges were excised with a scalpel until normal non-fibrotic anodermal tissue showed sufficient bleeding. The sentinel skin tag and hypertrophied papilla at the level of dentate line were excised when present. The tissue at the base of the fissure was curetted until there were clean muscle fibers of the IAS. There hasn't been any use of diathermy and careful attention was payed to avoiding damages of the IAS. Standard advancement anoplasty was performed using a flap of healthy skin tissue which was mobilized and then advanced with its blood supply to fill in the defect. The flap was secured without tension to the anal canal and the skin was closed tension free in a V-Y manner with interrupted rapid absorbable suture behind the advancement flap.

The patients were treated with intraoperative local injection of 30 U.I. of botulinum toxin A (Botox, Allergan Westport, Ireland) ²¹⁻²³or with local administration of post-operative nifedipine and lidocaine for 15 days after surgery (Antrolin[®])²⁴. Before surgery, all patients received a small volume of phosphate-saline enema.

Metronidazole was administered intravenously in a dose of 500mg 1h before surgery, subsequently, it was administered per os at the dosage of 250 mg for 7 days, three times daily.

During the first two weeks after the surgery, patients took variable doses of psyllium fibers. A laxative preparation (sennosides) was given orally to subjects who had not yet passed stools 3 days after surgery. Immediately after surgery, all patients received 100 mg of diclofenac intramuscularly for analgesia and were instructed to take only 100mg of nimesulide tablets as requires.

The goal of the study was the evaluation of MRP, MSP, USWA, incontinence and recurrence rate. A complete healing was defined as a complete epithelialization of the advancement skin flap. Recurrent CAFs were defined as those who occurred after the complete healing of the previous wound.

AI was assessed preoperatively and 6,12 and 24 months after surgery according to Pescatori's grading system [25]: A incontinence for flatus and mucus; B for liquid stool; C for solid stool; 1 for occasional; 2 for weekly and 3 for daily. Patients were discharged within 24 hours after surgery, afterwards they were examined until they were completely healed and they were also followed up until 24 months following the surgical procedure. Independently of the scheduled appointments, patients were seen on request.

STATISTICAL ANALYSIS

The data were analyzed by standard statistical methods and the results were expressed as means \pm standard deviation. Differences between continuous data were compared using Student *t* test for paired and unpaired samples, whereas differences between percentages were analyzed using Fisher test. Probability values of < 0,05 were considered significant.

Results

Demographic and clinical characteristics of the patients object to study are reported in Table I.

In all of the patients we recorded a fast post-operative resolution of clinical symptoms and we achieved a complete wound healing in all the patients within 40 days after surgery; none of them complained about pain, bleeding or itching 40 days after surgery. We recorded 7 cases of recurrences, 4 women and 3 men, the site of recurrence was always different from the primary location, all of them occurred within 2 years from the previous surgery and all were characterized by the persis-

TABLE I - Demographic and clinical characteristics of patients affected by CAF with hypertonic IAS.

	N°	%
GENDER		
Male	62	57
Female	46	42,5
Age (years)	32,9±13,1	
CAF		
Posterior	88	81,5
Anterior	20	18,5
Hypertrophied anal papilla	75	69,4
Skin Tags	65	60,2
Symptoms		
Pain	108	100
Bleeding	90	83,3
Pruritus	68	62,9
Duration (months)	$16,5 \pm 8,1$	

tence of IAS hypertonia. These patients underwent a medical treatment with implementation of fibres in the diet, employ of topical products containing nifedipine or lidocaine and anal dilatators. All of them responded to the conservative therapy with a complete healing.

ANAL INCONTINENCE

We recorded 7 cases of pre-operative AI (6,48%). In the immediate post-operative period, 2 of the latter, experienced a temporary worsening of the AI; after 6 months from surgery the grading come back to be similar than the one recorded pre-operatively. We observed only 3 "de novo" cases of post-operative AI all treated and healed after botulinum toxin injection; all of them had low grade and temporary alteration.

MANOMETRY FINDINGS

Pre-operative MRP findings were significantly higher when compared to healthy subjects (p = 0,0001), while MSP values were only slightly increased.

At 6,12, 24 months manometry follow up after surgery MSP values did not significantly differ when compared to the pre-operative ones and those recorded in healthy control subjects. MSP values were found to be slightly lower in women and anterior CAFs in comparison with men and posterior CAFs.

