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Local Anesthetic for Urinary Catheter Insertion: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Abbreviations

AMSTAR	a measurement tool to assess systematic reviews
CRBD	catheter related bladder discomfort
CRD	centre for reviews and dissemination
EMG	electromyography
MCC	maximum cystometric capacity
MeSH	medical subject headings
PICO	population intervention comparison outcomes
PRISMA	preferred reporting items for systematic reviews and meta analyses
PROSPERO	International prospective register of systematic reviews;
PVR	post-void residual
RCT	randomized controlled trial
SR	systematic review
UTI	urinary tract infection
UDS	urodynamic study
VAS	visual analog sale
VE	voiding efficiency

Context and Policy Issues

Urethral catheterization is a common procedure used in the management and diagnosis of bladder dysfunction.[1] A flexible plastic tube is inserted through the urethra to the bladder, which allows urine to drain freely or allows fluid to be added. Catheter material, duration of placement, diameter, or length can vary depending on the patient and medical purpose. Indwelling catheters remain in place for days to months after placement, and are commonly inserted by medical professionals.[1] Intermittent (in-and-out) catheters are removed shortly after insertion and bladder clearing. They can be inserted multiple times each day in a non-medical setting by patients or caregivers, as well as medical professionals.[2] A catheter may be used in a variety of contexts including patients recovering from surgery, or those with acute injuries or chronic illnesses that impair normal bladder function.[1]

Catheterization is associated with pain and discomfort.[2-4] Specific information on the incidence of catheterization and related pain in Canada is limited. A report from England detected a catheterization prevalence of 0.141-0.146% in the community,[5]which would represent approximately 50,000 individuals in Canada. This represents individuals with long-term indwelling catheters, and does not take into account individuals with catheters for short-term procedures. Another international study found catheter related bladder discomfort (CRBD) was experienced in 47% of patients who had catheters inserted during surgical recovery.[6] Although some individuals do not experience significant pain associated with catheterization, and others note that the level of pain is typically low (e.g., below 30 mm on a visual analog scale [VAS] where 0 represents “no pain” and 100 represents “most possible pain”),[7,8] it is important to know the best way to manage catheterization pain for those who experience it.

When catheters are inserted, aqueous lubricants can be used to reduce the risk of pain and discomfort, urethral damage, and procedure-related infection according to national evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England.[9] A lubricating gel containing local anesthetic, such as lidocaine, may provide additional pain reduction.[4,10] There are several commercial products available, with concentrations of lidocaine ranging from 2 to 5% and the required time interval between instillation and catheterization (incubation times) varying from 5 to 25 minutes.[11] In patients

with an in-tact urethra, lidocaine hydrochloride gel is generally considered safe for use with few associated adverse effects.[1,12] Manufacturers of several commercial brands warn that individuals with urethral lesions or injury are at risk for potential severe adverse effects due to systemic exposure.[1,2]

Although it is common practice in some jurisdictions to use local anesthesia to relieve pain during urinary catheterization, there has been a limited quantity of mixed evidence regarding the extent to which it reduces pain.[1,4] This inconsistency in findings might reflect inconsistency in the way it is used, including varying dosages, urinary instillation versus application to the catheter, and insufficient wait-time for the drug to take effect.[4] To address the inconsistency in previous studies, more information is required to determine the extent to which local anesthesia improves outcomes for urinary catheterization. The purpose of this report is to summarize the information available about the clinical effectiveness, cost-effectiveness, and guidelines for the use of local anesthesia during urinary catheterization in adults.

Research Questions

1. What is the clinical effectiveness of local anesthetic in adults undergoing urinary catheter insertion?
2. What is the cost-effectiveness of local anesthetic in adults undergoing urinary catheter insertion?
3. What are the evidence-based guidelines informing the use of local anesthetic in adults undergoing urinary catheter insertion?

Key Findings

This report reviewed the evidence from one systematic review with meta-analysis containing one relevant study, and six randomized controlled trials, to assess the clinical effectiveness of local anesthetic in adults undergoing urinary catheterization. Overall, there was evidence from four studies that compared to patients who received placebo, patients who received anesthetic (lidocaine) had significantly lower pain levels, or no difference in pain levels, both during and following catheter insertion. Two studies found that measures of urodynamic function were significantly different among those who received lidocaine compared to those received placebo, but results were inconsistent between the studies in terms of which metrics were different. The relevant study in the systematic review and one of the randomized controlled trials showed that pain level was significantly reduced when topical analgesics such as prilocaine or ketamine were added to lidocaine gel, compared to lidocaine gel only. One study in males found that those who received liquid paraffin lubricant had significantly less pain than those who received lidocaine gel during catheter insertion. The heterogeneity in findings may be due to differences in anesthetic doses; catheter type and size; gel application method; time intervals between instillation, catheterization, and outcome measures; reason for and duration of catheterization; population characteristics including sex and age; types of outcomes recorded; and comparison to placebo, alternative lubricant, or analgesic-augmented lidocaine gel. No economic evaluations or evidence-based guidelines were identified assessing the use of local anesthetic in urinary catheterization.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Ovid Medline, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were local anesthesia/anaesthesia and urinary catheterization. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and January 27, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults (≥ 18 years of age)
Intervention	Urinary catheter insertion performed with local anesthetic (e.g., lidocaine)
Comparator	Q1-Q2: Urinary catheter insertion performed without local anesthetic; urinary catheter insertion performed with alternative doses or types of local anesthetic Q3: No comparator required
Outcomes	Q1: Clinical effectiveness (e.g., pain, patient comfort, safety [e.g., rates of adverse events]) Q2: Cost-effectiveness Q3: Guidelines (e.g., recommendations regarding best practices and patient selection)
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, economic evaluations, non-randomized studies, guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2010. Primary studies identified in the search were excluded if they were reviewed in an included systematic review. Systematic reviews were excluded if their relevant reviewed studies were captured by another more recent or comprehensive included systematic review. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

One reviewer completed critical appraisal for all studies. The systematic review and meta-analysis was appraised using A Measurement Tool to Assess Systematic Reviews (AMSTAR) 2.[13] The included randomized controlled trials (RCT) and the non-randomized study were analyzed using the Downs and Black checklist.[14] Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 205 citations were identified in the literature search. Following screening of titles and abstracts, 182 citations were excluded and 23 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 16 publications were excluded for various reasons, and seven publications met the inclusion criteria and were included in this report. These comprised one systematic review, six RCTs, no economic evaluations, and no evidence-based guidelines. Appendix 1 presents the PRISMA[15] flowchart of the study selection.

Summary of Study Characteristics

The included SR[16] had broader inclusion criteria than the present review. Specifically, it included any form of anesthetic or analgesic intervention for the management of CRBD. One of the 29 included studies examined the effectiveness of a local anesthetic (i.e., compared lidocaine-prilocaine cream to lidocaine hydrochloride gel), and was therefore relevant to this report. Only the characteristics and results of this relevant study will be described in this report. Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

One SR with meta-analysis was included.[16] It was published in 2019, and summarized RCTs published between the inception of the searched databases and July 2018. Of the 29 RCTs identified in the SR, one was relevant to this report. In terms of primary studies, six RCTs were included.[8,17-21] No economic evaluations or evidence-based guidelines were identified.

Country of Origin

The systematic review[16] was conducted in the Republic of Korea, and the one included study that was relevant to this report was conducted in China. Three of the RCTs were conducted in the United States;[17-19] two were conducted in Israel;[21] one was conducted in Iran;[20] and the final occurred in Singapore.[8]

Patient Population

Participants in the one relevant RCT[22] in the included SR[16] were adult males at the Tianjin Union Medical Center in Tianjin (China) with American Society of Anesthesiologists physical status I-III, who were scheduled to undergo elective surgery requiring urinary catheterization.

The six RCTs included 451 participants, and study sample sizes ranged from 18 to 136. Four studies were conducted with only female participants,[8,17-19] and the other two with only males.[20,21] Four studies included patients that had catheters inserted for urodynamic analysis.[17-19,21] One study assessed patients that required catheterization during surgical recovery,[20] and another assessed patients requiring catheterization while admitted to a medical ward.[8] Five of the studies were conducted at major universities or university-affiliated hospitals in major cities.[17-21] One study was conducted in an unspecified acute care hospital in Singapore.[8]

Interventions and Comparators

The major intervention of interest was local anesthetic used for urinary catheterization. A variety of anesthetic application methods, dosages, and incubation times were used in the included studies, and were compared to aqueous and non-aqueous lubricants, or lidocaine gel augmented with an additional analgesic. The only relevant RCT reviewed in the included SR[16] compared 10 mL of 5% lidocaine gel instilled for 10 minutes before catheterization to 5 g of lidocaine-prilocaine cream (5% lidocaine and 25 mg/g prilocaine) applied to the catheter, and to the preputial sac, glans, and meatus for five minutes.[22] Four RCTs compared lidocaine hydrochloride gel to an equivalent volume of aqueous placebo lubricating gel.[8,17-19] Specifically, the lidocaine interventions in these studies were: 5 mL of 2% lidocaine hydrochloride instilled three minutes prior to catheterization,[17] two doses of 4% lidocaine hydrochloride 15 minutes apart,[18] 10 mL of 2% lidocaine instilled in the urethra for 10 minutes;[21] an unspecified volume of 2% lidocaine applied to the catheter,[19] and an unspecified dosage of 2% lidocaine, with an unspecified application method.[8] Of the RCTs that did not compare lidocaine to an aqueous lubricant, one compared 10 mL of 2% lidocaine instilled into the urethra for 10 minutes prior to insertion to 10 ml of liquid paraffin lubricant,[21] and the other compared an augmented gel (100 mg of ketamine dissolved in 2 mL of distilled water plus 5 mL of 2% lidocaine) to lidocaine alone (5 mL of 2% lidocaine with 2 mL distilled water).[20]

Outcomes

To assess the clinical effectiveness of local anesthesia during catheterization, the main outcomes of interest were measurements of bladder and urethral pain and discomfort. All of the studies used a VAS to assess pain. The most common version was a self-report scale for rating pain on a scale of 0-10 cm or 0-100 mm, where 0 indicates no pain and 10 cm (100 mm) means the most possible pain. Two of the reviewed articles specified a critically important difference of 1 cm,[21] and one study specified a critically important difference of 26 mm.[8] One study used the Wong-Baker Faces pain scale, which is a well-validated VAS that is suited to individuals who have difficulty using a number line.[19] Users indicated their level of pain by selecting a representative image from a series of facial expressions depicting increasing levels of pain. Each facial expression corresponds to a number on the classic VAS 1-10 scale. This study identified 1.5 as a critically important difference.

