

Medical Interventional Treatment of Adult Fistula-in-ano. A Pilot Study for Curative Response of Intra-tract Injections of Ceftazidime and Metronidazol

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ABSTRACT

The treatment of fistula in-ano is surgical but not always. Considering the recurrence and incontinence, alternative medical interventions may be required. 25 (18 males, 7 females) cases of referral perianal fistulas recruited in a randomized interventional clinical trial in hospitals affiliated to Jundishapur University, Ahwaz-Iran. The participants have been managed in three groups regardless of the type, age and gender by intermittent multiple intra-tract injections of selective drugs: Sodium Tetra Decyle Sulphate (STDS, 1%), Metronidazol and Ceftazidime during 15 months and were followed by ten months of treatment. 16 cases (64%) were completely cured for 10 months of follow up. 9 cases (36%) were recurred and referred for surgery. Metronidazol + Ceftazidim (5 cures versus 2 recurrences and 71.42% success) with STDS + Metronidazol (7 cures versus 3 relapses with 70% success) were more effective respectively. STDS + Ceftazidim group resulted in 4 cures versus 4 recurrences with 50% success. There were no significant differences between cured and recurrent fistulas considering gender, age, duration of involvement, number of injections, length of fistula and distance from anal verge. There was a significant relation between recurrence and anterior type of fistulas in the study ($P = 0.023$). Direct injection of selective drugs and antibiotics is curative and effective in treatment of perianal fistulas as the first step. Anterior fistulas, cavitated active fistulas and lack of patient's consent should not be considered.

Key words: Fistula in-ano, Perianal fistula, medical intervention, intra-tract drug injections.

INTRODUCTION

Perianal fistulas are mostly easy but difficult to imitate as a surgical treatable entity. Determination of the type and the pathway of this prevalent complication of cryptogenic perianal abscess for selecting the wide range of treatment from simple fistulotomy toward mucosal flap advancement or even diversion of rectum, is necessary. As surgery is the best treatment, both fistulotomy and fistulectomy are now commonly performed surgical procedures, however, in such procedures anal continence as the goal treatment and a full healing response may not be achieved¹⁻⁴. On the other hand, high, posterior curved, unilateral multi-orifice, bilateral multi-orifice (horseshoe) and recurrent fistulas are typically problematic and the sphincteric continence would be endangered by repeated

surgeries. Complicated fistulas are currently best treated by different invasive and noninvasive combined medical-surgical procedures. Yet, as a general concept, all these procedures besides other new techniques may not provide the ultimate for cure in all³; nevertheless, they have to be accomplished though as a rule, whenever the continence is being endangered, should regress and choose an alternative treatment strategy. Currently, there is no convincing accepted medical procedure alone as an alternative. Application of local antibiotics, chemotherapeutic drugs into the fistulas with inflammatory bowel disease (IBD), Fibrin glue injection and mixed seton or threads placement are examples of current treatment options. The main advocated advantages of individualized non-surgical minor invasive medical treatments are preserving anal continence in spite

of long-lasting healing processes as compared to surgery. Their effectiveness varies, however they are now being considered particularly in treatment of IBD. The aim of this study was to establish the efficiency and of direct local intra-tract injection of selective antiseptics as an independent treatment for fistula in-ano.

METHODS

This is a case series, interventional clinical study of selected cases for the study of referrals in our surgical clinics affiliated to Jundishapur University of Medical Science, Ahwaz-Iran. During 15 months from August 2011 to November 2012, patients referred for treatment of perianal discharges diagnosed as perianal fistulas by physical examination with their agreement and consent for this type of treatment were selected. Thirty patients were randomized in three groups regardless of age, gender and type of the fistula and were followed 10 months for complete cure. 5 cases were excluded due to late abortion to continue and poor compliance to the study protocol. Short anterior epithelialized superficial fistulas (up to 20 mm length) and active cavitated post abscess types and others with underlying disease (IBD) were also in the study exclusion criteria. Firstly, fistulas were probed by a fine blunt head semi-flexible plastic probe to find the direction, height and the length accompanied with injection of Povidin Iodine for determining the level of internal orifice during proctoscopy in outpatient. Three groups of drugs were selected on the bacterial basis of colorectal region for intra-tract direct injections at random; first, Sodium Tetra Decyl Sulphate (STDS) and Ceftazidim; second, STDS and Metronidazol; third, Ceftazidim and Metronidazol. We speculated that STDS has the ability to abrade internal tract epithelialization as a resistant ground and also a sclerosing detergent which could reinforce antibiotics to accelerate granulation and healing. Injections were performed very slowly about minutes through a fine blunt head injector needle to lodge the drug copiously into the tract, in a manner of "every other day injection" intermittently, which were followed twice weekly on the basis of discharges. For Metronidazol drip injection by the set from the external orifice was used. Following weeks, injections were continued