At 6 and 12 months manometry follow up after surgery MRP values were significantly lower as compared to the pre-operative ones (p=0,018), whereas they were still significantly higher than those measured in healthy controls (p=0,0286). At 24 months follow up after surgery MRP values were similar to those detected in healthy subjects (Table II).

	MRP values (mmHg)	p values
Healthy subjects	69,8 ±11,8	
Patients with CAPF		
Pre-operatively	95,3±8,5	0,0001
6 months after surgery	77,3±15,2	0,0018
12 months after surgery	76,1±19,5	0,0286
24 months after surgery	73,2±10,5	0,0642

TABLE II - MRP values in healthy subjects and in patients affected by CAPF, recorded before and after the surgical procedure.



Fig. 1: Detection of USWA in healthy subjects and in patients affected by CAPF, recorded pre-operatively and post-operatively. Statistically significant differences vs healthy subject:

pre-operatively p= 0,00011; 6 months after surgery p= 0,0028; 12months after surgery p=0,0230; 24 months after surgery p= 0,210.

The pre-operative presence of USWA was detected in 62 patients (57,4%); a comparison among healthy subjects showed a significant difference (p=0,00011). The presence of USWA was significantly reduced from 6 months follow up after surgery and it was similar to healthy controls; at 24 months follow up after surgery we did not recorded any differences concerning gender or CAF location (Fig 1).

Discussion

This study shows that IAS hypertonia and the high rate of USWA present in CAF with hypertonic IAS after fissurectomy and anoplasty with pharmacological sphincterotomy are considerably reduced at 6 months after surgery at after 24 months manometry values are similar to those detected in healthy controls. In all the patients subject to study we observed a fast resolution of clinical symptoms ad wound healing with a low incidence of post-operative complications and recurrences. We recorded only 3 cases of "de novo" AI, all temporary and low-grade alterations. These outcomes are similar than those obtained after LIS ^{26,27} or pneumatic balloon dilatation ^{.28} The role of hypertonia of the IAS in the pathogenesis of CAFs remains still unclear ²⁹. Several studies showed that a reduction of MRP levels with medical or surgical therapy is associated with a high incidence of fissure healing. The foundation of LIS is that the hypertone of the IAS reduces the irroration of the mucous-cutaneous transition zone, as little arterial branches are present in the depth of the muscle, so that its section improve its irroration ^{30,31} allowing a fast healing. Nevertheless, the diminution of MRP does not represent a prerequisite for CAF healing, however, Pitt et al. ³² in a double blindrandomized placebo-control trial observed that oral indoramin (α - adrenoreceptor antagonist) can reduced MRP values for the 35% without any satisfactory effect on fissure healing.

Ho et al. ³³ highlighted that LIS and pharmacological sphincterotomy with oral nifedipine produce a similar reduction of MRP values, but LIS was associated with a significantly higher rate of healing.

Thornton et al. ³⁴ observed a reduction of 17% of MRP values without correlation with clinical outcome after injection of botulinum toxin A, so the healing of the CAF does not come along with the reduction of MRP levels. Also, Pascual et al. ⁶ reported no significantly differences between healing and not healing CAF comparing manometric findings.

Madalinsky and Chodorowski ³⁵ theorized that a good response to surgical or pharmacological sphincterotomy could be related to the presence of conserved vascular endothelium which conditions the "stretchability" of the IAS by the increased preservation of muscular blood flow. Also some surgical procedures such as fissurectomy alone or fissurectomy associated with advancement flap showed a similar incidence of fissure healing compared with the sphincterotomy or the anal dilatation ^{26,28,36-39}.

The aid of CAF treatment is in healing the patient without immediate or long-time complications. The incidence of incontinence post-sphincterotomy or stretch of the IAS varies from zero in some studies to up to 31% in other cases. This extreme variability can depend on the extent of sphincterotomy, the definition of anal incontinence, and the differences in follow-up. Moreover, the treatment for AI has remarkable costs and the average total annual cost per person ranges around USD 17,166 ⁴⁰. AI, even if regarding only gas, is the most serious complication that can compromise quality of life and can be more disabling than CAF ^{10,41}. The AI can occur immediately or at a long distance after surgery and it can be temporary or permanent.

