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TECHNOLOGY IN MEDICINE (J PAXTON AND V KUMAR, SECTION EDITORS)

Current Updates in Rectal Infusion of Fluids and Medications

Bradford Macy[1] · **James H. Paxton**[2] · **Y. W. Francis Lam**[3]

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Abstract

Purpose of Review Rectal infusion is a feasible alternative for the immediate administration of medication and fluids when intravenous access is delayed, contraindicated, or unnecessary. Advances in medical device technology have made rectal infusion more practical and easier for medical care providers, and more comfortable for patients. This paper briefly reviews the history of therapeutic rectal infusion, including recent improvements in technology and the existing evidence for the use of this technique.

Recent Findings While ultrasound-guided peripheral intravenous (PIV) access techniques and other alternatives to landmark-based PIV catheter insertion have recently improved the ability of providers to overcome challenges related to difficult vascular access (DVA), these challenges are increasingly affecting patient outcomes, emergency department throughput, and the cost of medical care. In recent years, waves of parenteral drug, fluid, and supply shortages have affected hospitals. Concurrently, advances in rectal infusion technology have made rectal infusion easier, more comfortable, and more cost-effective than many parenteral options.

Summary The infusion of resuscitative fluids and medications via the rectal route has previously fallen out of favor due to concurrent improvements in IV access devices. However, this technique demonstrates the potential for a reemergence considering the current challenges facing healthcare providers and systems. Improvements in rectal infusion devices, coupled with an aging population, increased incidence of DVA, shortages in parenteral drugs, fluids, supplies and skilled staff, and the need for care improvements in the post-acute setting have contributed to a greater need for easy, safe and effective alternatives to IV infusion.

Keywords CLABSI · Macy catheter · Proctoclysis · DVA

Introduction

Rectal Infusion Technology

Until recently, techniques for proctoclysis (the rectal infusion of fluids and medications) remained relatively unchanged since the early twentieth century. Early rectal infusion catheters employed large diameter tubes with hard rubber plugs to hold them in place, often producing discomfort for patients (Figs. 1 and 2). Ballooned rectal catheters were later developed for elimination and collection of stool. However, these were developed to facilitate the passage of stool and were not designed for the comfortable delivery of medications and fluids. Reports of rectal wall necrosis related to these bowel management devices have historically led to increased concern among practitioners regarding the use of rectal catheters [1].

In 2014, the Macy Catheter® (Hospi Corporation, San Mateo, CA) was FDA-approved as the first device designed specifically to facilitate rectal access for the administration of fluids and medications. This catheter employs a 14-french tube with a 15-ml balloon that holds the catheter and infusate securely in the rectum (Fig. 3). The balloon used in this device is smaller and softer than typical formed stool in the rectum and exerts minimal pressure on the rectal wall, reducing the risk of iatrogenic bowel wall necrosis [2•]. Placement

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✉ Bradford Macy
brad.macy@hospicorp.com

James H. Paxton
jpaxton@med.wayne.edu

Y. W. Francis Lam
LAMF@uthscsa.edu

[1] Hospi Corporation, San Mateo, CA, USA

[2] Detroit Receiving Hospital, Wayne State University School of Medicine, Detroit, MI, USA

[3] University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

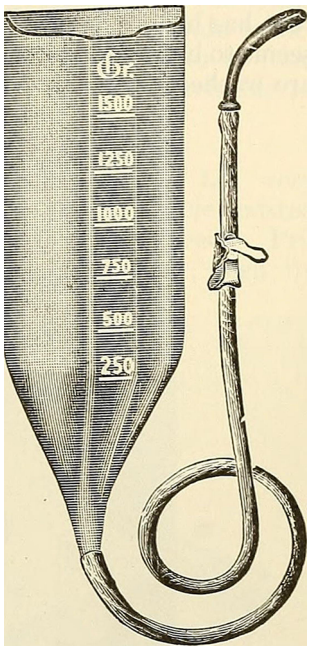

Fig. 1 Proctoclysis apparatus with fountain syringe, large rubber tube, and hard rubber tip (in JAMA 1909)

of the catheter requires minimal staff training and skill [3]. Initial placement requires a licensed clinician per FDA guidance, but a patient or caregiver can administer medication and fluids through the device and are able to replace the catheter after initial insertion if the device is expelled or removed for bowel movement [4]. Medications are given via the catheter in micro-enema (ME) form, defined as a low volume (usually under 20 ml) enema instilled into the rectum. Medications in solid form are crushed, and 10 ml water is added. Micro-enema medications are primarily absorbed in the distal one-third of the rectum. For proctoclysis, in which larger amounts of fluids are given, absorption occurs in the descending colon.