Three less common methods of measuring pain were also used. One study measured incidence of sedation (sleep) during postoperative recovery using the Ramsay Sedation Scale (which was used as an indirect measure of pain since pain may prevent sleep).[23] This study also measured total opioid consumption in the first 24 hours of recovery; opioid analgesic was provided as needed, and the amount administered was used as an indirect measure of pain since patients in pain would request more pain medication. A double-blind study determined the patients' expectations for pain during catheterization as well as their actual experience, and compared these between patients that received lidocaine hydrochloride gel, and those that received aqueous placebo. They also compared the physicians' impressions of the patients' level of pain between groups.[19] Another study interviewed patients undergoing urodynamic analysis about their willingness to receive the same type of catheterization lubricating gel in the future after receiving either lidocaine or liquid paraffin.[21]

Levels of CRBD were also measured in one RCT and the relevant RCT in the SR.[16,20,22] CRBD is typically assessed by an observer based on behavior and/or an interview and is

rated as none, mild, moderate, or severe. One of the RCTs used a three-point scale to measure CRBD during surgical recovery in patients that had been catheterized: 1) urge to urinate 2) urge to urinate with attempt to stand 3) urge to urinate with attempt to remove catheter.[20] The authors did not comment on the validity of this scale.

Secondary measurements of interest were urodynamic analysis outcomes, which measure bladder function and efficiency. Local anesthesia has a demonstrated effect on bladder function, which may be an important consideration for deciding whether local anesthesia is appropriate for certain patients.[17,18,24] Urodynamic testing was performed by a specialist in a medical setting according to a standardized protocol in three studies.[17,18,21] Common urodynamic outcomes of interest were voiding efficiency (VE), maximum cystometric capacity (MCC), post-void residual (PVR), and pelvic floor muscle electromyography (EMG) activity. One study where VE was a primary outcome identified a 30% reduction as a clinically significant change according to expert consultation.[18]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic Review and Meta-Analysis

Overall the SR study design was methodologically strong.[16] Major sources of bias were avoided by following PRISMA guidelines.[15,16] Major strengths of the SR included pre-registering the study with PROSPERO; using duplicate authors to search, screen, and extract data; and using a comprehensive search strategy. An important limitation was the absence of justification for only RCTs being eligible for inclusion. The authors diligently identified, analyzed, and explained the major study limitations wherever possible. Despite this, interpretation of the findings with respect to the present report was limited because only one of the included studies was relevant. This study was reviewed by two independent authors for risk of bias under the major domains of bias described in the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0.[13] The authors evaluated the study under each domain and assigned a rating of “high”, “low”, or “unclear’ risk of bias as follows: random sequence generation (low); allocation concealment (low); blinding of participants and personnel (low); blinding of outcome assessment (low); incomplete outcome data (low); selective reporting (high); other bias (high).

Randomized Studies

The six RCTs assessed in this report were all pre-registered and reported patient, intervention, comparison, and outcome (PICO) characteristics,[8,17-21] and four[8,17-19] reported distributions of principal confounders across groups, main outcome values, estimates of random variability, and probability values for all outcomes of interest. Of the other two RCTs, one provided all of these values, except for non-significant results in which specific probability values (P-values) were not reported.[21]. In the other RCT, VAS and CRBD were shown in a graph, but exact values were not reported; estimates of random variability for the opioid activity and sedation incidence outcomes were not provided; and actual probability values were not provided for VAS or CRBD outcomes.[20] A common limitation to the RCTs was their failure to report adverse events potentially resulting from the intervention, with the exception of one.[20] It was possible that adverse events did not occur because the exclusion criteria prevented individuals that were at risk for adverse events from participating in the study, and because there are few known adverse advents associated with lidocaine hydrochloride, but this should have been stated.

The external validity of all samples was limited by the setting. Facilities and staff present at the major university-affiliated medical centers where these studies primarily took place likely do not represent the facilities and staff at the typical urethral catheterization procedure outside of a major city center. Extensive exclusion criteria used in all but two studies also limited the extent to which the recruited sample represented the relevant patient population.[8,20] In one study inclusion criteria were extremely broad in order to allow for a more representative sample,[8] and in another external validity was strengthened by using a consecutive sample of patients receiving elective lumbar spine surgery requiring urinary catheterization during anesthesia. .[20] Internal validity strengths and weaknesses were variable across studies. Five studies were double blinded,[8,17-20] and one was single blinded where patients were not aware of the treatment,[21].

Randomization procedures were clearly described in all but one study,[20] and this study along with two others did not specify whether randomization was concealed until recruitment completion,[17,19] which could have reduced internal validity. Internal validity was also limited in the three groups that did not report specific time points during uroflow analysis. This is a potential limitation because lidocaine hydrochloride is relatively short-acting. Differences in the exact time point of each measurement during urodynamic testing could allow results to be affected by decreasing lidocaine waring off.

Two studies did not perform a power analysis to determine the required sample size a priori.[17,20] Two of the remaining studies did not reach the pre-determined sample size necessary to achieve power after due to drop outs after randomization.[18,19]

Summary of Findings

Additional details regarding the main outcomes and author conclusions of included publications are provided in Appendix 4.

Clinical Effectiveness of Local Anesthesia during Urinary Catheterization

Self-Reported Pain

All six of the RCTs measured pain (using a VAS) as an outcome.[8,17-21] Four RCTs conducted in females compared use of lidocaine gel to aqueous placebo as a catheterization lubricant.[8,17-19] One RCT found that the postprocedural pain level was significantly reduced in patients in medical wards that received 2% lidocaine compared to those that received placebo.[8] Another found no difference in mean pain level between lidocaine and aqueous placebo groups in healthy women undergoing urodynamic analysis, but the lidocaine group had significantly greater variability in VAS responses. The authors hypothesized that some patients may have experienced pain reduction due to lidocaine, but others still experienced pain related to the application or catheterization procedure.[18] Another study of healthy females undergoing urodynamic analysis found lidocaine produced a numerical twofold reduction in pain level compared to aqueous placebo, but this was not statistically significant.[17] This study notably did not include a power analysis, but the authors suggested the large difference might be clinically relevant even though it was not statistically significant.[17]

Two studies conducted in males compared use of 2% lidocaine gel to alternatives that were not the typical aqueous placebo.[20,21] One study found pain levels were greater in those who received 2% lidocaine gel during instillation and catheterization compared to those who received liquid paraffin lubricant, but there was no difference in VAS 5 or 30 minutes after

the procedure.[21] Another found adding 100 mg of ketamine to lidocaine gel reduced postsurgical VAS compared to lidocaine-only. [20]

Catheter-Related Bladder Discomfort

The incidence and severity of CRBD was the primary outcome for the included systematic review and meta-analysis.[16] In the systematic review, only one included study was relevant to the effect of local anesthesia on CRBD during surgical recovery. It was found that the incidence of moderate and severe CRBD was significantly lower in those who received 5% lidocaine-prilocaine compared to those who received 5% lidocaine cream at all time points within the first 60 minutes after catheterization.

In one RCT, it was found the incidence of CRBD was significantly reduced in patients who received 2% lidocaine gel containing 100 mg of ketamine compared to patients who received a standard 2% lidocaine gel.[20]

Urodynamic Analysis

Three of the RCTs reported urodynamic findings alongside pain outcomes.[17,18,21] All three found that use of lidocaine did not affect MCC or PVR compared to placebo.[17,18,21] Two of the urodynamic studies in females had conflicting findings regarding the effects of lidocaine gel on urine flow and pelvic floor EMG activity.[17,18] One found that compared to patients who received aqueous placebo, patients who received lidocaine anesthesia had significantly increased incidence of interrupted flow patterns and elevated pelvic floor EMG activity, but had no significant difference in average flow rate.[17] The other study showed the opposite; the group that received lidocaine had a significantly lower average flow rate compared to the group that received aqueous placebo, but there was no difference between groups in the incidence of intermittent flow pattern or elevated pelvic floor EMG activity.[18] These conflicting studies were conducted at the same institution, two years apart, using similar methodology, and shared three co-authors.

