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# A Randomized Controlled Trial of a Modified Cystoscopy Technique

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## Abstract

### Introduction

Pain, anxiety and embarrassment are well documented feelings in patients undergoing ambulatory diagnostic cystoscopy. In this study, we explored utilizing Peak-end theory in improving pain perception in patients undergoing diagnostic cystoscopy.

### Materials and Methods

We conducted a randomized clinical trial at the London Health Sciences Center for patients undergoing an ambulatory diagnostic cystoscopy for the first time. Males and females as well as allocation ratios were 1:1. The control arm received a standard cystoscopy. In the intervention arm the cystoscope was left for additional 2 minutes without further manipulation in the bladder before scope removal. The primary outcome was VAS pain scores after cystoscopy in both arms.

### Results

We present the preliminary results of 54 patients out of 61 patients recruited thus far in this ongoing study after exclusion of 7 patients. Baseline characteristics were balanced between the two arms. Mean VAS scores were lower in the intervention arm but not statistically significant (17.2 mm vs. 12.0 P=0.30). Post-cystoscopy anxiety scores were lower in the intervention group but were only statistically significant in the males' subgroup (3.4 vs. 0.96, P= 0.013).

### Conclusions:

Utilizing the tenets of the Peak-end theory in modifying an unpleasant ambulatory procedure like diagnostic cystoscopy showed a potential improvement in post-procedure pain and anxiety perception scores even at the preliminary and under-powered analysis. An interim-analysis will be performed after inclusion of 79 patients.

**Key words:** New cystoscopy technique, pain perception after cystoscopy, Peek-end theory, memory failure, behavioral psychology.

**Co-Authorship Statement:**

Khalil Hetou is the first author for all chapters of this thesis. Dr. Nicholas Power is the senior author for all chapters of this thesis.

Chapter 2 was co-authored by Ailsa Gan (co-first author) who helped in designing the methodology of the study as well as collected data. In addition, Dr. Joseph Chin and Dr. Jonathan Izawa co-authored chapter 2 in acknowledging their significant contributions in this study as co-investigators who recruited patients.

Khalil Hetou was responsible for the literature search and review in all chapters, sample size calculation and study design in chapter 2, data analysis and interpretation and illustrating all figures in the study.

**Dedication:**

To my parents: Hala and Chaker, as well as to my sisters: Ghaidaa, May, Serin and Salam who have been always supportive and inspirational.

To patients who suffer not only from their health conditions but also unfortunately because of our diagnostic procedures. I hope this work will help in alleviating this suffering and improve their overall experience at least when they undergo next time a diagnostic cystoscopy.

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1. VAS: Visual Analogue Scale.
2. BMI: Body Mass Index.
3. TURBT: Transurethral Resection of the Bladder Tumor.
4. LUTS: Lower Urinary Tract Symptoms
5. RBCs: Red Blood Cells
6. HPF: High power Field.
7. UDS: Urodynamic Studies.
8. VR: Virtual Reality.

# Chapter 1

# Introduction

## 1.1 Cystoscopy from the urologist's perspective

### *1.1.1 History of cystoscopy*

Visualizing the internal organs through natural orifices like mouth and urethral meatus using instruments from distance (endoscopy) has been attracting physicians since ancient times in an attempt to understand patient's symptoms and signs. Currently, endoscopy is much more differentiated and there is just about a special scope for each hollow organ: colonoscopy for colon, otoscopy for the ear and cystoscopy for the urinary bladder (1, 2).

Cystoscopy is a commonly performed procedure in urology clinics worldwide. It enables urologists to visualize the urethra and the bladder by introducing a scope through the urethral meatus. Before the invention of cystoscopy, diagnosing bladder tumors or stones was done using invasive methods. Open surgical exploration of the bladder through lower abdominal incisions was one of the common diagnostic tools to explore the bladder. Blind insertion of sounds and clamps into the urethra was a common method of trying to explore patients' lower urinary tract symptoms. Obviously, those invasive procedures

caused patients increased morbidity and were very low yield in clarifying patients' lower urinary tract symptoms (3).

It is well accepted that the German-Italian Phillip Bozzini was the first to use the "Lichtleiter", which is a German word that means the 'light conductor', to visualize multiple body cavities including the urethra (4). In 1806, Bozzini used an in-built beeswax candle with adjustable viewing ports (figure1). The device that Bozzini invented was not specific for one organ; he used it to visualize urethra, ear, gunshots tracts, etc.

Since 1806, endoscopy has gone through many technical modifications accompanied with advances in medical and mechanical knowledge. Endoscopy was also challenged at the beginning by some scientists from the medical community who believed that it was inferior to open surgical exploration of internal organs including the urinary bladder (5). Developers from the urologic community focused on 2 critical components: better light source and better fitting instruments (6).


***Figure 1:*** *Bozzini's original light conductor with specula. Courtesy of the History office at the European Association of Urology. (Int.Nitze-Leiter Research Society for Endoscopy/Nitze-Leiter Collection). http://history.uroweb.org/history-of urology/diagnosis/looking-into-the-body/bozzini-and-the-lichtleiter/.*

But it was not before 1879, when Maximilian Nitze developed the first usable endoscope used specifically to visualize the urethra and the bladder, the cystoscope. “A lucky break led me to the right path.” Those were Nitze’s own words when he described the coincidence as he was cleaning an eye-piece lens and was able to see an inverted image of Matthäus Church in Berlin across the street from his lab through that lens. That coincidence led him to the idea of creating a form of telescope to enable him to visualize internal organs (4). See Figure 2. The light source in the telescope he developed was attached on the distal part of the scope, offering maintained illumination throughout the procedure regardless of the angle the operator is working on. Moreover, he developed a water channel that ran through the scope to cool it down. Concepts of current rigid cystoscopy are based on Nitze’s model (figure 3).


***Figure 2:*** *Optical tube after Max Nitz. Courtesy of the History office at the European Association of Urology. From the Int. Nitze-Leiter Research Society for Endoscopy, Vienna/Reuter Collection. http://history.uroweb.org/history-of-urology/diagnosis/looking-into-the-body/nitzes-cystoscope/*

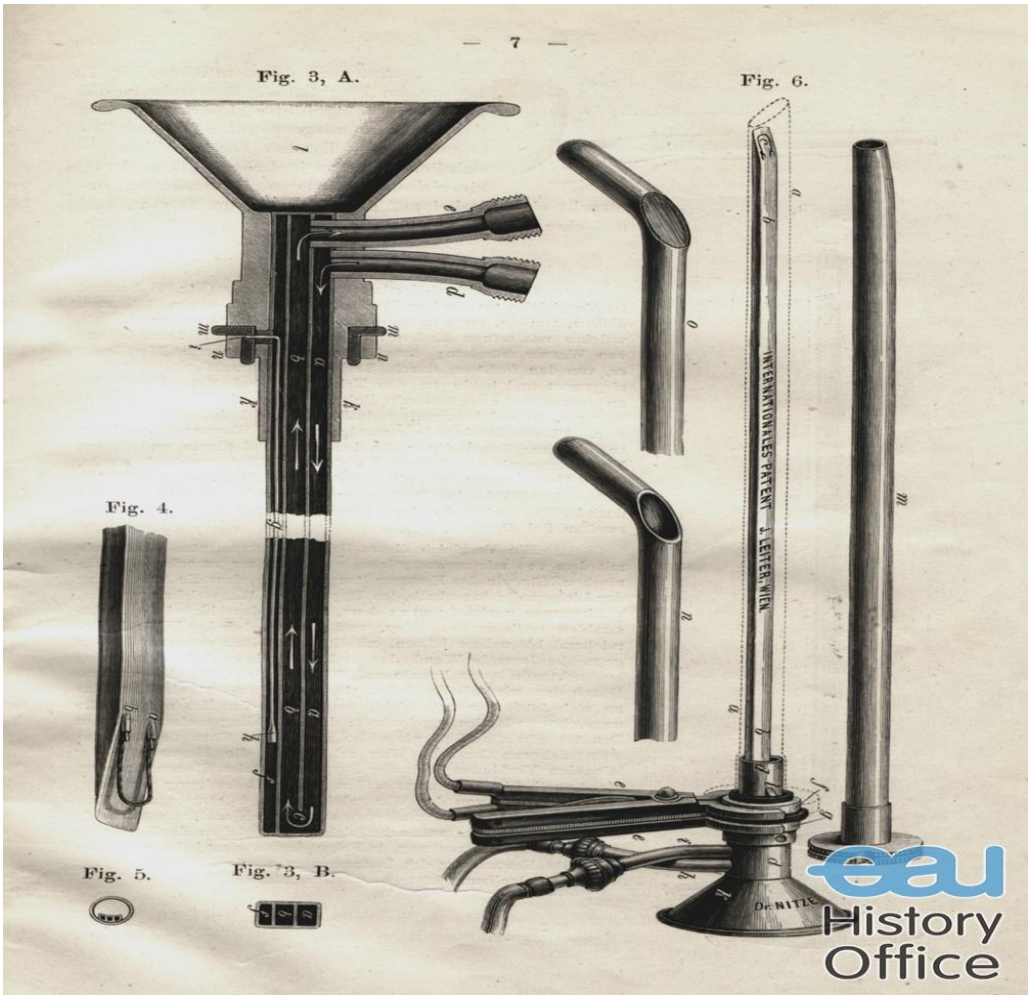



***Figure 3:*** *Woodcut of the first urethroscope and cystoscope built on the principle of the platinum wire filament based on Nitze's design. Courtesy of the History office at the European Association of Urology. From the collection of the Int. Nitze-Leiter Research Society for Endoscopy. http://history.uroweb.org/history-of-urology/diagnosis/looking-into-the-body/nitzes-cystoscope/*

A revolutionary step in the development of cystoscopes was the use of fiber optics (7). In 1951, a physicist named Harold Hopkins applied fiber optic technology to cystoscopies following its success in gastrointestinal tract visualization. A German company named Storz bought this patent. Its first flexible fiber optic cystoscope was introduced at the International Society of Urology in Munich in 1967. With this new system urologists worldwide have been using flexible cystoscopy with much better illumination and image definition than older cystoscopies. (Figure 4)

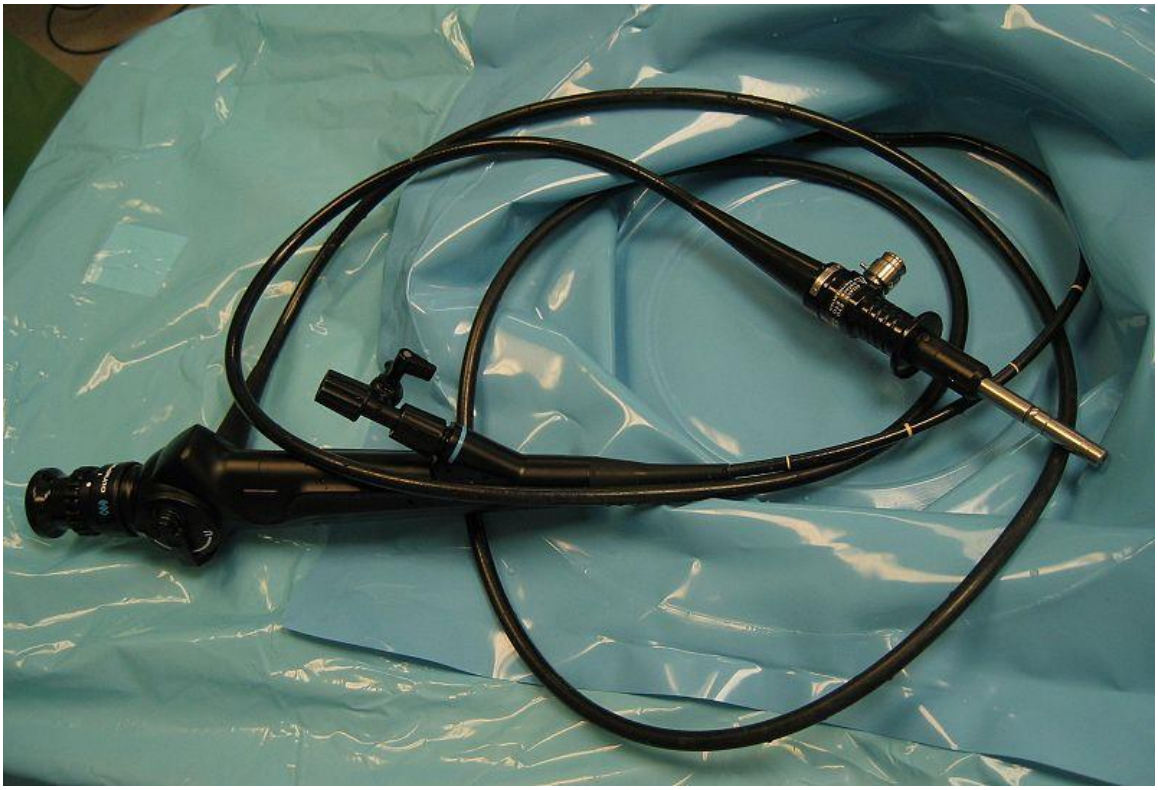


***Figure 4:*** *Flexible cystoscope with fiber-optic technology. Photograph taken by Michael Reeve, 25 April 2005. {{GFDL}}. https://commons.wikimedia.org/wiki/File:Cystoscope-med-20050425.jpg.*

Although still in use, fiber optics are vulnerable to break. In 1970, Boyle and Smith developed the charge-couple device (8). A sensor at the tip of the scope converts the optical image into a digital signal that can be transferred via the shaft of the endoscope to an image processor where a video signal is generated and displayed on a monitor. This latest advancement improved image resolution and durability of the cystoscope.

