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Refractory Anal Itching: Treatment *via* Injection of Methylene Blue with or Without Associated Corticosteroids

Fernando Fernández López* and Jesus Pedro Paredes Cotore

Department of Surgery, University of Santiago de Compostela (USC), Santiago de Compostela, Spain

Abstract

Background: The objective of this study was to determine whether there are differences in the efficacy of intradermal injection of methylene blue with and without corticosteroids for the treatment of refractory anal itching.

Material and Methods: Twenty patients whose anal pruritus was refractory to topical treatments were randomly divided into two groups. In Group A, 10 ml of 1% methylene blue and 100 mg of hydrocortisone were injected. In Group B, only 1% methylene blue was injected. A follow-up was carried out at 15 days post procedure, and a face-to-face consultation was held at 30 days post procedure. The condition was considered cured when the urge to scratch disappeared.

Result: At 8 weeks, 9 patients in group A (AM+HC) and 3 in group B were symptom-free. In those in whom treatment failed, four underwent a second injection of methylene blue, which provided complete relief at three to 8 weeks.

Conclusion: Perianal intradermal injection including methylene blue was effective in alleviating symptoms in 70% of patients. However, the study revealed that combined injection of methylene blue with corticosteroids did not improve the control of refractory anal itching symptoms.

Keywords: Methylene blue; Anal itching; Refractory; Hydrocortisone

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Correspondence:
Fernando Fernández López, Department of Surgery, Coloproctology Unit, Faculty of Medicine, University of Santiago de Compostela (USC), Santiago de Compostela, Spain, E-mail: fernando.fernandez@usc.es

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Introduction

Pruritus is an unpleasant and uncomfortable somatic sensation for individuals in which there is an important sensory and emotional component that directs and regulates an irresistible urge to scratch [1]. The objective of this study was to evaluate the effectiveness of methylene blue injection in the perianal skin of patients with chronic refractory idiopathic anal itching and to determine whether this effect could be strengthened through combination with corticosteroids.

Itching of neuropathic origin is caused by lesions in the afferent neural pathways without associated primary skin lesions (pruritus sine materia). Chronic anal itching corresponds to this subtype [2]. When, after correctly administering treatment, the duration of symptoms is prolonged for more than six weeks, itching is defined as refractory.

The correct diagnosis is based on careful anamnesis, a complete anorectal physical examination and complementary tests (anoscopy).

The treatment consists of general hygienic-dietary measures: sitz baths; drying the area without friction; and avoiding toilet paper, wet wipes and disinfectants, as well as the intake of coffee, chocolate, citrus fruits and soft drinks. Topical application of drugs such as corticosteroids, antifungals, local anaesthetics (lidocaine) and 0.006% capsaicin has been prescribed. Methylene blue has also been used, and its mechanism of action is likely the ablation of sensory nerve endings in the perianal skin [3]. This ablation translates into a disappearance of the urge to scratch, breaking the vicious circle in which, these patients are trapped. Some authors add corticosteroids to improve and accelerate the results [4], but there is no evidence of their efficacy.

Material and Methods

A prospective, randomized, open study of patients diagnosed with refractory pruritus was carried out between January 2021 and December 2024. The inclusion criteria were persistent symptoms for more than 6 weeks and having undergone two previous treatments without improvement.

Two weeks prior to methylene blue injection, the patients did not receive any topical treatment.

Table 1: Causes of Pruritus. Local and systemic Dermatological Causes.

Local Dermatological	Systemic Causes
Atopic dermatitis	Cholestasis
Contact dermatitis	Chronic kidney disease (uremic pruritus)
Urticaria	Opioids, ACEi, statins, hydroxychloroquine,
Psoriasis	Hyperthyroidism
Scabies	Diabetes mellitus
Pediculosis (lice)	Iron-deficiency anemia
Tinea (dermatophytosis)	Polycythemia vera
Candidiasis	Hodgkin lymphoma
Xerosis cutis	HIV
Lichen simplex	Sjögren syndrome
Lichen planus	Dermatomyositis
Prurigo nodularis	Neuropathic pruritus (post-stroke, MS, radiculopathy)
Photodermatoses	Psychogenic pruritus
Insect bites/popular urticaria	Pinworm infection
Dermatologic malignancy	

Patients with local or systemic dermatological pathology responsible for pruritus were excluded (Table 1).

Anorectal examination and endoscopy were performed for all patients to rule out associated proctological pathology.

Informed consent was obtained from patients, and patients were informed of the following possible minor side effects: blue colouration of the urine, a temporary perianal blue tattoo (Figure 1), occasional perianal sensory loss and temporary flatus incontinence.

The patients were randomized into 2 groups. In Group A, a perianal skin intradermal injection of 10 ml of 1% methylene blue (Luis Corbí Pharmacy Magistral Formula) and 100 mg of hydrocortisone (powder for injectable solution, Laboratories Lorien, SL) was administered. In Group B, only methylene blue was injected.

