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Review Article

Chemical Neurolysis in Proctology: A Narrative Review of Intradermal Methylene Blue for Anorectal Disorders

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ABSTRACT

Chronic anorectal disorders, including idiopathic pruritus ani and chronic anal fissure, frequently prove refractory to conservative management, while acute postoperative pain following procedures for anal fistula and hemorrhoidectomy remains a significant clinical hurdle. Perianal infiltration of methylene blue (MB) has emerged as a sophisticated neurolytic adjunct to address these challenges. By selectively targeting superficial sensory nerve terminals, it disrupts the chronic itch-scratch cycle and attenuates persistent pain pathways, providing relief that extends well beyond the duration of standard local anesthetics. This review examines the biochemical mechanisms of MB, along with its evolving clinical indications and refined injection techniques. While MB is a potent tool for achieving prolonged analgesia across these four key pathologies, clinical success necessitates precise delivery into the dermo-epidermal plane. When properly titrated to a 0.2% concentration, MB serves as a safe, cost-effective cornerstone of modern enhanced recovery protocols in proctology, effectively minimizing surgical morbidity and accelerating the return to daily activities.

Key words: Methylene blue, neurolysis, pruritus ani, hemorrhoidectomy, postoperative pain, proctology

INTRODUCTION

Methylene blue (MB), or methylthioninium chloride, is a phenothiazine derivative that holds a unique place in medical history as the first fully synthetic drug used in clinical practice. [1,2] Originally synthesized in 1876 by Heinrich Caro for the textile industry, its biological utility was quickly recognized by Paul Ehrlich, who pioneered its use in histology and the treatment of malaria. Chemically, MB is a heterocyclic aromatic organic chloride salt with a formula $C_{16}H_{18}ClN_3S$. It is also called methylthioninium chloride or Swiss Blue and is characterized by potent redox properties; it functions as a reversible oxidation-reduction system, allowing it to act as an electron donor or acceptor depending on the cellular environment. [3]

In the realm of pain and itch management, MB is utilized for its chemical neurolytic properties. [4] Within the field of proctology, the application of MB for idiopathic pruritus ani (PA) was first documented in the 1960s, though these early reports lacked standardized protocols. The seminal work of Eusebio et al. transformed the procedure by popularizing the modern intradermal injection technique. [5] This method targets the "itch-scratch cycle," a pathological feedback loop where chronic mechanical trauma leads to dermal lichenification and heightened nociceptor sensitivity.

Despite its documented efficacy, the clinical adoption of MB has historically been tempered by fears of tissue toxicity and skin necrosis. However, contemporary prospective

data from Sutherland et al. and longitudinal studies by Kim et al. and Samalavicius et al. have refined the safety profile of the drug and demonstrated that when administered correctly into the intradermal plane, MB is a safe and highly effective intervention for refractory anorectal disorders. [6–8]

This article aims to provide a structured narrative review of the indications, injection techniques, and clinical outcomes of MB neurolysis in proctology, establishing its place in the current therapeutic hierarchy for refractory anorectal pain and pruritus.

METHODS

A literature search was undertaken from September to October 2025.

Databases searched: PubMed, Embase, and Google Scholar.

Search period: From inception to October 2024.

Keywords/MeSH terms: "Methylene blue," "Pruritus ani," "Anorectal disorders," "Post-hemorrhoidectomy pain," "Analgesia," "Intradermal injection."

Inclusion criteria: Clinical trials, case series, and existing reviews (systematic or narrative) discussing the therapeutic use of MB in the perianal region.

Exclusion criteria: Studies using MB solely as a diagnostic dye (e.g., for sentinel lymph node mapping in cancer) without therapeutic analysis.

Pharmacological mechanism and neurolytic properties

The therapeutic efficacy of MB in treating chronic anorectal disorders lies in its unique ability to function as a selective neurolytic agent. While many topical treatments address surface inflammation, MB targets the underlying neurological dysfunction that characterizes the "itch-scratch" and "pain-sensitization" cycles (**Table 1**).

Selective nerve ablation

The primary mechanism of MB in proctology is the chemical destruction of sensory nerve endings. When injected intradermally, MB penetrates the nerve sheaths of the fine, unmyelinated C-fibers and small myelinated A-delta fibers. [4] These fibers are responsible for transmitting slow, dull pain and the sensation of pruritus.

