Reduction of Pain during Flexible Cystoscopy: A Systematic Review and Meta-Analysis

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Abbreviations and Acronyms

BCAN® = Bladder Cancer Advocacy Network

KQ = key question

PICOTS = Populations, Interventions, Comparators, Outcomes, Timing, and Study Design

VAS = visual analogue scale

Accepted for publication June 12, 2019.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

Supported in part by a Urology Care Foundation Residency Research Award, the Russell Scott, Jr., MD Urology Research Fund and PCORI (Patient-Centered Outcomes Research Institute) Contract 1089.

Supplementary references 31 to 42 for this article can be obtained at https://www.jurology.com.

No direct or indirect commercial, personal, academic, political, religious or ethical incentive is associated with publishing this article.

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Purpose: The BCAN (Bladder Cancer Advocacy Network) Patient Survey Network identified pain during intravesical procedures as a research priority for patients. Although intraurethral lidocaine is the standard of care in this setting, evidence of its use is equivocal. We systematically reviewed studies of interventions to reduce discomfort during cystoscopy and intravesical therapy of bladder cancer. We performed a meta-analysis of interventions using available randomized, controlled trials.

Materials and Methods: Search terms derived from the key questions were incorporated into the literature search constructed by a research librarian and the English medical literature from 1990 to 2017 was accessed. The initial search yielded 626 potential studies and the final review incorporated 62. We combined 12 trials into a meta-analysis with a random effects model of the efficacy of intraurethral lidocaine vs plain lubricant to reduce pain during flexible cystoscopy as measured on a 10-point visual analogue scale.

Results: Data from 12 randomized controlled trials in a total of 1,549 patients were included in the final intraurethral lidocaine meta-analysis. The standardized mean difference between visual analogue scale pain scores in patients who underwent flexible cystoscopy with intraurethral lidocaine and plain lubricant was −0.22 (95% CI −0.39−−0.05). Evidence was insufficient to evaluate other interventions to mitigate the discomfort of invasive bladder procedures.

Conclusions: Intraurethral lidocaine provides statistically significant pain reduction in men who undergo flexible cystoscopy, particularly with a longer dwell time. The evidence was insufficient for other tested interventions. A prospective study is needed to further clarify interventions to decrease patient discomfort during cystoscopy and other intravesical procedures in a diverse population.

Key Words: urinary bladder neoplasms; cystoscopy; pain, procedural; lidocaine; administration, intravesical

Cystoscopy is one of the most common invasive urological procedures undergone by patients without general anesthesia. Some patients require repeat procedures, including those with nonmuscle invasive bladder cancer requiring potentially indefinite surveillance.[1] Although

0022-5347/19/2026-1136/0
THE JOURNAL OF UROLOGY®
https://doi.org/10.1097/JU.0000000000000399
Vol. 202, 1136-1142, December 2019
Printed in U.S.A.

improvements in fiber optic technology have enabled flexible cystoscopy to largely supplant rigid cystoscopy, each procedure results in patient pain and anxiety.[2,3]

Attempts to reduce patient discomfort during cystoscopy have centered primarily on local anesthesia with intraurethral lidocaine. Although this has become commonplace, the evidence to support this practice is mixed. Two large meta-analyses have offered conflicting results regarding the benefit of intraurethral lidocaine,[4,5] leading others to perform additional randomized controlled trials in search of a definitive answer.[6–9] In the face of this uncertainty patients continue to demand evidence-based interventions to make urological care more comfortable.

The BCAN® Patient Survey Network recently identified pain reduction during cystoscopy as well as pain due to intravesical procedures for bladder cancer as research priorities for patients.[10] In response we systematically reviewed studies to evaluate interventions to reduce pain in partnership with a technical expert panel of bladder cancer specialists. We performed a meta-analysis of interventions in available randomized, controlled trials.

METHODS

Review Scope

This evidence synthesis focused on interventions that reduce discomfort from cystoscopy for all indications as well as intravesical interventions to treat bladder cancer. We developed preliminary KQs for this topic as well as eligibility criteria for the PICOTS framework for included studies. We refined the key questions and the PICOTS based on input from 6 key urology informants recruited from the BCAN Patient-Centered Outcomes and Policy Working Group. After a teleconference discussion of the draft KQs a survey was distributed to the key informants to ask about the PICOTS related to each KQ. Important changes to the KQ from this initial survey included examining interventions to reduce discomfort from cystoscopy and intravesical interventions for nonbladder cancer indications such as hematuria and recurrent urinary tract infections as well as the selection of pain as the most important outcome. A second survey confirmed that all 6 informants believed that the revised KQs comprehensively characterized the overarching topic and informed the study PICOTS. Supplementary Appendix 1 (https://www.jurology.com) shows the final revised KQs informing our search strategy.