The intervention was performed in the Major Outpatient Surgery Unit of the Hospital Clinic of the University of Santiago de Compostela under sterile conditions and with the patient in a lithotomy position. Loco-regional anesthesia was used in 18 patients, and intravenous sedation was used in two patients.

The solution was injected intradermally (Figure 2) into the perianal skin with a 10 ml syringe and a 22 Fr needle. The infiltration of methylene blue must be intradermal because the subcutaneous route is less effective. The patients were discharged at 6 hours after the procedure. Telephone follow-up was carried out at 15 days post procedure, and face-to-face consultation was held at 8 weeks post procedure.

Statistical analysis

Hypothesis testing for qualitative variables was performed using the chi-square ratio or frequency test. We determined whether the frequencies that occurred in the sample differed significantly from the frequencies that would be expected. The null hypothesis was that there would be no difference between the two groups (with or without corticosteroids) with respect to the dependent variable of "cure". Statistical significance was established at a threshold of $p<0.05$.

For the statistical analysis, the DATAtab Online Statistics Calculator (DATAtab e.U, Graz, Austria; https://datatab.es) was used.

Figure 1: Perianal tattoo with methylene blue.

Figure 2: Perianal subcutaneous infiltration of methylene blue.

Results

Twenty consecutive patients, 12 men (60%) and 8 women (40%), with a mean age of 53.3 years (range 21-78), were studied.

A chi-square test was performed, and no statistically significant association between a cure and corticosteroid use was observed (χ^2 (1) = 0.22, p = 0.639, Cramér's V = 0.1.). Therefore, on the basis of the current data, there were no statistically significant differences ($p>0.05$) between the two groups in terms of pruritus control, and the null hypothesis was not rejected.

Fisher's exact test revealed no statistically significant relationship between a cure and corticosteroids use ($p=1$).

Symptoms disappeared after eight weeks in 70% of the patients (n=14). There were 8 patients in Group B (80%) and 6 patients in Group A (60%). Among the 30% (n=6) who did not experience symptom relief, four received a second injection at 4 months. On this occasion, only methylene blue (without corticosteroids) was administered, which strengthened the overall effect. Complete symptom resolution was achieved in 90% of patients (with a single administration in 14 patients and with a second administration of only methylene blue in 4 patients).

Discussion

The sensation of pruritus seems to originate in the epidermal or subepidermal free nerve endings, especially through C fibres. Histamine is not the only mediator involved in itching and may not play a role in some cases, which explains why antihistamines are not always effective. Substance P, serotonin and prostaglandins

(especially prostaglandin E2) play as important of a role as histamine.

Methylene blue, known in the pharmaceutical field as methylthionine chloride, was synthesized in 1876 by the German chemist Heinrich Caro; it is an aniline-based dye for the textile industry and was soon used as a stain in microscopy [5]. Methylene blue is an organic dye with antiseptic properties and various clinical uses, including the treatment of methemoglobinemia or as a lymph node marker in oncological surgery [6]. The first description of methylene blue use in the treatment of pruritus was provided by Rygick [7] in 1968.

The mechanism of action of methylene blue has not been fully elucidated. Electron microscopy study observations suggest that methylene blue destroys sensory nerve endings in treated skin, thereby desensitizing perianal skin [8].

In the treatment of chronic idiopathic and refractory anal itching with methylene blue, after the use of 2 drugs, methylene blue was effective in 54% of patients at 6 weeks after a single application [4], and this percentage increased to 88% with a second topical application, with the effect being maintained over time, without recurrence of itching.

On the basis of therapeutic algorithms, some researchers propose the use of other drugs, such as topical capsaicin at 0.006% [9], which has been shown to provide symptomatic relief in 70% of patients, compared with 2% with placebo, after 4 weeks. However, some authors recommend caution regarding the safety of this treatment because capsaicin activates calcium- sensitive intracytoplasmic proteases and can cause irreversible damage to type C nerve endings. Furthermore, the dosage and duration of treatment have not been established.

Tacrolimus 0.1% ointment, administered locally on the transitional mucosa and perianal skin, is another therapeutic alternative, but the results have been suboptimal to date [10].

Our results in two treatment groups are similar to those obtained by other authors [11], although from a statistical point of view, we did not demonstrate that administering a combination of a corticosteroid and methylene blue provided therapeutic effects superior to those achieved by administering methylene blue alone.

In a systematic review [11], the use of methylene blue in the treatment of refractory anal itching was revealed to be relatively effective, with a recurrence rate of less than 5% per year and no serious complications. In our study, the complication rate was 4%, and in other studies [4,11], the most common complication was soiling secondary to a loss of sensitivity and perianal sensory discrimination, which remitted between 4 and 6 weeks.

In conclusion, intradermal administration of methylene blue in the treatment of refractory sine material anal itching was effective and safe, with minor and temporary complications. Rescue therapy via repeat treatment in patients for whom the initial treatment was ineffective strengthened the results, without the need for combined corticosteroids.

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