Other Metrics of Interest

One RCT found that patients who had 100 mg ketamine added to lidocaine gel prior to catheterization slept significantly more during recovery than those who had lidocaine-only gel.[20] The authors suggested this indicated they were not being kept awake by pain. This study also found that patients in the lidocaine-ketamine group required significantly less opioid pain management in the post-anesthesia care unit and ward during surgical recovery, compared to patients who received lidocaine-only gel. Another study that evaluated patients' and physicians' expectations and observations of pain during catheterization found patients that received lidocaine experienced a greater reduction in actual pain relative to expected pain, compared to the placebo group. [19] Similarly, the physicians rated the lidocaine group as being in less pain than the placebo group.[19] One study interviewed patients undergoing urodynamic study on their willingness to receive the same type of catheterization lubricating gel in the future after receiving either lidocaine or liquid paraffin, and found most patients were willing to receive the same lubricant in the future regardless which was used.[21]

Cost-Effectiveness

No relevant evidence regarding the cost-effectiveness of local anesthesia during urinary catheterization in adults was identified; therefore, no summary can be provided.

Guidelines

No relevant evidence-based guidelines for local anesthesia during urinary catheterization in adults were identified; therefore, no summary can be provided.

Limitations

There were major limitations to the available literature regarding the clinical effectiveness, cost-effectiveness, and guidelines for use of local anesthesia during catheterization. Notably, no relevant economic evaluations or guidelines were identified.

Regarding the clinical effectiveness of local anesthesia in adults undergoing catheter insertion, a large variety of catheter types and a variety of anesthesia doses were used across studies. In particular, the studies of urodynamic function required multiple catheterizations with different types of catheters;[17-19,21] certain types or larger gauges of catheters may produce more pain and discomfort, which could mask an effect of local anesthesia compared to placebo. Similarly, a low dose of anesthesia may not be as effective as a high dose, and may not significantly lower pain compared to placebo. The interventions, comparators, and outcomes in the studies in males and females were different, so it was not possible to determine whether findings may differ by biological sex.

The relevant RCT in the SR, and one of the RCTs reviewed here compared use of lidocaine to lidocaine combined with an additional analgesic or anesthetic.[20,22]. They did not include a placebo control group, making it difficult to interpret the findings with respect to whether the lidocaine alone had a meaningful clinical effect. Among the RCTs that compared use of lidocaine to aqueous placebo, there was heterogeneity in dosage (2% or 4% lidocaine) or method of administration (applied to the catheter or instilled in the urethra), reason for catheterization type and size of catheter (which may produce differing levels of sensitivity), outcome measurements, and intervals between dosage and measurement.[8,17-19] Two of the RCTs were in hospitalized patients requiring indwelling or intermittent catheters for treatment or recovery;[8,20] the remaining four were studies of urodynamic analysis.[17-19,21] The differing contexts limit the extent to which information from the two settings can be compared or synthesized since the reason for catheterization and the healthcare setting might impact a patient's perceptions of pain. Additionally, heterogeneity in mean age across limited comparability of results, as younger individuals have been found to experience more discomfort and pain during catheterization [25]

Lidocaine incubation times and in the interval between application and measurement time points was also heterogeneous. As noted in one of the studies, 2% lidocaine hydrochloride remains active for 30-60 minutes after application, and has a half-life of 90-120 minutes.[18] It is possible that studies that found no effect of lidocaine did not allow for long enough incubation. One study used 60 minutes from catheterization as an outcome measurement time point,[20] and others provided a 30-60 minute window of urodynamic testing,[17-19,21] or did not specify a time point.[8] If the lidocaine was administered before catheterization, and particularly if catheterization took a long time or multiple attempts, the drug effect may have been reduced at the 60-minute time point. In the studies where the measurement timeline was not specified, there was no way to know if variability in the interval between lidocaine application and pain measurement masked any important outcomes.

A common limitation for the RCTs was extensive exclusion criteria, including bladder or urinary tract related symptoms,[8,17-21] previous catheterization,[20,21] lidocaine or lubricant allergy,[8,19,21] and recent or current pregnancy.[8,17,18] While these were justified for the

purpose of the studies, it means these outcomes may not be representative of a large portion of the patient population at risk for requiring catheterization. A final important limitation inherent to all pain research was that the results were based primarily on self- or physician-reported scales (e.g., VAS or CRBD). Even for the scales that were well validated, this type of measurement may be more subject to bias than strictly quantitative measurements.

Taken together, these limitations emphasize the need for continued studies about the use of local anesthesia during urinary catheterization. Studies with the following characteristics may help to reduce uncertainty in the effectiveness of local anesthetic during urinary catheter insertion: comparison of common anesthetic dosages, incubations, and application methods; consistently reporting and adhering to relevant timelines; comparison of lidocaine-augmented drugs to both lidocaine and an aqueous placebo; and recruiting large enough sample sizes to achieve statistical power.

Conclusions and Implications for Decision or Policy Making

This report was comprised of one systematic review and meta-analysis (that contained one relevant RCT), and six RCTs regarding the clinical effectiveness of local anesthetic during urinary catheterization in adults. There was no information available regarding the cost-effectiveness of local anesthetic or guidelines regarding the use of local anesthetic in this population.

With respect to clinical effectiveness, the available studies were primarily conducted in women,[8,17-19] and in individuals undergoing urodynamic analysis.[17-19,21] Three studies were conducted in men,[20-22] and three considered patients that had catheters inserted during surgical recovery or after hospital ward admission.[8,20,22] The most common outcome was pain measured by VAS,[8,17-21] but CRBD[16,20] and urodynamic function[17,18,21] were also considered.

Overall, the findings suggested that pain was lower during and after catheterization, and urodynamic function was altered, in patients who received lidocaine compared to those who received aqueous placebo. Specifically, one study in women undergoing urodynamic analysis found when 2% lidocaine gel (compared to aqueous placebo) was applied to catheters, pain was lower during catheterization, but not after.[19] Two studies of healthy women undergoing urodynamic analysis found that urethral instillation of 2%[17] or 4%[18] lidocaine hydrochloride gel did not alter pain levels, but impaired urodynamic function, compared to aqueous placebo. Of these studies, one did not measure pain during catheterization, but found there was no difference in pain level after catheterization.[18] The other found a potentially clinically meaningful reduction in pain during and after catheterization when lidocaine gel was used compared to aqueous placebo, but this difference was not statistically significant.[17] A final study in women requiring catheterization after being admitted to a hospital ward found that post-procedural pain was significantly lower in those who received 2% lidocaine compared to those who received aqueous gel, but the method of application was not reported.[8] Different dosages, application methods, incubation times, and outcome measurement time points were used across studies.

The relevant RCT in the SR,[16,22] as well as one additional RCT, compared lidocaine combined with an additional topical analgesic to lidocaine alone.[20,22] One study in males found that CRBD was significantly lower in those who received combined lidocaine-ketamine gel compared to those who received lidocaine alone,[20] and the other noted that

those who received lidocaine-prilocaine cream had significantly lower CRBD relative to those who received lidocaine alone during catheter insertion.[16]

One study found that men who received a liquid paraffin lubricant experienced less pain compared to those who received 2% lidocaine gel during catheter insertion.[21] More research is needed to determine whether liquid paraffin provides comparable pain management to lidocaine gel in women.

Taken together, these studies provide a limited quantity evidence of intermediate quality to suggest that use of lidocaine gel during catheterization is be associated with lower pain levels and impaired urodynamic function in comparison to aqueous placebo.[8,17-19] Pain reduction may be improved by adding a topical analgesic such as ketamine[20] or prilocaine[22] in addition to lidocaine gel, and a paraffin lubricant may provide more pain reduction than lidocaine gel[21] which may be relevant for individuals that cannot use lidocaine. Additional research with larger sample sizes, consistent application and measurement protocols including strict timelines, and including both sexes may help to reduce uncertainty.