Study Selection

One of us (ALB), a research librarian, performed a formal search of the major medical citation databases, including PubMed®, Embase® and PsycINFO. The search was limited to English language abstracts published between January 1990 and December 2017. Search terms included cystoscopy, intravesical, pain, anxiety and discomfort.

Two of us (DR and BB) performed a dual review of all identified abstracts. From this cohort articles were selected for full text review if they described the results of randomized, controlled trials pertaining to the KQs identified by the Technical Expert Panel using a predetermined grading scale (supplementary Appendixes 2 and 3, https://www.jurology.com). In case of reviewer disagreement a third reviewer (JLG) examined the abstract or the complete manuscript. Meta-analysis was limited to randomized controlled trials in men who underwent flexible cystoscopy with 2% intraurethral lidocaine jelly or a similar product with slight variations resulting from differences among analogous commercially available products. Studies of female patients were excluded from the meta-analysis since they were limited in number and not thought to be directly comparable to studies of men due to differences in urethral anatomy.

Meta-Analysis

Meta-analysis was performed to evaluate the efficacy of intraurethral lidocaine. For the purpose of the meta-analysis the study treatment arms consisted of patients who underwent cystoscopy following the administration of intraurethral lidocaine of various quantities and dwell times. Patients treated with plain lubricating gel served as controls. In a small subset of studies no such control arm was available as these trials were primarily designed to investigate the effect of different dwell times of intraurethral lidocaine. For the purpose of the meta-analysis the cohorts of patients in these studies who underwent immediate cystoscopy after intraurethral lidocaine administration were grouped with the controls who received plain lubricant. This was done based on the biological implausibility of intraurethral lidocaine having an instantaneous effect according to a rigorous study demonstrating a peak plasma lidocaine concentration only 15 to 60 minutes after intraurethral instillation.[11] One trial did not report dwell time.[7] For the purpose of the analysis examining the effect of dwell time patients in this study were classified as having an exposure of 0 to 10 minutes due to reasoning that an unusually long dwell time would likely have been explicitly described.

The study primary outcome was pain measured on a VAS of 0 to 10 with higher scores signifying greater pain. The results of studies which reported VAS scores of 0 to 100 were adjusted by a factor of 10 to facilitate comparison.

Pooled adjusted estimates of differences in the means and 95% CIs in the treatment arms were estimated by random effects models using the DerSimonian-Laird method and visualized in forest plots[12] organized by dwell time. Random effect modeling was selected a priori to adjust for the heterogeneity of patient populations and exposure techniques. Statistical heterogeneity was measured with the random effects variance ($\tau 2$) and the I^2 statistic.[13] To account for potential differences in effect by dwell time we performed stratified analyses using treatment cut points of 0 to 10 and greater than 10 to 25

minutes. Analyses were done in Stata®, version 14.1 using the plug-in metan (University of Oxford, Oxford, United Kingdom).

RESULTS

We identified 626 potentially relevant studies, which underwent dual abstract review. Of the studies 62 underwent a full manuscript review (fig. 1). They included 12 trials which were combined for meta-analysis to evaluate the efficacy of intraurethral lidocaine vs plain lubricant to reduce pain during flexible cystoscopy (see table).

The 12 trials included 1,549 patients. Nine randomized trials specifically compared intraurethral lidocaine to plain lubricating gel and were included in this meta-analysis. Six of these studies indicated no difference[7,14–18] and 3 favored lidocaine.[6,19,20] Three additional studies designed to assess the effect of differences in intraurethral dwell time demonstrated no benefit to a longer intraurethral lidocaine dwell time.[8,9,21]

When combining these studies in the meta-analysis, the standardized mean difference between mean VAS pain scores in patients who underwent flexible cystoscopy with intraurethral lidocaine vs plain lubricant was −0.22 (95% CI −0.39−−0.05). In studies with a dwell time of 0 to 10 minutes there were consistent study findings ($I^2=9.2\%$, $p=0.36$) and a favorable difference was retained in the mean VAS score of the treatment group (fig. 2). While a more substantial benefit was seen for longer intraurethral lidocaine dwell times, the heterogeneity among study findings was significant, resulting in a wide CI of the combined difference in the means (−0.4, 95% CI −0.87−0.06).

