Reviews in Endourology

Intraurethral Lubricants: A Critical Literature Review and Recommendations

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Abstract

In current clinical practice, lidocaine gel is widely used as a local anesthetic lubricant before various forms of transurethral instrumentation. Over the past few years, the value of local anesthesia during urethral catheterization and flexible or rigid cystoscopy has been questioned. Strong data are lacking, and the results from the different studies are contradictory. As a result, the correct use of the intraurethral gels is, for the most part, left to individual preference. The purpose of this review is to provide an overview of the characteristics of the intraurethral gels, to assess the effectiveness, and to define evidence-based indications for their use.

Introduction

THE FIRST MENTION of a urethral lubricant in the form of olive oil and aqueous gels from plant gums goes back to antiquity. The use of a topical anesthetic in urology was reported in 1884, when Pease¹ described the use of cocaine during cystoscopy. Since then, numerous synthetic topical anesthetic-lubricant agents have been introduced, including lidocaine, tetracaine, tripeleminamine, silicone, and dyclonine. Lidocaine was synthesized by Lofgren and Lundqvist² in Sweden in 1943 and introduced in clinical practice in 1947.

In 1949, Haines and Grabstald³ were first to report the efficacy of intraurethral administration of 2% lidocaine in 250 patients who underwent cystoscopy. Similarly, in 1953, Persky and Davis⁴ reported that 2% lidocaine was a safe, rapid, and adequate anesthetic in a series of 622 cystoscopies. Since then, intraurethral lidocaine gel emerged as the anesthetic agent of choice based on its simultaneous role as lubricant and local anesthetic.

Controversial issues have been raised over the past few years regarding the need for local anesthesia during urethral instrumentation. Strong data are lacking, and results from the different studies are contradictory. Consequently, the correct use of the intraurethral gels, is for the most part, left to individual preference. The purpose of this review is to provide an overview of intraurethral gel characteristics, to assess the

current body of evidence on their effectiveness, and to define evidence-based indications for their use.

Evidence

A formal literature search was performed of the major medical citation databases, including Ovid Medline, PubMed, and Scopus. The formal search strategy was to include all related articles between 1949 and September 2008. This period was selected because of the pioneering paper of Haines and Grabstald³ on intraurethral lidocaine. Search terms were: pain, anesthesia, lidocaine, local anesthetics, intraurethral gel, cystoscopy, and catheterization. All randomized controlled trials (RCTs) and meta-analysis were included for the determination of efficacy and level of evidence. In all studies that referred to catheterization and cystoscopy, intraurethral plain lubricating gel was used in control groups and 2% lidocaine gel in treatment groups before the procedure. For all the mentioned studies, primary outcome was pain evaluation by a visual analog scale (VAS) pain score, scaled from 0 to 100 with 0 denoting no pain and 100 denoting the worst pain possible. The recommendations provided are rated according to the levels of evidence published by the U.S. Department of Health and Human Services, Agency for Health Care Policy and Research.⁵

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Based on the evaluation criteria mentioned above, 27 articles were selected. Four articles deal with urethral catheterization, 13 with cystoscopy (rigid and flexible), and 10 with variables that can alter anesthetic effectiveness, referred to in the article as improving factors.

The Ideal Lubricant

The clinical significance and the economic impact of the wide use of intraurethral lubricants in daily practice entail the need for a critical evaluation of their characteristics. Gel may guarantee safety, satisfactory lubrication to reduce friction and protect the mucosa during instrumentation, optimal visibility, fast and efficacious anesthetic effect, local control of the urethral microbial flora, and high electrical conductivity to prevent thermal injuries. In addition, it must be easily handled and cost effective. The accomplishment of the above requirements is needed to define an ideal gel.

The available intraurethral gels are composed of lidocaine, preservatives (methyl and propyl parabens), suspending agents (carboxymethylcellulose or hydroxyethylcellulose), and clorexidine. Depending on the combination of these constituents, four categories can be distinguished: Lubricant-anesthetic-disinfectant (Instillagel®, Farco-Pharma, GmbH, Cologne, Germany, Cathejell®, Montavit, Austria, AT; lubricant-disinfectant (Cathejell S®, Montavit, Austria, AT, Endosgel®, Farco-Pharma, GmbH, Cologne, Germany; lubricant-anesthetic (Xylocaine®, AstraZeneca LP, Wilmington, DE; and plain lubricant (K-Y Jelly®, Johnson & Johnson Medical, Arlington, VA, Lubrigel®, Major Pharmaceuticals, Livonia, MI.