until external orifice was being closed and its over skin was completely healed. Patients were followed up for early and late recurrence during the first and second week followed by monthly follow up until 3 and every two months for 6 months respectively; unless any discharges were reported. For recurrence, if the external orifice was active after injections, the second cycle was repeated until closure. In instances where recovery was not achieved or the patient did not accept the second session, patient was accounted as un-responsive and was referred for surgery. Cure was accepted as complete asymptomatic patient for at least over 10 months. The data were calculated and analyzed by independent sample test, T test, Spearman's correlation, Chi-square test where $p < 0.05$ was considered statistically significant (Pearson, Fisher) through the SPSS software.

RESULTS

There were 18 (72%) Male and 7 (28%) female, 28 – 63 (mean: 40.96) years old with 6 anterior and 19 posterior fistulas in which 15 were trans sphincteric and 10 Inter-sphincteric with short distance from anal verge (about: 1.3-3.6 Cm, mean: 2.428) without supra or extra-sphincteric or high type fistula. All were uni-tract with single orifice. Their internal orifices were juxta-dentate or below the dentate line mostly lateral and postero-lateral. The length of tract was between 28 - 57 mm (mean: 42.04). Duration of involvement until referral was 2 – 27 (mean: 5.76) months. The numbers of injections were between 6 -14 (Mean: 8.92). There were no complication and all of the symptoms of pain, inflammation, and discharges were dramatically subsided until the termination of injections and days before recurrence and patients were satisfied. 8 patients had intra tract injections of STDS + Ceftazidim in whom 4 were completely cured and 4 had recurrence after between 1-3 months (50% success) and 2 missed follow up. In second group, 10 patients were injected with STDS + Metronidazol that 6 of them had cure by first session of injections in follow up, however, 4 patients recurred after approximately 1-4 months. Two of recurrent fistulas received 5 and 8 times second session re-injections due to very low discharges and one cured until followed up (70% success). Other 3, referred to surgery after 3 months for bulging and new

symptoms. In the third group, 7 patients received Ceftazidime + Metronidazol injections. Five patients were cured and 2 had relapses (71.42% success)(Table1). One patient was a case of previous fistulectomy with two recurrences and re operation by seton placement during 20 months wherethe main tract was cured but has been referred again with an accessory tract in posterior side near the border of coccyx after 7 months. Overall, 16 (64%) patients were cured and had no symptom during 10 months of follow up and 9 (36%) relapsed. Of patients who had recurrence, relapse

intervals were in between 3 to16 weeks from recovery. From those were relapsed 5 fistulas (55.5%) with the length of 29-40 mm were anterior type and 4 (44.4%) were posterior with the length of 37-50 mm. There were no complications or incontinence. Comparing the results, there were no significant differences between cured and recurrent fistulas considering gender, age, duration of involvement, number of injections, length of fistula and distance from anal verge (Table2). However, there was a significant relation between recurrence and anterior type of fistulas in the study (P = 0.023)

Table 1: Injection of drugs and outcome. *No effectiveness that was referred for surgery. **Late rejections and follow up Abruptions who were omitted. [*] Only one was cured

Drugs	Injected patients		Cure	Recurrence No response*	Missed Follow up**	Number of Patients
	1 st session	2 nd session				
STDS + Cefta	8	0	4 (50%)	4	2	10 minus 2
STDS + Metro	8	2 [*]	7 (70%)	3	0	10
Metro + Cefta	7	0	5 (71.4%)	2	3	10 minus 3
Sum	23	2	16	9	5	25