### **1.1.2** *The current cystoscope and its properties*

There are two types of cystoscopes currently used worldwide in the urological community: the rigid and the flexible cystoscopes (9).

The current rigid cystoscope as described earlier is based on Nitze's model. It is composed of an optical lens, bridge sheath and obturator. Optical lenses are offered in different angles to serve different purposes. Bridges can accommodate more than one working channel. Because of that, the rigid cystoscope is more commonly used in the operating room where diagnostic, therapeutic and interventional procedures are usually needed and done through those working channels. In addition, because of their rigidity, they are easier to handle with one hand which gives the surgeon the ability to use the other hand to manipulate other instruments during the procedure.

The flexible cystoscope however is more commonly used in the outpatient setting because it causes less pain than rigid cystoscopy due to its thinner diameter and non-metallic material (10-12). Moreover, use of rigid cystoscopies was found to be associated with higher levels of anxiety prior to cystoscopy (13).

Although a single working channel can be incorporated into the flexible cystoscope, it is more commonly used for diagnostic purposes in the outpatient clinic (14). Regardless of its type, the cystoscope must be attached to a light source and irrigation source. Irrigation helps with opening the collapsed urethra and helps visualize the bladder.

Visualization during cystoscopy historically has been done by the surgeon directly looking in to the lens of the cystoscopy. With recent technological advances, now a days a camera is attached to the lens and its cable is attached to a video-endoscopic unit consisting of a fixed tower, monitor, light source and printer (14)

### 1.1.3 *The current technique of the outpatient cystoscopy:*

For a rigid cystoscope, the patient is usually positioned in lithotomy position both in males and females. With the flexible cystoscope the lithotomy position is not necessary. The male patient is usually positioned in a supine position where as the female patient is usually positioned in lithotomy or frog-leg position to facilitate passage of the scope into

the urethral opening (meatus). After disinfection of external genitalia, a lubricating gel is applied into the urethra. The tip of the cystoscope is then administered to the meatus.

Irrigation helps open the collapsed urethra. It also helps the surgeon to inspect the urethra for possible diseases as well as navigating the way to the bladder. Once in the bladder irrigation, helps inflate the bladder walls, stretching all folds that could harbor possible disease (15).

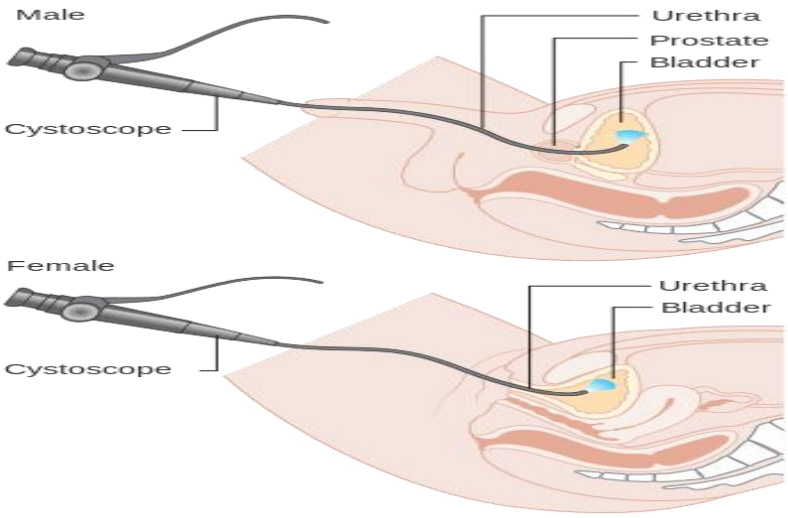



***Figure 5:*** *Diagram showing a cystoscopy for a man and a woman. Author: Cancer Research UK. 30 July 2014 (released by CRUK).*

*https://commons.wikimedia.org/wiki/File:Diagram_showing_a_cystoscopy_for_a_man_and_a_woman_CRUK_064.svg.*

Cystoscopy is performed in a systematic fashion. After insertion of the scope through the urethra, inspection of the ureteral orifices is done. Shape and color of urine efflux out of the orifices should be noted. Then inspection of all bladder walls is done. Advantage of the flexible cystoscope is its ability to deflect in different angles giving the surgeon the ability to visualize difficult areas of the bladder like the anterior bladder neck and anterior bladder wall (figure5). After the end of the procedure, the bladder is emptied, and the cystoscope is removed (15).

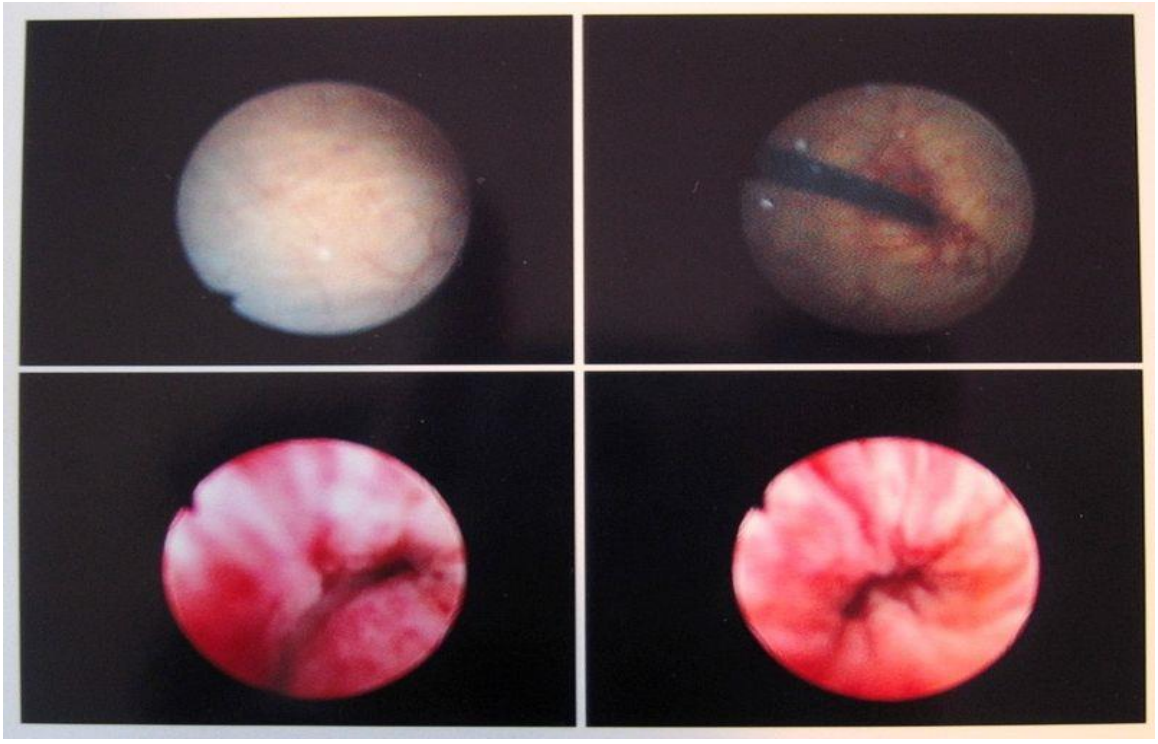


***Figure 6:*** *Images from a cystoscopy. The top two images show the interior of a bladder. The top left image shows the bladder wall, the top right shows the cystoscope passing into the bladder from the urethra. The bottom two images show an inflamed urethra. Author: Michael Reeve. 25 April 2005. https://commons.wikimedia.org/wiki/File:Cystoscopy-im-20050425.jpg.*

### 1.1.4 *Clinical applications of the cystoscope*

Blood in the urine is called hematuria. It could be gross or microscopic. Microscopic hematuria can be tested using urine dipstick and microscopic urinalysis. Dipstick color change indicating blood in urine is based on the fact that hemoglobin has a peroxidase like activity which catalyzes an oxidative reaction with the dipstick substance which changes color correlated with the amount of oxidation (16). See figure 7.

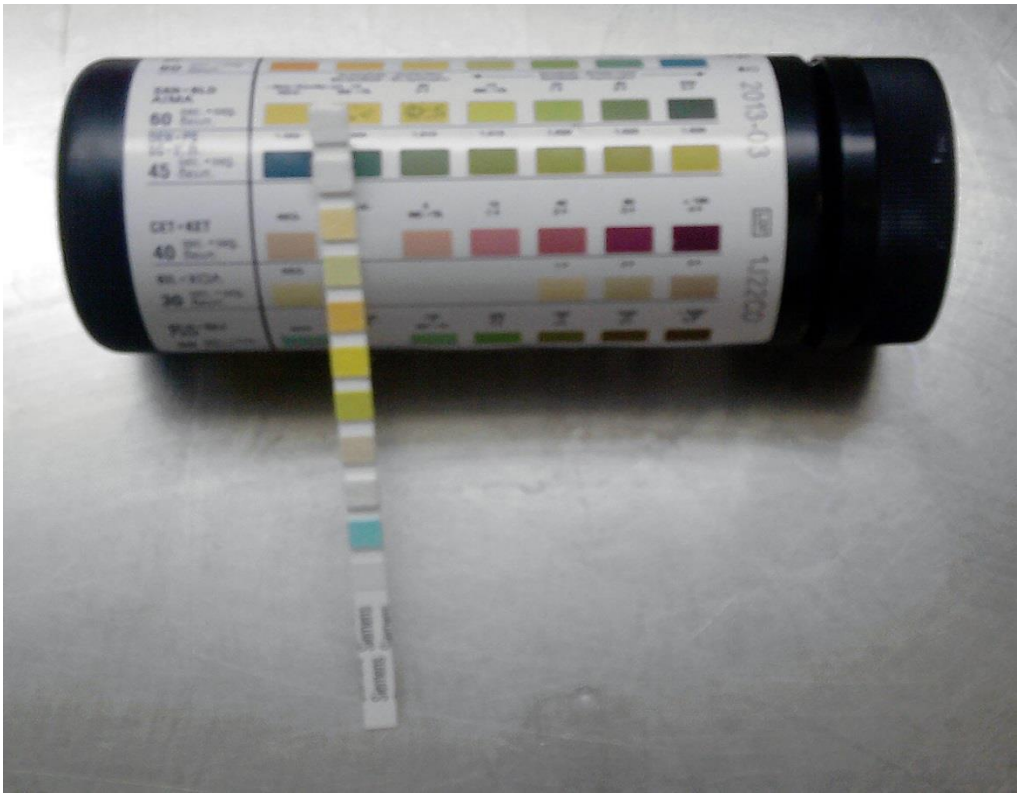


*Figure 7: A urine test strip photo. Author: Author: J3D3. 24 February 2012. https://commons.wikimedia.org/wiki/File:Chemstrip1.jpg.*