Rectal Infusion in Acute and Emergent Settings

While many emergent conditions require intravenous (IV) or intraosseous (IO) vascular access for the infusion of fluids and medications, rectal infusion can provide rapid delivery of fluids and medications while attempting or awaiting

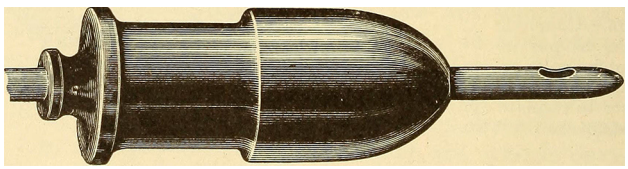

Fig. 2 Self-retaining tip with rubber catheter inserted. (in JAMA 1909)

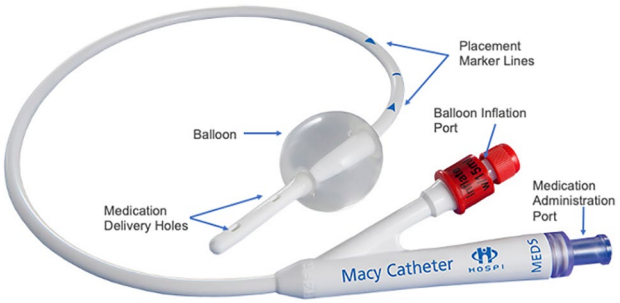

Fig. 3 The Macy Catheter: showing different components of the catheter. (Hospi Corporation)

IV placement. Proctoclysis can also provide an additional route of infusion for necessary fluids and medications, even after IV access has been established [5]. Administration of medication is at times desired prior to IV access or when IV access is unnecessary and the oral route is not possible, unsafe, or undesirable. Numerous medications demonstrate rapid and effective absorption kinetics when administered rectally, especially in ME form. Medications that have been safely and effectively delivered by the rectal route include many antiarrhythmics, antihypertensives, diuretics, antibiotics, antiepileptics, antipyretics, benzodiazepines, anticoagulants, sedatives, opioids, and NSAIDS (Table 1).

Venous collapse due to hypovolemia is a primary cause of difficult venous access (DVA) and can make even ultrasound-guided placement difficult or impossible [6]. Early rectal hydration may help to improve hypovolemia and enhance the provider's ability to obtain subsequent peripheral IV or central venous access.

The use of proctoclysis in non-critically ill patients presenting with DVA may obviate the need for peripheral intravenous (PIV) or IO vascular access if the patient's primary need for venous access is for the limited administration of fluids and medications. In rare cases, providers may feel compelled to establish a central venous catheter (CVC) when PIV access is deemed impossible, even if the patient does not require medications or other interventions that would otherwise require central venous access. Due to the complications and cost associated with CVC placement and use, many healthcare systems have initiated interventions to reduce the unnecessary use of CVCs. These methods have demonstrated effectiveness in reducing the rate of central line-associated bloodstream infections (CLABSI) [7]. The Michigan Appropriateness Guide for Intravenous Catheters (MAGIC) was developed by an international panel of experts to address inappropriate vascular access by providers. According to these guidelines, PIV placement is recommended (and CVC placement should be avoided) for patients who are not critically ill and require less than two weeks of anticipated therapy for the infusion of peripherally

compatible infusates, unless hemodynamic monitoring is necessary [8]. At present, the MAGIC does not specifically address the use of rectal catheters as an alternative to PIV catheters in this population.

Rectal infusion is particularly relevant to geriatric, pediatric, and palliative care patients as IV access is typically more challenging in these populations and invasive interventions such as CVC or IO catheter placement may be overly aggressive or considered prone to complication. In less emergent situations, providers should consider whether IV access is necessary, considering the potential risk and discomfort to the patient, as well as the associated resources required for their placement. Rectal infusion can facilitate earlier hospital discharge for patients who need non-oral medication and/or fluids but no longer require acute or emergent care. Patients with diagnoses of gastroparesis, migraine headaches, post-anesthesia-induced nausea and vomiting, hyperemesis gravidarum, or other conditions associated with the inability to tolerate oral medications and fluids may benefit from this approach. As rectal infusion is relatively easy to perform by lay persons, it can avoid parenteral therapy in the home which is expensive, more complicated for the patient and caregiver, and associated with an increased risk of complications.

Historical Perspective

The rectal infusion of medicinal substances and fluid appears to have originated in ancient Egypt and Mesopotamia. In these cultures, enemata (a.k.a., "clysters") were recommended as a monthly routine to cleanse the gastrointestinal system and to prevent decaying materials from entering the bloodstream. In ancient India, clysters are referenced in many of the main texts on medicinal treatments. The first report of medication delivery via the rectal route was noted in Egyptian papyri around 1500 BC, including over 800 different formulae [9, 10].

The use of clysters persisted in ancient Greece and Rome. During this era, use of this approach was advanced to include the administration of nutrients, astringents, antispasmodics, emollients, and anthelminthics [11]. Reports on the therapeutic use of enemata can be identified throughout the subsequent centuries, but it was not until the late nineteenth and early twentieth centuries that rectal infusions became popular within the medical community in Europe and the USA. From the late 1870s until the early twentieth century, enemata were considered standard of care for hydration and nutrition when patients could not tolerate oral fluid infusion, or the use of the oral route was medically contraindicated. The Index-Catalogue of the Library of the Surgeon General's Office (the predecessor to PubMed) records hundreds of citations on the use of enemata for hydration and nutrition, and this technique was included in the 2nd edition of D. Hayes Agnew's classic *Principles and Practice of Surgery* [12].

