Cooled (4ºC) lidocaine during office cystoscopy improves patient satisfaction and comfort: A prospective, randomized, double-blind, controlled study

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Abstract

Introduction: Office-based flexible cystoscopy is often associated with considerable discomfort in male patients. We devised this study to prospectively evaluate the efficacy of cooling intraurethral lidocaine jelly to 4ºC prior to use in office-based cystoscopy in an effort to reduce male patient discomfort.
Methods: A total of 600 male patients scheduled for office diagnostic cystoscopy were enrolled and randomized into three groups for a prospectively controlled, double-blind study. Each group received one of the three methods of intraurethral lubrication: plain room temperature lubricant (control) (CON), room temperature lidocaine (LI), or lidocaine at 4ºC (LI4ºC). Perceived pain was recorded on a Likert visual analog scale (VAS) of 1–10 where 0=no pain and 10=excruciating pain. Kruskal-Wallis test assessed the efficacy of cooling lidocaine compared to room temperature lidocaine and control. Subjective pain reporting was corroborated with instantaneous objective pulse rate recording eliminating perception bias.
Results: There was no significant difference in cystoscopy duration between all groups. Mean pain scores (mean ± standard deviation) were 4.05±0.91, 2.74±1.01, and 1.8±0.84, respectively, for groups CON, LI, and LI4ºC ($p=0.02$). There was a 32.34% reduction in the mean pain score of LI and a further reduction of 34.3% was achieved in LI4ºC when compared to CON. Body mass index (BMI) and prostate weight had a significant positive correlation with pain score, whereas no such correlation was found with age.

Conclusions: Cooling lidocaine to 4ºC provides additional analgesic benefit in men undergoing office cystoscopy and increases compliance.

Introduction

Cystoscopy is the most commonly performed procedure by the urologist. It is used for a variety of indications including bladder cancer surveillance, evaluation of hematuria, evaluation of lower urinary tract symptoms and recurrent urinary tract infections, etc.[1] A flexible cystoscope enables the procedure to be done in the office setting by minimizing the associated pain and discomfort in male patients. Various methods have been employed to further mitigate this perceived discomfort. These include use of intraurethral anesthetic agents, general anesthesia, pre-treatment with intramuscular narcotics, non-pharmacological replacement therapies, use of different lidocaine volumes, squeezing the irrigation liquid bag, simultaneous monitor visualization, nitrous oxide inhalation, slow delivery of local anesthetics, use of a specialized flexible cystoscope sheath, and transcutaneous electrical nerve stimulation, to name a few.[1-10] Despite all these options, office-based cystoscopy is still associated with patient discomfort and the use of intraurethral Lidocaine has been universally accepted as the most effective means to ameliorate procedure-related pain.[11]

It is well-documented that cooling of tissue leads to augmented effects of local anesthesia.[12-15] We hypothesized that cooling Lidocaine to 4ºC would enhance the local anesthetic effects and provide better compliance during office cystoscopies in male patients. The aim of this study was to evaluate the additional relief that could be obtained by cooling Lidocaine to 4ºC before cystoscopy. Our search of the existing literature did not find evidence of cooled intraurethral Lidocaine being compared prospectively in a randomized double-blind controlled fashion with any other type of anesthesia during office cystoscopy in male patients.

Methods

Study design and protocol

This was a prospective randomized double-blind controlled trial in absolute clinical equipoise.[16] Patient enrollment, randomization, and analyses are presented in a Consolidated Standards of Reporting Trials flow diagram (CONSORT) (Fig. 1).[17]

Hospital institutional review board approved (LCH-1-2020) 600 consecutive informed and consented male patients scheduled to undergo diagnostic office cystoscopy to be randomized into three groups (1:1:1 ratio), after excluding some, as per predetermined criteria. Given the large sample size, an α-level of 5% (2-sided) and a ß-level of 20% allowed our study to be sufficiently powered to detect small effects in all analyses.