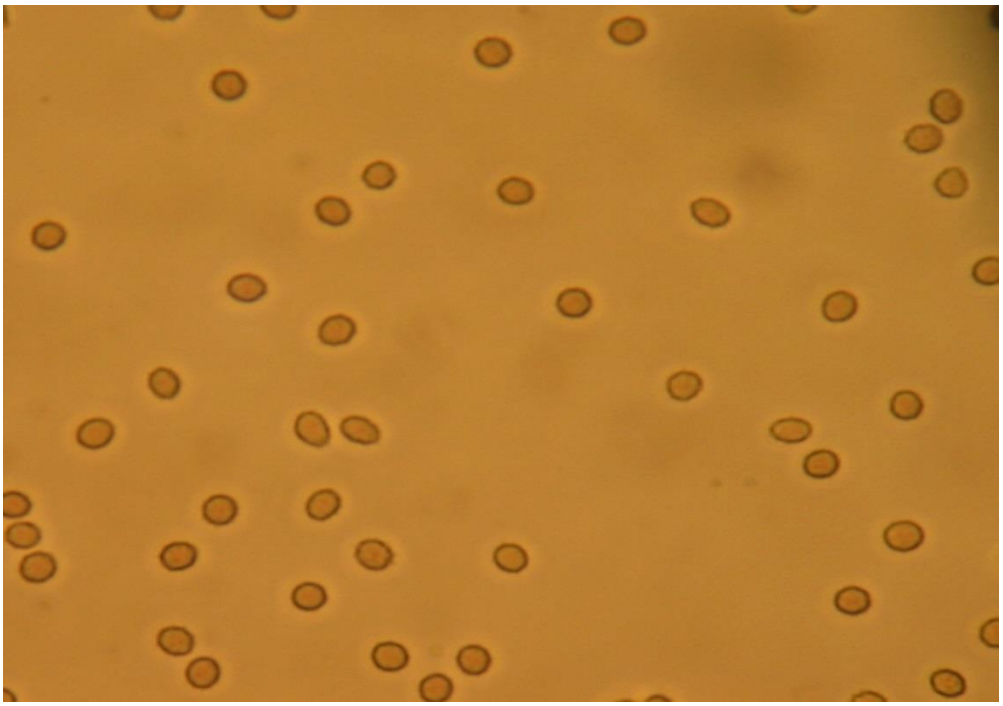


*Figure 8: Microscopic hematuria: Red blood cells in a urine sample seen under the microscope. Author: Bobjgalindo. 19 February 2005. https://commons.wikimedia.org/wiki/File:MicroHematuria.JPG*

Microscopic hematuria is defined as having more than 3 red blood cells (RBCs) per high power field (HPF) (16). See figure 8. Whether it is gross or microscopic, persistent hematuria after ruling out infection and other benign causes is an indication for referral to the urology clinic for further assessment (17). If confirmed, a cystoscopy is usually performed in the outpatient setting. The main aim of cystoscopy in the hematuria setting is to rule out the presence of malignant causes of hematuria from the lower urinary tract.

To date, cystoscopy has remained the gold standard of diagnosing bladder cancer. No other investigation available is able to replace cystoscopy. The Canadian, American and European urological guidelines recommend cystoscopy as the gold standard for diagnosing bladder cancer. (18-19).

Bladder cancer is the fifth most common cancer in Canada. About 9,000 Canadians are diagnosed with bladder cancer each year (20). The most common sign of bladder cancer is asymptomatic presence of blood in the urine. The confirmation of bladder cancer diagnosis is done by a diagnostic cystoscopy. If confirmed, the patient will undergo a procedure called trans-urethral resection of the bladder tumor (TURBT) (21). According to the pathological assessment after resection, a bladder tumor is classified as either non-muscle invasive or muscle invasive. 75% of patients with bladder cancer have non-muscle invasive bladder cancer (20). Depending on the microscopic appearance of the tumor cells and recurrence history, patient with non-muscle invasive bladder cancer might need adjuvant intravesical treatments to reduce recurrence and progression of the disease.

Because of its high recurrence rates (60-70%), surveillance strategies with regular cystoscopies have been developed by urologists worldwide and are recommended by all urological guidelines to assess for possible recurrence after TURBT and allow early intervention. Meaning that, every patient with non-muscle invasive bladder cancer requires regular ambulatory surveillance cystoscopies to assess for recurrence and/or

success of the intravesical treatments. The surveillance duration in cases of no recurrence might reach up to 5 years according to the European guidelines.

The standard of care for patients with muscle invasive bladder cancer is neo-adjuvant chemotherapy followed by radical surgical removal of the bladder, pelvic lymph nodes, and urinary diversion. However, in a sub-set of patients who are high risk for surgery due to age and/or comorbidities, a bladder preserving approach is undertaken which includes TURBT and a combined chemo-radiation regimen. Following this combined treatment; cystoscopy is of cardinal importance to assess treatment success as well as surveillance to assess for recurrence (22).

The lining urothelium of the bladder is in continuity with the lining urothelium of the ureter and the renal pelvis. Patients with upper tract urothelial cancer are at increased risk of developing bladder cancer. Therefore, surveillance cystoscopies are indicated in patients with previously treated upper tract urothelial cancer (23-24).

In addition to cystoscopy's role in malignant diseases, it plays a critical role in the evaluation of benign conditions that might affect the urinary tract. Persistent lower urinary symptoms (LUTS) including urgency, frequency, nocturia and dysuria in the absence of urinary tract infection is an indication for diagnostic cystoscopy not only to rule out bladder cancer but also to help in the assessment of potential diagnoses of benign bladder conditions like interstitial cystitis, chronic pelvic pain syndrome, and urethral stricture disease (25-27).

### 1.1.5 *Summary of cystoscopy from urologist's perspective*

Visualization of the lower urinary tract has undergone a significant evolution since the last century. Flexible cystoscopy is the most common type of cystoscope used in the ambulatory setting. It is usually performed while the patient is awake and with the use transurethral lidocaine-based lubricating gel. From a urologist's perspective, cystoscopy is an excellent tool to visualize the lower urinary tract. Over the years, cystoscopy has remained in all urological guidelines as the irreplaceable gold standard diagnostic and surveillance tool for bladder cancer as well as other benign and malignant urological diseases.

In the following section, we will explore cystoscopy from the patient's perspective. Since flexible cystoscopy is the type of cystoscopy investigated in this study, our critical analysis of the literature in the following sections will be focused on flexible cystoscopy.

## 1.2 Cystoscopy from patient's perspective.

### 1.2.1 *Before cystoscopy*

Like any other medical procedure, urologists approach patients requiring cystoscopy by explaining the indication based on their symptoms and signs. This is followed by explaining the steps of the procedure to the patient, potential side effects and what measures the urologist will perform to alleviate the pain which most commonly include lidocaine gel during the informed consent process.

At this point it might be clear and expected that patients feel uncomfortable, embarrassed and anxious as they anticipate an unpleasant painful procedure in a sensitive body area. This assumption has been investigated and confirmed. Yerlikaya et al performed a prospective clinical trial that compared pain perception in females after a diagnostic cystoscopy to that after urodynamic study (28). Urodynamic studies (UDS) is a dynamic investigation of the transport, storage and evacuation of urine. UDS in this study included introducing a Foley's catheter into the bladder and filling the bladder to certain points to assess for filling pressure and leaking pressure points as well as a rectal catheter that helped in assessing abdominal pressure. The study did not only show pain perception from cystoscopy is higher than that associated with urodynamic studies but also pain anticipation was even higher than pain scores obtained after cystoscopy. Patient's anxiety before cystoscopy although logically expected has been examined and conformed too. Biardeau et al performed a prospective clinical trial assessing anxiety, embarrassment and

pain in patients undergoing cystoscopy and urodynamic studies (29). In the cystoscopy group, 93.7 % (Age 18-50 years) reported a degree of anxiety before cystoscopy. Older patients reported less anxiety levels. In addition, anxiety and embarrassment were statistically correlated.

### 1.2.2 *During cystoscopy:*

Pain associated with cystoscopy has been the focus of many urologists for a long time. The first reported article in PubMed goes back to 1946 when Felber published an abstract titled "Does cystoscopy need to be painful?" (29). Since then, many articles have been published about patient's pain and discomfort associated with cystoscopy and potential interventions to manage that pain.

Studies investigating pain associated with cystoscopy usually use the Visual Analogue Scale to give pain a value. VAS values in studies assessing pain associated with cystoscopy are variable. Highest mean VAS scores associated with cystoscopy reported by Walker et al was 6.6 in the control group (31). However, other studies like Cornel et al reported mean VAS score as low as 1.55 in the control group (32). Biardeu et al in their study including 101 patients who received flexible cystoscopy for the first time, 59,4 % reported some level of pain. Moreover, pain during different steps of the procedure was investigated. It was found that pain during cystoscope insertion was the highest 2.8 +/-

3.1 compared to pain during gel installation 0.7 +/- 2.1 and cystoscope removal 0.7 +/- 2.1. The pain peak-phase was confirmed by another study by Poletajew et al. In their comparative analysis, peak-pain levels were recorded at the time of insertion of the scope in both study arms (33)

Greenstein et al study in pain associated with diagnostic cystoscopy included the largest population sample in the literature. He examined pain associated with cystoscopy in 1,320 patients. In subgroup analysis that included only patients who had flexible cystoscopy, they found that pain scores were significantly lower in first timers compared to repeaters. In addition, his results confirmed the fact discussed earlier that flexible cystoscopy compared to rigid cystoscopy caused less pain (34).

### 1.2.3 *After cystoscopy*

No long-term study examined correlation between higher pain perception after cystoscopy and less compliance for future repeat cystoscopies. However, one study explored patient's willingness to repeat cystoscopy at the time of first cystoscopy. Kwon et al asked participants about their willingness to repeat cystoscopy in their comparative interventional trial (35). They found that patients who had higher VAS scores were less willing to repeat cystoscopy. Although no long-term data exists, this finding suggests pain as a potential cause for noncompliance for a repeat cystoscopy if indicated.

### *1.2.4 Summary of patient's perspective*

Patients planned to undergo ambulatory flexible cystoscopy for the first time anticipate pain and have anxiety about the procedure even before the initiation of the procedure. Cystoscopy even in its flexible form is associated with pain, anxiety and embarrassment during the procedure. Pain levels associated with cystoscopy were reported using VAS scores in the literature and were variable among studies. Males reported average higher VAS scores than females. However, most patients report a certain level of pain and anxiety associated with the procedure. Higher VAS scores were associated with less willingness to repeat the procedure in one study that might impact patient's compliance if surveillance cystoscopy is indicated.

## 1.3 Current Approaches in the Literature to Alleviate Pain Perception Associated with Cystoscopy

### 1.3.1 *Assessment of Pain associated with Cystoscopy in the Literature*

Pain and discomfort associated with ambulatory cystoscopy has been acknowledged by the urologic community. This is demonstrated by the literature published from different countries across the world, as well as recent publications in management of pain

associated with cystoscopy that highlight the ongoing efforts to improve patients' experience during this unpleasant procedure.

Studies that examined pain associated with flexible cystoscopy used the visual analogue scale (VAS) to assess patients' pain associated with the procedure. This test has established performance across clinical specialties in assessing pain (36). The scale is graded from 1 to 10. 1, representing the least amount of pain and 10 representing severe amount of pain. The patient will draw a line between these 2 values to represent the amount of pain he/she felt during the procedure. The test has many forms that follow the same concept. Although there are other tests that assess pain like Likert and Borg scales, the VAS showed superiority over those tests (37).

Current approaches in management of pain and discomfort associated with cystoscopy are divided into pharmacological and non-pharmacological approaches. Pharmacological approaches include interventions that include a pharmacological product given to the patient that aims to relieve the pain associated with cystoscopy. A non-pharmacological approach includes a form of distraction that could be utilized during cystoscopy with the intention to improve patients' overall experience and pain perception.