In July of 1881, President James A. Garfield was shot and critically wounded. A 0.44 caliber bullet penetrated his abdomen, ultimately resting posterior to his pancreas. By August 3rd, he was septic and no longer able to receive oral fluids or nutrition. His medical team provided "nutrition" with an enema consisting of blood and beef extracts. Unfortunately, the president died on September 19th, but the medical team was able to maintain hydration and nutrition for more than a month utilizing proctoclysis [13, 14].

On September 6th, 1901, yet another president was shot. President William McKinley was shot by an anarchist at the Pan-American Exhibition in Buffalo, NY, with two 0.32 Caliber bullets, one of which penetrated his abdomen. His physicians performed an emergency celiotomy (i.e., laparotomy) on-site at the fairground clinic. He was immediately given an enema of saline for resuscitation and blood volume replacement followed by rectal salt and sugar infusions the following day. On day 3, he began receiving daily nutritive enemata consisting of eggs, beef juice, and even whiskey! It is not surprising that his doctors noted that, "the rectum was becoming irritable and did not retain the nutritive enemata" [15]. President McKinley died on September 14th, 1901, but during his 1 week of medical treatment, doctors relied primarily on the rectal route for hydration, nutrition, and medication delivery.

The practice of nutritive enemata lost popularity in the early twentieth century. With improvements in the science of biochemistry, a series of early studies suggested that the rectal route provided poor absorption of nutrients, such as fats and proteins [16, 17]. Although these discoveries led to decreased use of rectal nutrition, rectal fluid hydration became increasingly popular over the first half of the century. Dr. John B. Murphy was primarily responsible for promoting the use of proctoclysis for fluid delivery. The so-called "Murphy Drip" was first described in the 1909 issue of the *Journal of the American Medical Association* [18]. As Dr. Murphy described the importance of proctoclysis at that time, "next to the conservative technique of the operative procedure, proctoclysis is second in importance as a life-saver. It rapidly restores blood pressure, it improves the capillary circulation, it quiets the thirst, it eliminates the septic products" [19].

Rectal rehydration remained standard of care through the First World War, when it was used extensively to treat soldiers wounded on the battlefield [20]. As intravenous access techniques improved during the early to mid-twentieth century, reliance upon proctoclysis continued to decline.

Proctoclysis as an alternative or addition to intravenous delivery of medication and fluid witnessed a re-emergence with the invention and FDA clearance of the Macy Catheter® in 2014. This method was added to Reichman's

Emergency Medicine Procedures in 2018. Chapter 91 on proctoclysis states that, "in recent years, the Macy Catheter has been successfully used to facilitate proctoclysis with fewer complications and higher satisfaction among patients receiving palliative care, those in the Emergency Department, and those in the Intensive Care Unit. The Macy catheter has proven that proctoclysis can be used as an alternative and efficient route for medication and fluid infusion in the modern era" [21•].

A Review of the Literature

Studies on the Macy Catheter

In the Emergency Department

In a small case series report in the ED setting, Lyons et al. reported success with hydration and medication administration in three patients with difficult venous access (DVA) who were poor candidates for CV line placement using the Macy Catheter® (MC). Patients were rectally administered tap water for hydration, lorazepam for agitation, aspirin for anticoagulation, ondansetron for nausea, acetaminophen for fever, and methimazole for hyperthyroidism. They found catheter placement easy and well tolerated by patients with rapid onset of clinical response. They conclude that, "this device may be an appealing alternative route to medication and fluid administration for a variety of indications in acute and critical care settings" [22].

A case report in the ED reported lactulose retention enema on a patient with hepatic encephalopathy on three separate ED visits. On all three encounters, the patient received a lactulose enema via catheter. In this report, the catheter was placed in under 5 min and lactulose was administered quickly and easily. The enema was easily retained for the required time and the patient tolerated the procedure well. They described the method minimized potential cleanup and exposure to body fluids compared to previous techniques and increased the comfort and effectiveness of the retention enema by facilitating longer retention time [23].

In the Inpatient Palliative Setting

During the early COVID pandemic in 2020, severe parenteral drug shortages were experienced in parts of the USA. New Jersey was one of the hardest states hit. The MC was employed in the acute care setting for patients transitioning to palliative care and an end-of-life care plan to preserve parenteral medication for the care of patients on ventilatory support [24•].

In the Intensive Care Unit

In another case report, the MC was used to control the shivering reflex during induced hypothermia for cardiac arrest. The shivering reflex was effectively suppressed with MC delivered APAP 650 mg and buspirone 30 mg. Aspirin was also given via the MC for anti-platelet effects. The patient was able to reach a core temperature of 33 °C [3].