IAS has an essential role to preserve the faecal continence, it is a smooth muscle that maintains sustained tone in the basal state, and it is fatigue resistant ^{13,14,18}. Myogenic IAs tone mostly originates from the tonic contraction of circular smooth muscle cells ^{42,43} and it is modulated by RhoA/ROCK proteins ³⁷, arachidonic acid and metabolites ⁴⁴ and intrinsic myenteric neuros, which also tonically release NO. The IAS section can be functionally compensated immediately after surgery. However in some patients the progression from functionally compensated to functionally uncompensated anal sphincter damage may occur. Delayed incontinence may be associated with other cofactors accumulating over time, or more likely, anal fissure surgery may accelerate the physiological age related weakening of the anal sphincter mechanism.

Conclusion

This study shows that hypertonic IAS and the frequent detection of USWA in patients affected by CAPF normalize after 24 months from fissurectomy and anoplasty. Moreover, we did not record any "de novo" case of AI, while the recurrence incidence rate has been found to be similar to LIS.

Riassunto

Il ruolo dell'aumento del tono dello sfintere anale interno nella patogenesi delle ragadi anali croniche (CAF) è a tutt'oggi dibattuto. La sfinterotomia laterale è la procedura chirurgica più frequentemente impiegata sebbene sia associata ad un incidenza di incontinenza anale postoperatoria del 14%. L'obbiettivo del nostro studio è quello di valutare, oltre alla guarigione delle CAF, se le alterazioni manometriche pre-operatorie nei pazienti affetti da CAF con ipertono sfinterico, si normalizzassero dopo asportazione della ragade e anoplastica con lembo mucocutaneo di scorrimento a V-Y nei pazienti con CAF. Sono stati studiati 108 pazienti affetti da CAF con ipertono.

I risultati dello studio mostrano una guarigione di tutte le ferite entro 40 giorni dall'intervento chirurgico; sono stati osservati 7 casi di recidiva trattati efficacemente con terapia medica e 3 casi di incontinenza anale post-operatoria "de novo", tutti temporanei e di lieve entità. La maximum resting pressure e la presenza di ultraslow wave activity pre-operatorie , a 24 mesi dall'intervento chirurgico, sono simili a quelle dei soggetti sani. L'alto tasso di guarigione in assenza di incontinenza anale post-operatoria permanente, e la normalizzazione dei valori manometrici, suggeriscono che quest'approccio "sphincter preserving" risulta valido per il trattamento delle ragadi anali croniche con ipertono sfinterico.

References

1. Mapel DW, Schum M, Von Worley A: *The epidemiology and treatment of anal fissures in a population-based cohort.* Tech Coloproctol, 2012; 16:9-19.

2. Patti R, Famà F, Barrera T, Migliore G, Di Vita G: Fissurectomy and anal advancement flap for anterior chronic anal fissure without

hypertonia of the internal anal sphincter in females. Colorectal Dis, 2010; 12:1127-30.

3. Bove A, Balzano A, Perrotti P, Antropoli C, Lombardi G, Pucciani F: *Different anal pressure profiles in patients with anal fissure*. Tech Coloproctol, 2004; 8:151-56.

4. Pascual M, Pera M, Courtier R, Gil MJ, Parés D, Puig S, Andreu M, Grande L: *Endosonographic and manometric evaluation of internal anal sphincter in patients with chronic anal fissure and its correlation with clinical outcome after topical glyceryl trinitrate therapy.* Int J Colorectal Dis, 2007; 22:963-67.

5. Anaraki F, Foroughifar T, Laleh Hossein S, Etemad O: *Evaluation of outcomes in fissurectomy and V-Y advancement flap for the treatment of chronic anal fissure*. J Coloproctol (RIO J), 2018; 38:132-36.

6. Santander C, Gisbert JP, Moreno-Otero R, McNicholl AG, Maté J: Usefulness of manometry to select patients with anal fissure for controlled anal dilatation. Rev Esp Enferm Dig, 2010; 102:691-97.

7. Garg P, Garg M, Menon GR: Long-term continence disturbance after lateral internal sphincterotomy for chronic anal fissure: A systematic review and meta-analysis. Colorectal Dis, 2013; 15:e104-17.