### 1.3.2 *Pharmacological interventions*

The most commonly used pharmacological intervention before the initiation of cystoscopy is delivering a lidocaine-based gel through the urethra. Many preparations have been made available in the market for this purpose with different amounts of gel and lidocaine concentrations. Furthermore, the use of the transurethral lidocaine-based gel is variable among urologists regarding amounts used, indwelling time and penile clamping after introduction of the gel.

Our literature search demonstrated conflicting results about the efficacy of transurethral lidocaine gel in alleviating pain associated with cystoscopy (38, 39). David et al reported the most recent systemic review and meta-analysis (40). The review included 4 randomized clinical trials with a total patient population of 411 male patients. Patients were randomized to either receiving transurethral lidocaine gel (intervention) or transurethral plain gel (placebo). Although 3 of the 4 studies included showed no evidence of VAS score differences between the 2 arms, meta-analysis showed that patients in the lidocaine gel arm were 1.7 times less likely to develop moderate to severe pain (score of 3 or higher). In addition, the study did highlight its limitations which include mainly variability of the amount of gel introduced and dwelling times of gel in the urethra before cystoscopy start.

Ho et al investigated whether the lidocaine part of the lubricating gel is causing pain upon instillation. They performed a prospective double-blind study and found that

instillation of lidocaine-based gel was more painful for patients than plain gel suggesting an irritating effect of lidocaine itself to the urothelium that adds negatively to the overall patient experience (41).

Other studies examined whether a longer indwelling time of the lidocaine gel increases this intervention's efficiency. Losco et al performed a prospective comparative trial where he randomized men to either undergo flexible cystoscopy with insertion of lidocaine-based gel either immediately prior to cystoscope insertion or after a 3-min interval. This modified gel insertion technique however showed no significant differences in VAS scores (42).

Although transurethral lidocaine-based gel is the most commonly used pharmacological intervention, researchers investigated other pharmacological interventions. Nadeem et al investigated the role of a diclofenac suppository taken by the patient 1 hour before cystoscopy in addition to lubricating plain gel compared to use of only plain lubricating gel (43). 60 patients were randomized to either group. The intervention arm had statistically significant lower VAS scores, which might question the value of lidocaine in the lubricating gel. The indications for cystoscopy in both groups in this study were variable ranging from first timers, to repeaters and cystoscopy with stent removal which confounded the results and acted as one of the study limitations.

The previously cited study by Poletajew et al was a randomized controlled trial. They proposed that the inefficiency of transurethral gel is that it does not reach the posterior urethra. For that, a catheter was inserted after transurethral gel administration to aid in distributing the gel material to the posterior urethra before the initiation of cystoscopy. There were no statistically significant differences between the 2 arms in VAS scores at the time of cystoscopy, but patient's perception of the procedure was better in the intervention arm. Other outcomes confirmed the fact that was reported by other studies that the number of previous cystoscopies is inversely related with VAS scores.

### 1.3.3 *Non-pharmacological interventions*

The most investigated non-pharmacological interventions in alleviating patients' pain and discomfort during cystoscopy was the use of music as a method of distraction. A pair of headsets is offered to the patient and he/she listens to music of his/her choosing. In another setting, music is played in the cystoscopy suite. Kyriakides et al reported the most recent systemic review and meta-analysis examining the role of music in different urological procedures including diagnostic flexible cystoscopy (44).

In this meta-analysis, three randomized clinical trials were included in the cystoscopy setting. Anxiety and VAS-pain scores were significantly lower with the use of music during cystoscopy. Although studies included were of high quality, performance bias was

the only weakness in those trials due to lack of blinding which is unavoidable in such studies.

Allowing the patient to visualize the cystoscopy examination on the monitor while lying during the cystoscopy procedure was investigated as non-pharmacological intervention to alleviate pain associated with cystoscopy. Two randomized control trials from Soomro et al and Zhang et al showed statistically significant lower VAS scores in the intervention arms (45, 46). However, another previously cited randomized clinical trial by Cornel et al showed no significant difference between the 2 arms. No systematic review was found in the literature that examined this intervention.

Less commonly investigated interventions include hand-holding during cystoscopy. The previously cited study by Kwon et al in their randomized clinical trial assigned a nurse that held the patient's hand during cystoscopy in the intervention arm. 81 patients were randomized to either a standard cystoscopy or with hand-holding. VAS scores were significantly lower in the intervention group.

With the rapid development of virtual reality and its applications, investigators at the Triple Army Medical Center in the United States examined the role of VR in lowering patients' pain perception with cystoscopy. In their randomized clinical trial Walker et al (cited earlier) randomized a total of 45 patients to either standard cystoscopy with the use of VR helmet as a distraction during cystoscopy or standard cystoscopy alone. This study however did not show any difference in VAS scores between the 2 arms.

Hruby et al investigated the effect of transcutaneous electrical stimulation in the lower abdominal area in improving patients' pain associated with cystoscopy (47). In their randomized control trial that included 148 patients, no significant difference in VAS scores in the electrical stimulation group compared to placebo.

Another randomized clinical trial investigated increasing the pressure of the irrigation during flexible cystoscopy on pain perception. Pressure was manipulated by increasing the height of the irrigation fluid bag from the bed. Higher irrigation pressure was associated with lower discomfort and pain scores than patients who received lower irrigation pressure during flexible cystoscopy (48).

### 1.3.4 *Summary of current interventions*

Interventions in the literature that were investigated to alleviate pain associated with cystoscopy were either pharmacological or non-pharmacological. Our literature search showed variable outcomes in the most commonly used pharmacological intervention which is transurethral lidocaine-based gel. Only the use of music during cystoscopy showed evidence to have effect in reducing pain and discomfort. Other interventions

were less rigorously studied and most of them showed no impact on patients' pain perception.

The past and recent publications reviewed, show the huge efforts from the international urological community in exploring ways to improve patients experience during cystoscopy. Even the use of more personal, expensive and complicated technology and medications were considered by those investigators to alleviate pain associated with cystoscopy. This reflects the keen interest in improving overall patients' experience with diagnostic cystoscopy.

An optimal intervention would be that of low costs, minimal side effects and be simple to perform. Before we introduce the intervention investigated in this study, we will in the following section describe how we assess experiences in different ways and how understanding that assessment might open the door for a modified technique in cystoscopy that might improve patient's pain perception.

Tables 1 and 2 summarize current interventions published in the literature with the intent to alleviate pain associated with the flexible cystoscopy.

| ***Pharmacological Intervention*** | ***Comments*** |
|---|---|
| Transurethral lidocaine-based gel | Systematic review and analysis showed no significant difference in VAS in 3 out 4 included studies. However, patients were less likely to develop moderate to severe pain if they had lidocaine gel. |
| Diclofenac suppository | 1 study that is limited by variability in sample population. |
| Modified application of the lidocaine-based gel to reach the posterior urethra | 1 study. No significant difference between 2 arms. |

Table 1: Summary of current pharmacological interventions in alleviating pain associated with flexible cystoscopy.

| ***Non-pharmacological Intervention*** | ***Comments*** |
|---|---|
| Music | Systematic review and meta-analysis showed evidence of VAS score decrease with music. |
| Visualizing the procedure | 3 RCTs, 2 showed significant decrease and the 3rd did not show any difference. No systematic review and meta-analysis available. |
| Patient's hand-holding during the procedure | Only 1 study that showed lower VAS scores in the intervention arm. |
| Virtual reality | Only 1 study that showed no significant difference. |
| Increasing irrigating pressure during the procedure. | Only 1 study that showed lower VAS scores in the intervention arm. |

Table 2: Summary of current non-pharmacological interventions in alleviating pain associated with flexible cystoscopy.

## 1.4 The Peak-end Theory

### *1.4.1 Types of Experience Evaluation*

There are 2 types of experience evaluation (49). Instant evaluation, which is providing a specific intensity of an effect at a specific moment: like asking a person how are you right now? And the other type of evaluation is remembered, which is a retrospective evaluation of a certain experience, for example: How was the movie?

The 2 types have distinct features that have been investigated. In instant evaluation, there is a moment to moment feedback that is recorded which gives an accumulative overall effect of that experience. Whereas in remembered feedback, there is a global evaluation of the entire experience. It could be a short visit to the urologist or an evaluation of a 1-week long vacation.

The significance of differentiating between these 2 types of evaluation comes from the fact that when patients are asked about their pain after an unpleasant medical procedure they provide a form of retrospective remembered global evaluation. Although there is some controversy of memory's weight in impacting future decisions (50) retrospective evaluation is the type of evaluation that people depend at least partly on for future decisions. The impact of retrospective global evaluation today goes beyond self-decisions. People share their different experiences on-line as well as on different

social media platforms. Sharing personal global evaluations might have impact on others planning to be part of the same or similar experience (51, 52).

### 1.4.2 *Retrospective Global Evaluation*

The remembered retrospective global evaluation has been examined in multiple animal and human experiments in the literature. 3 distinct features of this type of evaluation were identified: Peak-end rule, duration neglect and violation of monotonicity.

#### 1.4.2.1 *Peak-end rule*

Humans evaluate life experiences whether it was pleasant or not on daily basis whether it was their vacation or a movie that they saw. One would expect that their retrospective evaluations are based on an average of all the individual moments of that vacation or the individual clips of that movie. But, when we recall a movie or any specific experience, we do not recall each clip or moment. We would rather recall certain clips and moments.

Kahneman et al examined further remembered evaluation and its characteristics and features. He hypothesized that retrospective evaluation is based on an average between

the peak event and the event at the end of that experience. This is based on 2 known psychological biases in memory: peak and recency biases. High intensity incidents within an experience outweigh less intense moments. We tend also to remember the most recent moments rather than the more remote ones. The accuracy of the Peak-end rule was challenged by Kahneman et al in multiple experiments (53, 54).

In his experiment with Redelmeier, Kahneman explored the Peak-end rule in the medical setting. They hypothesized that this theory might have an application on pain perception associated with an unpleasant medical procedure. They performed a prospective clinical trial where they randomized over 600 participants into either standard colonoscopy (control) or to standard colonoscopy extended by leaving the scope for 3 minutes in the rectum at the end of the colonoscopy. Thus, creating a less aversive end to the procedure. Pain assessments during the procedure (instant evaluations) as well as 1 hour after the procedure (global, remembered evaluation) were measured with ten-point intensity scale. Not only did patients in the intervention arm have statistically significant lower VAS scores but also compliance rates with repeat colonoscopies if indicated were higher in the intervention arm. Participants' recollections were strongly associated with the momentary instant peak and end moments (55).

The peak-end rule extend applies even for longer- term memories. In another experiment, Kahneman recruited patients with clinically confirmed rheumatoid arthritis to evaluate their pain status 7 times a day. These assessments were compared with their overall pain perception a day after that week is over. He found that a simple average of the peak

instant evaluation reported during an episode and of the evaluation reported at its end predicted subsequent global evaluations at least as accurately as the average of instant assessment.

The peak-end rule opened the doors for Kahneman and his colleagues to explore the next 2 features of retrospective global evaluation.

#### 1.4.2.2 *Duration neglect*

In his experiment with Redelmeier, Kahneman noted that although the procedure was longer in duration in the intervention arm and the scope was left in the rectum, it was ended with less aversive event compared to the actual colonoscopy which includes scope manipulation and irrigation. This according to authors contributed to the study resulting in lower VAS scores in the intervention are. Longer duration did not apparently influence participants' retrospective evaluations.

In another experiment, Kahneman and colleagues recruited 32 college students to 2 unpleasant experiences. The one shorter in duration included students emerging their hands into bowl of cold water (14 $C^0$) for 60 seconds. Then in the longer experiment they kept their hands into bowl of cold water for 60 seconds and then the water was warmed to 15 $C^0$ (still experientially cold) and they kept their hands for extra 30 seconds. Students were not told before the experiment of both durations. When asked about which

experiment would they prefer to repeat, the majority chose the longer experiment as they felt it was more comfortable.