Table 2: Comparing the mean of variants related to recurrence and their P values

Variant	Recurrence	Mean	SD	Minimum	Maximum
Age	No	41.07	7.815	28	54
	Yes	40.8	11.173	30	63
Distance. from Anal Verge (Cm)	No	2.28	0.587	1.3	3
	Yes	2.65	0.738	1.5	3.6
Tract length (mm)	No	41.47	9.219	30	57
	Yes	42.9	7.894	28	53
Duration of involvement	No	6.67	6.149	2	27
	Yes	4.4	1.43	3	7
Number of injections	No	8.53	1.767	6	12
	Yes	9.5	2.635	7	14

Table 3: Comparing Recurrence, Anterior type of fistulas based on Goodsall Law and gender

Chi-square test	Fisher's Exact Test. Sig (2- sided)
Recurrence x type of fistula (Pearson chi –square P = 0.013)	P = 0.023
Gender x type of fistula	P = 0.298
Gender x Recurrence	P = 0.378

and gender had no meaningful difference compared to recurrence and the type (Table3).

DISCUSSION

Treatment of fistula-in-ano has a fluctuated remedy, originated from multi factorial causes that directly affect the therapeutic outcome. Selective therapeutic protocols depend on fistula's anatomy and patient's habitual conditions. Long lasting constipation, high protein-fat diets and crypt bacterial reservoir are existing factors that facilitate resistance against healing. Having their considered, insight necessitates changing the glance more towards medical interventional remedy for most fistulas. Since, ancient medicine had experienced the thought of using thread or seton weltering to materials working as antiseptics for managing the fistula in ano, medical interventions had been propounded (Ksharsootra by Indian physician Sushruta in the 600 BC)^{1,5}. Although, nowadays, surgery alone is the promising ultimate cure in simple fistulas however, saving the continence as a rule, has withdrawn it in the complex types. For instance, advancement flap is considered the gold standard for complex fistula; however it is associated with up to 31% post operative minor incontinence and also more than 12% major incontinence³. The procedure fails in one in three patients⁶, which are about 2-5 times more than fistulotomy – fistulectomy with or without seton⁷. Seton placement alone has been substantially more effective in complex type with least incontinence⁸. Furthermore, sphincter saving procedures like plug placement, ligation of intersphincteric fistula tract (LIFT), Bio LIFT and stem cell injections are associated with technical disadvantages and were not trialed in details to be used with confidence as the standard methods^{9,10}; although, advocated reports are available¹¹⁻¹³. Application of alternative medical interventional treatments has been also well introduced. Fibrin Glue injection postulated that it possess safe and feasible usage in infants and children¹⁴; However, in adults have been shown to have led to unsatisfactory outcomes compared to staged mucosal flap surgery in complex and IBD base fistulas^{15,16}. Furthermore, the glue is accepted to be mostly promising in comparison to conventional surgery especially in simple fistulas^{16,17} and even

alone without accompanied procedures¹⁸. Its presented overall success was 83.3%¹⁹ and 67.6% in high fistulas²⁰. Yet, antibiotics are not clinically postulated to be directly curative alone in fistula but their effects were advocated for use, especially about Metronidazol and Silver phosphate^{6,21}. As etiology, bacterial colonization and active internal recto-fistula communication besides following tract epithelialization are three well known important causes for corrupting the healing and closure of the fistula. In general, destruction of any two, leads to repair and omission of fistula in a controlled ground. Antibiotics in such circumstances are supplementary alternatives. We believe that if bacterial colonization and tract epithelialization is eliminated successively, internal mucosal orifice would rapidly repair and internal communication will cut. Since, STDS is a sclerosing drug, it has been used to destroy the tract epithelial cobblestone and also support antibiotics to suppress the bacterial overgrowth. Therefore, the ground for granulation formation will be facilitated to progress and thus, the tract will be obliterated and fibrosed. Based on our results, similarly, both STDS + Metronidazol group and Ceftazidime + Metronidazol were shown to be more effective in fistulas medical treatment (70 & 71.4% success rate respectively) with less recurrence compared to group. This may insist on the substantial role and direct effect of Metronidazol compared to ceftazidime. On the other hand, from the point of recurrence, the sum of relapses (5 recurrences of 6 anterior types) was strongly correlated to anterior type fistulas according to Goodsall law ($P = 0.023$) (table3). Presumably, straight and shorter pathway of anterior types as they were in the lower range of tract length (29-40 mm), with more fecal or infected drainages due to fast epithelialization, play a role in tract resistance. Overall, in the study, lack of incontinence and independent treatment success rate of 64% are acceptable. Consequently, it can be suggested that mixed selected antibiotics will be optimistically effective in the first step of treating fistula-in-ano among selective situations. However, since the patients requested to be free of symptoms and persuading into full recovery immediately, they have to be explained for long lasting. To avoid least complications, safe suggestion would be: patient selection, step treatment and close follow up. Step treatment can be medical material