In the Hospice and Palliative Care Setting

An early case study in 2016 described hospice agency use of the MC. In this study, they identified the ability to give ongoing medications comfortably and effectively at home without the need for moving or re-invading the patient's rectum with each dose to be a major benefit. Another major benefit identified was the avoidance of symptom management delay as oral medications already present at the bedside could be used by grinding the tablets, adding water, and injecting them in ME form. They found the catheter to be easy to place, comfortable for the patient, and reported "consistently excellent outcomes" in patients for whom the oral route has failed [4].

One study done in the hospice inpatient setting and home found use of the MC to be cost-effective, saving the agency about $402 for every catheter utilized, when compared to the use of parenteral medication. The authors conclude that, "the rectal administration catheter has improved the ability of Hospice Buffalo to facilitate quick and effective symptom management while simultaneously decreasing costs and improving nursing efficiency" [25].

Comparative Comfort

A three-arm crossover pharmacokinetic study performed using healthy volunteers compared ME doses given via the MC to suppository. Subjects rated the comfort of placement and medication administration via the MC compared to suppository administration. Of the 19 MC placements, the subjects rated MC placement and medication administration as "not uncomfortable" compared to suppositories, which were reported as "mildly uncomfortable" ($P < 0.05$) [26].

One large hospice in Ohio currently utilizes the MC as the first option prior to parenteral medication in both inpatient and home hospice patients. One year after adoption of the MC, a Likert survey was sent to 391 nurses within the organization. This survey included 191 nurses, 49% of those asked to respond with experience in both MC and subcutaneous medication delivery. Part of the survey asked nurses to

evaluate the comfort of the MC compared to subcutaneous medication delivery. They found that 70% of respondents considered the MC more comfortable for patients, and 13% found it equally comfortable when compared to subcutaneous medication delivery [27].

In a small case series including ten patients in four skilled nursing facilities, medication and/or proctoclysis was provided with the MC in eleven separate instances. The catheter was well-tolerated, and hydration was achieved in all incidences with no reported discomfort [28].

Studies on Proctoclysis

The effectiveness and tolerability of proctoclysis for hydration was well-established in the medical literature and medical practice during the early twentieth century. Daily rectal infusion volumes exceeding 8 L were reported by Murphy to be well tolerated, although no empirical studies were done and reports were anecdotal. The Murphy method for the treatment of peritonitis consisted of fast gravity infusion of an average of 1.5 pints (720 ml) normal saline over 40–60 min, followed by a 1-h rest period. This process was repeated every 2 h for an average infusion rate of 360 ml/h [18, 19].

One early study compared the use of tap water to normal saline (NS) for proctoclysis in 400 post-operative patients. Both tap water and saline were effectively absorbed, as evidenced by similar urine outputs in both groups. The authors report that the water group absorbed an average of 400 ml more (2444 cc/24 h) than the NS group (2041 cc/24 h), although they do not describe how this absorption was measured. The authors also noted that patients given NS required twice as much water by mouth to relieve thirst. This study supports the conclusion that NS can be used effectively for volume replacement and that rectal water infusion can be used to treat a free water deficit [29].

More recent studies have been completed demonstrating the effectiveness and comfort of proctoclysis. Bruera et al. [30] conducted a multi-site prospective, open study of 78 patients with terminal cancer. In this study, patients received proctoclysis at four different medical centers. Infusion of normal saline in 2 cases and tap water in the remaining 76 cases was administered at a rate of 250 ± 63 cc/h. Hydration was maintained for 15 ± 8 days. Most patients received daily intermittent infusions for an average daily volume of 1038 ± 202. Volumes up to 400 ml/h were tolerated in some cases. For the 78 patients receiving multiple daily infusions during a treatment period averaging more than 2 weeks, there were only four incidences of leakage, five instances of pain during infusion, and nine incidences of enema effect. No other complications were noted. The mean visual analogue score for discomfort after infusion with (0 = no discomfort, 100 = worst possible discomfort) was 19 ± 14. Four patients (5%) refused to continue hydration due to the discomfort of insertion. This study used a 22-French nasogastric tube inserted 40 cm into the rectum [30].

In the small case series mentioned above under "Studies on Comfort," ten patients in four skilled nursing facilities received proctoclysis with the MC in eleven separate instances. Hydration was successful in 100% of cases, based upon improvement of vital signs or decrease in lethargy. In all instances, regular tap water was infused rectally through a gravity feeding bag. Infusion volumes varied from 60 to 250 ml/h. The duration of infusion varied from 2 to 48 h. Infusions were stopped when the patient returned to oral intake. Hospital transfer was avoided in 78% of patients for whom their condition was serious enough to warrant transfer without this treatment option [28].

Studies on Rectal Medication Pharmacokinetics

Numerous authors have previously discussed the pharmacokinetics and pharmacodynamics of rectal medication absorption in detail [31–34]. In summary, many medications are effectively and reliably absorbed via the rectum. The rectal mucosa is highly vascularized with a high percentage of absorptive cells. There is a partial first pass avoidance for blood returning to the central venous circulation from the distal one-third of the rectum. Table 1 provides a list of medications that have shown effective absorption and/or demonstrated clinical effectiveness when given rectally either by ME or suppository.

