

Efficacy of Argentum-Quartz Solution in the Treatment of Perianal Fistulas: A Preliminary Study

Tomasello Giovanni^{1, 8&}, Tralongo Pietro^{2&}, Di Trapani Benedetto^{3, 8&}, Carini Francesco¹, Sinagra Emanuele^{4, 8}, Oueidat Doreid^{5, 6, 7}, Tarek Bou Assi⁶, Jurjus Abdo^{5&}, Leone Angelo^{2*}

1. Department of Experimental Biomedicine and Clinical Neuroscience, Section of Human Anatomy, University of Palermo, Palermo 90133, Italy;

2. Department of Experimental Biomedicine and Clinical Neuroscience, Section of Histology, University of Palermo, Palermo 90133, Italy;

3. Chief Unit of Surgery, "Clinica Torina", Palermo 90100, Italy;

4. Fondazione Istituto S. Raffaele-G. Giglio, Gastroenterology and Endoscopy Unit, Cefalù 90146, Italy;

5. Department of Anatomy, Cell Biology and Physiological Sciences, Faculty of Medicine, American University of Beirut, Beirut 1107-2020, Lebanon;

6. Department of Laboratory Medicine, Hôpital Psychiatrique de la Croix, Jal el Dib, Beirut 60096, Lebanon;

7. Makhzoumi Foundation, Health Department, American University of Beirut, Beirut 1107-2020, Lebanon;

8. IEMEST, Euro-Mediterranean Institute of Science and Technology, Palermo 90139, Italy

ABSTRACT

Objective: Nowadays, an optimal and effective medical surgery remains the gold standard for perianal fistulas. Hereby we reported preliminary results in favor of using Argentum-quartz solution for both primary and recurrent perianal fistulas.

Methods: Three patients with intersphincteric and extrasphincteric fistulas were enrolled. Argentum-quartz solution was administrated twice a week for a period of 4 weeks, followed by a pause of 8 days and then another 4 weeks of treatment, totally 16 administrations. After treatment, all patients were monitored for a 4-month follow-up.

Results: Complete closures of 2 extrasphincteric fistulas and a partial closure with absence of inflammation and superative phenomena in the intrasphincteric fistula were both manifested.

Conclusion: Selective treatment of perianal fistulas with an argentum-quartz solution is safe and effective, and may represent a reliable alternative.

Key words:

Perianal fistula

Argentum

Quartz

Intersphincteric fistula

Extrasphincteric fistula

Introduction

Surgery has always been recognized as the gold standard for the management of perianal fistulas. However, the surgical procedures are associated with several complications including anal incontinence, preoperative bleeding and high rates of recurrence^[1-5]. At present, there are no available efficacious medical therapies

and all of the alternative procedures that have emerged, such as injection of fibrin glue or use of collagen plug, have not been found to be optimal in treating anal fistulas^[6-7]. Based on Park's criteria, fistulas are classified into 4 types, namely intersphincteric, trans-sphincteric, suprasphincteric and extrasphincteric. If the involved

*Corresponding Author:

Leone Angelo, E-mail: angelo.leone@unipa.it

[&]These authors share the first authorship.

anatomical area starts from the dentate line through the internal sphincteric muscle and courses downward to the anal verge or spreads to the rectum, fistulas are classified, respectively, as low or high-track intersphincteric. On the other hand, a trans-sphincteric fistula crosses the internal sphincter and the lower portion of external sphincter, and extends to the ischioanal fossa. Moreover, a suprasphincteric fistula extends over the puborectalis and exits through the ischioanal fossa. These are worrisome and difficult to treat. Finally, an extrasphincteric fistula usually results from trauma, anorectal disease and pelvic infection^[4]. Therefore, the colorectal surgeon proctologist often involved in dealing with this disease, implements only surgical treatments in these cases^[5]. Clinical evaluations are basically based on the extent of fistulas and the involved sphincteric apparatus.