Although 15 $C^0$ was still unpleasant for the human body, it is less unpleasant than 14 $C^0$. Having a less aversive ending affected how those students evaluated retrospectively their experiences. In addition, this experiment confirmed the suggested feature of remembered evaluation which duration neglect is and further enforced the concept of the peak-end rule. Participants evaluated their experiences based on the average between peak and end phases regardless of the duration (56).

Kahneman examined this phenomenon in a type of evaluation that involved non-tactile stimulus. With his previously cited study, with Fredrickson (53), Kahneman made participants view aversive film clips and pleasant film clips that varied in duration and intensity. They provided real-time ratings of affect during each clip and global evaluations of each clip when it was over. Another group of students viewed these same clips and later and ranked them retrospectively by either pleasant or unpleasant. Retrospective evaluations appear to be determined by a weighted average of "snapshots" of the actual affective experience, as if duration did not matter.

1.4.2.3 *Violations of monotonicity*

Monotonicity from a psychological perspective is one of the principles in decision making. If we were to decide between two alternatives but one has a higher outcome than the other, than that option is deemed better. As logical as it might sound, Birnbaum in his study explored monotonicity and when people violate it in decision making (57). In his experiment he asked undergraduate students to choose between guaranteed amounts of money and gambles. Each of the 30 gambles was presented for comparison with 2 groups of money amounts. Means of those amounts were intentionally put higher in group 2 than in 1 to investigate the impact of contextual effects. Instructions clearly stated that they should prefer amounts of money if they exceeded the most a gamble could offer and prefer a gamble to any amount less than the least amount a gamble would offer. Despite instructions promoting monotonicity satisfaction, 70% of participants showed at least one violation of monotonicity. 50% violated it more often than they satisfied it and 25 % satisfied it more than they violated it. Subgroup analysis for the 2 groups were made and showed difference percentages of choosing gamble over a sure amount of money. He concluded that comparison judgments are not always simple and straight forward comparison of values but are instead influenced by the distributions that form the context of choice.

In the experiment described earlier by Kahneman (56), students were asked which experiment they would repeat. They were asked to make a choice between two similar alternatives. Both experiments were considered aversive experiences (cold water). Following monotonicity, one would expect more students will choose the shorter in duration experiment with less total pain. However, the clear majority chose the longer in duration experiment because of its less aversive ending.

### 1.4.3 *The Peak-end theory: potential applications*

As noted earlier patient's pain perception after an unpleasant medical procedure is based on retrospective global evaluation rather than instant evaluations. When a person retrospectively evaluates an experience, whether a pleasant or an unpleasant one, he/she will not replay the whole experience in his/her mind to evaluate. Because of peak and recency biases, only specific snapshots will be remembered, and the evaluation will be based on the average of those specific snapshots. Moreover, as described earlier retrospective evaluation appears to be independent of duration.

Retrospective evaluation and Peak-end theory interpretation of global evaluation added a new way of looking into how seniors evaluate their life in general and quality of life (58). Moreover, characteristics of global evaluation and its effects on memory based on Peak-

end theory motivated research in business development to explore ways to improve overall customer satisfaction (59, 60).

Kahneman and Redelmeier were the first scientists to explore this theory application in the medical setting to improve overall patient experience in colonoscopy. However, the use of intravenous opioids is part of the standard of care in patients undergoing this type of procedure. This might make it challenging to delineate the real effect of their intervention on post procedure VAS scores. To the best of our knowledge, Peak-end theory concepts have not yet been examined in unpleasant medical procedure where intravenous opiates are not traditionally used.

## 1.4 The purpose of this study and specific aims

### *1.5.1 Purpose Statement*

The purpose of this research is to evaluate the feasibility and efficiency of modifying the cystoscopy procedure by prolonging the end-phase with less aversive maneuvers based on the peak-end theory to improve patient's pain perception after ambulatory diagnostic flexible cystoscopy.

### *1.5.2 Specific aims*

1. Examine the feasibility and effectiveness of the peak-end theory in the flexible cystoscopy setting on lowering pain perception scores.

2. Assessment of pain associated with flexible cystoscopy at our institution.

## 1.5 Hypothesis

We hypothesized that prolonging the end phase of the cystoscopy with a less aversive phase by leaving the cystoscope for an additional 2 minutes in the bladder without further manipulation will lead to lower post interventional VAS scores than in patients receiving standard cystoscopy.

## 1.7 Significance

Cystoscopy has been and is still currently the gold standard diagnostic tool in many urologic diseases, mainly bladder cancer. In addition, it is irreplaceable by any other investigational diagnostic modality. Recurrence is a hallmark feature of bladder cancer making cystoscopy a frequent surveillance procedure that millions of patients around the world must undergo for years.

Pain perception associated with flexible cystoscopy is an ongoing clinical challenge for urologists worldwide. This is evident by the amount of literature published on pain associated with the procedure as well as investigational trials for interventions that could lead to lower pain perception associated with the procedure. Scientists considered simple and inexpensive as well as complex and very expensive interventions with minimal yield most of the times.

Improving patients' pain perception will improve their overall experience. In addition, future decisions depend on their evaluation of the experience that they had during cystoscopy. Therefore, by improving patients' experience with flexible cystoscopy, we decrease the chances for noncompliance where a repeat cystoscopy is warranted.

Currently, people share their experiences not only with their families and friends but also on multiple social medical platforms. In addition, more people are researching procedures and medical information via blogs on the internet. Patient experiences with cystoscopy

might be shared with people that might need cystoscopy in the future. Improving patients' experiences will act as an indirect positive impact on people in whom cystoscopy is warranted but are concerned with the pain and discomfort associated with it.

The peak-end theory concept offers a very low-risk profile intervention to improve a patient's perception. In addition, there are no direct costs that the healthcare provider, the government or the patient must cover.

# Chapter 2

# Materials and Methods

## 2.1 Study Design

This is a randomized prospective single blinded study collecting quantitative data (pain perception as measured using a visual analogue scale) after a diagnostic only flexible cystoscopy for patients who have not had cystoscopy before. The study compared a modified technique based on the Peak-End theory's concepts by prolonging the end phase with a less aversive maneuver.

The study has been approved by the University of Western Ontario Research Ethics Board and approved by Lawson Research Institute Board. Recruitment started in September 2017. Co-investigators at the Urology Clinic at the Victoria Hospital of London Health Sciences Center recruited patients on the day of their scheduled cystoscopy.

The only surgeons who performed cystoscopies for the purposes of this study are Drs. Power, Izawa, and Chin. The 3 surgeons were neither involved in the randomization process nor in data extraction and analysis. Data collection was performed by the nursing staff at the clinic and they were not involved in data extraction or analysis.

## 2.2 Inclusion and Exclusion Criteria

Inclusion criteria were: 1. all patients with ages from 18 to 60 years old planned to have an ambulatory diagnostic flexible cystoscopy for the first time. 2. Males and females were included. To assess for potential confounders previously described in the literature we have designed recruitment to include equal numbers of males and females in each arm and only first timers.

Exclusion criteria included:

1. Patients who underwent cystoscopy before
2. Patients with congenital or acquired urinary tract anomalies.
3. Patients with chronic pain or on chronic pain medications.
4. Cystoscopies that involved additional interventions along with cystoscopy were excluded.
5. Patients with previous pelvic or urethral surgeries or radiation were excluded.
6. Patients planned to undergo rigid cystoscopy were excluded.
7. Patients currently taking medication for chronic pain (e.g. opioids, TCAs) will be excluded from the study.
8. Patients with history of chronic anxiety or on any anxiolytics.

## 2.3 Outcomes

The primary outcome of this study is to compare the mean VAS scores after flexible cystoscopy for the first time in the standard cystoscopy group with the modified group in the ambulatory setting at our institution.

Secondary outcomes include:

1. Anxiety levels before flexible cystoscopy
2. Anxiety levels after flexible cystoscopy

## 2.4 Sample Size Calculation

### *2.4.1 Effect size and VAS score difference.*

An important component of sample size calculation is effect size. As clinicians we are interested in not only a statistically significant difference in VAS scores between the 2 arms, but also a difference that is clinically relevant.

In our literature search, most studies looking into clinically significant VAS score differences, evaluated those measurements according to instant and minute to minute

evaluation in the emergency department for acute pain rather than a retrospective evaluation after the procedure. Based on those studies, a clinically significant difference varied from 12 mm to 30 mm on the 100 mm VAS (61, 62). Sadovsky et al suggested that a clinically significant VAS difference depends on the severity of the basal VAS score. Kelly et al, however found that basal VAS scores do not really affect clinically significant VAS scores (63).

In this study, VAS scores were evaluated in a retrospective manner. As we have discussed earlier, there are some key differences between retrospective and instant assessments of experiences. In the Redelmeier et al study, a 5 mm difference was noted between the 2 arms of the study in the retrospectively collected data.

We assumed an expected mean VAS score of 3.48 cm with standard deviation of 1.53, based on the Greenstein et al study. Simulating the retrospective effect of this technique on patients described in Redelmeier study, we assumed an effect change of 0.5 cm on VAS score scale. Considering a power of 0.8 and 0.05 level of significance, we proposed a sample size of 296 patients with 1:1 allocation ratio.

If an effect size of 10 mm was considered, a total of 79 patients will suffice. Based on our literature search on clinically significant VAS score differences discussed earlier and the

difference noted in the Redelmeier et al trial, we planned an interim analysis after recruiting 79 patients. If results showed significant difference of 10 mm or more then we will terminate the study.

Because of slow recruitment we submitted the analysis of only 61 patients. However, future analysis will remain as planned in the statistical design.

## 2.4 Methodology

Sealed study packages have pre-randomized study numbers for both interventions. Study numbers were randomized to both arms using the Medsharing® mobile application. Because we had a preliminary sample size of more than 100, simple randomization sequence of study numbers was performed. Randomization, allocation process and creation of the master list were done by Khalil Hetou. Each study number was pre-randomized and its allocated arm was noted in the master list. Study number allocations were not known to the investigators. Equal number of packages was allocated in each arm. Gender stratification was performed by labeling equal numbers of males and females in each arm.

Patient assignment to in investigator was predetermined so that each investigator performs similar number of intervention and controls as well as of males and females. 2 investigators had exactly the same number of patients assigned. Only one investigator had 8 more patients than the other 2 investigators. Please see figure 9.

The study packages were sealed and put in a safe place at the urology clinic where access is only granted to official personal. Each investigator was assigned 2 boxes. One box labeled for males that has equal numbers of intervention and control (pre-randomized) study packages. The other box labeled for females that have equal numbers of intervention and control (pre-randomized) study packages. All study packages were identical from the outside except for the study number. Investigators were blinded to the master list.

The study package included a sealed envelope with instruction to the investigator about which arm this patient was randomized to. Instruction envelope shall be opened only at the time of cystoscopy.

In addition, the study package contained a letter of information, consent form, a pre-intervention survey, post-intervention survey and a debriefing form.

296 closed envelopes were created. Envelopes were gender stratified with 1:1 male to female ratio. 148 blue envelopes for men and 148 green envelopes for women were created. Once the patient was deemed a candidate for the trial and consented, the gender matched closed envelope will be attached to his/her file. Dr. Chin will receive 96 (48 blue and 48 green) closed envelopes. Dr. Izawa will get the same amount and type of envelopes. Dr. Power will get 104 envelopes (52 blue and 52 green).

Once patients have been informed and have completed the consent form, they were given a short pre-procedure survey to fill assessing demographic, history of cystoscopy (to confirm first-time cystoscopy), and pre-cystoscopy anxiety levels. This survey confirmed that the participant is first timer in cystoscopy. In addition, age, level of education, pre-intervention level of anxiety and BMI were collected and analyzed to assess for potential confounders.

The standard group had a cystoscopy performed by the current standard technique defined in chapter 1. Modified intervention included the routine procedure with the addition of a two-minute period prior to removal of the scope from the urethra during which no activity was to occur. During this period, the physician-initiated discussions of findings and directions of care while leaving the scope in-situ without further manipulation or irrigation. In routine care, this discussion began after removal of the scope. In modified care, the discussions began during the two-minute period of inactivity and continue after the scope has been removed. For accurate measurement of the 2-minute period in the modified group, a digital clock was installed in each cystoscopy room to help the surgeon and nursing staff to determine time to remove the scope accurately.