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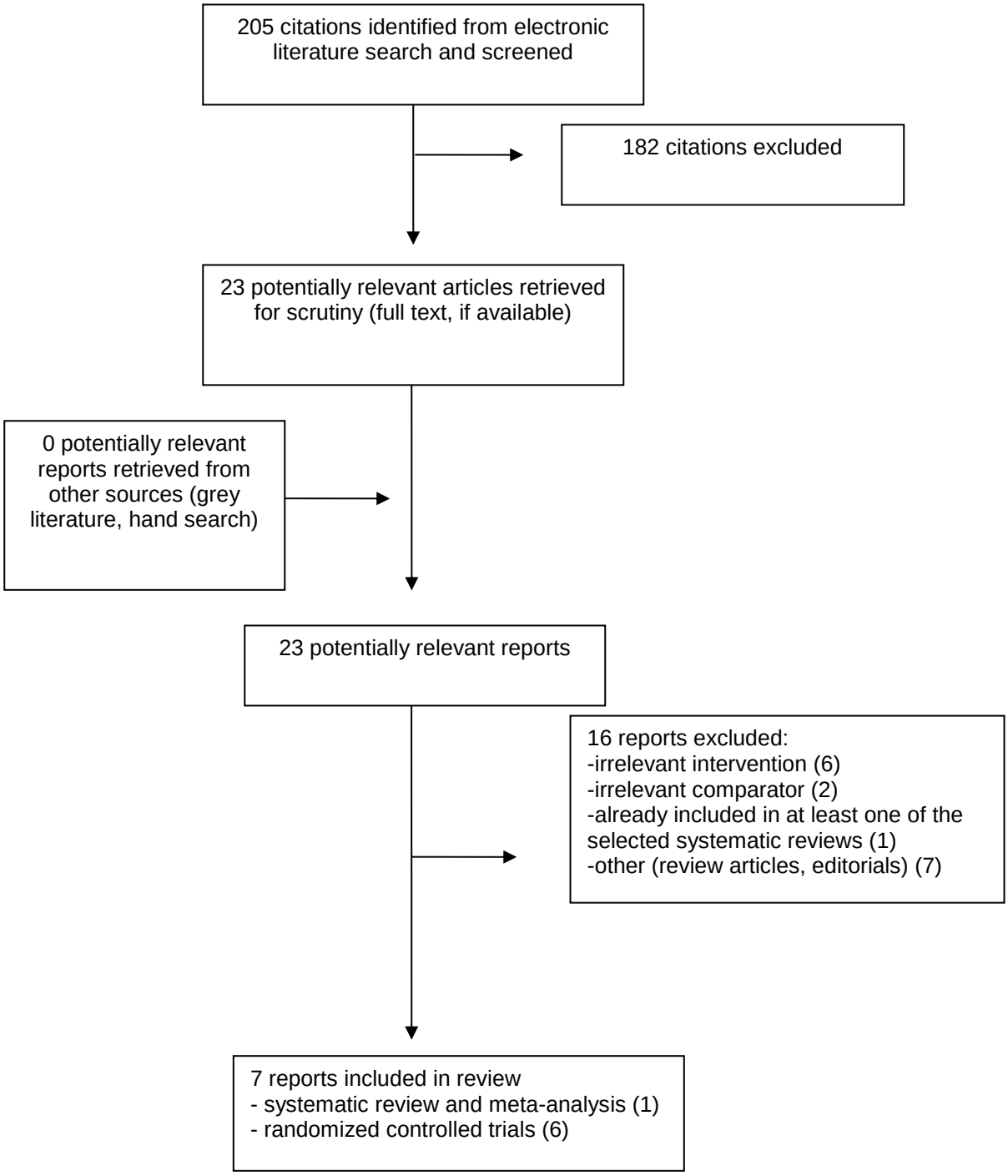
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Review and Meta-Analysis

First Author, Publication Year, Country	Study Designs and Number of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Hur et al., 2019,[16] Republic of Korea	**Objective:** Compare the efficacy of interventions to prevent and treat CRBD after urologic surgery **Study design:** Arm-based network meta-analysis of RCTs **Literature search strategy:** -Cochrane Central Register of Controlled Trials [Central, Issue 7 of 2017], Embase database, and Med-line via PubMed were searched from inception to July 2017 by two authors working independently -The same authors reviewed titles and abstracts for eligibility -Bibliographies of this and previous meta analyses were also searched -Search was updated with revisions in July 2018 -1,458 titles initially screened; 362 duplicates eliminate; 1081 fail to meet inclusion criteria; 21 of 50 remaining were excluded after full-text examination; 29 RCTs were included	-Studies included 2841 adult patients undergoing any urologic surgery with postoperative catheterization -Significant heterogeneity in sex, age, surgery type and duration, and Foley catheter size	This meta-analysis summarized studies of the following 15 pre- or perioperative drugs or interventions: amikacin, dexmedetomidine, gabapentin, glycopyrrolate, butylscopolamine, ketamine, oxybutynin, resiniferatoxin, solifenacin, darifenacin, tolterodine, tramadol, dorsal penile block, lidocaine-prilocaine cream, and pudendal nerve block. The relevant study for this report assessed the clinical effectiveness of lidocaine-prilocaine (local anesthetic) compared to lidocaine-only in urinary catheterization	**Clinical outcome**: Severity or incidence of postoperative CRBD **Follow-up**: Studies that included peri- or postoperative measurement of CRBD at 0, 1, or 6 hours after surgery were included

First Author, Publication Year, Country	Study Designs and Number of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Number of studies included: 29 studies were included; 1 examined lidocaine-prilocaine cream and was relevant to the current report **Quality assessment tool:** GRADE approach			

CRBD =catheter relate bowel discomfort; GRADE = grading of recommendations assessment development and evaluation; RCT = randomized controlled trial.

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Randomized Studies				
Kisby et al., 2019,[17]United States	**Objective:** Determine whether voiding efficiency and urodynamic parameters are decreased by intraurethral anesthesia in healthy females **Study Design:** Single center, double blind, prospective randomized placebo-controlled trial **Setting:** Duke University from October to December 2016; recruitment through electronic and print advertisements	**Inclusion Criteria:** Healthy women able to provide informed consent and agree to study risks **Exclusion Criteria:** Neurologic condition; interstitial cystitis or bladder pain syndrome; current or recurrent UTI; ≥1+ blood/dipstick urinalysis suspicious for UTI; BMI greater than 40; pregnancy; less than 6 weeks postpartum or breastfeeding; pelvic organ prolapse at or beyond hymen; consumption of alcohol within 24 hours and anticholinergic medications within one week prior to study; taking anti-	**Intervention:** Intraurethral administration of 5 mL of 2% lidocaine gel for three minutes prior to urodynamic study with in-and-out, and indwelling catheterization **Comparator:** Intraurethral administration of 5 mL of plain aqueous gel (KY Jelly; Reckitt Benckiser) for three minutes prior to urodynamic study with-in and-out and indwelling catheterization	**Clinical Outcomes:** Pain level (measured with VAS) during and after catheterization; urodynamic analysis outcomes (incidence of interruption of flow; incidence of elevated pelvic floor EMG activity; flow rate; VE; PVR; MCC) **Length of Follow-Up:** Not specified; all measurements were collected in a single 30-60 minute session, but the duration of testing and specific time point of each measurement were not reported

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		muscarinic for overactive bladder; taking psychiatric medications and others listed on the Anticholinergic Risk Scale; more than two replies of “sometimes” or more on LUTS Questionnaire **Number of Participants:** N = 23 (n = 11 in lidocaine group; n = 12 in placebo group) **Mean age, years (SD):** Lidocaine: 30 (9.6) Placebo: 33 (9.2) **Mean BMI, kg/m^2 (SD):** Lidocaine: 23 (3.7) Placebo: 25 (5.0) **Sex:** Female **Catheter:** In-and-out; dual sensor 8F		
McKee et al., 2019,[18] United States	**Objective:** Determine if intraurethral anesthesia decreased VE and catheterization pain, and impacted urodynamic parameters in healthy adult females **Study Design:** Single center, double blind, prospective, randomized, placebo-controlled trial **Setting:** Duke University from October to December 2018; recruitment through	**Inclusion Criteria:** able to agree to risks of study and give informed consent **Exclusion Criteria:** pelvic organ prolapse past the hymen; neurologic condition including stroke in the last six months; bladder pain syndrome; recurrent UTIs; BMI > 40; pregnancy at time of consent; positive urine dip and UTI symptoms; ≥+1 blood on urine dip; >2 replies of ≥ “sometimes” on the LUTS questionnaire;	**Intervention:** Intraurethral administration of 5 mL of 4% lidocaine gel; two doses, 15 minutes apart prior to urodynamic analysis requiring urinary catheterization **Comparator:** Intraurethral administration of 5 mL of plain aqueous gel (KY Jelly; Reckitt Benckiser); two doses, 15 minutes apart	**Clinical Outcomes:** Pain level (measured with VAS) during and after catheterization; urodynamic analysis outcomes (incidence of interruption of flow; incidence of elevated pelvic floor EMG activity; flow rate; VE; PVR; MCC) **Length of Follow-Up:** Maximum of 60 minutes between second drug administration and end of uroflowmetry study

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	electronic and print advertisements	abnormal baseline uroflowmetry; consumption of alcohol or caffeine within 24 hours; consumption of anticholinergic medications during week prior to the study **Number of Participants:** N = 18 (n = 8 in lidocaine group; n = 10 in placebo) **Mean age, years (SD):** Lidocaine 30 (5); placebo 32 (10) **Mean BMI, kg/m^2 (SD):** Lidocaine 24 (4.2); placebo 26 (6.9) **Sex:** Female **Catheter:** in-and-out; dual sensor 8F		
Etezadi et al., 2018,[20] Iran	**Objective:** Determine if intraurethral instillation of ketamine-lidocaine gel reduces catheter related bladder discomfort after urethral catheterization **Study Design:** Single center, double-blind, randomized controlled trial **Setting:** Department of Neurosurgery, Sina Hospital, Tehran University of Medical Sciences	**Inclusion Criteria:** Candidates for elective two-level laminectomy/ discectomy under general anesthesia **Exclusion Criteria:** patient refusal of catheterization; history of drug addiction and taking gabapentin; clinical evidence of past lower urinary system diseases requiring medical intervention; history of neurologic disorder, severe heart or liver disease, or overactive bladder; disk disease with sphincter	**Intervention:** Urethral lubrication with 5 mL of 2% lidocaine hydrochloride gel with 2 mL (100mg) of ketamine during administration of a 16 Fr Foley catheter **Comparators:** Urethral lubrication with 5 mL of 2% lidocaine hydrochloride with 2 mL distilled water	**Clinical Outcomes:** -Primary outcome was incidence of CRBD in the recovery room; recorded as: 1) feeling of urination 2) feeling of urination and try to sand up 3) agitation, strong vocal response, and attempts to pull out catheter -Postsurgical pain level (measured with VAS) -Incidence of sedation (sleep) assessed with Ramsay Sedation Scale (used as an indirect measure of pain since pain may prevent sleep)