Exclusion criteria

Female patients (120), patients who declined to participate (2), patients who had undergone prior cystoscopy (43), patients with chronic analgesic usage (32), patients undergoing therapeutic procedures (52), patients with known urethral stricture disease or prior urethral surgery (11), patients undergoing cystoscopy under general anesthesia (4), patients with general anxiety disorder screener score (GAD-7) ≥ 10.[7]

Randomization

Coordinator computer-generated randomization sequence allocated patients into three groups in a 1:1:1 ratio. The allocation sequence was concealed in sequentially numbered opaque sealed envelopes to prevent randomization disclosure to patients and the investigator. The three groups were as follows:

CON: Plain lubricant jelly at room temperature (24ºC) was instilled into the urethra (n=200).

LI: Viscous 2% Lidocaine at room temperature (24ºC) was instilled into the urethra (n=200).

LI4ºC: Viscous 2% Lidocaine cooled to 4ºC was instilled into the urethra (n=200).

Pre-procedure counselling

Fellows not actively involved in the study counseled and explained the trial methodology to all included patients without discussing the anticipated benefits of one allotment arm over the other, thus eliminating any response bias. Performance and verification bias were eliminated by double-blinding. A single experienced urologist performed all cystoscopies in the office. Primary endpoint of the study was a recording of self-reported pain, perceived during cystoscopy, using a standardized and validated Likert visual analog scale (VAS) graded 0 to 10 (0= painless, 10= worst pain ever).[18] (Fig 2). Along with pain quantification, we added two standardized and validated questions to be answered on the same VAS scale:

1. How satisfied were you with this procedure?
2. If medically necessary, how willing would you be to return for this procedure?

Cystoscopy procedure

A prior urine culture confirmed absence of infection in all patients. Pre-procedural single dose oral levofloxacin 500 mg was given to each patient. Patient was blinded to his group allotment. Aqueous-based iodophor-containing products such as Betadine® were used for skin disinfection. An Oximetro® fingertip pulse oximeter was attached to the left index finger to continuously monitor pulse rate during the procedure. After being positioned in the lithotomy position, patients in the CON group received 10 ml of intraurethral plain lubricating gel, those in LI group received 10 ml of intraurethral 2% Lidocaine gel at room temperature, and patients in LI4ºC

group received 10 ml of intraurethral 2% Lidocaine cooled to 4ºC, administered by a registered nurse over two minutes followed by the application of a penile clamp to prevent retrograde flow of viscous fluid and to provide standardization of the contact time with the urethral mucosa. A commonly used reliable digital stopwatch (iPhone X®) was used to keep time. A disposable curtain was then installed, and the physician donned two sets of sterile gloves to ensure his blinding to the type and temperature of the lubricant used. After five minutes and draping, flexible cystoscopy was conducted with appropriately sterilized 0º viewing intuitive Karl Storz® flexible cystoscope (model number 11272 VNU) (Karl-Storz Inc., Tuttingen, Germany), having an external diameter of 16 Fr and working length of 37 cm, utilizing 40 cm of water pressure. Procedure time was kept by the nursing assistant and was measured from insertion until extraction of the scope's tip from the external urethral meatus. Immediately after cystoscopy, another urology trained nurse who was unaware of the patient's study arm allotment assisted the patient into the supine position and recorded the change in magnitude of the pulse rate, pain score, and responses to the questions of procedural satisfaction and likelihood of tolerating repeat cystoscopy. Absence of the physician while scoring eliminated courtesy bias in favor of the physician, which could have resulted in a lower reported score.

Statistical analysis

After group allotment one patient each from CON and LI were excluded from statistical analysis as shown in Fig 1, leaving 598 patients to be statistically analyzed. ANOVA was used to compare continuous data in the three groups. Shapiro-Wilk test was conducted in order to determine normality of pain score distribution in each group. Non- parametric tests were used for statistical analysis, as Shapiro-Wilk test was significant. Kruskal-Wallis test was performed to assess if the means of pain score in each group had a statistically significant difference. Dwass-Steel-Critchlow-Fligner test was then used as a post hoc test to define which groups were different in their mean pain scores. For comparing answers to the adjunct questions on the continuous VAS scale, Kruskal-Wallis test followed by Dwass-Steel-Critchlow-Fligner pairwise comparisons was used in post hoc setting. In each group, a two-tailed Wilcoxon signed rank test was conducted to examine whether there was a significant change in the pulse rate within each group. BMI, prostate weight (as determined by radiological imaging), and age were correlated with pain scores using Spearman correlation analysis. Cohen's standard was used to evaluate the strength of the relationship. All statistical analysis was performed using jamovi.[19]

Results

Data are represented as mean ± SD. Demographic characteristics, mean age, procedure duration, and preprocedural data analyses did not differ significantly between the three groups. (Table 1). Pain levels ≥ 5 were reported in 62 patients (31.1%) in CON and none in the other two groups.