As previously discussed, duration neglect is one of the hallmark features of the Peak-end theory. Although variability in the length of the procedure between patients was expected, it was not analyzed. Moreover, no maximum or minimum limit was given for the surgeon on the duration of cystoscopy as part of the inclusion or exclusion criteria.

After the procedure, patients were asked to rate the pain and anxiety they experienced during the procedure on two-100 mm Visual Analogue Scales. After they completed the post-interventional survey, patients received a debriefing form that includes specifics of the procedure, information and links about the peak-end theory that they can follow and contact information of the investigator in case they had questions or concerns.

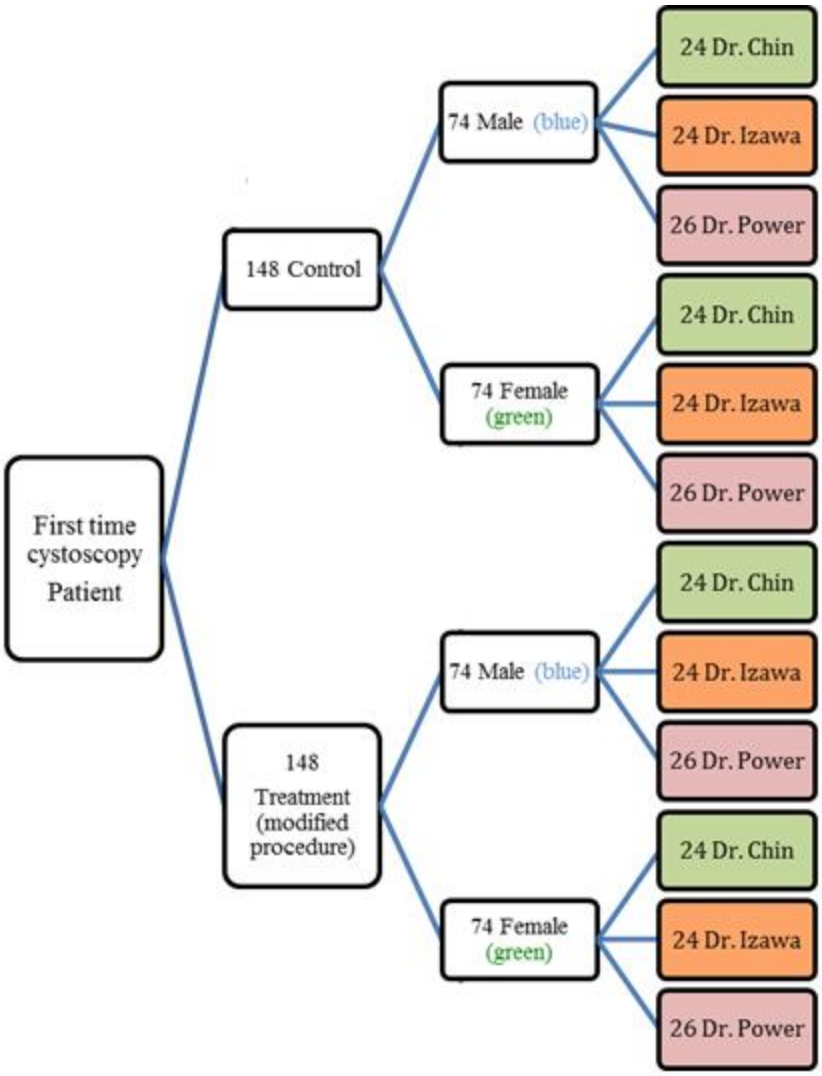



**Figure 9:** Schematic diagram showing assignment of patients in each arm and to the 3 co-investigators.

## 2.5 Statistical analysis

### *2.6.1 Visual Analogue Scale in statistical analysis*

There are some disagreements in the literature on how to handle VAS scores in statistical analysis and how VAS measurements behave in different statistical tests (60, 64). However, according to our literature search, only one study by D. Franklin et al (65) investigated VAS score in an objective manner using simulating software that challenged VAS measurements in different parametric and non-parametric tests. The goal of that study was to evaluate the effectiveness of several statistical tests to compare VAS measurements among groups using a computer simulation.

Data was collected from two studies published by the University of Iowa hospitals and clinics' obstetric anesthesia department. They examined whether women in the early epidural analgesia group had better obstetric outcome than women who had intravenous morphine or oxytocin. VAS measurements were taken in a standard fashion from women in all these 3 groups.

VAS measurements were randomly selected with replacement from the measured VAS distributions. Then various statistical tests were run. These two steps were repeated 3999 times using a computer simulation program. Each time a new random sample was drawn.

Null-hypothesis in this study was true, meaning that there was no difference among the groups. None of the statistically tests suggested significant difference exists. T-test and ANOVA showed greater power than other parametric tests. A five category VAS has as high power as the corresponding continuous VAS.

A possible drawback of this study included being a single center study and the data distribution was close to normal distribution, which is not necessarily true for data from other centers or in a multi-center setting. Therefore, conclusions could not be applied if >16% of patients in any group ranked their pain as 0 or 10 cm.

Authors concluded that t and ANOVA are good choices to compare VAS measurements among groups. However, these results may not be reliable if >16% of patients rank their pain at one of the two extremes.

### *2.6.2 Statistical Analysis overview*

The principal analysis will be comparing VAS scores between standard cystoscopy and the modified cystoscopy. All statistical evaluations were performed using STATA IC for Mac version 15.0 software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). A test of normality using Shapiro-Wilk test was applied to the data in both arms and subcategories to determine the use of either parametric or non-parametric tests.

The outcome variable examined (continuous vs. categorical) further dictated the type of test used in analysis, with a level of significance set to $\alpha=05$.

# Chapter 3

## Results

Because of unexpected slow recruitment, results submitted with this thesis represent preliminary data on 61 patients recruited from September 2017 till July 2018. Recruitment is still on-going, and an interim analysis will be performed after including 79 patients.

Out of 61 patients, 7 patients were excluded due to one of the following reasons: 1. Repeat cystoscopy (n=4). 2. Withdrew consent (n=1). 3. Post-procedure survey was unfilled (n=2). None of the patients were excluded because they were not able to complete the cystoscopy in both arms. Only per-protocol analysis was performed.

Of included patients in the analysis, 33 cystoscopies were performed by Dr. Chin (13 modified and 20 standard), 19 cystoscopies were performed by Dr. Power (13 modified and 6 standard) and 2 cystoscopies were performed by Dr. Izawa (both were standard)

54 patients were included in the current data analysis. 27 patients in the standard arm and 27 in the modified arm. Age in both arms as well as mean BMI and mean pre-cystoscopy anxiety in the standard arms passed the test of normality. However, BMI and pre-anxiety cystoscopy in the intervention arm did not pass the test of normality. Nevertheless, we took the liberty of using a parametric test (t-test) to compare means because each arm had

enough participants (>15). Test of proportion was used to calculate the difference of education in both groups.

Baseline characteristics for both the intervention and standard arms were well balanced and are summarized in Tables 1 and 2.

| Variable | Standard Arm | Modified Arm | P-Value |
|---|---|---|---|
| Gender Male (%) | 15 (55.5) | 13(48.1) | 0.90 |
| Gender Female (%) | 12 (44.4) | 14 (52.0) | 0.90 |
| Mean age (SD) | 58.3 (14.6) | 56.7 (16.2) | 0.71 |
| Mean BMI (SD) | 26.7 (4.7) | 29.5 (7.7) | 0.12 |
| Mean Pre-cystoscopy anxiety (SD) | 5.1 (2.99) | 4.3 (3.1) | 0.30 |

- **Table 3:** Baseline characteristics between the 2 arms including males and females

| Educational Level | Standard Arm | Modified Arm | P-Value |
|---|---|---|---|
| Below High School | 0 | 1 | 0.30 |
| High School | 9 | 8 | 0.70 |
| College/University | 15 | 15 | 0.89 |
| Post-graduate | 3 | 2 | 0.67 |

- **Table 4:** Educational level comparison between the 2 arms including males and females. One missing value in the standard arm

Gender stratified analysis was performed for baseline characteristics. Age as well mean pre-cystoscopy anxiety scores passed the normality tests. Means and t-tests were used to compare these two variables. However, data in the BMI intervention group did not pass the normality test. Therefore, we compared medians of BMI in both arms using.

Baseline characteristics comparison showed no significant differences between the 2 arms in females and is summarized in tables 3 and 4.

| Variable | Standard | Modified | P-Value |
|---|---|---|---|
| Mean age (SD) | 52.8 (13.6) | 46.5 (15.7) | 0.30 |
| Median BMI | 22.85 | 25.8 | 0.31 |
| Mean Pre-cystoscopy anxiety (SD) | 4.33 (2.7) | 4.83 (3.09) | 0.65 |

**Table 5:** Baseline patients' characteristics female group in both arms

| Educational Level | Standard Arm | Modified Arm | P-Value |
|---|---|---|---|
| Below High School | 0 | 1 | 0.95 |
| High School | 3 | 4 | 0.84 |
| College/University | 7 | 8 | 0.45 |
| Post-graduate | 2 | 1 | 0.45 |

**Table 6:** Educational levels in females in both arms

Age, BMI and pre-cystoscopy anxiety scores passed the Sahpiro-Wilk test of normality and a t-test was used to compare these variables between two arms in the males' subgroup. Baseline characteristics comparisons between the 2 arms in males showed also no significant differences and are summarized in tables 5 and 6.

| Variable | Standard | Modified | P-Value |
|---|---|---|---|
| Mean age (SD) | 62.7 (14.4) | 66.8(11.2) | 0.41 |
| Mean BMI (SD) | 28.5 (4.4) | 29.7 (6.8) | 0.58 |
| Mean Pre-cystoscopy anxiety (SD) | 5.9 (3.04) | 3.46 (3.19) | 0.053 |

**Tables 7:** Baseline patients' characteristics male group in both arms

| Educational Level | Standard Arm | Modified Arm | P-Value |
|---|---|---|---|
| Below High School | 0 | 0 | NA |
| High School | 6 | 4 | 0.72 |
| College/University | 8 | 7 | 0.80 |
| Post-graduate | 1 | 1 | 0.90 |

**Table 8:** Educational levels in males in both arms.

Mean VAS scores were lower in the intervention group combined (males and females) compared to the standard group combined (17.2 vs. 12.5). However, this difference was not statistically significant (P=0.30).

We further analyzed VAS score variable as a categorical one, where VAS scores from 1 to 3 were considered mild, >3 to 6 moderate and >6 to 10 severe. A fourth category of no pain was added if patient reported no pain. We performed a chi-square test to look for differences in these categories between the 2 arms.

There were more patients reporting no pain in the intervention arm (n=7) than in the standard arm (n=5). Similar number of patients reported mild pain in both arms (n=18). 3 patients reported moderate pain in the standard arm compared to the intervention arm. One patient reported severe pain in the standard arm compared to no patients in the intervention arm. However, those differences were not statistically significant (P=0.80). Table 7 summarizes the frequency of reported pain in both arms according to VAS category.

| Arm | No Pain | Mild Pain | Moderate Pain | Severe Pain | Total |
|---|---|---|---|---|---|
| Standard | 5 | 18 | 4 | 1 | 27 |
| Intervention | 6 | 18 | 2 | 0 | 27 |
| Total | 12 | 36 | 6 | 1 | 54 |

**Table 9:** Frequency of reported pain category in both arms including males and females in each arm.

In the females' subgroup, VAS scores did not pass the normality test in the intervention arm, so we compared the median in both groups. The median VAS score was found to be higher in the standard arm (7.5) compared to the intervention arm which was 2.5. This difference however was not statistically significant with Wilcoxon-Rank sum test (P=0.4).