Interestingly, the use of silver nitrate in the treatment of trachea-bronchial fistulas has been reported^[8]. In addition, our research group has previously reported the ability of silver and quartz

to reduce bacterial infection and to stimulate the proliferation and differentiation of fibroblasts^[9]. This prompted us to carry out a pilot trial to evaluate the possibility of treating primary and recurrent perianal fistulas with topical administration of argentum and quartz as a valid alternative to surgical practices.

Materials and Methods

General data

Three patients with intersphincteric and extrasphincteric fistulas were enrolled (Table 1). One of the enrolled subjects was also affected by Crohn’s disease diagnosed endoscopically, histologically and radiologically. The subjects with abscessed fistulas were excluded from the present study. Informed consent was obtained from all patients prior to their inclusion in the study. All procedures have been performed in accordance with Declaration of Helsinki ethical standards.

Table 1 Fistula Classifications and Relevant Clinical Outcomes of Three Patients

Age (years old)	Gender	Fistula classification	Clinical outcomes
42	Male	Extrasphincteric fistula	Complete closure
60	Male	Intrasphincteric fistula	Partial closure (absence of inflammatory suppurative events during follow-up).
29	Male	Extrasphincteric fistula	

Methods

Argentum-quartz solution marketed in Italy by WALA was packaged in a 1 mL vial, and the content of vial was drawn into a 1 mL insulin syringe (Figure 1). A catheter was placed into the fistula using a 20 gauge×1.26 inches of “pink” venflon (1.1 mm×32.0 mm) (Figure 2). Argentum and quartz were already available in Italian Pharmacopoeia (AIFA) and sold by prescription in pharmacies as a homeopathic medicine^[10].

Argentum-quartz solution was administrated twice a week for a period of 4 weeks, followed by a pause of 8 days and then another 4 weeks of treatment, a total of 16 administrations. After completion of treatment, all patients were monitored for a 4-month follow-up.

Results

During observation period, one patient with intersphincteric fistula had an exacerbation of Crohn’s disease with clinical symptoms characterized by abdominal colic and diarrhea. Consequently, a contextual treatment was offered with mesalazine orally, at a dose of 800 mg 3 times a day, and cortisone, prednisone 25 mg/tablet per day for 20 days. After

treatment, despite the failure in achieving a complete fistula closure, Crohn’s disease symptoms vanished. Therefore, Argentum-quartz solution was able to prevent the onset of inflammatory suppurative events in the fistula secondary to Crohn’s disease. In this case, partial healing may be due to the well-known higher complexity in treating intersphincteric rather than extrasphincteric fistulas or to the need for a longer treatment duration and follow-up observation period.

Argentum-quartz solution was given to a 42-year-old patient with relapse of perianal fistula who underwent the surgery one year ago, and a complete healing was achieved (Figures 3-4). Moreover, another patient with extraphincteric fistula was also healed completely after treatment with Argentums-quartz solution.

Discussion

Sometimes, the surgery doesn’t represent a solver procedure due to fistula recurrence after several months or years. Therefore, the patients as they try to avoid new surgical procedures are willing to accept an alternative treatment with administration of Argentum-quartz solutions. are willing to accept an alternative treatment with administration of Argentum-quartz solution as they try to avoid new



Figure 1 Argentum-quartz solution was packaged in a 1 ml vial and an insulin syringe was employed for administration.



Figure 2 Introduction of the Catheter Within Fistula for the Administration of Argentum-Quartz Solution (This photo did not portray the patients enrolled in our study.)



Figure 3 Scar in the Fistula Orifice of the 42-year-old Man Previously Undergoing Fistulectomy (Periodical blood arised from the lesion.)

surgical procedures. The present work was prompted to demonstrate the efficacy of Argentum-quartz solution as a valid non-surgical therapy leading to a more comfortable perianal fistula healing.

Patients with inflammatory bowel diseases (IBDs), such as Crohn's disease, ulcerative colitis (UC) and indeterminate colitis, often undergo pyogenic, suppurative complications. In these patients, the inflammation of the anorectal mucosal compartment favors the onset of such complications which are most commonly represented by pyogenic infection. The



Figure 4 After 30 days of treatment, a complete orifice fistula closure and clinical resolution were observed.