Mean pain scores (M±SD) were 4.05 ± 0.91, 2.74 ± 1.01, 1.8 ± 0.84 respectively for CON, LI, and LI4ºC. Shapiro-Wilk test demonstrated that pain scores were not distributed normally in all 3 groups based on an alpha of 0.05. CON ($W = 0.89$, $p < .001$), LI ($W = 0.88$, $p < .001$), LI4ºC ($W = 0.80$, $p < .001$). Kruskal-Wallis test showed that the mean pain scores were significantly different between the 3 groups (χ^2 (2)=300, p < .001). Post hoc pairwise comparison done by Dwass-Steel-Critchlow-Fligner revealed statistically significant difference in the inter-group mean pain scores (Table 1), (Figure 3). There was a 32.34% reduction in the mean pain score as compared to control when Lidocaine was used as anesthetic and a further reduction of 34.3% in mean pain score as compared to control when Lidocaine was cooled to 4ºC.

Two-tailed Wilcoxon signed rank test revealed a statistically significant intragroup change in the pulse rate. CON (Z = -12.23, p < .05), LI (Z = -12.17, p <0.01), and LI4ºC (Z = -12.13, p < .01). Kruskal-Wallis revealed no significant differences in the duration of cystoscopy between the 3 groups (χ^2 (2)=5.3, p= .09), with the mean duration of 3.11 minutes for CON, 2.92 minutes for LI, and 2.98 minutes for LI4ºC.

A statistically significant difference in satisfaction scores was seen between CON and LI and LI4ºC whereas no significant difference was observed between LI and LI4ºC. Similarly, although there was a statistically significant difference between CON and the other two groups regarding how willing they would be to return for the procedure if necessary, there was no significant difference between LI and LI4ºC (Table 1).

Spearman correlation analysis between BMI and pain scores in each group demonstrated a significant positive correlation in varying degrees, implying increasing pain with increasing BMI. CON ($r_s = .05$, $p = .001$), LI ($r_s = .39$, $p = .02$), LI4ºC ($r_s = .52$, $p < .001$). (Fig 4). A positive correlation in each group was also found between prostate weight and pain score, although this was not statistically significant. CON ($r_s = .05$, $p = .3$), LI ($r_s = .04$, $p = .6$), LI4ºC ($r_s = .05$, $p < .5$). (Fig 5). No significant correlation in any direction was observed between patient age and pain score in any group. CON ($r_s = -0.004$, $p = .91$), LI ($r_s = .03$, $p = .48$), LI4ºC ($r_s = .02$, $p < .74$). (Fig 6).

No patient required additional anesthetic agents or sedatives for insufficient pain relief, even after the procedure.

Justification of exclusions

Although studies of pain perception among women undergoing cystoscopy do exist, we intentionally restricted this study to men, as female urethral anatomy is not directly comparable to male. Possibility of confirmation bias and persistence of conservatism bias in patients who had undergone prior cystoscopy made them ineligible for this study. Ongoing analgesic consumption would be inappropriate for any pain assessing study. Patients who had prior urethral pathology or procedure would potentially have altered local anatomy or pain perception, and hence these

patients were excluded. Multiple studies have demonstrated anxiety leading to decreased pain tolerance and enhanced pain assessment.[20,21] GAD-7 was the standardized and validated self-reported instrument utilized in this study, wherein a score of ≥ 10 categorized patients with clinically significant anxiety and hence they were excluded.[22]

Discussion

Perceived discomfort, anxiety, and pain associated with office cystoscopy has been a deterrent for many patients to undergo this procedure. Urologists currently employ various pain management strategies, with intraurethral Lidocaine being the most common method used to circumvent this issue. We performed this double-blind study to evaluate the additional relief that could be obtained by cooling Lidocaine to 4ºC before flexible cystoscopy in male patients.