- **Chemical neurolysis:** MB induces a localized toxic effect on these nerve terminals, causing them to degenerate. This effectively "numbs" the perianal skin to the specific frequencies of sensation that trigger the urge to scratch.
- **Regeneration delay:** Unlike local anesthetics, which block sodium channels temporarily, MB provides long-term relief because the nerve endings must physically regenerate before sensation returns—a process that can take several months to a year. [7]

Redox-mediated cellular impact

Chemically, MB is a potent redox cycler. In the cellular environment, it oscillates between its oxidized form and its reduced form, leucomethylene blue. This cycling interferes with the oxidative phosphorylation process within the mitochondria of highly active cells, such as sensitized nociceptors. [3]

- **Mitochondrial dysfunction:** By disrupting the electron transport chain, MB can induce apoptosis (programmed cell death) in the overactive sensory neurons responsible for chronic pain and itching.
- **Nitric oxide inhibition:** MB is a known inhibitor of guanylate cyclase, which reduces the production of cyclic GMP (Guanosine monophosphate). Since the nitric oxide-cGMP pathway is heavily involved in pain signaling and vasodilation, its inhibition results in a potent analgesic effect. [9]

Anti-inflammatory signaling (the inflammasome pathway)

Recent molecular research has highlighted that MB's benefits extend beyond simple nerve destruction. It plays a crucial role in modulating the innate immune response:

- **NLRP3 inflammasome inhibition:** As documented by Ahn et al., MB inhibits the activation of the NLRP3 inflammasome, a protein complex that triggers the release of pro-inflammatory cytokines like IL-1β (Interleukin-1 beta). [10] By suppressing this pathway, MB reduces the neurogenic inflammation that often accompanies chronic PA.

Breaking the "itch-scratch" cycle

The culmination of these mechanisms—nerve ablation, redox interference, and inflammasome inhibition—allows for a "physiological reset" of the perianal skin. By removing the sensory stimulus (the itch), MB prevents the patient from scratching. This cessation of mechanical trauma allows the lichenified, damaged skin to restore its natural barrier function, which is often the key to permanent resolution. [6]

Table 1: Summary of mechanisms of action of methylene blue.

Mechanism	Target	Clinical outcome
Neurolysis	C-fibers and A-delta fibers	Direct cessation of itch/pain transmission.
Enzyme inhibition	Guanylate cyclase	Reduced nociceptive signaling and inflammation.
Redox cycling	Mitochondria	Long-term sensory "numbing" through nerve degeneration.
Inflammasome suppression	NLRP3 complex	Reduction in local pro-inflammatory cytokines.

Clinical technique and injection protocol

The clinical success of MB is highly dependent on the precision of the injection technique. While historical complications were often linked to deep subcutaneous administration, modern protocols emphasize a standardized intradermal approach to maximize neurolysis while protecting the underlying sphincter muscles (**Table 2**).

Pre-operative preparation

Most studies, including Sutherland et al. and Mentes et al., recommend performing the procedure under sedation or general anesthesia due to the significant discomfort associated with the initial injection. [4,6]

- **Positioning:** The patient is typically placed in the lithotomy or prone jack-knife position to allow for optimal exposure of the perianal region.
- **Skin preparation:** The area is cleansed with an antiseptic solution (e.g., povidone-iodine). It is crucial to clearly demarcate the zone of lichenification or the area of "maximal itch" before starting.

The MB solution

The solution is rarely injected in its pure form. To manage immediate post-operative pain and ensure even distribution, a mixture is prepared:

- **Concentration:** 1% MB is the gold standard.
- **The mixture:** It is frequently mixed with a local anesthetic (such as 0.5% bupivacaine or 1% lidocaine) in a 1:1 ratio. This creates a total volume of roughly 10 to 20 mL, depending on the surface area of the affected skin.

Injection technique

The goal is to deliver the agent into the dermal-subcutaneous junction, where the fine sensory nerve endings terminate, as depicted in **Figure 1**.

- **The "Fan" technique:** Using a fine-gauge needle (typically 25G or 27G), the clinician performs a series of radial or "fan-shaped" injections.
- **Intradermal placement:** The needle is inserted just beneath the skin surface. A successful injection is often characterized by the appearance of a "peau d'orange" (orange-peel) effect and immediate blue staining of the skin.
- **Coverage area:** Injection should extend from the perianal skin up to the dentate line (the anorectal junction) to ensure all sensory fibers contributing to the pruritus are addressed.