8. Griffin N, Acheson AG, Tung P, Sheard C, Glazebrook C, Scholefield JH: *Quality of life in patients with chronic anal fissure*. Colorectal Dis, 2004; 6:39-44.

9. Di Vita G, Patti R, Barrera T, Arcoleo F, Ferlazzo V, Cillari E: Impact of heavy polypropylene mesh and composit light polypropylene and polyglactin 910 on the inflammatory response. Surg Innov, 2010; 17:229-35.

10. Patti R, Territo V, Aiello P, Angelo GL, Di Vita G: *Manometric* evaluation of internal anal sphincter after fissurectomy and anoplasty for chronic anal fissure: A prospective study. Am Surg, 2012; 78:523-27.

11. Rao SS: *Pathophysiology of adult fecal incontinence*. Gastroenterology, 2004; 126(1 Suppl 1):S14-22.

12. Bharucha AE: *Pelvic floor: anatomy and function.* Neurogastroenterol Motil, 2006; 18:507-19.

13. Ram E, Alper D, Stein GY, Bramnik Z, Dreznik Z: Internal anal sphincter function following lateral internal sphincterotomy for anal fissure: A long-term manometric study. Ann Surg, 2005; 242:208-11.

14. McNamara MJ, Percy JP, Fielding IR: A manometric study of anal fissure treated by subcutaneous lateral internal sphincterotomy. Ann Surg, 1990; 211:235-38.

15. Peker K, Yilmaz I, Demiryilmaz I, Inal A, Işik A: *The effect of lateral internal sphincterotomy on resting anal sphincter pressures*. Turk J Med Sci, 2014; 44:691-95.

16. Remes-Troche JM, Rao SS: *Neurophysiological testing in anorectal disorders*. Expert Rev Gastroenterol Hepatol, 2008; 2:323-35.

17. Patti R, Almasio PL, Arcara M, Sparacello M, Termine S, Bonventre S, Di Vita G: *Long-term manometric study of anal sphinc-ter function after hemorrhoidectomy.* Int J Colorectal Dis, 2007; 22:253-57.

18. Jones OM, Ramalingam T, Lindsey I, Cunningham C, George BD, Mortensen NJ: *Digital rectal examination of sphincter pressures in chronic anal fissure is unreliable*. Dis Colon Rectum, 2005; 48:349-52.

19. Patti R, Famà F, Tornambè A, Asaro G, Di Vita G: *Fissurectomy* combined with anoplasty and injection of botulinum toxin in treatment of anterior chronic anal fissure with hypertonia of internal anal sphincter: A pilot study. Tech Coloproctol, 2010; 14:31-6.

20. Patti R, Guercio G, Territo V, Aiello P, Angelo GL, Di Vita G: Advancement flap in the management of chronic anal fissure: A prospective study. Updates Surg, 2012; 64:101-6.

21. D'Orazio B, Geraci G, Martorana G, Sciumé C, Corbo G, Di Vita G: Fisurectomy and anoplasty with botulinum toxin injection in patients with chronic anal posterior fissure with hypertonia: A long-term evaluation. Updates Surg, 2020; DOI: 10.1007/s13304-020-00846-y. Ahead of print.

22. D'Orazio B, Sciumé C, Famà F, Bonventre S, Martorana G, Corbo G, Calì D, Terranova G, Di Vita G, Geraci G: Surgical sphincter saving approach and topical nifedipine for chronic anal fissure with hypertonic internal anal sphincter. Chirurgia 2020; 115: 590-99.

23. Pescatori M, Anastasio G, Bottini C, Mentasti A: *New grading* and scoring for anal incontinence. Evaluation of 335 patients. Dis Colon Rectum, 1992; 35:482-87.

24. Sahebally SM, Walsh SR, Mahmood W, Aherne TM, Joyce MR: Anal advancement flap versus lateral internal sphincterotomy for chronic anal fissure. A systematic review and meta-analysis. Int J Surg, 2018; 49:16-21.

25. Sileri P, Stolfi VM, Franceschilli L, Grande M, Di Giorgio A, D'Ugo S, Attina' G, D'Eletto M, Gaspari AL: *Conservative and surgical treatment of chronic anal fissure: Prospective longer term results.* J Gastrointest Surg, 2010; 14:773-80.