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		problem as clinical symptom; history of urinary tract catheterization **Number of Participants:** N = 136 (n = 68 per group in the ketamine and control groups) **Mean age, years (SD):** Total 45.32 (10.6); ketamine group 44.13 (12); control group 45.3 (9.7) **Mean BMI, kg/m2 (SD):** NR **Sex:** Male **Catheter:** 16F Foley's		-Opioid consumption for first 24 hours after surgery, where 0.5 mg/kg IV pethidine was administered in the recovery room as rescue analgesia if needed **Length of Follow-Up:** -CRBD and VAS were measured upon arrival to PACU and at 1, 2, and 6 hours post-surgery -Opioid consumption was recorded for 24 hours post-surgery
Özel et al., 2017,[19] United States	**Objective:** Determine if 2% lidocaine gel reduces pain during urodynamic testing compared to an aqueous lubricant control **Study Design:** Single center, double blind, prospective, randomized, placebo-controlled trial **Setting:** The Los Angeles County + University of Southern California Urogynecology Clinic from November 2011 to April 2012	**Inclusion Criteria:** Women scheduled to undergo urodynamic testing at the study center **Exclusion Criteria:** Unable to read or write English or Spanish; contraindication to urodynamic testing; allergy to lidocaine gel or aqueous lubricant; active lower UTI or genital tract infection; unable to give informed consent **Number of Participants:** N = 88 (n = 40 in the lidocaine group; n = 48 in the placebo group) **Mean age, years (SD):** Lidocaine 52.8 (9.1)	**Intervention:** Application of 2% lidocaine gel (2% Lidocaine Hydrochloride Jelly; Akorn) to all instrumentation prior to insertion into the urethra during urodynamic investigation following a standardized protocol; instrumentation included an 8-Fr red robin catheter and dual sensor air-charged catheter in the bladder and urethra **Comparator:** Application of water-based lubricant (Surgilube; Fougera) to all instrumentation prior to insertion into the urethra during urodynamic	**Clinical Outcomes:** **-**Primary outcome was pain after placement of urodynamic catheter (assessed by the Wong-Baker Faces Pain Scale,[26] a form of VAS) -Secondary outcomes were physician observations of pain and embarrassment with urodynamic testing; patient expectation of pain and embarrassment with urodynamic testing; pain after cotton-tipped swab test; pain 30 minutes after study completion **Length of Follow-Up:** Up to 30 minutes after study completion; pain was

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Placebo 50.2 (9.4) P = 0.19 **Mean BMI, kg/m^2 (SD):** Lidocaine 31.1 (4.5) Placebo 30.1 (4.7) P = 0.33 **Sex:** Female **Catheter:** 8Fr Red Robin	investigation following a standardized protocol	assessed at baseline; after the cotton-tipped swab test; after placement of the urodynamic catheter
Stav et al., 2015,[21] Israel	**Objective:** Compare the effect of intraurethral instillation of 2% lidocaine gel to liquid paraffin on pain during catheterization in urodynamic study **Study Design:** Single center, single-blind (patients only), randomized controlled study **Setting:** May to September 2013; location not specified; authors are affiliated with Assaf Harofeh Medical Center, Zerifin	**Inclusion Criteria:** Men referred to out-patient multi-channel urodynamic study to evaluate lower urinary tract symptoms **Exclusion Criteria:** Analgesic use within 24 hours; active UTI; urethral stricture; indwelling urethral catheter; pre-existing urethral pain; lidocaine or paraffin allergy; inability to complete forms **Number of Participants:** N = 40 (n = 20 per group in the lidocaine and paraffin groups) **Mean age, years (SD):** Lidocaine: 66 (11) Paraffin: 67 (14) P = 0.95 **Mean BMI, kg/m^2 (SD):** Lidocaine: 28.4 (4.7) Paraffin: 29.2 (5.3) P = 0.34 **Sex:** Male	**Intervention:** 10 mL of 2% lidocaine gel instilled in urethra for 10 minutes **Comparator:** 10 mL of sterile liquid paraffin solution instilled in urethra for 10 minutes	**Clinical Outcomes:** Pain level (measured with VAS); self-reported willingness to use same anesthetic; urodynamic outcomes (PVR, MCC) **Length of Follow-Up:** Five time points: baseline prior to instillation; immediately post-instillation; immediately after urodynamic catheter introduction; 5- and 30 minutes after catheter removal

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Catheter: 6F and urodynamic		
Chan et al., 2014,[8] Singapore	**Objective:** Determine if 2% lignocaine gel reduces pain compared to aqueous lubricant gel in urethral catheterization **Study Design:** Single center, double-blind, randomized controlled trial **Setting:** Acute care hospital in Singapore between November 2011 and April 2012	**Inclusion Criteria:** All females over the age of 21 admitted to medical wards requiring indwelling or intermittent urethral catheterization **Exclusion Criteria:** Altered mental state; decreased visual acuity preventing VAS completion; current pregnancy; allergy to treatment or control gels **Number of Participants:** N = 52 (n = 26 per group in the 2% lignocaine and aqueous control groups) **Mean age, years (SD):** 67.2 (13.1) **Mean BMI, kg/m^2 (SD):** **Sex:** Female **Catheter:** Intermittent (n = 23) and indwelling (n = 29)	**Intervention:** 2% lignocaine gel used as lubricant to reduce pain during urethral catheterization; dosage descried as [sic] “the usual amount” **Comparator:** aqueous gel	**Clinical Outcomes:** -Mean and median pain level (measured with VAS) as indication of patient’s pain perception **Length of Follow-Up:** One preoperative and one postoperative VAS measurement was taken

BMI = body mass index; CRBD = catheter related bladder discomfort; EMG = electromyography; IQR = interquartile range; IV = intravenous; LUTS = lower urinary tract symptoms; MCC = maximum cystometric capacity; PACU = post anesthesia care unit; PVR = post-void residual; N = study sample size; n = group sample size; NR = not reported; SD = standard deviation; UTI = urinary tract infection; VAS = visual analog score; VE = voiding efficiency.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[27]

Strengths	Limitations
Hur et al., 2019 [16]	

• Research question and inclusion criteria included components of PICO
• Report explicitly stated that review methods were established prior to conducting the review
  ○ Followed PRISMA guidelines[15]
  ○ Registered with PROSPERO
  ○ Deviations from the protocol were justified
• A comprehensive literature search strategy was used
• Study selection was performed, and data were extracted, in duplicate. Consensus was achieved on included articles and data
• Excluded studies were listed and justified
• Detailed characteristics were provided for included studies including design, setting, timeframe, and PICO metrics
• Cochrane Handbook for Systematic Reviews was used to inform assessment of risk of bias for individual studies[13]
• Authors justified and appropriately weighted data for meta-analysis
• Authors confirmed absence of conflicts of interest
• Authors performed statistical tests for small study bias
	• Authors did not justify use of only RCTs
	• Literature search strategy parameters and outcomes were not stated explicitly in the report, but were tabulated in the supplement
	• Five of the 29 included studies were “low” risk of bias, the remaining included studies were “high” or “unclear” risk of bias
	• The study relevant to this report received the following risk of bias evaluation by authors:
	  ○ random sequence generation (low)
	  ○ allocation concealment (low)
	  ○ blinding of participants and personnel (low)
	  ○ blinding of outcome assessment (low)
	  ○ incomplete outcome data (low)
	  ○ selective reporting (high)
	  ○ other bias (high)
	• Individual funding sources were not mentioned in the report
	• Authors identified and investigated a large degree of heterogeneity between studies
	• Authors acknowledge that network meta-analysis results must be interpreted cautiously due to high study heterogeneity and unclear/ high risk of bias, but did not analyze possible impact of risk of bias on meta-analysis
	• Small study bias identified by statistical tests was stated, and authors acknowledged that small study size in reviewed studies limits interpretation of findings

AMSTAR = a measurement tool to assess systematic reviews; PICO = population intervention comparator outcome; PRISMA = preferred reporting items for systematic reviews and meta-analyses; PROSPERO = International prospective register of systematic reviews; RCT = randomized controlled trial.