“primummovens” responsible for the onset of suppurative fistulas is represented by the infection of Lieberkuhn's recto-anal glands. The contact of enteropathogenic bacteria with the crypts triggers mucosal inflammation. The latter is associated with a subsequent aggravation of an inflammatory process, responsible for the penetration of pyogenic flora into adipose-sphincteric deep tissues, leading to the formation of a perirectal abscess cavity^[1]. Histological studies performed on biopsies demonstrated the presence, between the internal and external anal sphincters, of a substantial aggregation of glands greatly affected by the inflammatory process. This phenomenon leads to cryptitis and extends to surrounding tissue including perirectal adipose tissue. Hence, the abscess spreads to the skin through perirectal sphincteric structures, leading to the formation of abscesses and frankly purulent fistulas^[1]. Anatomical studies conducted by Chiari in 1878 and then by Hermann and Desfosses in 1880, described infectious small glands in the anus that are adjacent to the internal sphincteric muscle. Subsequently, Parks performed a selective study involving 30 consecutive cases of fistula-in-ano, in which serial sectioning of removed fistulous track revealed cystic dilatation and infection of anal glands in 90 percent of cases^[2]. All these findings suggest that small glands in the anus represent a usual precursor to infection.

As mentioned above, fistulous pathology connected to a septic-pyogenic framework is particularly debilitating for affected people. Pain and defecation difficulties are the main symptoms of the disease. The presence of a perianal abscess should be ascertained and, if present, should be drained urgently^[3]. In general, fistulas flattening and fistulectomy represent the more conservative interventions. Recently, less invasive and more conservative treatment has been taken in consideration as a valid alternative to surgery in order to preserve the integrity of the anatomical structures. Indeed, it was reported that the use of fibrin glue could stimulate tissue repair capacity^[6, 7]. The

auto-resolution capacity of inflammatory processes is very limited. Thus, the resulting tissue framework is characterized by an infiltrate of neutrophils and by relevant cytotoxic and cyto-destructive enzymes together with oxygen free radicals. The latter can induce an active tissue necrosis not balanced by efficient reparative processes.

Argentum nitricum, also known as silver nitrate, is used in the treatment of various disorders. The solid form possesses antiseptic properties and is used in the treatment of epistaxis, warts and nail granulomas^[11-13]. The liquid form is used for filarial chyluria and prophylaxis of neonatal conjunctivitis^[14, 15]. In addition, silver nitrate has also been used for tubal sterilization due its corrosive properties^[16]. The studies on murine perianal tissue investigated the effect of Argentum-quartz solution and revealed its ability in stimulating the proliferation of fibroblasts and a consequent tissue repair^[9, 17]. Furthermore, Fayaz *et al.*^[18, 19] reported that silver nanoparticles could synergistically cooperate with antibiotics for production of collagen fibers, favoring tissue healing. The mechanism responsible for this therapeutic effect seems to be due to the capacity of silver nanoparticles in inhibiting the action of special cyto-detrimental peptidoglycan and cellular DNA damage^[20]. Moreover, nanoparticles reduce the levels of acute phase proteins, such as hemopexina, haptoglobin and serum amyloid protein (SAP). Argentum and quartz synergistically leverage the antiseptic properties of silver and those fibro-reparative of quartz^[21]. The properties of components of argentum and quartz are recognized and reported in various research results^[22-24]. They, therefore, are justified by international studies dealing with the treatment of perianal fistulas. Application of preparations based on silver has been tested on murine models of pulmonary diseases and has been employed for tracheo-bronchial fistulas^[8, 25-27]. The above data lead us to believe that administration of argentum and quartz presents an antiseptic activity against pyogenic and enteropathogenic bacteria, thus inducing attenuation of mucosal inflammation and stimulating fibroblast activity with the “fully recovered” tissue. The most common aerobic pathogens isolated from perianal abscesses are escherichia coli, proteus vulgaris, staphylococcus aureus, streptococcus species, and the two most common anaerobic organisms are bacteroides and peptostreptococcus^[28-29].