In general, medications in ME form tend to be absorbed quicker and with less intra-subject variability than the suppository form [35]. This can be explained by the fact that suppositories must melt (with a fatty base) or dissolve (with an aqueous base) in the rectum prior to drug absorption across the mucosal membrane. The time required for this can be quite variable, depending upon the dryness of the rectum and the presence of stool in the rectal cavity. Microenemas, on the other hand, can be delivered to the mucosa in a readily absorbable form.

Several studies comparing rectal suppositories to ME doses of the same drug also demonstrate this phenomenon. Jensen et al. (1985) found indomethacin to achieve Cmax in 20 min via ME versus 40 min PO and 60 min by suppository [48]. Moolinaar et al. (1980) studied diazepam given by several routes (IM, ME, PO, and suppository). The ME delivery had a fastest Tmax with least intrasubject variability. Tmax by ME was achieved in ($17 \text{ min} \pm 6 \text{ min}$) compared to IM ($95 \text{ min} \pm 39 \text{ min}$), PO ($52 \text{ min} \pm 40 \text{ min}$), and suppository ($82 \text{ min} \pm 20 \text{ min}$). AUC for all routes was essentially the same, but there was a significant difference in Cmax between the ME (369 ng/ml) vs the suppository (272 ng/ml) [67].

A three-arm crossover study by Lam et al. also demonstrated earlier absorption, overall higher blood concentrations

Table 1 Rectal medication comparative bioavailability and clinical effectiveness studies

Drug class	Medication	Dosage form studied ME = micro-enema Supp = suppository	Rectal bioavailability or clinical effectiveness	References and notes
Opioid analgesics	Morphine	ME [35] ME vs oral [36]	Similar to oral	Pain relief onset 10 min (ME) vs. 60 min (oral) [35] Tmax (ME) = 30 min [36]
	Oxycodone	Supp [37–39]	Similar to oral	Analgesia onset (supp) 30 min–1 h [37–39]
	Methadone	ME vs oral [40] ME [41] ME vs supp [42]	80–90% of oral	Tmax (ME) 1.4 h vs (oral) 2.8 h [40] Analgesia onset (ME) 30 min [41] Absorption (ME) 80% of oral vs (supp) 35–58% of oral [42]
	Hydromorphone	Fatty supp vs oral [43, 44]	65–70% of oral	[43, 44]
Anesthetics	Lidocaine	ME vs oral [45]	200% of oral	Extensive first pass avoidance [45]
	Ketamine	Supp vs oral [46]	150% of oral	Plasma concentrations similar for oral and rectal [46]
NSAIDS/APAP	Aspirin	Supp vs oral [47]	Similar to oral	[47]
	Indomethacin	ME vs IM vs Supp vs IV [48]	80% of IV	Tmax (ME) 20 min. vs (IM) 40 min vs (supp) 60 min [48]
	Ibuprofen	ME vs oral [49]	87% of oral	Tmax (ME) 1.1 h vs (oral) 33 min [49]
	Ketoprofen	Supp vs oral vs IM [50]	Same as IM 73–93% of oral	[50]
	Naprosyn	Supp vs oral [51]	Similar to oral	Studies done on both suppository and oral solution [51]
	Acetaminophen	Supp vs oral [52]	Similar to oral	As aqueous suspension [52]
Corticosteroids	Dexamethasone	Supp. and ME [33] Supp [53]	Clinical effectiveness	Satisfactory results obtained in several studies [33] Case study on Benadryl, Reglan, Dexamethasone Supp (BRD) — effective for malignant bowel obstruction [53]
Antidepressants	Imipramine	Supp [54]	Similar to oral	[54]
	Clomipramine	Supp [54]	Similar to oral	[54]
	Doxepin	Rectal gelatin capsule	Therapeutic levels	[55]
	Amitriptyline	Supp [56]	Clinical effectiveness	Case study: clinical effectiveness [56]
	Trazodone	Supp [57]	Clinical effectiveness	Clinically effective [57]
Anticholinergics	Atropine	ME vs IM [58, 59] ME [60]	32% of IM [59]	(ME) clinically as effective as (IM) [58] Tmax (ME) 15–33 min [59, 60]
	Hyoscyamine	Sublingual study only [61]	100% absolute bioavailability	[61]
Benzodiazepines	Lorazepam	ME vs IV [62] IM vs oral vs SL [63] Case study [5]	80% of IV [62] Clinically effective [5, 64]	Tmax (ME) 1.12 h vs (IM) 2.25 h vs (oral) 2.37 h vs (SL) 2.35 h [62, 63] Seizure control (ME) in 37 s average [64] Agitation control (ME) < 1 min [5]
	Diazepam	ME vs oral vs supp [65]	Similar to oral	Tmax (ME) 17 min. vs (IM) 95 min. vs (supp) 82 min. vs (oral) 52 min. [65]
	Midazolam	ME vs oral [66] ME [67] ME vs IV [68]	Similar to oral	Improved sedation (ME) vs (oral) [66] (ME) acceptable in children ages 2–7 Tmax 16 min in children [67] Tmax 31 min in adult males [68]