Post-operative management

Following the procedure, immediate care focuses on preventing infection and managing patient expectations:

- **Tattooing:** Patients must be counseled to ensure that the skin will remain stained blue or green for several weeks.
- **Sensory changes:** Patients should be warned of perianal numbness (dysesthesia), which is the intended clinical effect.
- **Hygiene:** Normal perianal hygiene is encouraged, but aggressive scrubbing of the stained area should be avoided to prevent skin breakdown.

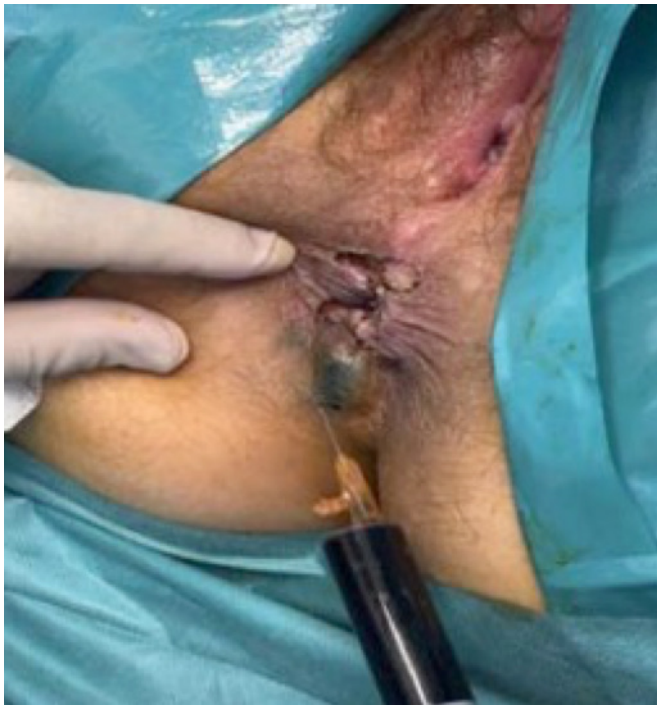

Figure 1: Perianal subcutaneous infiltration of methylene blue. Image Source: Fernández López and Pedro Paredes Cotore. [13] Image reused under Creative Commons Attribution License.

Table 2: Technical comparison of treatment protocols.

Study	Anesthesia	Volume/concentration	Key technical note
Eusebio et al. [5]	Local/sedation	0.5%–1% MB	Popularized the multiple-puncture intradermal approach.
Sutherland et al. [6]	General/spinal	1% MB + 0.5% Bupivacaine	Injected 1 cm beyond the margins of the affected skin.
Kim et al. [7]	Local/sedation	1% MB (5 mL) + Lidocaine	Used a smaller volume with high precision in chronic cases.
Mentes et al. [4]	General	1% MB (15 mL total)	Employed a "rescue" second dose protocol for incomplete responders.

Complications and safety profile

While intradermal MB injection is generally considered safe, the potential for adverse events remains a primary concern for clinicians. Data from major studies (**Table 3**) indicate that complications are typically transient and closely related to injection depth and volume rather than drug toxicity itself. [6,11]

Minor and expected side effects

These effects are considered part of the clinical process and do not usually signify a failure of the procedure:

- **Skin discoloration:** 100% of patients experience blue or greenish "tattooing" of the perianal skin as depicted in **Figure 2**. This typically fades over 4 to 8 weeks as the skin cells desquamate. [6]
- **Perianal hypoesthesia:** A "numb" sensation is the intended result of neurolysis. However, some patients find the lack of sensation distressing (dysesthesia) for the first few weeks. [6]
- **Local pain:** Transient burning or soreness at the injection site is common for 24 to 48 hours, usually managed with oral analgesics. [6,11]

Sensory and functional complications

The most frequently reported "true" complication involves the sensory discrimination of the anal canal.

- **Transient incontinence:** Approximately 14% of patients in the Sutherland et al. study reported difficulty distinguishing between flatus and stool. [6]
- **Mechanism:** This is not due to muscle damage but rather the "numbing" of the sensory nerves that provide the brain with feedback about rectal contents.
- **Resolution:** In almost all documented cases, this sensory discrimination returns to normal within 6 weeks as the nerves begin to recover or the patient adapts.

Major complications: The risk of necrosis

Historically, the fear of skin necrosis (tissue death) limited the use of MB.