injections (selective antibiotics as was shown in the study or alternatively fibrin glue), seton placement (cutting²² or simple), fistulotomy or fistulectomy "using manometry" respectively. For recurrence or incontinence as complex fistulas: fistulotomy and simultaneously sphincter repair^{23,24}, LIFT, advancement flaps and plugs, based on surgeon's experiences is suggested. In addition, we

believe. However this would require further studies to investigate in more population.

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REFERENCES

- Ramesh PB. Anal fistula with foot extension-treated by Kshara sutra (medicated seton) therapy: A rare case report. *Int J Surg Case Rep.* 2013; **4**(7):573-576. Doi: 10.1016/j.ijscr.2013.04.004.
- Tobisch A, Stelzner S, Hellmich G, Jackisch T, Witzigmann H. Total fistulectomy with simple closure of the internal opening in the management of complex cryptoglandular fistulas: long term results and functional outcome. *Dis Colon Rectum.* 2012; **55**(7):750-5. Doi: 10.1097/DCR.0b013e3182569b29.
- Kee Ho Song. New techniques for Treating an Anal fistula. *J Korean Soc Coloproctol.* 2012; **28**(1):7-12. Doi: 10.3393/jksc.2012.28.1.7 PMID: PMC3296947
- Toyonaga T, Matsushima M, Kiriu T, Sogawa N, Kanyama H, Matsumura N, Shimojima Y, Hatakeyama T, Tanaka Y, Suzuki K, Tanaka M. Factors affecting continence after fistulotomy for intersphincteric fistula-in-ano. *Int J Colorectal Dis.* 2007; **22**(9):1071-5 (ISSN:0179-1958).
- Pasta V, Redler A, Amabile MI, Merola R, Monti M. Personal technique for treatment of perianal fistulas in outpatients. *Ann Ital Chir.* 2012; **83**(3):269-72.
- Van Onkelen RS, Mitalas LE, Gosselink MP, van Belkum A, Laman JD, Schouten WR. Assessment of microbiota and peptidoglycanin perianal fistula. *Diagn Microbiol Dis.* 2013; **75**(1):50-4. Doi: 10.1016/j.diagmicrobio.2012.09.012.
- Rosa G, Lolli P, Piccinelli D, Mazzola F, Bonomo S. Fistula in ano: anatomoclinical aspects, surgical therapy and results in 844 patients. *Tech Coloproctol.* 2006; **10**(3): 215-21. (ISSN: 11234-6337)
- Sileri P, Cadeddu F, D'Ugo S, Franceschilli L, Del Vecchio Blanco G, De Luca E, Calabrese E, Capperucci SM, Fiaschetti V, Milito G, Gaspari AL. Surgery for fistula-in-ano in a specialist colorectal unit: a critical appraisal. *BMC Gastroenterol.* 2011; **11**:120 (ISSN:1471-230X).
- de la Portilla F, Rada R, Jimenez-Rodriguez R, Diaz-Pavon JM, Sanchez-Gil JM. Evaluation of a new synthetic plug in the treatment of anal fistula: results of a pilot study. *Dis Colon Rectum.* 2011; **54**(11): 1419-22. Doi: 10.1097/DCR.0b013e31822c4d59.
- Gupta PJ, Gupta SN, Heda PS. Which treatment for anal fistula? Cut or cover, Plug or paste, loop or lift. *Acta Chir Iugosl.* 2012; **59**(2): 15-20.
- Sirikurnpiboon S, Awapittaya B, Jivaoaisarnpong P. Ligation of intersphincteric fistula tract and its modification: Results from treatment of complex fistula. *World J Gastrointest Surg.* 2013; **5**(4):123-8. Doi: 10.4240/wjgs.v5.i4.123.
- Han JG, Yi BQ, Wang ZJ, Zheng Y, Cui JJ, Yu XQ, Zhao BC, Yang XO. Ligation of the intersphincteric fistula tract plus a bioprosthesis anal fistula plug (LIFT-Plug): a new technique for fistula-in-ano. *Colorectal Dis.* 2013; **15**(5):582-6. Doi: 10.1111/codi.12062.
- Mushaya C, Batlett L, Schulze B, Ho YH. Ligation of intersphincteric fistula tract