Table 5: Strengths and Limitations of Clinical Studies using Downs and Black Checklist[14]

Strengths	Limitations
Randomized Studies	
Kisby et al., 2019[17]	

Reporting
• Objective was clearly described
• Main outcomes were clearly described in introduction or methods
• Characteristics of patients were clearly described
• Interventions of interest were clearly described
• Distributions of principal confounders were clearly described for each group
• Main findings were clearly described
• Estimates of random variability of main outcome data were provided
• Characteristics of patients lost to follow-up were described
• Actual probability values were recorded for main outcomes
Internal Validity
• Participants were blinded to intervention
• Those measuring outcomes were blinded to the intervention
• Analyses were planned a priori, and no unplanned analyses occurred
• Appropriate statistical tests were used
• Compliance with interventions was reliable
• Main outcome measures were valid and reliable
• Participants in different groups were recruited from the same population
• Participants in different groups were recruited over the same period of time
• Participants were randomized to intervention groups
• Only one patient dropped out after randomization; this likely did not have a substantial effect on outcomes
Power
• The study had sufficient power to detect a clinically important effect at alpha = 0.05
	Reporting
	• Important adverse events potentially resulting from intervention were not reported
	  ○ This might be because individuals at higher risk of experiencing adverse events were not included due to the exclusion criteria, or because there were few adverse events associated with lidocaine hydrochloride gel
	External Validity
	• Those asked to participate were not representative of entire recruitment population
	  ○ Exclusion criteria limit sample representation
	• Participants were representative of entire recruitment population
	  ○ Demographic information of excluded individuals was not reported or compared to study sample
	• Staff and setting were representative of the treatment most patients receive
	  ○ The staff and infrastructure at a specialized, university-affiliated medical clinic in a major city center may not represent the staff and medical infrastructure available during the average urethral catheterization procedure
	Internal Validity
	• The length of time between intervention and outcome was not specified; multiple measurements were performed immediately post-procedure, and group differences in the interval to each test could bias outcome
	• Authors did not specify whether randomized intervention assignment was concealed until recruitment was complete
	• Potential confounders were identified, but a statistical test to detect between-group differences was not run

McKee et al., 2019[18]	
Reporting • Objective was clearly described • Main outcomes were clearly described in introduction or methods • Characteristics of patients were clearly described • Interventions of interest were clearly described • Distributions of principal confounders were clearly described for each group • Main findings were clearly described	Reporting • Important adverse events potentially resulting from intervention were not reported External Validity • Unable to determine if those asked to participate were representative of entire recruitment population ○ Extensive exclusion criteria limited the extent to which the population in this study represented all potential candidates

Strengths	Limitations
• Estimates of random variability of main outcome data were provided • Characteristics of patients lost to follow-up were described • Actual probability values were recorded for main outcomes Internal Validity • Participants were blinded to intervention • Those measuring outcomes were blinded to the intervention • The use of "data dredging" was avoided • The time between intervention and outcome were consistent between groups • Appropriate statistical tests were used • Compliance with interventions was reliable • Main outcome measures are valid and reliable • Participants in different groups were recruited from the same population • Participants in different groups were recruited over the same period of time • Participants were randomized to intervention groups • Randomized intervention assignment was concealed until recruitment was complete • Patients lost to follow-up were taken into account in analysis	• Unable to determine if participants were representative of entire recruitment population ○ A comparison of the population asked to participate, and the recruitment population was not provided • Staff and setting were not representative of the treatment most patients receive ○ The staff and infrastructure at a specialized, university-affiliated medical clinic in a major city center were likely not representative of the staff and medical infrastructure available during the average urethral catheterization procedure Internal Validity • Analyses did not adequately adjust for confounding ○ Potential confounders were identified and reported for each group, but a statistical analysis to compare confounding variables between groups was not reported Power • The study did not have sufficient power to detect a clinically important effect at alpha = 0.05 ○ An appropriate power analysis was conducted and an attempt was made to recruit appropriate sample sizes, but due to exclusion criteria and individuals declining to participate the lidocaine group did not have large enough sample size according to their power calculation
Etezadi et al., 2018[20]	
Reporting • Objective was clearly described • Main outcomes were clearly described in introduction or methods • Characteristics of patients were clearly described • Interventions of interest were clearly described • Distributions of principal confounders were clearly described for each group • Main findings were clearly described for opioid use after surgery • Estimates of random variability of main outcome data were provided for opioid activity and sedation incidence • Characteristics of patients lost to follow-up were described • Potential adverse effects related to ketamine administration were explained, but authors did not state whether adverse events occurred or were measured • Actual probability values were recorded for main outcomes of CRBD, opioid requirement, and sedation incidence	Reporting • Exact values for VAS and CRBD findings were graphed but not reported numerically • Estimates of random variability of main outcome data were not provided for opioid activity and sedation incidence • Actual probability values were not provided for VAS External Validity • It was not possible to determine if participants represented the entire recruitment population because demographics of excluded individuals were not described • Staff and setting were not representative of the treatment most patients receive ○ The staff and infrastructure at a specialized, university-affiliated neurosurgical clinic in a major city center were likely not representative of the staff and medical infrastructure available during the typical urethral catheterization procedure Internal Validity

Strengths	Limitations
External Validity • Invited participants were representative of the entire recruitment population since a consecutive sample was taken and no exclusions were reported Internal Validity • Participants were blinded to intervention • Those measuring outcomes were blinded to the intervention • The use of "data dredging" was avoided • The length of follow up or time between intervention and outcome are consistent, or accounted for in analysis • Appropriate statistical tests were used • Compliance with interventions was reliable • VAS was a valid and reliable pain scale • Participants in different groups were recruited from the same population • Participants in different groups were recruited over the same period of time • Participants were randomized to intervention groups • No patients were lost from the original recruitment sample	• Authors stated the study was double blind, but did not explain how randomization was achieved or how long blinding lasted • Authors stated there were no differences between groups in potential confounding variables, but did not report a significance test Power • Power analysis was not provided
Özel et al., 2018 [19]	

Reporting
• Objective was clearly described
• Main outcomes were clearly described in introduction or methods
• Characteristics of patients were clearly described
• Interventions of interest were clearly described
• Distributions of principal confounders were clearly described for each group
• Main findings were clearly described
• Estimates of random variability of main outcome data were provided
• Characteristics of patients lost to follow-up have been described
• Actual probability values have been recorded for main outcomes
Internal Validity
• Participants were blinded to intervention
• Those measuring outcomes were blinded to the intervention
• The use of "data dredging" was avoided or reported
• The length of follow up or time between intervention and outcome were consistent, or accounted for in analysis
• Appropriate statistical tests were used
• Compliance with interventions was reliable
• Main outcome measures were valid and reliable
  ○ Validated Wong-Baker Faces Pain Scale [26] was used for actual pain assessment
	Reporting
	• Important adverse events potentially resulting from the intervention were not reported
	  ○ It is possible that adverse advents were limited because potential participants likely to experience an adverse event (e.g. those with UTI or allergy) were excluded
	External Validity
	• Unable to determine if those asked to participate were representative of entire recruitment population
	  ○ Extensive exclusion criteria limit the extent to which the population in this study represented all potential candidates
	• Unable to determine if participants were representative of entire recruitment population
	  ○ A comparison of the population asked to participate, and the recruitment population were not provided
	• Staff and setting were not representative of the treatment most patients receive
	  ○ The staff and infrastructure at a specialized, university-affiliated, urogynecology clinic in a major city center were likely not representative of the staff and medical infrastructure available during the average urethral catheterization procedure
	Internal Validity

Strengths	Limitations
• Participants in different groups were recruited from the same population • Participants in different groups were recruited over the same period of time • Participants were randomized to intervention groups • Analyses adequately adjusted for confounding • Patients lost to follow-up were taken into account in analysis	• Authors did not state the validity and reliability of questionnaires used to compare patients' pain and embarrassment with expectations, and physicians' assessment of pain had been previously validated • Did not report if randomized intervention assignment was concealed until recruitment was complete Power • The study did not have sufficient power to detect a clinically important effect at alpha = 0.05 ○ Appropriate power analysis were conducted and initially a sufficiently large n was enrolled, but after randomization the lidocaine group was smaller than necessary to achieve the desired power
Stav et al., 2015a [21]	
Reporting • Objective was clearly described • Main outcomes were clearly described in introduction or methods • Characteristics of patients were clearly described • Interventions of interest were clearly described • Distributions of principal confounders were clearly described for each group • Main findings were clearly described • Estimates of random variability of main outcome data were provided • No patients were lost to follow up; relevant criteria were reported for patients excluded after recruitment • Actual probability values have been recorded for significant main outcomes Internal Validity • Participants were blinded to intervention • The use of "data dredging" was avoided or reported • The length of follow up or time between intervention and outcome were consistent, or accounted for in analysis • Appropriate statistical tests were used • Compliance with interventions was reliable • Main outcome measure of VAS was valid and reliable • Participants in different groups were recruited from the same population • Participants in different groups were recruited over the same period of time • Participants were randomized to intervention groups • Groups were equivalent with respect to identified potential confounders • No patients were lost to follow up	Reporting • Important adverse events potentially resulting from intervention were not reported ○ Adverse events may have been avoided because exclusion criteria removed patients likely to have adverse evens • Actual probability values have not been recorded for main outcomes that were not significantly different External Validity • Those asked to participate were not representative of entire recruitment population ○ Single-center study; extensive exclusion criteria; and all male Participants limit extent to which sample was representative • Participants were not representative of entire recruitment population ○ Demographics of excluded participants were not reported or compared to sample recruitment population • Staff and setting were not representative of the treatment most patients receive ○ Single center does not represent broad settings for urinary catheterization Internal Validity • Those measuring outcomes were not blinded to the intervention • Main outcome measure of self-reported willingness to use same lubricant in the future was based on a non-validated scale

Strengths	Limitations
Power • The study had sufficient power to detect a clinically important effect at alpha = 0.05	
Chan et al., 2014[8]	