In the females' groups, none of the patients in both arms reported severe pain. 1 patient reported moderate pain in the intervention arm. 8 patients reported mild pain in the intervention group compared to 9 in the standard of care group. 5 patients reported no pain in the intervention arm compared to 3 patients in the standard arm. However, those differences were not statistically significant using the Spearman's Rank test (P=0.50). Table 8 summarizes the frequency of reported pain according to VAS category in the females' subgroup.

| Arm | No Pain | Mild Pain | Moderate Pain | Severe Pain | Total |
|---|---|---|---|---|---|
| Standard | 3 | 9 | 0 | 0 | 12 |
| Intervention | 5 | 8 | 1 | 0 | 14 |
| Total | 8 | 17 | 1 | 0 | 26 |

**Table 10:** Frequency of reported pain category in both arms in the females' subcategory.

VAS scores in the males' subgroup did not pass the normality test. Median VAS score in the standard arm was higher 12 compared to 11 in the modified arm. This difference was not however statistically significant (P=0.91)

Two patients reported no pain in the standard arm compared to 1 in the intervention arm. 1 patient reported severe pain in the standard arm compared to 0 in the interventions arm. More patients reported moderate pain in the standard arm (n=4) compared to the intervention arm (n=1). Those differences were however not statistically significant (P=0.31). Table 9 summarizes the frequency of reported VAS category in both arms in the males' subgroup.

| Arm | No Pain | Mild Pain | Moderate Pain | Severe Pain | Total |
|---|---|---|---|---|---|
| Standard | 2 | 8 | 4 | 1 | 15 |
| Intervention | 1 | 11 | 1 | 0 | 13 |
| Total | 3 | 19 | 4 | 1 | 28 |

**Table 11:** Frequency of reported pain category in both arms in the males' subcategory.

Table10 includes combined and gender-stratified comparative analysis of VAS scores between the 2 arms.

| Outcome | Standard | Modified | P-Value |
|---|---|---|---|
| Mean Pain VAS both (SD) | 17.2 (20.0) | 12 (13.8) | 0.30 |
| Median Pain VAS Females | 7.5 | 2.5 | 0.40 |
| Median Pain VAS Males (SD) | 12 | 11 | 0.91 |

**Table 12:** Mean VAS scores in combined group as well as median VAS scores in gender stratified sub-groups

Post cystoscopy anxiety scores data failed the normality test in the combined group as well as in the gender subcategories. Median post cystoscopy anxiety scores in the intervention arm was higher than in the intervention arm (1 vs. 0). The difference was not statistically significant (P=0.057).

The median post cystoscopy anxiety scores in the females' subgroup was higher in the standard arm compared to intervention (0.5 vs. 0) which was statistically not significant (P=0.91).

Post-cystoscopy anxiety score in the male subgroup passed the normality test. Mean post cystoscopy anxiety scores were significantly higher in the standard arm compared to the modified arm (3.4 vs. 0.96).

Table 13 includes group and gender-stratified comparative analysis of post cystoscopy anxiety scores between the 2 arms.

| Outcome | Standard | Modified | P-Value |
|---|---|---|---|
| Median Post cystoscopy Anxiety: Both | 1.0 | 0 | 0.057 |
| Mean Post cystoscopy Anxiety: Females (SD) | 0.5 | 0 | 0.91 |
| Mean Post cystoscopy Anxiety: Males (SD) | 3.4 (3.14) | 0.96 (1.1) | **0.013** |

**Table 13:** Comparative results of post cystoscopy anxiety scores in both males and females as well as in gender stratified groups

Future directions include continuing the recruitment until 79 patients accrue. At this stage an interim analysis will be performed. If a statistically significant difference of 10 mm between the 2 arms is found, the study will be terminated. Otherwise, we will continue recruiting until we reach 296 patients. As for analysis, further sub-group analysis will be performed including inter-surgeon variability and independent variables associated with VAS scores of more than 3.

# Chapter 4

# Discussion

## 4.1 Overview

Our literature search demonstrated mild to moderate levels of pain associated with cystoscopy. Nevertheless, since the invention of the flexible cystoscope researchers have been looking into different interventions to alleviate the pain associated with this simple procedure. That we believe highlights the efforts that urologists are putting in to improve patient's overall experience with cystoscopy.

This study represents the first clinical application of Peak-end theory in diagnostic cystoscopy. Although Redelmeier et al performed a similar study with colonoscopy and extracorporeal shockwave lithotripsy; intravenous sedation was usually part of the standard of care in such procedures which might impact patient's retrospective evaluation and judgment as well as confounding pain and discomfort levels. In ambulatory diagnostic cystoscopy, however, intravenous sedation is not a standard of care, which makes exploring the weight of this theory in our study less confounded.

The randomized controlled nature of the presented study as well as gender stratification and selection of only first timers addressed known confounders demonstrated in our literature search. In addition, other baseline characteristics that could act as potential confounders were collected and analyzed.

Compared to all interventions in the literature that aimed to alleviate pain associated with cystoscopy, the intervention investigated in this study is attractive in many ways. It is simple to learn, perform and to teach. It does not include the use of any instruments or medications that might cause side effects to the patient. This makes it an intervention with absolutely no direct costs to the patient, hospital or the health-care system. Moreover, there was no need for extra or specially trained personnel to perform it.

Biardeau et al explored the exact peak phase of this procedure. In his study cited previously, peak pain was reported by patients at the time of insertion of the cystoscope. In our study we created a new end-phase that constituted of no manipulation or irrigation for 2 minutes.

Baselined characteristics were well balanced between the 2 arms. However, in the subgroup analysis Pre-cystoscopy anxiety scores were higher in the standard arm compared to the modified arm. This was however not statistically significant and we could not find a scientific explanation for that difference. Preliminary data analysis showed lower mean VAS scores in intervention arm in the general sample population as well as in the gender stratified subgroups. However those differences were statistically not significant. Differences in the male subgroup were more prominent than in the female

group, which might predict a significant benefit in this subgroup. Moreover, more patients reported severe and moderate pain especially in the males' group. But this was also not statistically significant.

Mean anxiety scores post-procedure showed lower mean scores in the intervention arm in the general sample population as well as in the gender stratified subgroups. Differences however were statistically significant in the total population as well as in the male subgroup only. Similar to mean pain VAS scores, the differences in the male subgroup were more prominent than those in the female sub-group.

These findings, though at the preliminary analysis level, did support thus far the results of previous experiments done on peak-end theory. Adding a less aversive end-phase to an aversive experience will result in better overall evaluation of that experience regardless of the duration and with violation of monotonicity.

## 4.2 Limitations

### *4.2.1 Variables difficult to analyze*

As in the Redelmeier study, our research is a proof-of-concept study on the psychology of memory. Previous painful experiences like trauma or pregnancy might enhance the variability in pain thresholds among patients and their pain perception assessment after cystoscopy.

There are many factors that might affect patients' ability to recall. In addition, there are many factors that might affect patients' perception of pain. Although pre-anxiety scores were assessed in this study, there are other factors and technicalities that patients face sometimes when they are in the clinical environment: traffic on their way to the hospital, concerns about their family and children, waiting times, negative interactions they had on that day, weather, etc. that all may affect memory and retrospective evaluation (66, 67).

No literature is available on whether certain physician-patient communication before cystoscopy might help in alleviating pain and anxiety associated with cystoscopy. Moreover, no data is available to evaluate whether physician's gender or type of personality might affect pain associated with cystoscopy.

Cystoscopy performed for the first time might have different types of indications as illustrated in the introduction. Although no evidence is available, some patients might be more anxious if they were told that the indication of cystoscopy is because of suspicious for malignancy based on pre-cystoscopy imaging reports for example compared to other patients with no previous knowledge of suspicion for malignancy. No stratification was done for indication of cystoscopy. We believe that if there were any effect of indication on pain and anxiety scores post-cystoscopy, it will be balanced between the 2 arms because of the randomized nature of the study.

Patients filled their post-cystoscopy evaluations after cystoscopy is done. They usually needed few minutes, to put their clothes back on, between the end of the procedure and filling the post-cystoscopy form. This time was not standardized among study participants. Standardization would be technically challenging in a busy clinic. Although

we believe that there was most probably variability in the duration of the time between the end of cystoscopy and filling the forms among participants, this variability is minimal. Moreover if that variability had any effect on pain and anxiety perception, it will be balanced between the 2 arms because of the randomized nature of the study.

Although similar numbers of patients were assigned at the time of study design among the 3 investigators, variability of assignment occurred at the time of the current interim-analysis and potential early termination of study in the future. We believe that we could have avoided this variability if we had only one investigator.

### *4.2.2 Risk of bias*

By blinding the investigator from the study arm at the time of patient recruitment, we have only partially managed selection bias. Investigators have self-screened patients during their initial interaction at the clinic. Patients whom the co-investigators felt they might have difficulty in understanding written and verbal instructions because of language barrier and/or mental difficulties were excluded by the co-investigators. Nevertheless, we believe that this type of bias, although present, affected both the control and intervention arms equally making its potential impact on the results of this study low. However, we believe that this might affect the generalizability and external validity of the technique in the general population.

In addition, since the investigator was un-blinded at the time of the procedure, he was aware of the study arm the patient was enrolled in before the procedure, which adds the risk of possible performance bias. This type of bias could have been avoided by asking the investigator to perform only the standard cystoscopy, which is part of the management in both arms, and then he can leave the room. If the patient was randomized to the control arm, the nurse can pull the cystoscope right after the physician leaves the room. In contrast, if the patient was randomized to the intervention arm the nurse will remove the cystoscope 2 minutes after cystoscopy is performed. In both scenarios, the investigator would not have known which study arm the patient was randomized to.

### *4.2.3 Possible indirect costs*

Although one of the strengths discussed earlier of this concept was lack of direct costs, there are potential indirect costs to this intervention. Adding 2 minutes to the procedure means adding more time per patient. In a typical busy urological clinic with more than one cystoscopy procedure per session, this might create a challenge for the surgeon as well as for the staff who is trying to manage patients' flow in a timely manner. This might force the staff to reschedule other patients which in return adds to the waiting times.

This leads to another challenge in defining the minimum amount of time to make the end-phase of certain aversive experience less aversive. In this experiment as well as in the Redelmeier experience a fixed time interval was used (2 -3 minutes), which was not

based on any calculation or certain reference. It would be interesting to know if we reduced this interval to 1 minute and still have the same effect as 2 or 3 minutes.

# Chapter 5

## Conclusions

Diagnostic cystoscopy has been developing since the last century. It is evident that diagnostic cystoscopy remains a gold standard in diagnosing and following up bladder cancer and other urological malignancies. Its clinical significance extends further in evaluating other benign urological diseases. Despite advancements in medical diagnostics, cystoscopy is currently an irreplaceable tool for the urologists.

Diagnostic cystoscopy is associated with anxiety, embarrassment and pain for the patient. Pain in particular is more prominent in males, first timers and the use of rigid cystoscope. Even with the use of flexible cystoscopy, most patients report certain levels of pain and discomfort. Even the most common intervention used to alleviate pain associated with cystoscopy demonstrated variable outcomes. There is an unmet need in better understanding patients' pain perception to improve patients' overall experience.

Future decisions are based at least partially on retrospective evaluations. Moreover, assessments of experiences shared with others are usually retrospective evaluations. Improving overall patients' pain perception after an unpleasant procedure like outpatient cystoscopy will not only have potential impact on compliance for future surveillance cystoscopies but also indirectly impact future patients with cystoscopy experiences are shared.

Peak-end theory characteristics were applied in medical and non-medical applications to improve customer/patient satisfaction. In our study we demonstrated that creating a less aversive end-phase by leaving the scope in the bladder without further manipulation is both safe and feasible and caused no side effects to patients. Moreover, our preliminary data analysis showed lower VAS pain scores and anxiety scores after the procedure in the intervention arm. Although results were for the most part not statistically significant because of early and underpowered analysis, we believe that results are promising and coincide with the principles of retrospective evaluation investigated in other experiments.

We believe that this intervention has added a promising non-pharmacological tool to alleviate patients' pain and anxiety perception associated with cystoscopy. Future prospective trials needed to evaluate the value of this intervention if combined with other interventions studied in the literature.