- compared with advancement flap for complex anorectal fistula requiring initial seton drainage. *Am J Surg.* 2012; **204**(3): 283-9. Doi: 10.1016/j.amjsurg.2011.10.025
14. Osman MA, Elsharkawy MA, Othman MH. Repair of fistula in-ano in children using image guided Histoacryl injection after failure of conservative treatment. *J Pediatr Surg.* 2013; **48**(3):614-8. Doi: 10.1016/j.jpedsurg. 2012.11.029.
 15. van der Hagen SJ, Baeten CG, Soeters PB, van Gemert WG. Staged mucosal advancement Flap versus Staged Fibrin Sealant in the treatment of complex perianal fistula. *Gastroenterol Res Pract.* 2011; **2011**: 186350. Doi: 10.1155/2011/186350.
 16. Yeung JM, Simpson JA, Tang SW, Armitage NC, Maxwell-Armstrong C. Fibrin glue for the treatment of fistulae in ano-a method worth sticking to? *Colorectal Dis.* 2010;**12**(4):363-6 (ISSN1463-1318).
 17. Cirocchi R, Santoro A, Trastulli S, Farinella E, Di Rocco G, Vendettuali D, Giannotti D, Redler A, Coccetta M, Gulla N, Boselli C, Avenia N, Sciannameo F, Basoli A. Meta-analysis of fibrin glue versus surgery for treatment of fistula-in-ano.
 18. Singer M, Cintron J, Nelson R, Orsay C, Bastawrous A, Pearl R, Sone J, Abcarian H. Treatment of fistula-in-ano with fibrin sealant in combination with intra-adhesive antibiotics and/or surgical closure of the internal fistula opening. *Dis Colon Rectum.* 2005; **48**(4): 799-808 (ISSN: 0012-3706).
 19. Maralcan G, Baskon I, Aybasti N, Gokalp A. The use of fibrin glue in the treatment of fistula-in-ano: a prospective study. *Surg Today.* 2006; **36**(2):166-70 (ISSN:0941-1291).
 20. Queralto M, Portier G, Bonnaud G, Chotard JP, Cabarrot P, Lazorthes F. Efficacy of synthetic glue treatment of high cryptoglandular fistula-in-ano. *Gastroenterol Clin Biol.* 2010; **34**(8-9): 477-82 (ISSN:2210-7401).
 21. Blaker JJ, Pratten J, Ready D, Knowles JC, Forbes A, Day RM. Assessment of antimicrobial microspheres as a prospective novel treatment targeted towards the repair of perianal fistulas. *Aliment Pharmacol Ther.* 2008; **28**(5): 614-22. (ISSN:1365-2036).
 22. Kamrava A, Collins JC. A decade of selective use of adjustable cutting seton combined with fistulotomy for anal fistula. *Am Surg.* 2011; **77**(10):1377-80.
 23. Arroyo A, Perez-Legaz J, Moya P, Armananzas L, Lacueva J, Perez-Vicente F, Candela F. Fistulotomy and sphincter reconstruction in the treatment of complex fistula-in-ano: long-term clinical and manometric results. *Ann Surg.* 2012; **255**(5): 935-9. Doi: 10.1097/SLA.0b013e31824e9112.
 24. Ratto C, Litta F, Parello A, Zacccone G, Donisi L, De Simone V. Fistulotomy with end- to-end primary sphincteroplasty for anal fistula: results from prospective study. *Dis Colon Rectum.* 2013; **56**(2):226-33. Doi: 10.1097/DCR.0b013e31827aab72