It is believed that this study is the first to explore the utility of the concomitant injection of argentum and quartz in the treatment of anorectal fistulas. Two previous studies have reported the

effectiveness of topical silver nitrate irrigation for anal fistulas, but did not investigate the synergistic effect of argentum and quartz^[30, 31]. The expected complications from traditional surgical procedures, such as perioperative bleeding and anal stricture, were not encountered in the patients included. Complete clinical healing was observed in 2 out of 3 patients after injection of Argentum-quartz solution. It should be noted that this procedure was performed on an outpatient basis without any anesthetic requirement, thus providing a big advantage over the known surgical procedures. It was proved to be a good therapeutic alternative to classical surgical approaches. It is also compatible with the concomitant administration of anti-inflammatory drugs employed in the treatment of IBDs. However, this study also has several limitations. One is the relatively small sample size. The other is short period of follow-up. The third one is short of comparison of the results of this procedure with available surgical techniques. However, the positive results obtained in the patients encourage us to increase both number of enrolled patients and the follow-up period. Furthermore, these preliminary data lead us to seriously consider Argentum-quartz solution in the treatment of perianal fistulas associated or not with IBDs. However, it is too early to tell whether these encouraging results of conservative management with argentum and quartz will stand the test of time. Therefore, a larger study with a longer follow up to assess the effectiveness of this non-invasive procedure is in order. And our team is currently enrolling a larger cohort of patients and observing them for a longer follow-up period with the potential of a multi-center study.

In conclusion, these preliminary results demonstrate that selective treatment of perianal fistulas with an argentum-quartz solution is safe and effective, and may represent a reliable alternative.

Declaration

The authors of this manuscript declare that they have no conflict of interest.

References

- 1 Bjarnsholt T, Kirketerp-Møller K, Jensen PØ, et al. Why chronic wounds will not heal: a novel hypothesis. *Wound Repair Regen*, 2008, 16(1): 2-10.
- 2 Parks AG. Pathogenesis and treatment of fistula-in-ano. *Br Med J*, 1961, 5224: 463-9.
- 3 Tonkić A, Borzan V. Treatment of fistulizing Crohn's disease. *Acta Med Croatica*, 2013, 67(2): 191-4.
- 4 Gafni-Kane A, Goldberg RP, Spitz JS, et al. Extrasphincteric perianal fistulae after sacrospinous fixation for apical