Our results support the findings of Rajiv Goyal et al.[23] Despite being marred by a very small number of participants in their study and absence of a control arm, they reported significant benefits of cooling Lidocaine for cystoscopy. Likewise, despite the low power of their study, Thompson and Thompson et al. also reported beneficial effects of cooling Lidocaine during cystoscopy.[24] Although controversy exists about the exact amount of Lidocaine to be used and its dwelling time, literature suggests 10 ml for 5 minutes is the optimal volume and duration.[25,26] We used 10 ml of Lidocaine with 5 minutes of dwell time based on these studies.

Patients in LI and LI4ºC were significantly more willing to undergo repeat cystoscopy and were more satisfied with the procedure as compared to those in CON, suggesting that Lidocaine alone, irrespective of its temperature, was sufficient in ensuring patient compliance with repeat cystoscopy. In contrast to the reported effect of age on pain scores, our study found no such correlation.[27] This discrepancy could be accounted for because many of the reported series included rigid cystoscopy in contrast to our sole use of flexible cystoscopy. On the contrary, BMI and prostate weight were found to have a significant correlation with pain scores in our study.

Limitations

More than 2/3rd of participants in our study were of one ethnicity, thereby limiting the generalizability of our results to other ethnic groups. Future studies incorporating a more ethnically heterogeneous population needs to be devised to better account for possible genetic predisposition to pain perception. The pain scale we utilized had descriptive terms as terminal anchoring points and intermittent lines demarcating different levels of the scale. It is reported that clustering of observations close to the lines and anchoring points does happen in a small percentage of reporting. A more subtle scale without such clustering needs to be devised and used for more precise data collection. Patient viewing of the procedure on a monitor was not controlled for in the study; consequently, the possibility of visual diversion leading to alleviated pain, anxiety, or discomfort cannot be eliminated.

Strengths

Strengths of this study include its prospective, randomized, double blind design as well as the use of objective pulse rate determination to corroborate subjective pain perception and thereby eliminate perception bias. The fact that a single surgeon performed all office cystoscopies also controlled for differences in procedure technique, which could influence pain perception as well.

Conclusions

The findings of this present study suggest that cooling Lidocaine to 4ºC for office cystoscopies in male patients provides a cost-effective, non-labor-intensive method of giving additional analgesia. It also increases patient compliance for future cystoscopy by significantly reducing pain perception.

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Figures and Tables

Fig. 1. CONSORT diagram of the study. CON: plain lubricant at room temperature; GAD: generalized anxiety disorder score; LI: lidocaine at room temperature; LI4ºC: Lidocaine gel cooled to 4 ºC; VAS: visual analog scale.