# Appendices

Western Research

Research Ethics

**Western University Health Science Research Ethics Board**
**HSREB Delegated Initial Approval Notice**

**Principal Investigator**: Dr. Nicholas Power
**Department & Institution**: Schulich School of Medicine and Dentistry\Surgery,London Health Sciences Centre

**Review Type**: Full Board
**HSREB File Number**: 109345
**Study Title**: A Randomized Control Trial of a Modified Cystoscopy Method to Reduce Pain Perception

**HSREB Initial Approval Date**: August 30, 2017
**HSREB Expiry Date**: August 30, 2018

**Documents Approved and/or Received for Information**:

| Document Name | Comments | Version Date |
|---|---|---|
| Western University Protocol | | 2017/08/20 |
| Letter of Information & Consent | | 2017/08/20 |
| Data Collection Form/Case Report Form | Pre-procedure Survey | 2017/08/17 |
| Data Collection Form/Case Report Form | Post-procedure Survey | 2017/08/17 |
| Other | Debriefing form | 2017/08/14 |
| Other | Protocol References | 2017/08/20 |

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

**Appendices (continued)**



**A Randomized Control Trial of a Modified Cystoscopy Method to Reduce Pain Perception**

**Letter of Information and Consent**

**Principal Investigator**
Dr. Nicholas Power
Victoria Hospital,

**Co-Investigators**
Dr. Jonathan Izawa
Dr. Joseph Chin
Dr. Khalil Hetou
Ailsa Gan (M3)

You are being invited to participate in a study that examines a modification to routine cystoscopy (scope in the bladder) procedure. This modification aims to decrease pain perception during the procedure. You are invited to participate because you are receiving diagnostic cystoscopy as part of your care.

The goal of the study is to find a better way to perform diagnostic cystoscopy so that the patient experiences the least amount of pain. We aim for quality improvement of the current methods of cystoscopy to achieve a better patient experience.

This study tests a modification in cystoscopy technique to see what effects it has on you as you receive your cystoscopy procedure. This technique has not been tested in cystoscopy, but a similar technique was tested in patients receiving colonoscopy, a different procedure, and found to successfully reduce pain perception. Up to 296 patients will participate in this study and we anticipate that up to 296 will be enrolled at this institution. This study will take up to one year to complete. It is expected that you will be in the study for 1 appointment.

If you agree to participate, you will be asked to complete one questionnaire that takes less than 5 minutes before and after the procedure. Sealed envelopes containing instructions for the intervention group (standard vs. modified) will be prepared for individual patients according to a randomization schedule. This means that you are put into a group by chance, and there is no way to predict which group you will be assigned to. You will have a 50/50 chance of being placed in either group. You will not know whether you are in the standard or the modified cystoscopy group. The modified procedure is a simple change in technique and does not pose any additional risk to you should you be placed in

this intervention group. You will receive a debriefing letter after completion of the post-procedure survey detailing the modification in technique.

Collected data will be stored on the hospital's network drive with a firewall implemented by the hospital that can only be accessed through a password-protected computer on a secure network. All paper collected will be stored in a locked cabinet in an office in the department of urology. The data collected will be kept for 15 years as per Lawson's data retention policy. After this period, an investigator on the research team will delete all data.

Participation in this study is voluntary. There is no known risk to your participation in this study. Breach of privacy is always a risk. This modification does not pose any additional risks of harm over the standard procedure. You may refuse to participate at any time with no effect on your future care. Information that has already been transferred to the research database will not be able to be withdrawn, as it would compromise the findings of the research that had already been completed. If you wish to stop your participation just let your urologist or Dr. Power's research coordinator know. You do not waive any legal rights by signing the consent form. If the results of the research are published or presented at scientific meetings, your name will not be used.

Representatives of The University of Western Ontario's Health Sciences Research Ethics Board may contact you or require access to your study-related records to monitor the conduct of the research. Representatives from Lawson Health Research Institute may require access your study record for quality assurance purposes.

If you have any questions about this research, please contact your urologist or Dr. Power's research coordinator, Kaydee Connor ##########.
If you have any questions about your rights as a research participant or the conduct of the study you may contact the Scientific Director of the Lawson Health Research Institute at##########.

**Appendices (continued)**


**A Randomized Control Trial of a Modified Cystoscopy Method to Reduce Pain Perception**

**CONSENT FORM**

**Principal Investigator:**
Dr. Nicholas Power

**Co-Investigators**
Dr. Jonathan Izawa
Dr. Joseph Chin
Dr. Khalil Hetou
Ailsa Gan (M3)

Please check this box if you are willing to be contacted for future research. ☐

I have read the Letter of Information and have had the nature of the database explained to me. All questions have been answered to my satisfaction. I agree to take part in the study.

---
Name of participant (Print)

---
Signature of participant

---
Date

---
Name of person conducting consent discussion (Print)

---
Signature of person conducting consent discussion

---
Date

**Appendices (continued)**


PATIENT QUESTIONNAIRE: PRE-PROCEDURE

Date _____

Please complete the following questions to the best of your ability:

1) Age _____

2) Weight _____

3) Height _____

4) Gender

☐ Male

☐ Female

☐ Other: please specify _____

5) Highest education level completed

☐ Below high school

☐ High school

☐ University or College

6) Have you ever had a cystoscopy before?

☐ Yes

☐ No

7) Please rank the anxiety level you are experiencing right now with respect to the cystoscopy procedure you are about to receive.


None at all

Extreme anxiety

**Appendices (continued)**

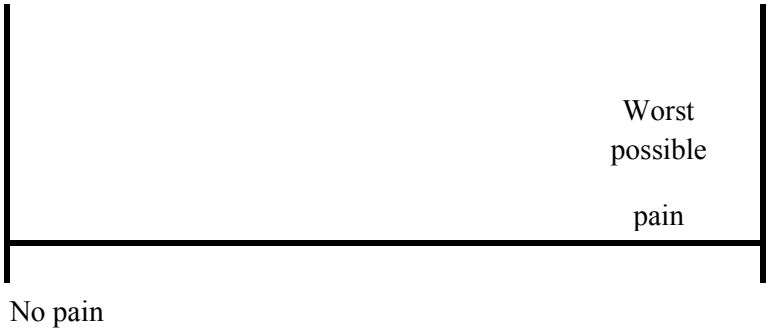
PATIENT QUESTIONNAIRE: POST-PROCEDURE

Date _____

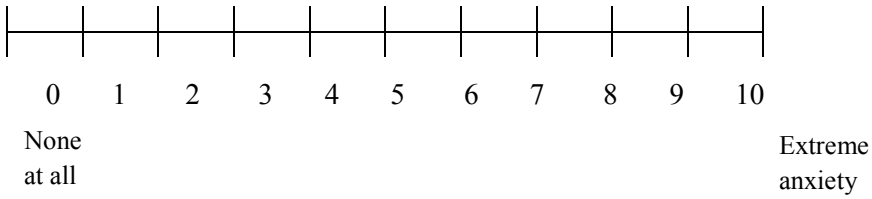
Please complete the following questions to the best of your ability:

VISUAL ANALOGUE SCALE

1) How painful was the cystoscopy procedure that you just received?
Please mark on the scale with a vertical line.




2) Please rank the anxiety level you are experiencing right now.



# DEBRIEFING FORM

**Project Title:** A Randomized Control Trial of a Modified Cystoscopy Method to Reduce Pain Perception

**Principal Investigator:** Dr. Nicholas Power
Affiliation: Schulich School of Medicine and Dentistry/Urology
Contact Information:

Thank you for your participation in this study. The purpose of this study was to evaluate patient experience of cystoscopy using a modification of procedure. We are hoping to achieve a reduction in pain perception. The modification technique was selected based on the "peak-end phenomenon" which explains that the most important moments of a recalled event are the peak and the end of the experience. We applied this by modifying the routine procedure to include laying the cystoscope down at the end and remaining inactive for a period of two minutes before removal of the scope. This does not pose any additional risk to you, but withholding of this information was to avoid potentially increasing participant anxiety before the procedure.

As a reminder, the results are confidential and all data collected is de-identified. If you have any questions or concerns, please contact Dr. Power.

Here are some references if you would like to read more.

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Thank you,

Ailsa Gan, Schulich School of Medicine and Dentistry
Dr. Khalil Hetou, Schulich School of Medicine and Dentistry/Urology
Dr. Nicholas Power, Schulich School of Medicine and Dentistry/Urology
Dr. Joseph Chin, Schulich School of Medicine and Dentistry/Urology
Dr. Jonathan Izawa, Schulich School of Medicine and Dentistry/Urology

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**Vita**

# Khalil Hetou

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## *Education and Training*

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|---|---|
| 2017 – Present | SUO Fellow at the University of Western Ontario |
| 2017 – Present | Masters of Science in Surgery candidate. University of Western Ontario |
| 2017 – 2018 | Global Clinical Scholar Research Training Program. Harvard Medical School. |
| 2016 – 2017 | Urologic Chemotherapeutics fellowship at the Klinikum Bremen Mitte. Bremen, Germany. |
| 2010 – 2016 | Urology Resident at the Klinikum Bremen Mitte. Bremen, Germany. |
| | Earned the German Board of Urology (FA) on 25.05.2016. |
| | Earned the European Board of Urology (FEBU) on 03.06.2017. |
| 2009 – 2010 | Rotating Internship. Jordan University Hospital. Amman, Jordan. |
| 2002 – 2008 | University of Jordan School of Medicine. |
| | Visiting Student at The University of Toronto Medical School |
| | Earned the M.B.B.S degree in June, 2008. |

## *Examinations and Certifications*

• Passed the Medical Council of Canada Evaluating Exam (MCCEE)

• Passed the Medical Council of Canada Qualifying Part 1 Exam (MCCQE1)

• Educational Commission for Certification of Foreign Medical Graduates (ECFMG) certified.

## *Activities and Memberships*

- EAU Guidelines Office Associate: Hypogonadism Panel
- EAU Guidelines Office: 2012 Abstract reviewer: Systematic Review and Individual Patient Data Meta-analysis of Randomized Studies Comparing a Single Immediate Instillation of Chemotherapy after TURBT to TURBT alone.

- Canadian Urological Association (CUA). Candidate Member.
- The German Society of Urology Residents (GESRU): Member.
- The German Society for Urology. Junior Member.
- The European Association of Urology. Junior Member.
- The American Association of Urology. International Resident in Training Member.

## *Abstracts*

- Mean of maximum standardized uptake value (SUV) from PET imaging: a possible predictive parameter for locally advanced prostate cancer. K. Hetou, G. Bauman, J. Thiessen, M. Moussa, I. Rachinsky, Z. Kassam, S. Pautler, M. Dewar, T. Lee, J. F. Valliant, A. Ward, J. Chin.

- Laparoscopic Robot Assisted Reconstruction of a Retrocaval Ureter. Case report. K.Hetou, R.Schnell, A. Plümpe, A.Shardan. M. Kuehl, D. Lazica, C. Schwenke, S. Melchior.

- Primary Testicular Lymphoma. Klinikum Bremen Mitte Experience. K.Hetou, L.Franzaring, S. Melchior.

- MRI-Guided Transurethral Ultrasound Ablation in Patients with Localized Prostate Cancer: 3-Year Outcomes of a Prospective Phase I Study. J. Chin, J. Relle, M. Dewar, K. Hetou, T. Kuru , G. Hatiboglu, I. V. Popeneciu, J. Hafron,

- M. Roethke, M. Mueller-Wolf, Z. Kassam, R. Staruch, M. Burtnyk, D. Bonekamp, H. Schlemmer , S. Pahernik.

- Comparative effectiveness of salvage cryosurgery and high intensity focused ultrasound for radio-recurrent prostate cancer: A regression analysis. M. Peters, M. Dewar, K. Hetou, J. Noteboom, R. Tersteeg, J. Van Der Voort Van Zyp, P. Violette, G. Bauman, J. Chin.

- Salvage Radical Prostatectomy versus Salvage Cryotherapy for Localized Radio-recurrent Prostate Cancer: Comparative Long-Term Outcomes. M. Dewar, T. Lyon, R. Karnes, H. Abed, K.Hetou, J. Chin, S.Boorjian.