- prolapse. *Obstet Gynecol*, 2011, 117(2 Pt 2): 438-40.
- 5 Dudukgian H, Abcarian H. Why do we have so much trouble treating anal fistula? *World J Gastroenterol*, 2011, 17(28): 3292-6.
 - 6 Limura E, Giordano P. Modern management of anal fistula. *World J Gastroenterol*, 2015, 21(1): 12-20.
 - 7 Maralcan G, Başkonuş I, Aybasti N, et al. The use of fibrin glue in the treatment of fistula-in-ano: a prospective study. *Surg Today*, 2006, 36(2): 166-70.
 - 8 Stratakos G, Zuccatosta L, Porfyridis I, et al. Silver nitrate through flexible bronchoscope in the treatment of bronchopleural fistulae. *J Thorac Cardiovasc Surg*, 2009, 138(3): 603-7.
 - 9 Tomasello G, Bellavia M, Damiani F, et al. Argentum-quartz solution in the treatment of anorectal fistulas: is it possible a conservative approach? *Med Hypotheses*, 2012, 79(4): 542-3.
 - 10 Cingolani E. The Italian Pharmacopoeia from 1800 to 1892. *Med Secoli*, 1993, 5(1): 115-38.
 - 11 Mudunuri RK, Murthy MA. The treatment of spontaneous epistaxis: conservative vs cauterization. *J Clin Diagn Res*, 2012, 6(9): 1523-4.
 - 12 Lwegaba A, Phillips A, Kiraru R. Silver nitrate may be far superior to podophyllin in clearing HPV external anogenital warts. *West Indian Med J*, 2008, 57(1): 63-5.
 - 13 Erdogan FG. A simple, pain-free treatment for in-grown toenails complicated with granulation tissue. *Dermatol Surg*, 2006, 32(11): 1388-90.
 - 14 Nandy PR, Dwivedi US, Vyas N, et al. Povidone iodine and dextrose solution combination sclerotherapy in Chyluria. *Urology*, 2004, 64(6): 1107-09.
 - 15 Dunn PM. Dr Carl Crede (1819-1892) and the prevention of ophthalmia neonatorum. *Arch Dis Child Fetal Neonatal Ed*, 2000, 83(2): 158-9.
 - 16 Ringrose CA. Office tubal sterilization. *Obstet Gynecol*, 1973, 42(1): 151-5.
 - 17 McAnulty RJ. Fibroblasts and myofibroblasts: their source, function and role in disease. *Int J Biochem Cell Biol*, 2007, 39(4): 666-71.
 - 18 Fayaz AM, Balaji K, Girilal M, et al. Biogenic synthesis of silver nanoparticles and their synergistic effect with antibiotics: a study against gram-positive and gram-negative bacteria. *Nanomedicine*, 2010, 6(1): 103-9.
 - 19 Kwan KH, Liu X, To MK, et al. Modulation of collagen alignment by silver nanoparticles results in better mechanical properties in wound healing. *Nanomedicine*, 2011, 7(4): 497-504.
 - 20 Taglietti A, Diaz Fernandez YA, Amato E, et al. Antibacterial activity of glutathione-coated silver nanoparticles against Gram positive and Gram negative bacteria. *Langmuir*, 2012, 28(21): 8140-8.
 - 21 Arce JM, Tatay AI, Luna ML, et al. In vitro study of the antimicrobial properties of silver ion-releasing polyurethane foam. *Cir Esp*, 2011, 89(8): 532-8.
 - 22 Ryu HS, Bae IH, Lee KG, et al. Antibacterial effect of silver-platinum coating for orthodontic appliances. *Angle Orthod*, 2012, 82(1): 151-7.
 - 23 Liu X, Lee PY, Ho CM, et al. Silver nanoparticles mediate differential responses in keratinocytes and fibroblasts during skin wound healing. *ChemMedChem*, 2010, 5(3): 468-75.
 - 24 Nasiri E, Hosseinimehr SJ, Azadbakht M, et al. The healing effect of arnebia euchroma ointment versus silver sulfadiazine on burn wounds in rat. *World J Plast Surg*, 2015, 4(2): 134-44.
 - 25 Park HS, Kim KH, Jang S, et al. Attenuation of allergic airway inflammation and hyperresponsiveness in a murine model of asthma by silver nanoparticles. *Int J Nanomedicine*, 2010, 5: 505-15.
 - 26 Shen FH, Fan XY, Liu BC. Decrease of cyclin D1 and CDK4 protein and their related factors induced by quartz in human embryonic lung fibroblasts. *Chinese Journal of Industrial Hygiene and Occupational Diseases*, 2008, 26(7): 391-4.
 - 27 Mehta D, Mehta C, Wadhwa S, et al. Silver nitrate in interventional pulmonology: treating a case of persistent bronchopleural fistula. *J Bronchology Interv Pulmonol*, 2011, 18(2): 184-7.
 - 28 Goldstein EJ, Citron DM, Merriam CV, et al. Comparative in vitro activity of ceftaroline, ceftaroline-avibactam, and other antimicrobial agents against aerobic and anaerobic bacteria cultured from infected diabetic foot wounds. *Diagn Microbiol Infect Dis*, 2013, 76(3): 347-51.
 - 29 Zomorodian K, Rahimi MJ, Taheri M, et al. The cutaneous bacterial microflora of the bodybuilders using anabolic-androgenic steroids. *Jundishapur J Microbiol*, 2014, 8(1): e12269.
 - 30 Demirel AS. Silver nitrate cauterization for anal fistulas with high blind tract chemical therapy in complicated anal fistulas. *Euroasian J Hepato-Gastroenterol*, 2013, 3: 49-53.
 - 31 Attaallah W, Tuney D, Gulluoglu BM, et al. Should we consider topical silver nitrate irrigation as a definitive nonsurgical treatment for perianal fistula? *Dis Colon Rectum*, 2014, 57(7): 882-7.