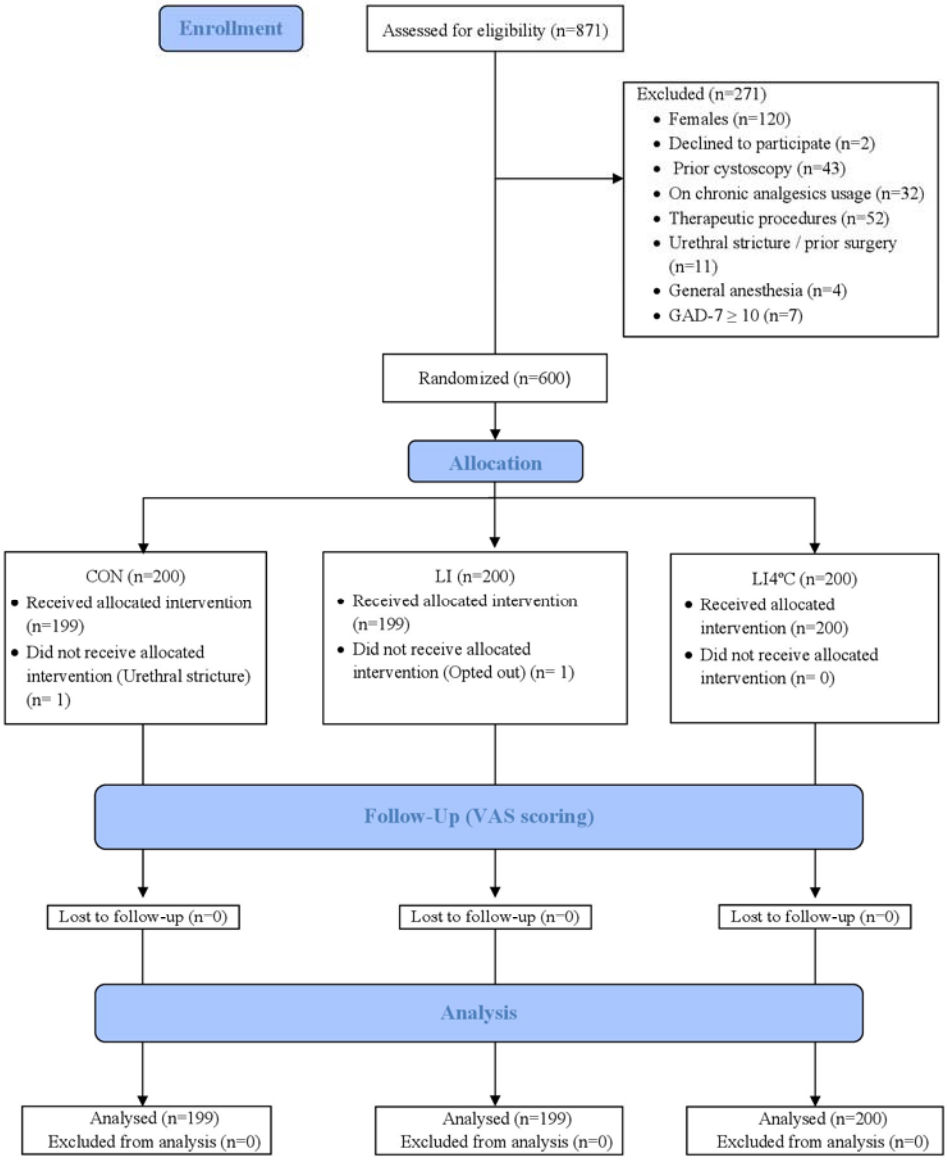

Fig. 2. The used visual analog scale.

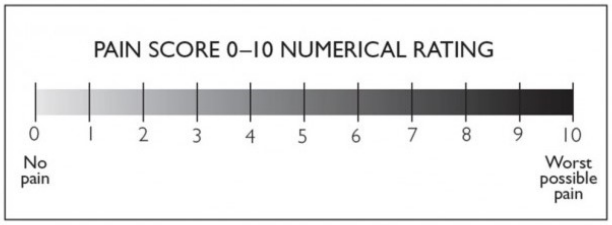

Fig. 3. Distribution of pain scores across three groups. CON: plain lubricant at room temperature; LI: room temperature lidocaine gel; LI4ºC: lidocaine gel cooled to 4 ºC.

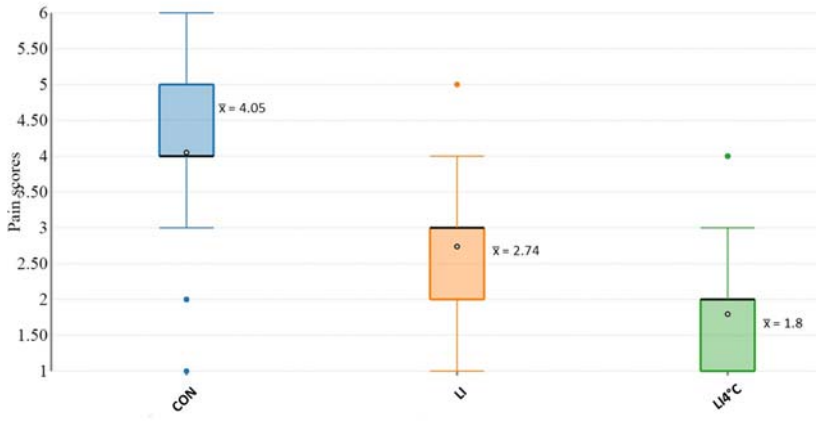

Fig. 4. Scatterplots between body mass index and pain scores in each group with added regression line. CON: plain lubricant at room temperature; LI: room temperature lidocaine gel; LI4ºC: lidocaine gel cooled to 4 ºC.