Other studies examined variables of lidocaine administration which may also have a role in patient discomfort (supplementary table, https://www.jurology.com). Because they were heterogenous, they were insufficient to perform a meta-analysis. Khan et al studied 100 patients who underwent instillation of 11 ml intraurethral lidocaine for 2 or 10 seconds and found that slower administration resulted in less pain.[22] Three studies examined the use of different lidocaine gel volumes,[16,20,23] of which 2 demonstrated less pain with an instillation volume of 20 ml.[20,23] Other studies examined the temperature of instilled intraurethral gel with equivocal or conflicting results.[24,25]

The impact of watching cystoscopy was examined in several additional studies. In 3 trials it was suggested that patients who watched the cystoscopy on video experienced less pain[26–28] while another 3 showed no benefit.[29,30,31] Male patients may have experienced a greater benefit than female patients, although there was a risk of bias in these studies. Four trials demonstrated that listening to music during cystoscopy reduced pain.[32–35]

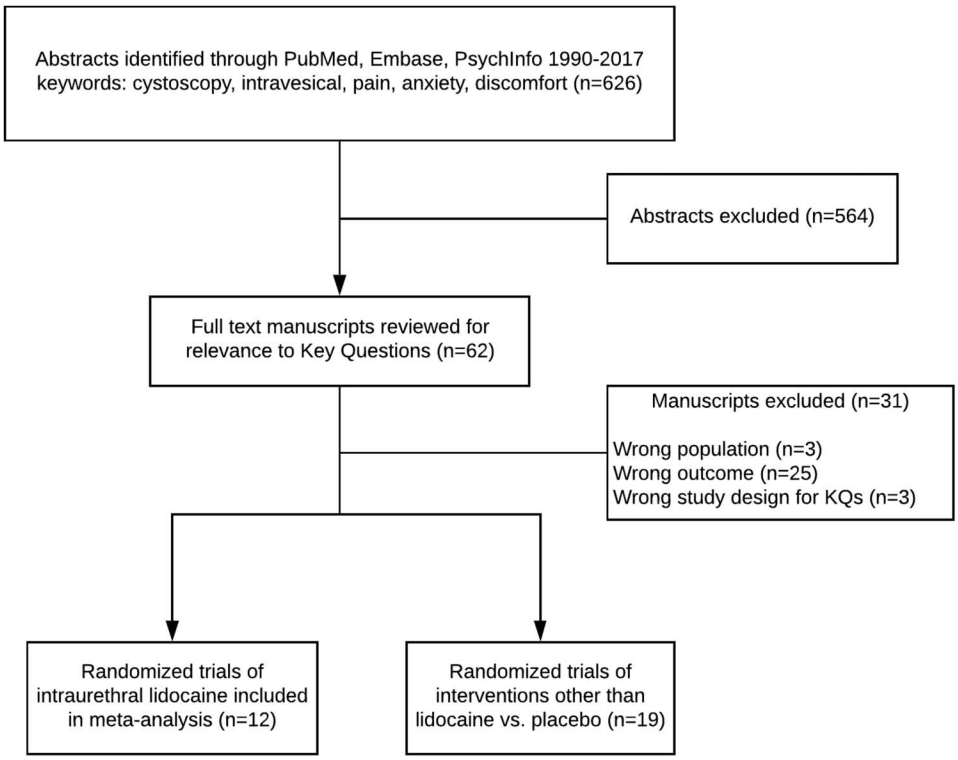

Figure 1. Literature flow

Meta-analysis of effect of intraurethral lidocaine vs plain lubricant on pain during flexible cystoscopy in 1,549 men