26. Renzi A, Izzo D, Di Sarno G, Talento P, Torelli F, Izzo G, Di Martino N: *Clinical, manometric, and ultrasonographic results of pneumatic balloon dilatation vs. lateral internal sphincterotomy for chronic anal fissure: A prospective, randomized, controlled trial.* Dis Colon Rectum, 2008; 51:121-27.

27. D'Orazio B, Geraci G, Famà F, Cudia B, Martorana G, Sciumé C, Corbo G. Terranova G, Bonventre S, Di Vita G: Long term outcomes of fissurectomy and anoplasty for chronic anterior anal fissure without hypertonia: low recurrences and continence conservation. Ann Ital Chir, 2020. S0003469X20034727, Ahead of print.

28. Schouten WR, Briel JW, Auwerda JJ: Relationship between anal pressure and anodermal blood flow. The vascular pathogenesis of anal fissures. Dis Colon Rectum, 1994; 37:664-69.

29. Klosterhalfen B, Vogel P, Rixen H, Mittermayer C: Topography of the inferior rectal artery: A possible cause of chronic, primary anal fissure. Dis Colon Rectum, 1989; 32:43-52.

30. Pitt J, Dawson PM, Hallan RI, Boulos PB: A double-blind randomized placebo-controlled trial of oral indoramin to treat chronic anal fissure. Colorectal Dis, 2001; 3:165-68. 31. Ho YH, Tan M: Ambulatory anorectal manometric findings in patients before and after haemorrhoidectomy. Int J Colorectal Dis, 1997; 12:296-97.

32. Thornton MJ, Kennedy ML, King DW: Prospective manometric assessment of botulinum toxin and its correlation with healing of chronic anal fissure. Dis Colon Rectum, 2005; 48:1424-31.

33. Madaliński M, Chodorowski Z: *Relation between botulinum toxin and nitric oxide donors in the treatment of chronic anal fissure*. Med Sci Monit, 2005; 11:HY1-5.

34. Abramowitz L, Bouchard D, Souffran M, Devulder F, Ganansia R, Castinel A, Suduca JM, Soudan D, Varastet M, Staumont G: *Sphincter-sparing anal-fissure surgery: A 1-year prospective, observational, multicentre study of fissurectomy with anoplasty.* Colorectal Dis, 2013; 15:359-67.

35. Patel CA, Rattan S: Cellular regulation of basal tone in internal anal sphincter smooth muscle by RhoA/ROCK. Am J Physiol Gastrointest Liver Physiol, 2007; 292:G1747-56.

36. Hancke E, Suchan K, Völke K: Anokutaner Advancement-Flap zur sphinkterchonenden chirurgischen Therapie der chronischen Analfissur. Coloproctology, 2020; 42: 270-76.

37. Vershenya S, Klotz J, Joos A, Bussen D, Herold A: *Combined* approach in the treatment of chronic anal fissures. Updates Surg, 2015; 67:83-9.

38. Mandaliya R, DiMarino AJ, Moleski S, Rattan S, Cohen S: Survey of anal sphincter dysfunction using anal manometry in patients with fecal incontinence: A possible guide to therapy. Ann Gastroenterol, 2015; 28:469-74.

39. Topal U, Eray IC, Rencüzoğulları A, Dalcı K, Yalav O, Alabaz Ö: The effect of anorectal manometric examination on the surgical treatment plan in chronic anal fissure. Ann Ital Chir, 2020; 9: \$0003469X20030997.

40. Opazo A, Lecea B, Gil V, Jiménez M, Clavé P, Gallego D: Specific and complementary roles for nitric oxide and ATP in the inhibitory motor pathways to rat internal anal sphincter. Neurogastroenterol Motil, 2011; 23:e11-25.

41. Opazo A, Aguirre E, Saldaña E, Fantova MJ, Clavé P: *Patterns of impaired internal anal sphincter activity in patients with anal fissure.* Colorectal Dis, 2013; 15:492-99.

42. de Godoy MA, Rattan N, Rattan S: Arachidonic acid metabolites follow the preferential course of cyclooxygenase pathway for the basal tone in the internal anal sphincter. Am J Physiol Gastrointest Liver Physiol, 2009; 296:G727-34.