Table 1 (continued)

Drug class	Medication	Dosage form studied ME = micro-enema Supp = suppository	Rectal bioavailability or clinical effectiveness	References and notes
Anti-epileptics	Phenobarbital	ME vs oral [69] ME vs suppository [26]	Similar to oral [69]	(ME) showed faster absorption, improved overall absorption, decreased variability vs (supp) [26]
	Levetiracetam	Supp vs oral [70]	Similar to oral	Tmax (Supp) 190 min vs (oral) 90 min [70]
	Lamotrigine	ME vs oral [71]	63% of oral	[71]
	Valproic acid	Supp vs oral [72]	Similar to oral	[72]
	Carbamazepine	ME vs oral [73] Rectal gelatin capsule [55]	Similar to oral [73]	[73] Therapeutic levels [55]
Anti-emetics	Metoclopramide	Supp vs IV [74] ME case study ($N = 1$) [75]	100% absolute bioavailability [74]	Therapeutic blood levels [74] (ME) Controlled gastroparesis symptoms [75]
	Prochlorperazine	Supp [76]	Clinically effective	Suppositories available commercially [76]
	Promethazine	Supp [77]	70–97% of oral	[77]
	Ondansetron	ME vs oral [78] Supp vs oral [79]	ME similar to oral [78] Supp 50% of oral [79]	(ME) Cmax, Tmax, and bioavailability similar to oral [78] (Supp) bioavailability 50% vs oral [76]
Antibiotics	Amoxicillin	Supp [80]	87—99% of oral	Study used hydrophilic suppository [80]
	Erythromycin	Supp vs IV [81] Oral vs IV [82]	≅150% of oral [81, 82]	Suppository 54% of IV [81] Oral 32% of IV [82]
	Ampicillin	Supp [83]	Plasma concentrations well above MIC	Rapidly absorbed, therapeutic plasma concentrations, same therapeutic effect rectal (89% cured) vs oral group (86% cured) $N = 683$ [83]
	Sulfamethoxazole-trimethoprim	Supp [84]	Similar serum concentrations given rectal (TID) vs oral (BID)	Steady state blood levels achieved Serum concentrations comparable to oral with same dose given TID rectal vs BID oral [84]
	Metronidazole	Supp [85]	80% of oral	PEG (supp) compared to oral suspension [85]

Table 1 (continued)

Drug class	Medication	Dosage form studied ME = micro-enema Supp = suppository	Rectal bioavailability or clinical effectiveness	References and notes
Cardio-active medications	Flecainide	ME vs oral vs IV [86]	98% of IV and 126% of oral [86]	Rapid Tmax for ME (11 min) vs oral tab (51 min) [86]
	Lidocaine	ME vs oral [87]	200% of oral	Extensive first pass avoidance [87]
	Nifedipine	Supp vs oral [88]	Similar to oral [88]	AUC comparable (oral) vs (supp) [88] Anti-hypertensive effects at 30 min lasting 7 h, heart rate increase associated with oral dosing did not occur with rectal dosing [89]
	Metoprolol	Supp vs oral [90]	Similar to oral	AUC for (oral) vs (supp) not significantly different (0.05). (Supp) effective in lowering heart rate by (avg. 19 bpm) and BP by (syst. 14 mmhg/dia. 15 mmhg) [90]
	Propranolol	Supp [91]	200% of oral	Significant first pass avoidance noted [91]
	Verapamil	PEG supp vs fatty supp vs oral [92]	PEG supp similar to oral	Faster Tmax 33 min (PEG supp) vs 2.1 h oral. (Fatty supp) AUC 50% oral [92]
	Digoxin	No PK studies	Clinical effectiveness	Therapeutic effects noted [93, 94] NOTE: early studies (1924 and 1932) with digitalis extracts
Anti-psychotics/ neuroleptics	Chlorpromazine	Supp vs IV [95]	Clinically effective	Supp as effective as IV in controlling restlessness and dyspnea in EOL patients [95] Commercial suppositories available
	Haloperidol	No PK studies	Clinical effectiveness	Anecdotal reports support clinical effectiveness administered rectally [96]
	Olanzapine	No PK studies	Clinical effectiveness	Suppository found clinically effective for delirium and N/V [97]
	Quetiapine	Supp vs oral vs topical	Supp 189% of oral	No topical absorption noted [98]
Diuretics	Furosemide	No PK studies	Clinical effectiveness	Therapeutic effect similar to oral at same dose [99]
	Bumetanide	Supp vs oral [100]	52–62% compared to oral	Sufficient diuretic effects obtained after rectal dosing [100]
Anticoagulants	Warfarin	Supp [101]	Therapeutic PT ranges	Therapeutic PT ranges achieved within 24 h (N = 23) [101]

and less variability with phenobarbital tablets compounded into suppositories compared to the same medication suspended in water. Phenobarbital (PB) tablets were ground and suspended in water to produce two different volume MEs (6 ml and 20 ml). Blood levels were drawn for the first 12 h for determination of PB concentrations and characterization of early absorption profile. The PB concentrations for both the 6 ml and 20 ml MEs remained consistently higher than suppository concentrations. Blood levels at 10 min were 12 times that of the suppository for the 20 ml ME and 8 times the suppository for the 6 ml ME. The achievable concentrations for the 20 ml ME were consistently higher than that of the 6 ml ME, demonstrating the effect of fluid volume in facilitating absorption from these MEs [26].