References (study group)	No. Pts	Vol (cc)	Dwell Time (mins)	Mean VAS Score ± SD	Result
Birch et al:[14]					No difference
Plain lubricant	63	10	15	1.4 ± 2.0	
Lidocaine	75	10	15	1.2 ± 2.1	
Borch et al:[6]					Favors lidocaine
Plain lubricant	24	10	15	3.4 ± 1.4	
Lidocaine	26	10	15	2.0 ± 1.1	
Chen et al[15]					No difference
Plain lubricant	46	20	15	2.5 ± 1.1	
Lidocaine	45	20	15	2.8 ± 1.1	
Chitale et al[7]			Not reported		Noninferior
Plain lubricant	51	11		2.2 ± 2.6	
Lidocaine	51	11		2.0 ± 1.9	
Choong et al:[19]					Favors lidocaine, more than 25 mins
Plain lubricant, immediate cystoscopy	20	20	5	3.7 ± 2.8	
Lidocaine, immediate cystoscopy	23	20	5	3.3 ± 2.0	
Plain lubricant, delayed cystoscopy	21	20	25	4.6 ± 2.7	
Lidocaine, delayed cystoscopy	26	20	25	1.8 ± 1.4	
Herr and Schneider:[21]					No difference
Lidocaine, immediate cystoscopy	145	10	0	1.8 ± 1.1	
Lidocaine, delayed cystoscopy	143	10	10	1.7 ± 1.1	
Holmes et al:[20]					Favors 20 cc lidocaine
Plain lubricant, 10 cc	38	10	10	2.5 ± 1.6	
Lidocaine, 10 cc	32	10	10	2.7 ± 2.1	
Plain lubricant, 20 cc	36	20	10	3.1 ± 1.9	
Lidocaine, 20 cc	41	20	10	1.8 ± 1.9	
Losco et al:[8]					No difference
Lidocaine, immediate cystoscopy	25	20	0	1.1 ± 1.1	
Lidocaine, delayed cystoscopy	25	20	3	1.2 ± 1.1	
McFarlane et al:[16]					No difference
Plain lubricant, 10 vs 20 cc	20	20	15	4.1 ± 1.8	
Lidocaine, 10 vs 20 cc	19	20	15	3.2 ± 1.7	
Palit et al:[17]					No difference
Plain lubricant	70	11	0	2.8 ± 2.2	
Lidocaine	70	11	15	3.0 ± 2.3	
Panach-Navarrete and Martínez-Jabaloyas:[9]					No difference
Lidocaine, immediate cystoscopy	110	12	0	2.4 ± 2.3	
Lidocaine, delayed cystoscopy	132	12	5	2.0 ± 2.0	
Rodríguez-Rubio et al:[18]					No difference
Plain lubricant	86	10	5	2.1 ± 1.5	
Lidocaine	86	15	5	2.0 ± 1.2	

Other interventions which were evaluated included virtual reality based distraction, which showed no benefit in 1 study,[36] and bag squeeze. The latter is the practice of briefly increasing hydrostatic pressure in the irrigation fluid as the cystoscope traverses the urethral sphincter, which was associated with decreased pain during cystoscopy in 2 studies.[37,38]

We found no suitable studies with which to evaluate the remaining KQs, including randomized trials of techniques to decrease discomfort during intravesical treatment of bladder cancer (eg intravesical immunotherapy or chemotherapy) or the efficacy of complementary and/or alternative medical interventions in patients undergoing intravesical treatments or procedures.

DISCUSSION

To our knowledge this is the first systematic review addressing a series of questions identified by patients with bladder cancer. While multiple interventions have been studied to decrease discomfort, only studies on the intraurethral administration of lidocaine prior to cystoscopy provided sufficient data for meta-analysis (supplementary table, https://www.jurology.com, and see table).[6-9,14-21] We found that watching the cystoscopy on a screen, listening to music or a bag squeeze may decrease discomfort but the evidence was insufficient to support these interventions in routine practice. In our meta-analyses intraurethral lidocaine administration was associated with a −0.22 (95% CI −0.39, −0.05) standardized mean difference in the VAS pain score, which was statistically significant.

Flexible cystoscopy is a common clinic procedure associated with substantial discomfort and anxiety.[4,5,39] Most studies of how to reduce this discomfort have focused on the role of intraurethral lidocaine. Two meta-analyses of 817[4] and 411[5] patients reached conflicting results with one demonstrating a benefit from intraurethral lidocaine but the other showing no difference. In response to