- **Superficial versus deep:** Necrosis is highly associated with injecting MB too superficially into the epidermis (causing sloughing) or too deeply into the subcutaneous fat (causing fat necrosis). [11]
- **Modern incidence:** In modern series using the 1% concentration and intradermal technique, the incidence of major necrosis is near 0%. Kim et al. and Mentes et al. reported no cases of necrosis in their combined cohorts. [4,7]

Risk mitigation strategies

To ensure safety, the literature emphasizes several "best practices":

1. **Concentration control:** Higher concentrations greatly increase the danger of tissue toxicity; thus, never exceed 1%.
2. **Aspiration:** To make sure the needle is not in a blood vessel, aspirate before injecting.

Table 3: Complications of methylene blue injection.

Complication	Estimated frequency	Duration/prognosis
Skin tattooing	100%	Temporary (4–8 weeks)
Local pain	15%–20%	24–72 hours
Sensory incontinence	7%–14%	Reversible (within 6 weeks)
Skin necrosis	<1%	Rare with proper technique
Recurrence of itch	10%–20%	May occur after 1–3 years

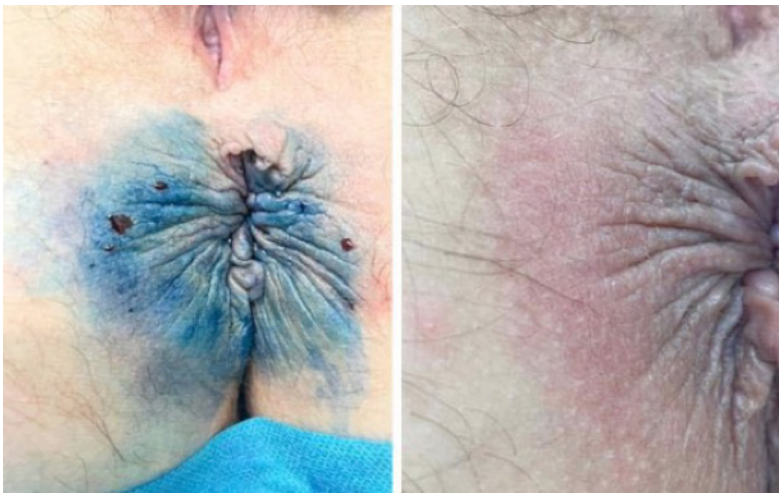

Figure 2: Perianal tattoo with methylene blue. Image Source: Fernández López and Pedro Paredes Cotore. [13] Image reused under Creative Commons Attribution License.

3. **Strict intradermal plane:** The needle needs to stay inside the dermis. Inflammatory nodules are more likely if the needle penetrates deeper into the fat layers.
4. **Avoidance of "Pooling":** Make sure the solution is dispersed uniformly. Local blood flow may be jeopardized by high-pressure "bolus" injections delivered in one spot.

Clinical indications

The emerging literature mentions the following situations where MB is used.

Refractory idiopathic PA

Idiopathic PA represents some of the most frustrating challenges in clinical proctology. Patients are often in their fourth or sixth decade of life, and men are affected four times more frequently than women. Despite not being cancerous, PA has a significant negative influence on social functioning and psychological health, which frequently results in a self-sustaining "itch-scratch-infection" cycle. The condition is categorized as "intractable or refractory" when common conservative treatments, like dietary changes, careful cleanliness, and topical corticosteroids, are ineffective. [12–14] In such refractory cases, the shift in therapeutic focus from topical suppression to sensory modulation has been tried, and intradermal or subcutaneous injection of MB has emerged as a potent therapeutic agent, as depicted in **Table 4**.

While clinical applications of MB for PA date back to 1960, the seminal work by Eusebio et al. is widely credited with establishing and popularizing the contemporary intradermal injection protocol. [5] The studies by Kim et al. and Samalavicius et al. offer critical insights into the longitudinal efficacy of MB, providing follow-up data spanning three to five years. [7,8] Such extended observation periods are rare in the literature for this procedure. These findings are particularly significant as they demonstrate the treatment's ability to provide sustained relief and break the chronic itch-scratch cycle long after the initial chemical neurolysis of the perianal nerve endings.

The study by Sutherland et al. serves as a critical benchmark for the safety and efficacy of intradermal MB injections. [6] The authors found a stunning 96% improvement rate in their prospective examination of 49 patients, with more than half of the group (57%) attaining total symptom clearance following a single therapy. A follow-up injection resulted in a 100% remission rate for individuals with persisting symptoms, highlighting the procedure's reliability in cases with PA. Beyond its effectiveness, the Sutherland trial is often noted for its strong safety statistics, and when MB was given using the contemporary intradermal approach, the authors observed no significant side effects. Although 14% of individuals had acute incontinence, which was completely reversed in 6 weeks.