Rapid Tmax and clinical effectiveness have been reported with ME-administered lorazepam. One study of lorazepam absorption via ME demonstrated a Tmax of 1.12 h with similar AUC to IV [62]. The Tmax for lorazepam in this study is about twice as fast as that for oral, sublingual, and IM demonstrated in another study, (2.37 h for oral), (2.35 h for sublingual), and approximately the same for IM (1.15 h) [63]. Both diazepam and lorazepam in ME form have been demonstrated to work extremely fast in controlling status epilepticus (SE). In a study done on children, ME doses of diazepam were effective in controlling SE in an average of 38 s ($N=19$) and lorazepam in an average of 37 s ($N=6$) [64]. In one case study, a 41-year-old woman presented to the emergency department in alcohol withdrawal. As the patient was too agitated to obtain IV access, a Macy Catheter was placed, and 2 mg lorazepam was administered. Immediate improvement in agitation, orientation, and tachycardia was achieved in under 1 min [22].

In some instances, ME delivery has been shown to achieve a faster Tmax, Cmax and onset of action when compared to oral delivery. Micro-enema administered flecainide has demonstrated a similar AUC to IV and a Tmax of 11 min vs. 52 min given orally by tablet. The Cmax achieved via ME was almost twice that of the tablet at 0.29 mg/L, when compared to the oral tablet of 0.14 mg/L [86]. In a triple crossover study done by Moolinaar et al., a 5-ml ME of 10 mg morphine at a pH of 4.5 was associated with an AUC, Tmax, and Cmax similar to oral dosing of 10 mg morphine given orally in 100 ml water. But when the same dose and volume of ME was adjusted to a pH of 7.4, Cmax increased by almost two-fold and AUC increased by 1.5-fold [36]. In a comparative study on clinical effectiveness, significant pain relief was noted for morphine via ME at 10 min versus 60 min administered orally [37]. The Tmax for methadone was shown by Dale et al. to be 1.2 h via ME vs 2.8 h orally with AUC of 88% compared to oral [39, 40]. Ripamonti et al. achieved onset of significant pain relief in an average of 30 min with methadone given via ME [41]. In another study, methadone absorption via ME suspension was 80% of oral vs. suppository absorption of 35–58% of oral absorption [42].

Practical Guidelines for Proctoclysis

Indications

Proctoclysis can facilitate earlier treatment in patients for whom IV access is difficult, delayed, or unnecessary. It can facilitate the immediate administration of fluids and medications while awaiting PIV or CVC placement. Hydrating patients by proctoclysis may improve the ease of subsequent PIV placement, thereby avoiding CVC or IO access altogether when it is otherwise not indicated. Proctoclysis is not a first-line option for resuscitation, but in the presence of hypovolemic shock or other scenarios when massive and immediate fluid resuscitation are critical and difficult to initiate or achieve, rectal fluid infusion can provide additional fluids alongside parenteral methods of fluid delivery [5].

Proctoclysis may also facilitate rapid hospital discharge for patients who do not require acute care, other than for the non-oral delivery of fluid and medication. Many patients could benefit from home-based hydration and medication via the rectal approach, including those diagnosed with hyperemesis gravidarum, migraine headaches, or gastroparesis.

Patient Positioning

During rectal infusion, the patient should be positioned on their left side, allowing fluid to drain from the rectum into the descending colon by gravity (Fig. 4). The right side-lying position should be avoided, as fluid pressure will build in the rectum and fluid cannot flow by gravity into the colon where most of the fluid absorption occurs. The patient may have the head of the bed elevated for comfort or temporarily turn on their back if necessary.

Fluids

Fluids administered by the rectal route can be either hypotonic or isotonic. Saccharide solutions should be avoided. While absorption of sugars in the colon is possible, bacterial degradation of sugars may produce gas and patient discomfort [102]. Hypotonic fluids (e.g., tap water, one-fourth NS, or one-half NS) can be used for hydration in patients with free water deficit. Normal saline solution can be used for fluid volume replacement in cases of hypovolemia. Ringer's solutions with calcium and potassium additives were prepared by hospitals for proctoclysis in the early twentieth century, but no studies have been done on the absorption of calcium and potassium via the colon.