Characteristics

Safety

Despite the large safety range, undesired effects from the high blood levels of lidocaine or allergic reactions to lidocaine, to preservatives, to the suspending agent and/or to chlorexidine have been registered.⁶⁻⁸

Several clinical studies have suggested the safety of intraurethral use. Eardley and associates⁹ found that the instillation of 400 mg lidocaine gel before transurethral resection of the prostate results in plasma concentrations safely below the toxic levels. Ouellette and colleagues¹⁰ reported that plasma concentration after the intraurethral administration of 218 to 550 mg of 2% lidocaine never reached levels that caused systemic toxicity, and Birch and Miller¹¹ confirmed the low peak concentration after intravesical administration of 400 mg of lidocaine.

Excessive amounts, short intervals between doses, and long duration of urethral exposure can result in high plasma levels of lidocaine or its metabolites and serious adverse effects. In addition, mucosal integrity may play an important role. In cases of severe or multiple urethral injuries, absorption across the damaged mucosa is rapid, and a high peak systemic concentration from the absence of the hepatic first-pass effect can be reached. Central nervous system (CNS) toxicity usually precedes the cardiovascular effects of the drug, because it occurs at lower plasma concentrations.¹² Direct effects on the heart include slow conduction, negative inotropism, and eventually cardiac arrest.¹³

Lubricant action

Carboxymethyl and hydroxyethyl cellulose are polysaccharide derivatives of cellulose. These highly hydrosoluble substances confer the lubricant properties of the intraurethral gels. Their adhesion to the mucosa reduces friction by creating a slippery barrier between urethra and instruments.¹⁴

Anesthetic action

Lidocaine or lidocaine hydrochloride or 2-(diethylamino)-2,6-acetoxylicidide is a lipid-soluble tertiary amide able to penetrate the hydrophobic components of the cell membranes and to exert local anesthetic action by blocking the voltage operated sodium channels.¹⁵ Today it is known that pain of tubular organs such as the urethra is produced by mechanical stretching. Shear stress forces stimulate urothelial cells to release adenosine triphosphate that subsequently act on P2X_{2/3} nociceptive receptors on suburothelial sensory nerve terminals, which then relay impulses to the CNS to be registered as pain.¹⁶

Lidocaine acts on these suburothelial nerves by inhibiting neuronal impulse propagation and/or generation. Topical anesthesia, however, does not efficiently block pain sensation of the entire urethra because of the complex innervation of the rhabdosphincter, and passage of the membranous urethra results as the most painful part of cystoscopy.¹⁷⁻¹⁹

Anti-infective properties

Johnson and coworkers²⁰ reported that local anesthetics not only serve as agents for pain control, but also possess antimicrobial activity and can be considered as an adjunct to traditional antimicrobial use in the clinical or laboratory setting. Sperling and colleagues²¹ investigated the disinfectant action of Instillagel in symptomatic patients with nongonococcal urethritis and found that eradication of the infection was obtained in 81.2% of patients, results comparable with systemic antibiotic treatment effectiveness.

Electrical conductivity

The importance of gel electrical conductivity to prevent urethral stenosis during transurethral resection was first reported by Flachenecker and associates²² Investigators found that when the conductivity of the gel is equal to or higher than that of the urethra, the dispersion of current between the surface of the resection instrument and urethra is uniform and the current density is low. In cases of low conductivity gel (insulator), electrical current is concentrated in a few points along the sheath where the amount of gel is low or absent, damaging the tissue and causing scar formation. Electrical conductivity of tissues that are highly perfused, such as the urethra, range between 4 and 6 mS/cm, and, consequently, the ideal conductivity of a gel must be at the same range.²³

Clinical Use

With the restriction of the limited number of RCTs and with the small overall number of patients included, we tried to obtain conclusions about the clinical efficacy of the intraurethral lidocaine gel.

Urethral catheterization

Siderias and coworkers²⁴ compared the efficacy of intraurethral lidocaine gel with that of a plain lubricant during male urethral catheterization and found a statistically significant reduced pain associated with the use of the anesthetic gel [level of evidence (LVE)=Ib, A]. In a similar trial, Tanabe and associates²⁵ reported that the most of the women in their study, urethral catheterization was not very painful, and no difference was noticed in pain scores associated with the type of lubricant used before the procedure [Ib, A]. In children who were 4 to 11 years old, pain score and observer-rated behavioral distress was significantly lower in the lidocaine gel group than in the lubricant group²⁶ [Ib, A]. This was not valid, however, for children younger than 2 years. Vaughan and colleagues²⁷ found that lubricant with 2% lidocaine gel was not helpful in alleviating pain that was associated with the procedure [Ib, A].