These findings suggest that while the procedure involves a temporary "sensory reset" of the perianal skin, it does not pose a long-term risk to anal sphincter function or tissue integrity. The study used "Patient Symptom Scores" as a primary endpoint, moving the focus from "clinical appearance" to the patient's actual quality of life and emphasized that the goal is not just to "numb" the skin, but to physically break the cycle of chronic irritation, allowing the skin to finally heal. For patients with "end-stage" PA where the skin has become lichenified and thickened, MB infiltration often serves as the only successful alternative to aggressive surgical excision. By providing a prolonged period of anesthesia (often lasting several months to a year), MB allows the perianal skin to return to its normal physiological state.

Hemorrhoidectomy

Recent literature strongly supports the integration of MB into postoperative protocols for hemorrhoidectomy to address the significant challenge of acute perianal pain (**Table 5**). A comprehensive 2025 meta-analysis of randomized controlled trials confirmed that MB significantly attenuates visual analogue scale (VAS) scores from the initial 12-hour period through the seventh postoperative day. [16] This sustained effect is particularly valuable in proctology, as it addresses

Table 4: Clinical studies on methylene blue for pruritus ani.

Author(s) and year	Concentration	Success/resolution	Complications
Jia et al. [15]	Various (meta-analysis)	76.1% (single dose); 85.4% (double)	Low recurrence; no severe necrosis.
Kim et al. [7]	1% (5 mL) + Lidocaine	90.6% at 6 weeks; 85.5% at 3 years	Transient pain (14.6%); tattooing.
Samalavicius et al. [8]	1% (15 mL total)	80% early; 20% success at 5 years	Temporary numbness and tattooing.
Sutherland et al. [6]	1%	96% improved; 57% resolved	Transient incontinence (14%); numbness.
Mentes et al. [4]	1% (15 mL total)	93.3% after "rescue" 2nd dose	Mild local pain; no serious events.
Eusebio et al. [5]	0.5%–1%	~87% significant improvement	Inflammatory response; discoloration.

Table 5: Outcomes of methylene blue injection for post-hemorrhoidectomy pain.

Study	Population	Concentration	Key outcome
Long et al. [19]	180 patients	0.1% vs. 0.2%	0.1% is safer for anal function.
Zhu et al. [16]	Meta-analysis	Various	Confirmed pain reduction through Day 7.
Babu et al. [18]	51 patients	0.2%	Reduced hospital stay and POD-7 pain.
Tato et al. [17]	68 patients	0.16%	Pre-emptive infiltration is highly effective.

pain during the first few bowel movements, a period typically associated with peak patient distress. Beyond direct pain scores, systematic evidence indicates a dramatic reduction in the requirement for rescue analgesia, which may lower the risk of opioid-related side effects such as constipation—a condition that can further complicate hemorrhoid recovery.

The clinical success of the intervention is closely tied to the timing and concentration of the injection. Tato et al. highlighted the benefits of pre-emptive infiltration using a 0.2% MB solution (titrated as 2 mL of 1% MB in 8 mL of 0.75% ropivacaine), suggesting that early blockage of pain pathways may prevent central sensitization. [17] Similarly, Babu et al. utilized a 0.2% concentration (4 mL of 1% MB in 16 mL of 0.5% bupivacaine), demonstrating that this specific titration significantly shortens hospital stays to an average of 2.27 days and provides robust relief up to the seventh postoperative day. [18]

Recent data suggest a ceiling effect where higher doses may compromise safety without providing additional analgesic benefit. Specifically, Long et al. demonstrated that while 0.1% and 0.2% concentrations offer comparable analgesia, lower concentrations are often clinically preferred to minimize the risk of transient anal incontinence or skin necrosis. [19] Collectively, these studies suggest that while MB does not increase traditional surgical complications like infection or secondary hemorrhage, careful titration to a 0.2% concentration is an effective balance for achieving sensory denervation while preserving anal sphincter function.