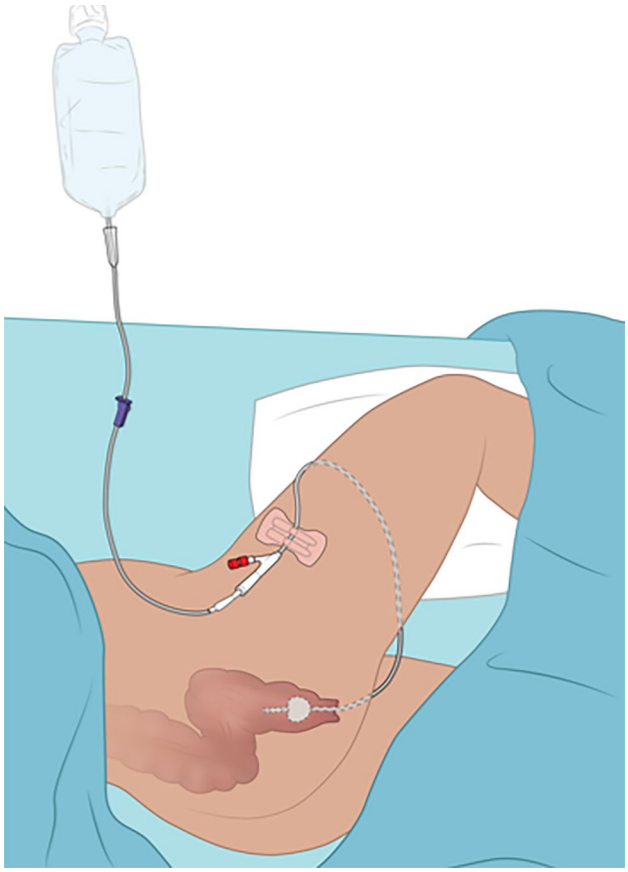

Fig. 4 Proctoclysis via the Macy Catheter (Hospi Corporation)

Infusion Rate

Based upon previous studies, rapid infusion rates of up to 400 ml/h appear to be well tolerated for short durations of a few hours [18–20, 30]. To achieve this rate of infusion, an enteral feeding pump can be employed or pressure can be applied with a gravity bag. For extremely rapid infusion, fluid boluses with a 60-ml enteral syringe pushing at a rate of 60 ml over 15 to 30 s have been done in emergent settings [5]. In non-emergent situations, keeping infusions to about 250 ml/h or less can avoid overdistension of the colon and patient desire for the expulsion of fluid. Intermittent infusions of a few hours, followed with rest periods of a few hours between infusions, allow the bowel to absorb the water and return to a resting (i.e., unstretched) position while also allowing for bowel movement. Table 2 provides a quick review of the preparation and procedure for proctoclysis.

Conclusions

A strong foundational evidence base exists for the effectiveness of proctoclysis and the rapid and effective absorption of a large number of medications delivered by micro-enema. The rectal infusion of medications and fluids can provide a viable alternative to IV access, facilitating immediate and rapid treatment when IV access is delayed, contraindicated, or unavailable. Proctoclysis can support parenteral methods by improving the ease of peripheral IV access in cases of DVA. While ultrasound-guided PIV placement has improved the clinician's ability to obtain IV access, the incidence of DVA continues to rise. Fields et al. found that 1 in 10 patients treated in the emergency department are considered to have difficult venous access [103].

Hospitals have recently been challenged by unprecedented shortages of skilled nursing staff causing further delay in the placement of both PIV and CVC lines and increased risk of injury and discomfort. Multiple PIV attempts cause discomfort for the patient, a burden on staffing and produce longer throughput in the ED [104•]. For patients with existing PIV access, rectal infusion can provide an additional route of fluid and medication delivery to provide medications not deliverable by the IV route and provide additional fluids during resuscitation. Lastly, numerous hospitals have faced parenteral drug, fluid, and supply shortages. Training ED and in-hospital staff on rectal infusion procedures may be beneficial as shortages continue.

More research is needed to support increased acceptance and use of this method in the acute care setting. Clinical protocol development is lacking for the use of proctoclysis as a means of improving the likelihood of PIV access in DVA, as are studies exploring reductions in the use of IO infusions, CVC use, and the associated discomfort and complications associated with rectal infusion. Increased use

Table 2 Proctoclysis quick guide

Patient positioning and preparation	1. The patient should be positioned on their left side during and for 30 min after the infusion. 2. If feasible, have the patient evacuate their bowels prior to the procedure. 3. Place chux or incontinence brief under patient.
Fluid types	Hypotonic solutions (1/4 NS, 1/2 NS, H2O (oral rehydration solutions)) Isotonic solutions (NS) Solutions with sugar are NOT recommended
Infusion/bolus rate	Infusion method: up to 400 ml per hour for 1–2 h with rest periods in-between spanning 2–4 h Bolus method: up to 250 ml every 30 min pushed at a rate of 60 ml over 15–30 s

of rectal infusion techniques to facilitate hydration and/or medication administration could decrease the current burden on the health care system and further decrease the risk of iatrogenic infections, morbidity, and mortality associated with the use of other techniques to achieve hydration and non-emergent medication administration [105].

Declarations

Conflict of Interest Mr. Macy is the inventor of the Macy Catheter. He receives a salary and owns stock in Hospi Corporation, producer of the Macy Catheter. The other authors have no financial or proprietary interest in any material discussed in this article.

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