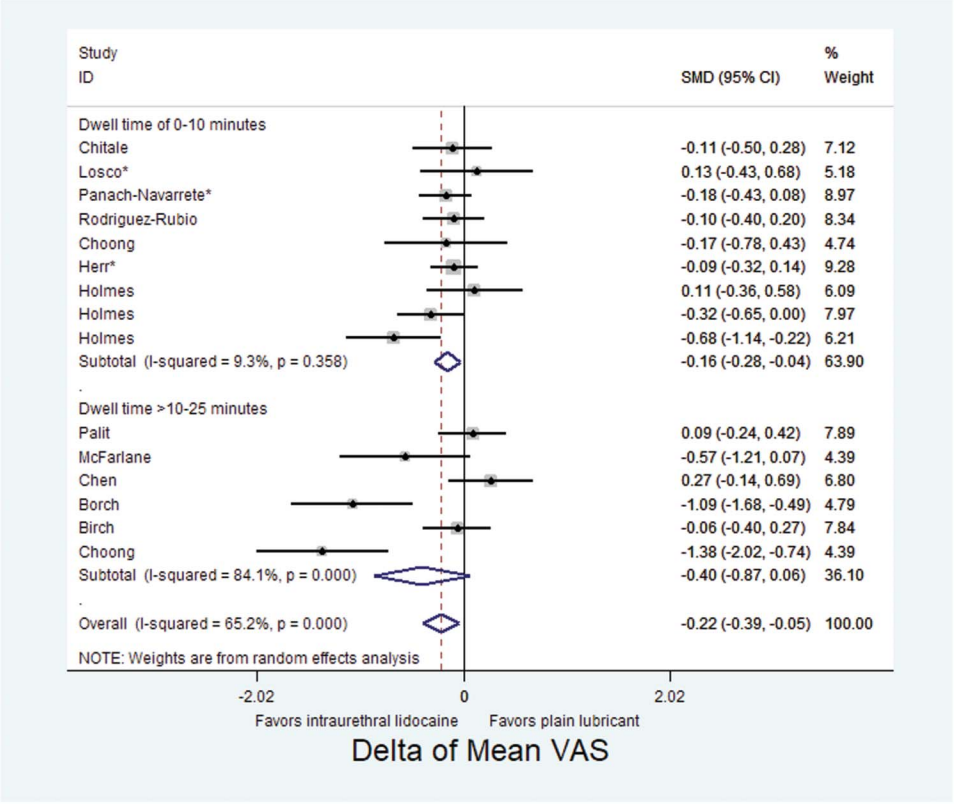

Figure 2. Meta-analysis of effect of intraurethral lidocaine vs plain lubricant on pain during male flexible cystoscopy. Asterisk indicates studies in which control groups included lidocaine with immediate cystoscopy rather than plain gel.

demand from the community of patients with bladder cancer we systematically reviewed the literature of patient discomfort during intravesical procedures. Meta-analysis of randomized trials with a total of 1,549 patients demonstrated a statistically significant benefit to intraurethral lidocaine compared to plain lubricant with respect to pain during cystoscopy.

The concept of local anesthesia for cystoscopy is not new. An 1884 report found that intraurethral cocaine had "charming results," although this approach failed to stand the test of time.[40] More recently, multiple randomized trials have been done to compare intraurethral lidocaine to plain lubricant. These studies have been limited due to the lack of standardization among cystoscopy protocols across centers. As a result studies have varied with respect to the volume of lidocaine gel used and the duration of intraurethral dwell time, among other variables.

Although many presume that intraurethral lidocaine has a benefit, this assumption is not without cost. Lidocaine jelly is substantially more expensive than plain lubricant with reported estimates ranging from a twofold to a 200-fold greater expense.[6,14,15,21] This is ultimately a cost which patients and the greater health care system absorb. If intraurethral lidocaine is effective, it may represent high value spending.

Intraurethral dwell time is also an important consideration. If prolonged dwell time is necessary for lidocaine to have an effect, patients must experience longer appointments with prolonged periods of anticipatory anxiety before cystoscopy begins.[8] Urologists must consider the opportunity cost of clinic space and time.