Cystoscopy

Rigid cystoscopy. Stein and associates²⁸ compared the efficacy of 2% intraurethral lidocaine gel to plain lubricant in pain management during cystoscopy. In this study, the intraurethral dwell time was 5 and 10 minutes, but the amount of gel was not reported. Using a VAS, the investigators found no difference in pain perception between patients (men and women) who received lidocaine or plain lubricant. [Ib, A]. In contrast, Goldfischer and colleagues²⁹ found that 30 mL of lidocaine gel dwelling in the urethra for 20 minutes before cystoscopy offers no advantage over plain lubricant regarding pain control during cystoscopy in women. It can, however, significantly decrease pain in men [Ib, A].

The importance of the gel amount during cystoscopy is reported by Brekkan and coworkers.³⁰ They evaluated the influence of instilled volume (11 vs 20 mL) in pain perception and found a significant pain reduction in the group of male patients with the use of 20 mL of the anesthetic lubricant. No difference was found among the two groups of women [Ib, A]. In a recent study by Choe and associates,³¹ however, a statistical significant reduction in pain score was found after application of anesthetic gel in women during cystoscopy [Ib, A].

Flexible cystoscopy. The advent of flexible cystoscopy and digital chip technology has significantly increased tolerability during cystoscopy. Consequently, the value of lidocaine gel in alleviating pain during this procedure has been reevaluated by many authors with contradictory results.^{32–38} Patel and coworkers³⁹ performed a meta-analysis of the results of the above clinical trials. Pooled data, including more than 800 male patients from nine trials, identified no statistically significant difference in the efficacy of pain control between 2% lidocaine and plain gel during flexible cystoscopy [Ia, A]. More recently, the same results have been reported by Chitale and colleagues⁴⁰ in a RCT study [Ib, A]. No studies have been found regarding the need for local anesthetics during flexible cystoscopy in women.

Cost-effectiveness

The cost-effectiveness of intraurethral gel use has been less frequently argued. Considering the wide use, however, cost is

an important issue. McFarlane and associates³⁸ found that the cost savings at their institute would be more than \$5000 a year if lidocaine gel was eliminated from all outpatient cystoscopy procedures. Chen and colleagues³⁵ reported that lidocaine gel is more than three times more expensive than plain gel in Taiwan. Patel and coworkers³⁰ reported that the cost of 10 mL of lidocaine gel, which is \$4.64 *vs* \$0.86 for 4 ounces of plain gel at their institution, is not reimbursed and must be borne by the urology practice.

Improving Factors

The instillation of topical anesthetics provokes discomfort and may negatively influence pain perception of the procedure.⁴¹ Several studies examined strategies to overcome discomfort during urethral instillation to increase clinical effectiveness of lidocaine gel.

Decreasing pain during initial instillation

Temperature. Thomson and coworkers⁴² investigated the role of temperature in the perception of pain during gel instillation. They found that the reduction of the gels temperature at 4°C was significantly caused less pain compared with gels at 22°C or 40°C. They postulate that this is a cryoanalgesic phenomenon relating to the temperature of the gel and its thermal effect on nociceptors [Ib, A]. In a similar study, Goel and Aron⁴³ confirmed the previous results [Ib, A].

Delivery rate. Pain in tubular and sacular organs is caused by distension. Consequently, instillation gel rate may influence the extent of urethral distention and pain perception. Khan and colleagues⁴⁴ compared 2 *vs* 10 sec intraurethral gel delivery rate into 100 patients and found that the instillation discomfort, which may influence perceived pain in the entire procedure, may be significantly reduced by slowing gel administration rate [Ib, A].

Chemical composition. The role of chemical composition as a cause of pain during instillation was studied by Ho and associates.⁴⁵ They found statistically less discomfort in patients who received plain aqueous gel compared with the group who received lidocaine-chlorhexidine gluconate gel [Ib, A]. Jayathillake and coworkers⁴⁶ randomized 141 patients to receive either urethral gel that contained 10 mL of 2% lidocaine with 0.05% chlorhexidine gluconate or K-Y gel and 2% lidocaine solution. They found no significant difference in pain at insertion, during, or immediately after flexible cystoscopy. Pain during first void, however, was statistically greater in patients in whom gels that contained chlorhexidine were used [Ib, A].

Decreasing pain during cystoscopy

Volume of local anesthetic. The value of adequate volume during rigid cystoscopy was outlined by Goldfischer and associates²⁹ and confirmed by Brekkan and coworkers³⁰ and Holmes and colleagues.³⁶ They found that a minimal volume of 20 mL is necessary to increase anesthetic efficacy.