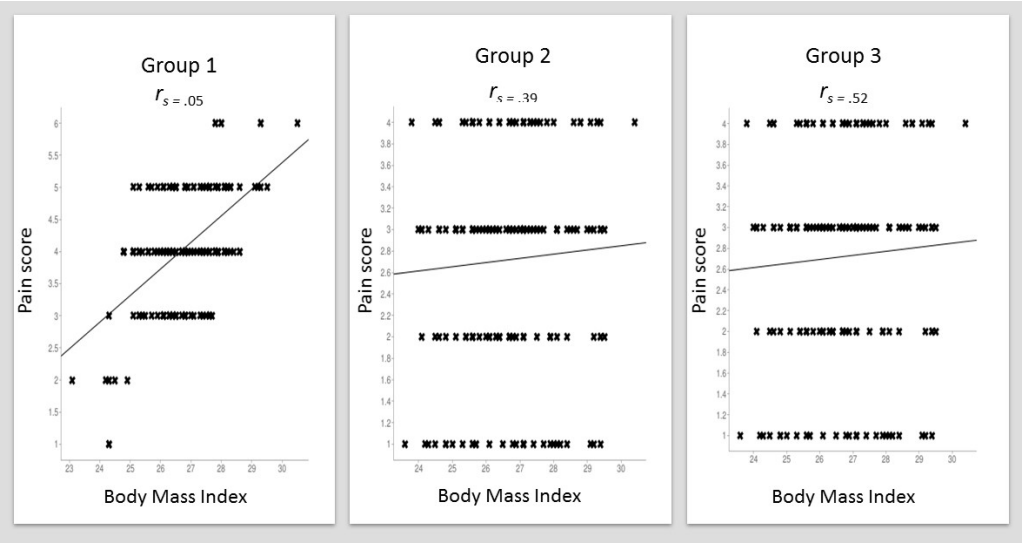

Fig. 5. Scatterplots between prostate weight and pain scores in each group with added regression line. CON: plain lubricant at room temperature; LI: room temperature lidocaine gel; LI4ºC: lidocaine gel cooled to 4 ºC.

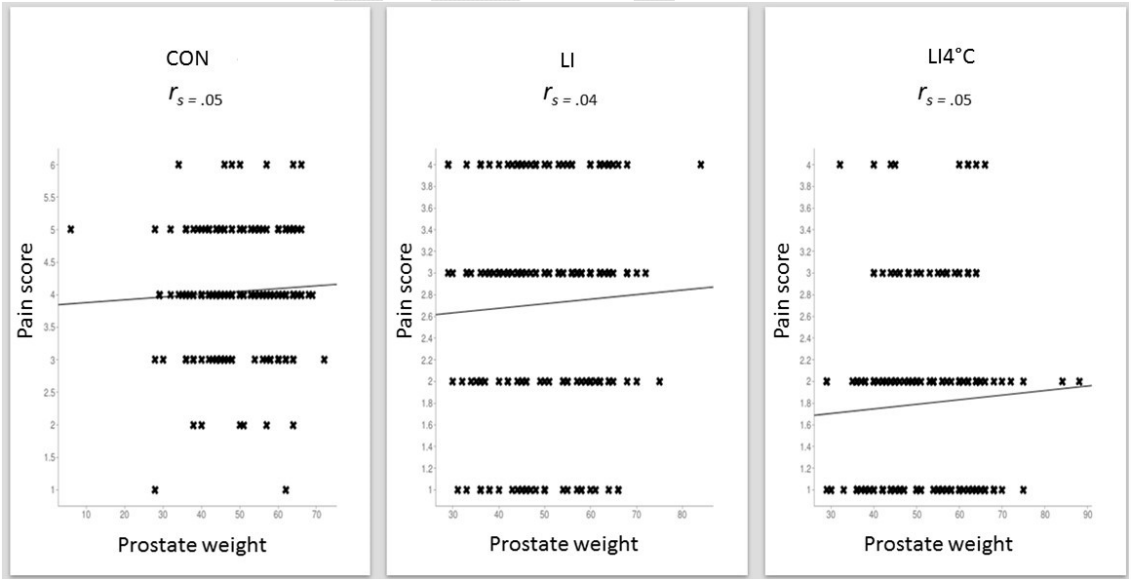

Fig. 6. Scatterplots between age and pain scores in each group with added regression line. CON: plain lubricant at room temperature; LI: room temperature lidocaine gel; LI4ºC: lidocaine gel cooled to 4 ºC.