The finding that the speed of intraurethral lidocaine administration is associated with pain is supported by our anecdotal experience. The volume of lubricant gel used is also likely to be important. To establish a measure of urethral volume Dawkins et al filled the urethra of 50 men with lubricant gel until it was seen to pass through the bladder neck on transabdominal ultrasound.[41] This study demonstrated a mean urethral volume of 16 cc (range 12 to 20) in men, suggesting that the difference between the commercially available 10 and 20 ml vials of lidocaine based lubricant may be clinically meaningful.[41]

Aside from intraurethral anesthesia, several adjuncts to cystoscopy are supported by varying degrees of evidence. Differences in methodology preclude a meta-analysis of watching cystoscopy on video[26–30,31] and listening to music, although they

appear to be associated with decreased pain.[32–35] Other interventions with less evidence offer promising avenues for future research, including virtual reality based distraction, which has been associated with reducing pain and anxiety during nonurological office based procedures, and increasing hydrostatic pressure with cystoscope insertion.[37,38]

Our study adds to the literature by demonstrating a statistically significant benefit to intraurethral lidocaine before flexible cystoscopy, particularly after dwell times of greater than 10 minutes. By synthesizing data from 12 trials in a total of 1,549 patients during 20 years this study provides greater power to discriminate the benefit of intraurethral lidocaine than prior meta-analyses did, which were also limited by inconsistent results. This study aligns a research question with patient priorities for improving bladder cancer care. Our results are also broadly generalizable, given the ubiquity of clinic cystoscopy across urology practices.

Many study limitations are inherent to the literature on which it is based. 1) The meta-analysis of intraurethral lidocaine includes only studies of men because of the paucity of analogous literature in female subjects. Although the authors of most primary studies indicated that there are differences in female urethral anatomy which limited comparison with men, we cannot state that the identified benefit applies to women who undergo cystoscopy. Future studies should ensure adequate power to make conclusions about interventions which reduce cystoscopy discomfort in men and women.

2) The ethnic and racial composition of study populations has almost never been described. In the absence of knowing to what degree underrepresented minorities have participated in these studies, the generalizability of our result is limited even further.

3) Our meta-analysis involved an assumption which we believed was clinically appropriate but may have introduced bias. Three of the 12 analyzed trials were designed to assess the effect of differences in intraurethral dwell time rather than a comparison of lidocaine with plain lubricant.[8,9,21] We made an a priori decision to include the placebo cohorts of these studies, which comprised patients who underwent immediate cystoscopy after intraurethral lidocaine administration. We did this based on the biological implausibility of an immediate effect of intraurethral lidocaine, equating it to plain lubricant.[11] If this assumption is invalid, it would have biased our results toward the null by inflating the benefit of the control plain lubricant cohort, further supporting our finding of a benefit from intraurethral lidocaine. We repeated the current meta-analysis while excluding these 3 studies and obtained nearly identical results.

4) While our study demonstrated statistical significance, it was not designed to evaluate clinical significance. Others have described a decrease of 1.3/10 as potentially meaningful in VAS scores.[42] Intraurethral lidocaine does not appear to provide this benefit.

Despite these limitations we present a meta-analysis demonstrating the positive effect of intraurethral lidocaine along with a systematic review of the literature created in response to research priorities described in the BCAN Patient Survey Network. A meta-analysis of 12 trials in a total of 1,549 patients during 20 years revealed a statistically significant benefit for intraurethral lidocaine compared with plain lubricant to reduce pain during cystoscopy. Important gaps in our current knowledge include an understanding of the potential benefit of other adjuncts to cystoscopy, how patient demographics impact the benefit of these interventions, how we can reduce the discomfort and anxiety associated with other intravesical procedures, such as intravesical instillations of immunotherapy for bladder cancer, and how these procedures impact other patient centered outcomes such as anxiety and compliance with care. Further prospective study is required if our goal is to arrive at a consensus protocol for clinic cystoscopy which minimizes patient discomfort.

CONCLUSIONS

Intraurethral lidocaine provides a statistically significant reduction in pain in men who undergo flexible cystoscopy, particularly with a longer dwell time. The evidence is insufficient to recommend other interventions. Further prospective study is needed to clarify methods to decrease patient discomfort during cystoscopy and intravesical interventions.

ACKNOWLEDGMENT

Judy Mayer-Connery assisted with patient comfort during cystoscopy at our institution. BCAN Patient Centered Outcomes and Policy Working Group key informants assisted with study KQ and PICOTS iterative development, including Drs. Kamal Pohar, Department of Urology, Ohio State University, Columbus, Ohio; Karim Chamie, Department of Urology, David Geffen School of Medicine at UCLA, Los Angeles, California; Matthew Nielsen, Department of Urology, University of North Carolina, Chapel Hill, North Carolina; and Scott Gilbert, Department of Urology, H. Lee Moffitt Cancer Center, Tampa, Florida.

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