Urethral exposure time. There are two studies, already mentioned, that deal with time exposure before rigid

cystoscopy. Stein and associates²⁸ [Ib, A] found no difference in pain reduction during rigid cystoscopy after intraurethral exposure time of 5 and 10 minutes compared with Goldfisher and colleagues²⁹ who found that an exposure time of 20 minutes is necessary for significant pain reduction [Ib, A]. Eggersmann and coworkers⁴⁷ showed, in a randomized, double-blind, placebo-controlled study that measured sensory thresholds of the male urethra, that the pain-relieving effect of lidocaine gel needs an exposure of more than 10 minutes.

Choong and colleagues,³² in a study that consisted of two consecutive parts, tried to study the importance of the exposure time of lidocaine gel in pain reduction during flexible cystoscopy. In the first part of the study, 90 men were assigned to four groups who received 20 mL of 2% lidocaine gel or plain aqueous gel over a 5- or 25-minute exposure time. This showed a significant difference in pain reduction for patients who received 2% lidocaine gel over an exposure time of 25 minutes. Sixty men entered the second part of the study, to compare pain perception between exposure times of 15 and 25 minutes; no difference was detected between these exposure times. The authors concluded that intraurethral delivery of 20 mL of 2% lidocaine gel over an exposure time of 15 minutes is preferred.

Combination treatment. Demir and associates⁴⁸ assessed the efficacy of intraurethral lidocaine (group 1) *vs* the combination of DMSO with lidocaine (group 2) in male patients undergoing rigid cystoscopy. Exposure urethral time was 15 minutes and 5 minutes in group 1 and group 2, respectively. Immediately after cystoscopic examination, pain was scored on a VAS. They found that dimethyl sulfoxide with lidocaine caused significantly less delivery discomfort and less pain perception in a shorter exposure time.

Fields for Future Research

Various new minimally invasive techniques, including thermal-based therapies, bipolar resection, laser therapy, and other new modality treatments, have been developed for the management of lower urinary tract symptoms caused by benign prostatic obstruction. The wide acceptance and application of the new high-energy techniques may generate the need

for new specialized products for the protection of the urethra. Recently, Faul and coworkers⁴⁹ reported the importance of intraurethral gel quality and conductivity as a preventive factor with regard to urethral thermal injury and stenosis during bipolar transurethral resection.

Indications for Proper Use

Available data suggest that anesthetic lubricants are needed during catheterization in men and children older than 4 years. Plain lubricants are sufficient during catheterization in women and in flexible cystoscopy in men. A slow instillation rate of more than 20 mL of cooled anesthetic gel, with an exposure time of 10 to 20 minutes decreases initial pain perception and increases patient tolerance during rigid cystoscopy (Table 1).

Although there are no data, it is common sense that in patients who are under anesthesia, the use of anesthetic lubricants is not justified. The use of the less-expensive plain lubricants may contribute to the overall safety and cost reduction. The use of disinfectant lubricants may be useful in reducing infections after urethral manipulation; however, chlorhexidine appears to significantly increase the levels of pain and urgency.

Conclusions

While the available evidence for best practice in terms of treatment is continuously evolving, the important issues regarding the correct use of intraurethral gels are, for the most part, left to individual preference. Data indicate that for catheterization in women and for flexible cystoscopy in men, the need of an anesthetic-lubricant gel is questionable. Appropriate use, in terms of instillation rate, amount, and dwell intraurethral time, may be helpful during rigid cystoscopy in men. In the modern era of minimally invasive treatments of lower urinary tract symptoms, however, further studies that address specific issues are needed.

Disclosure Statement

No competing financial interests exist.

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TABLE 1. INDICATIONS FOR THE PROPER USE OF INTRAURETHRAL ANESTHETIC GEL

Procedure			Intraurethral anesthesia	LVE
Cystoscopy	Rigid	Male	+ ^a	Ib: A
		Female	Inc	—
	Flexible	Male	—	Ia: A
		Female	b	—
Catheterization	Pediatric ^c		+	Ib: A
	Male		+	Ib: A
	Female		—	Ib: A

^aInstillation rate ≥ 10 sec, volume ≥ 20 mL, temperature of 4°C, exposure time of 10 to 20 minutes.

^bNo data.

^cChildren older than 4 years.

LVE = level of evidence; Inc = inconclusive.

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Abbreviations Used

CNS = central nervous system

RCT = randomized controlled trial

VAS = visual analog scale