Reporting
• Objective was clearly described
• Main outcomes were clearly described in introduction or methods
• Characteristics of patients were clearly described
• Interventions of interest were clearly described
• Distributions of principal confounders were clearly described for each group
• Main findings were clearly described
• Estimates of random variability of main outcome data were provided
• All participants remained in the study after randomization
• Actual probability values have been recorded for main outcomes
External Validity
• Those asked to participate were somewhat representative of the entire potential recruitment population
  ○ Broad inclusion criteria increases likelihood population represents the extensive variety of indications for urinary catheterization
Internal Validity
• Participants were blinded to intervention
• Those measuring outcomes were blinded to the intervention
• The use of "data dredging" was avoided or reported
• Appropriate statistical tests were used
• Compliance with interventions was reliable
• Main outcome measures were valid and reliable
• Participants in different groups were recruited from the same population
• Participants in different groups were recruited over the same period of time
• Participants were randomized to intervention groups
• Groups were equivalent in all potential confounders reported
• All participants remained in the study after randomization
Power
• The study had sufficient power to detect a clinically important effect at alpha = 0.05
	Reporting
	• Important adverse events potentially resulting from intervention were not reported
	External Validity
	• Those asked to participate were not representative of entire recruitment population
	  ○ Sample was less representative of population due to exclusion criteria
	• Participants were not necessarily representative of the entire recruitment population
	  ○ Demographics for excluded recruits were not reported or compared to study population
	• Staff and setting were not necessarily representative of the treatment most patients receive
	  ○ Single center data likely does not represent all settings for broad inclusion criteria
	Internal Validity
	• The length of time between intervention and outcome measurement were not reported specifically, and may not be consistent
	• Authors did not specify whether randomized intervention assignment was concealed until recruitment was complete
	• Authors stated that groups were not significantly different with respect to potentially confounding characteristics, but no statistical test was reported

NS = Not significant; UTI = urinary tract infection; VAS = visual analog score.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings of Included Systematic Review and Meta-Analysis

Main Study Findings	Authors' Conclusion
Hur et al., 2019 [16]	

A systematic review and network meta-analysis of the effect of 16 drugs and interventions for postoperative CRBD at 0, 1, and 6 hours after surgery; 29 studies and 2841 patients were included
 	
Relevant primary study:
Lidocaine-prilocaine was the only local anesthetic in the 16 interventions included in the systematic review. Lidocaine-prilocaine compared to lidocaine alone was examined in one of the included studies.[22]
• A prospective, randomized, case-control STROBE study to determine whether intraurethral 5% lidocaine with 25 mg prilocaine cream reduced CRBD relative to 5% lidocaine in male patients recovering from anesthesia
• CRBD was assessed 15, 30, 45, and 60 minutes post-surgery
• Lidocaine-prilocaine decreased moderate and severe CRBD compared to lidocaine [OR]: 0.055, 95% [CI]: 0.021-0.144, P = 0.01
• Lidocaine-prilocaine reduced CRBD incidence and severity (frequency %)
  ○ None
  ▪ 15 minute
  • lidocaine-prilocaine: 86%
  • lidocaine: 30%
  • P < 0.05
  ▪ 30 minute
  • lidocaine-prilocaine: 79%
  • lidocaine: 30%
  • P < 0.05
  ▪ 45 minute
  • lidocaine-prilocaine: 93%
  • lidocaine: 55%
  • P < 0.05
  ▪ 60 minute
  • lidocaine-prilocaine: 94%
  • lidocaine: 73%
  • P < 0.05
  ○ Mild
  ▪ 15 minute
  • lidocaine-prilocaine 11%
  • lidocaine 34%
  • P < 0.05
  ▪ 30 minute
  • lidocaine-prilocaine: 13%
  • lidocaine: 38%
  • P < 0.05
  ▪ 45 minute
  • lidocaine-prilocaine: 7%
  • lidocaine: 31%
  • P < 0.05
  ▪ 60 minute
  • lidocaine-prilocaine: 6%
  • lidocaine: 15%
  • P < 0.05
  ○ Moderate
  ▪ 15 minute
	"In conclusion, our first network meta-analysis of the interventions preventing CRBD after surgery demonstrated that gabapentin 1200 mg p.o. was ranked best in decreasing the overall incidence of CRBD and tolterodine was ranked best in decreasing the severity of CRBD during the 6 hours after surgery. However, our results were limited by the small number of study for each intervention and the heterogeneous patients with a different distribution of age, gender, and type of surgery." [16] (p. 206-207)
	
	The authors did not make specific conclusions about the use of lidocaine-prilocaine cream in comparison to lidocaine alone for postoperative CRBD management

Main Study Findings	Authors' Conclusion
• lidocaine-prilocaine 3% • lidocaine 9% • P = = NS ▪ 30 minute • lidocaine-prilocaine: 8% • lidocaine: 14% • P = NS ▪ 45 minute • lidocaine-prilocaine: 0% • lidocaine: 14% • P < 0.05 ▪ 60 minute • lidocaine-prilocaine: 9% • lidocaine: 12% • P < 0.05 ○ Severe ▪ 15 minute • lidocaine-prilocaine 0% • lidocaine 0% • P = = NS ▪ 30 minute • lidocaine-prilocaine: 0% • lidocaine: 18% • P < 0.05 ▪ 45 minute • lidocaine-prilocaine: 0% • lidocaine: 0% • P = NS ▪ 60 minute • lidocaine-prilocaine: 0% • lidocaine: 0% • P = NS • Authors concluded that lidocaine-prilocaine applied to the urinary catheter was an efficient and safe intervention to reduce severity and incidence of CRBD	

CI: confidence interval; CRBD = catheter related bladder pain; OR = odds ratio; STROBE = strengthening the reporting of observational studies in epidemiology.

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Randomized Controlled Trials	
Kisby et al., 2019[17]	
A single center double blinded randomized placebo-controlled study in which 23 women were randomized to receive intraurethral instillation of either 5 mL 2% lidocaine gel, or aqueous lubricant placebo for three minutes prior to urodynamic analysis Summary of findings: • Pain (measured by VAS) was not significantly different between groups at any time point ○ VAS during catheterization, median (IQR) ▪ Lidocaine: 24 (12-41)	"In this pilot study of healthy female volunteers, intraurethral 2% lidocaine gel did not decrease voiding efficiency during uroflow. However, a greater proportion of participants who received lidocaine demonstrated elevated EMG activity and an interrupted urinary flow pattern during pressure-flow studies. […] It is notable that at all time points, the lidocaine group did have a trend toward higher VAS scores and wider interquartile ranges than the placebo group (Table 3). In addition, the lidocaine group

Main Study Findings	Authors' Conclusion
▪ Placebo: 12 (3.0-29) ▪ P = 0.35 ○ VAS at 100 mL filling, median (IQR) ▪ Lidocaine: 1.0 (0.0 – 7.0) ▪ Placebo: 0.0 (0.0 – 2.0) ▪ P = 0.35 ○ VAS at MCC, median (IQR) ▪ Lidocaine: 11 (1.0 – 18) ▪ Placebo: 5.0 (0.0 – 14) ▪ P = 0.53 • Urodynamic function was affected by lidocaine ○ Incidence of interruptions in flow; n (%) ▪ Lidocaine: 4 (36) ▪ Placebo: 0 (0) ▪ P = 0.02 ○ Incidence of elevated pelvic floor EMG activity; n (%) ▪ Lidocaine: 8 (73) ▪ Placebo: 3 (25) ▪ P = 0.02 • There were no significant between-group differences for other urodynamic outcomes of interest; P > 0.05 ○ Average flow rate, mean (SD) ▪ Lidocaine: 16.9 (3.85 mL/s) ▪ Placebo: 17.1 (7.46 l/s) ▪ P = 0.15 ○ VE, mean (IQR) ▪ Lidocaine: 89.5 (82.5-91.7) ▪ Placebo: 89.3 (85.9-93.9) ▪ P = 0.74 ○ PVR, mean (IQR) ▪ Lidocaine: 50.0 (30.0-150 mL) ▪ Placebo: 45 (26.3-58.8 mL) ▪ P = 0.35 ○ MCC, mean (SD) ▪ Lidocaine: 387 (173 mL) ▪ Placebo: 421 (178 mL) ▪ P = 0.65	experienced a twofold higher increase in pain (increase 0–24 mm vs 0–12 mm) after catheterization as compared with the placebo group."[17] (p. 268-269)
McKee et al., 2019 [18]	
A single center double blinded randomized prospective controlled trial in which 18 healthy female patients were randomized to receive two intraurethral 5 mL doses of either 4% lidocaine or aqueous placebo prior to urodynamic study involving urinary catheterization Summary of findings: • Pain (measured by VAS) were not significantly different between groups after catheterization ○ Lidocaine VAS (SD): 36.9 (26.8 mm) ○ Placebo VAS (SD): 26.7 (12.8 mm) ○ P = 0.34 ○ There was greater variability in VAS responses in the lidocaine group; P = 0.003 • Average flow rate per voided volume was significantly reduced in lidocaine group ○ Lidocaine flow rate (SD): 0.02 (0.01 s^{-1}) ○ Placebo flow rate (SD): 0.04 (0.02 s^{-1}) ○ P = 0.04	"We found that intraurethral 4% lidocaine does not decrease VE. Our work corroborates other researchers' findings that urethral sensory feedback may have a role in regulating urinary flow and output during human micturition. In addition, intraurethral 4% lidocaine does not alter VAS pain scores following catheterization. We would therefore not recommend intraurethral lidocaine prior to or during routine UDS of healthy women as it may impact the diagnostic results without reducing pain." [18] (p. 133)