Fistula in ano

The postoperative phase of anal fistula surgery is often characterized by significant somatic pain due to open wound beds or the presence of setons, which act as local irritants. Recent clinical trials have sought to address this by utilizing the neurolytic and anti-inflammatory properties of MB. In a landmark 2024 double-blind, randomized controlled trial (RCT) involving 34 patients undergoing fistulectomy for simple anal fistula, Jeo et al. investigated the analgesic efficacy of adjuvant MB. [20] Participants were divided into two equal cohorts (n = 17): an experimental group receiving subcutaneous MB (4 mL, 1%) and intravenous ketorolac (30 mg, TID), and a control group receiving ketorolac monotherapy. Utilizing a VAS for assessment, the authors observed significantly lower pain scores in the MB group during the first 72 hours post-surgery ($P < 0.05$). However, by the seventh postoperative day, analgesic requirements and pain intensity were comparable between both groups ($P > 0.05$), suggesting that by acting as an adjuvant to systemic NSAIDs, MB enhances the early-phase analgesia.

Qin et al. specifically investigated the efficacy of different MB concentrations in elderly patients undergoing fistulectomy. [21] Their study concluded that concentrations as low as 0.05% and 0.1% provide equivalent analgesic relief to higher doses, but the lower concentration (0.05%) significantly reduced the risk of temporary anal incontinence, making it a safer profile for geriatric populations.

In the context of fistulectomy, the application of MB serves a critical role beyond immediate pain scores by significantly enhancing patient tolerance for postoperative wound care and frequent dressing changes. Given that fistula wounds are typically managed by secondary intention, the localized analgesia provided by MB is essential for maintaining patient compliance and ensuring the perianal hygiene necessary for optimal healing.

Anal fissure

The therapeutic goal in managing chronic anal fissure (CAF) is to break the "pain-spasm-ischemia" cycle. While Lateral Internal Sphincterotomy (LIS) is the established surgical standard for reducing sphincter hypertonicity, the immediate postoperative period is often characterized by intense somatic pain at the anoderm tear site. MB has emerged as a verified adjunct to manage this pain through the localized destruction of dermal sensory nerve endings.

Evidence from prospective trials conducted by Tan and Seow-Choen suggests that the intradermal application of MB significantly extends the analgesic window following sphincterotomy. [22] In a cohort of 24 patients treated with a combination of MB and lignocaine (4 mL of 1% MB, 16 mL of 1% Lignocaine), pain intensity remained clinically negligible during the critical first four days of recovery. By the fifth postoperative day, patients reported a complete absence of pain. The study suggested that this approach not only provides high-quality pain control but also supports rapid recovery, as evidenced by a 79% healing rate at two weeks and a total absence of perianal complications.

Furthermore, recent advancements have explored non-surgical applications. Lobascio et al., in a phase II randomized pilot trial, investigated a topical ointment combining MB and glyceryl trinitrate (GTN). [23] The study demonstrated that MB-based ointments significantly reduced severity scores and achieved a 77% healing rate over a 40-day course. This evidence positions MB as a promising innovative agent in the non-operative conservative management of fissures, potentially sparing patients from the risks associated with surgical sphincterotomy.

From a systematic perspective, Zhu et al. confirm in a meta-analysis that MB is an effective intraoperative adjunct for various perianal surgeries, including those for fissures. By significantly reducing the requirement for rescue analgesia in the first seven days, MB helps patients avoid the constipation often associated with opioid use—a complication that can directly impede the healing of the fragile fissure tract. [16]

CONCLUSIONS

The role of perianal MB in anorectal surgery has transitioned from a niche treatment for intractable PA to a powerful adjuvant for perioperative pain management across a spectrum of disorders, including anal fissure, anal fistula, and post-hemorrhoidectomy recovery. MB has a long-lasting analgesic effect that overcomes the drawbacks of short-acting local anesthetics by blocking dermo-epidermal sensory pathways. Current evidence indicates that a 0.2% concentration is the clinical benchmark for success. This concentration effectively modulates sensory input for up to seven days, significantly reducing the need for rescue analgesics and shortening hospital stays without compromising the integrity of the anal sphincter or surrounding cutaneous tissue.

The success of this intervention remains strictly dependent on the precise plane of infiltration; targeting the sensory nerve endings within the perianal skin is vital to achieving denervation while avoiding deeper complications. As standardized protocols for volume and titration continue to emerge, the integration of 0.2% MB stands to become a cornerstone of enhanced recovery protocols, offering a safe and effective solution for reducing the significant postoperative morbidity typically associated with anorectal procedures.

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Figures 1 and **2** have been reused as they appear in Fernández López and Pedro Paredes Cotore [13] under the terms of the Creative Commons Attribution License. The author expresses gratitude to the publishers for having kept the article available for Open Access.

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