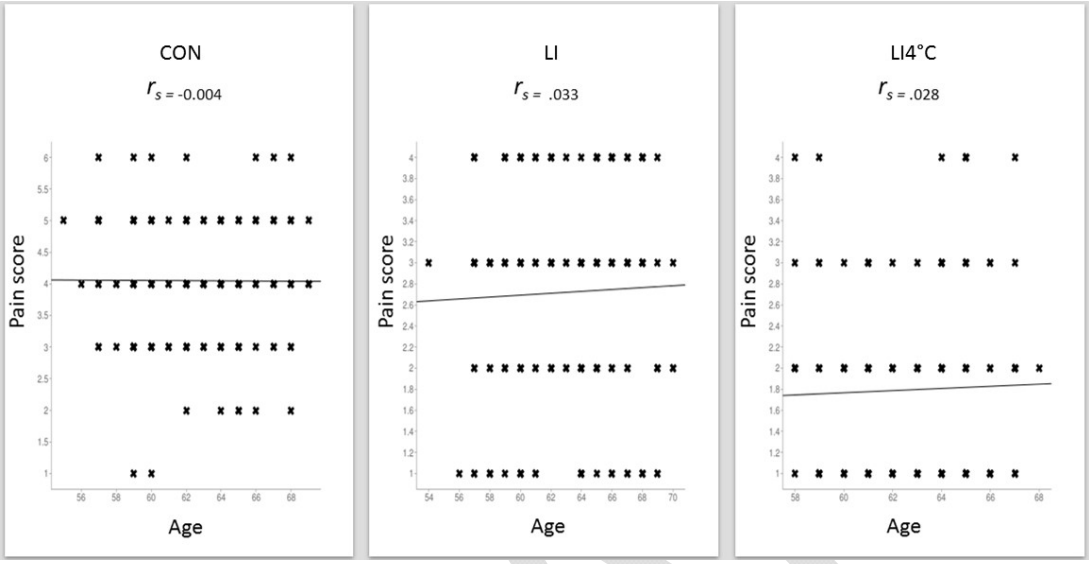

Table 1. Demographics and other intra procedural data depicted					
Parameter	**CON**	**LI**	**LI4ºC**	**p**	**Post-hoc test results**
Age Mean ± SD IQR	62.4±3.1 5	63±3.6 6	63±3.1 4	0.26*	NA
BMI Mean ± SD IQR	26.8±1.1 1.5	26.6±1.4 1.9	25.7±1.5 2.1	0.1*	NA
Prostate weight Mean ± SD IQR	49.8±10.7 18	50.4±11 18	51.4±11.2 18.5	0.34	NA
Procedure duration (mins) Median IQR	3 2	3 2	3 2	0.09**	NA
Magnitude of change in pulse rate Median IQR	10 6	8 5	4 4	0.002**	CON ≠ LI, p=0.002 LI ≠ LI4ºC, p=0.006 CON ≠ LI4ºC, p=0.020

Satisfaction level with procedure Median IQR	 6 1	 8 1	 9 1	 0.024**	 CON ≠ LI, p=0.001 LI = LI4ºC, p=0.061 CON ≠ LI4ºC, p=0.023
Willingness for future cystoscopies Median IQT	 7 2	 8 2	 8 1	 0.031**	 CON ≠ LI, p=0.027 LI = LI4ºC, p=0.130 CON ≠ LI, p=0.010
Mean pain score Mean ± SD Median IQR	 4.05±0.91 4 1	 2.74±1.01 3 1	 1.8±0.84 2 1	 0.02**	 CON ≠ LI, p=0.02 LI ≠ LI4ºC, p=0.03 CON ≠ LI4ºC, p=0.01

*Analysis of variance. **Kruskal-Wallis test, followed by Dwass-Steel-Critchlow-Fligner pairwise comparisons (post-hoc test). CON: Plain lubricant at room temperature; LI: lidocaine at room temperature; LI4ºC: lidocaine cooled to 4ºC; NA: not applicable.