Main Study Findings	Authors' Conclusion

• Other urodynamic findings were not significantly different between lidocaine and placebo groups
  ○ VE, median (IQR)
  ▪ Lidocaine: 93(91, 94 %)
  ▪ Placebo: 92(75, 95 %)
  ▪ P = 0.81
  ○ PVR, median (IQR)
  ▪ Lidocaine: 51 (32, 72.25 mL)
  ▪ Placebo: 51 (32, 72.25 mL)
  ▪ P = 0.42
  ○ MCC, mean (SD):
  ▪ Lidocaine: 359 (104 mL)
  ▪ Placebo: 411 (197 mL)
  ▪ P = 0.76
  ○ Intermittent flow pattern n (%)
  ▪ Lidocaine: 2(25)
  ▪ Placebo: 4 (44)
  ▪ P = 0.62
  ○ Elevated pelvic floor EMG activity n (%)
  ▪ Lidocaine: 1 (12.5)
  ▪ Placebo: 3 (33)
  ▪ P = 0.59	

Etezadi et al., 2018 [20]	

A single center double blinded randomized prospective controlled trial in which 136 men requiring urinary catheterization after two-level laminectomy/discectomy were randomized to receive intraurethral instillation of 5 mL of 2% lidocaine hydrochloride gel containing either 2 mL (100 mg) ketamine, or 2 mL distilled water
 	
Summary of findings:
• CRBD incidence was significantly reduced in the ketamine group at PACU entry, 1 hour, and 2 hours post-surgery compared to lidocaine-only but was not significantly different between groups at 6 hours post-surgery
  ○ P < 0.001
• Mean postsurgical VAS was lower in the ketamine group than the control group at all time points
• Sedation incidence during recovery period was 72% in ketamine group, and 11% in control
  ○ P = 0.008
• Opioid requirement in the postoperative period was lower in the ketamine group than the control group
  ○ PACU opioid requirement
  ▪ Ketamine-lidocaine group n (%): n=8 (11.7%)
  ▪ Lidocaine control group, n (%): n=37 (54.4%)
  ▪ P = 0.003
  ○ Ward opioid requirement
  ▪ Ketamine-lidocaine group n (%): n=4 (5.8%)
  ▪ lidocaine, n (%): n=14 (12.5%)
  ▪ P = 0.008
	"Intraurethral instillation of 100 mg ketamine with 5 mL lidocaine gel before bladder catheterization is an effective technique for reducing the incidence and severity of postoperative CRBD and overall patient-reported pain severity."[20] (p.1059-1060)

Main Study Findings	Authors' Conclusion
Özel et al., 2018 [19]	

A single center double blind randomized controlled trial in which 88 women were randomized to receive either 2% lidocaine gel or aqueous placebo prior to urodynamic study
 	
Summary of findings:
• Lidocaine group had a lower Wong-Baker pain score after urodynamic catheter placement compared to placebo group, mean (SD)
  ○ Lidocaine: 1.4 (1.9)
  ○ Placebo: 3.9 (3.0)
  ○ P < 0.001
• Lidocaine group had a smaller increase in pain score from baseline to immediately after urodynamic catheter placement compared to placebo group, mean (SD)
  ○ Lidocaine: 1.0 (2.1)
  ○ Placebo: 2.9 (2.8)
  ○ P < 0.001
• There was no difference between groups in pain score 30 minutes after study completion, mean (SD)
  ○ Lidocaine: 0.7 (1.2)
  ○ Placebo: 1.2 (2.0)
  ○ P = 0.19
• There was no difference between groups in change in pain score after study completion (30 minutes after urodynamic catheter placement) compared to baseline, mean (SD)
  ○ Lidocaine: 0.4 (1.4)
  ○ Placebo: 0.4 (1.8)
  ○ P = 0.86
• Lidocaine group had significantly reduced actual pain relative to expectation of pain, compared to placebo; scores were based on a five-point Likert scale where 1 is much better, and 5 is much worse than expected
  ○ Lidocaine median: 1
  ○ Placebo median: 2
  ○ P = 0.005
• Lidocaine group had significantly reduced pain score compared to placebo group according to physicians' assessment; scores were based on a 1 to 10 scale, where 1 is least pain
  ○ Lidocaine median: 2
  ○ Placebo median: 3
  ○ P = 0.008
• There was no difference between groups in actual embarrassment relative to expected embarrassment
  ○ Lidocaine median: 2
  ○ Placebo median: 2
  ○ P = 0.05
	"Our data reveal that 2% lidocaine gel, when applied to the 12-Fr single-use latex urinary catheter, […] and urodynamic catheters decreases pain during urodynamic testing, although pain levels 30 minutes after the procedure were similar in women who received the lidocaine gel versus lubricant alone. Participants in the 2% lidocaine gel group believed their level of pain to be much lower than expected, and physicians believed that women who received lidocaine gel had less pain over the water-based lubricant group." [19] (p. 1300)

Stav et al., 2015a [21]	
A single center, single blind (patients) prospective randomized controlled study to compare catheter-related pain perception with urethral instillation of a 2% lidocaine or paraffin lubricating gel for urinary catheterization during urodynamic analysis Summary of findings:	"The current study has shown that liquid paraffin causes significantly less instillation pain in the male urethra than 2% lidocaine gel. Pain scores were significantly better during the instillation of the lubricant and during the delivery of the urethral catheter. Our results suggest that intraurethral liquid paraffin is a

Main Study Findings	Authors' Conclusion

• VAS were significantly higher in lidocaine group compared to paraffin group immediately after lubricant instillation; mean (SD)
  ○ Lidocaine: 4.2 (1.5)
  ○ Paraffin: 2.6 (0.9)
  ○ P < 0.001
• VAS were significantly higher in lidocaine group compared to paraffin group immediately after catheterization; mean (SD)
  ○ Lidocaine: 4.8 (1.5)
  ○ Paraffin: 3.5 (1.1)
  ○ P < 0.01
• Pain scores did not differ between groups at 5- and 30 minutes after catheter removal
  ○ Lidocaine: 1.4 (0.7)
  ○ Paraffin: 1.5 (1)
  ○ P = NS
• Pain scores did not differ between groups at 5- and 30 minutes after catheter removal
  ○ Lidocaine: 0.6 (0.4)
  ○ Paraffin: 0.7 (0.6)
  ○ P = NS
 	
• Willingness to have the same anesthetic in the future was not significantly different between groups
  ○ Lidocaine
  ▪ Very willing: n = 11
  ▪ Fairly: n = 6
  ▪ Reluctant: n = 2
  ▪ Not at all: n = 1
  ○ Paraffin
  ▪ Very willing: n = 12
  ▪ Fairly: n = 6
  ▪ Reluctant: n = 2
  ▪ Not at all: n = 0
  ○ P = NS
• PVR, mean (SD)
  ○ Lidocaine: 46 (32 mL)
  ○ Paraffin: 62 (49 mL)
  ○ P = 0.25
• MCC, mean (SD)
  ○ Lidocaine: 444 (208 mL)
  ○ Paraffin: 446(171 mL)
  ○ P=0.97
	good option for urethral lubrication during catheterization. Further studies were needed to evaluate the efficacy of liquid paraffin in pain reduction during other common-urological procedures such as cystoscopies."[21] (p. 453)

Chan et al., 2014[8]	

A single center double blind prospective randomized controlled trial in which 52 women over the age of 21 admitted to a hospital ward were randomized to receive either 2% lignocaine gel (intervention) or aqueous gel (control) as lubricant during urethral catheterization
 	
Summary of findings:
• Postprocedural pain was reduced in patients that received 2% lignocaine gel as lubricant during urethral catheterization compared to those that received aqueous gel
  ○ Postprocedural VAS
  ▪ Lignocaine, mean (SD): 8.7 (8.3)
	"This study yielded a statistically significant result that 2% lignocaine reduced pain more than using aqueous gel for female catheterization. After reviewing these results, we recommend the use of 2% lignocaine gel in female catheterization. This study provides evidence for change in current practice in the hope of reducing procedural pain for female patients during urethral catheterization."[8] (p.144)

Main Study Findings	Authors' Conclusion
▪ Aqueous, mean (SD): 19.3 (14.2) ▪ Lignocaine, median [range]: 6.6 [0.0-32.7] ▪ Aqueous, median [range]: 18.2 [0.0-70.0] ▪ P = 0.019 • The median VAS was significantly reduced from pre- to postprocedural time points in the 2% lignocaine group, but not the aqueous group ○ 2% lignocaine group ▪ Preprocedural VAS, median [range]: 22.0 [0.0-97.5] ▪ Postprocedural VAS, median [range]: 6.6 [0.0-32.7] ▪ P < 0.001 ○ Aqueous gel group ▪ Preprocedural VAS, median [range]: 16.5 [0.0-50.0 ▪ Postprocedural VAS, median [range]: 18.2 [0.0-70.0] ▪ P = 0.716	

BMI = body mass index; CRBD = catheter related bladder discomfort; EMG = electromyography; IQR = interquartile range; IV = intravenous; LUTS = lower urinary tract symptoms; MCC = maximum cystometric capacity; PACU = post anesthesia care unit; PVR = post-void residual; N = study sample size; n = group sample size; NR = not reported; NS = not significant; SD = standard deviation; UTI = urinary tract infection; VAS = visual analog score; VE = voiding efficiency.