

Systematic Review

Several interventions to alleviate pain in male patients undergoing office-based flexible cystoscopy: a systematic review and meta-analysis

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Submitted: 16 March 2021 Accepted: 1 April 2021 Published: 22 July 2021

Abstract

Background: The purpose of this study was to explore the ability of nonpharmacologic adjuvant interventions to alleviate pain in male patients during flexible cystoscopy (FC) under local anesthesia. **Methods:** Electronic databases including PubMed, the Cochrane Library, and Embase were searched to identify eligible clinical trials from inception to 31 December 2020, with no language restrictions. Two independent reviewers used Cochrane Collaboration tools to assess the selection criteria, methodological rigor and risk of bias. Statistical analyses were performed using STATA 14.2. **Results:** In total, 717 studies were initially identified, and fourteen randomized controlled trials were ultimately included. We observed that patients who underwent FC with higher irrigation pressures had significantly lower pain scores on the visual analog scale than their counterparts with lower irrigation pressure during FC (weight mean difference (WMD): -1.43; 95% confidence interval (CI): -1.72 to -1.14) with no between-study heterogeneity ($p = 0.661$). There were no significant differences in pain between immediate or delayed FC groups under the same local anesthetic (standard mean difference (SMD): -0.19; 95% CI: -0.39 to 0.01). A pooled analysis of three studies including 340 male patients showed that men who observed the cystoscopy on the monitor had significantly lower pain ratings compared to those who did not view the operation on the monitor (SMD: -0.64; 95% CI: -1.14 to -0.15). Two studies, including a total of 272 patients, assessed the influence of listening to music on pain and anxiety in male patients during FC. Our meta-analysis found that music significantly improved patient pain (WMD: -0.92; 95% CI: -1.29 to -0.54). Hand-holding and urination during FC also relieved pain and anxiety in male patients undergoing FC. **Conclusions:** We observed that elevated irrigation pressure, real-time cystoscopy visualization, and music therapy alleviated pain in male patients undergoing FC. Well-designed trials are needed to confirm our findings.

Keywords: Flexible cystoscopy; Music; Pressure; Bag squeeze; Real-time visualization

1. Introduction

Cystoscopy is a common office-based examination in many urology clinics. This procedure is indicated for common conditions such as hematuria, suspected bladder tumors, recurrent urinary tract infections, and lower urinary tract symptoms [1,2]. However, a majority of patients are afraid of the procedure because they believe it will be painful [2]. In 1973, Tsuchida Seigi and Sugawara Hiroatsu first introduced flexible cystoscopy (FC), as a potentially more comfortable alternative to rigid cystoscopy (RC) [3]. Subsequently, FC has been routinely performed in many outpatient urology departments, and several studies indicate that FC is more tolerable than RC [4,5]. The European Association of Urology (EAU) guidelines state that FC increases compliance relative to RC for instillation in the urethra under topical anesthetics, especially in male patients due to prostate, tight sphincter, and longer urethra [6]. Even so, it can be difficult to optimally relieve pain and anxiety during FC.

Previous studies have shown that intraurethral lidocaine reduces pain in patients undergoing FC, particularly with longer procedure durations [7–9]. The recent increase in the number of studies investigating nonpharmacologic approaches to improving pain in male patients undergoing

FC has attracted our attention. Thus, our aim was to explore the potential application of nonpharmacologic interventions to reduce pain in men undergoing FC.

2. Methods

2.1 Search strategy

We performed a thorough literature search to retrieve potential publications in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10]. From inception to 31 December 2020, we searched PubMed, Embase and the Cochrane Library without language restriction. In addition, reference lists of relevant articles were hand-searched to ensure a comprehensive search. The keywords or mesh terms used in our meta-analysis were “flexible” and “cystoscopy”. We provided the following search tactic used in PubMed: (flexible (Title/Abstract)) AND (((((((((((Cystoscopy (Title/Abstract)) OR (Cystoscopies (Title/Abstract))) OR (Cystoscopic Surgical Procedures (Title/Abstract))) OR (Cystoscopic Surgical Procedure (Title/Abstract))) OR (Procedure, Cystoscopic Surgical (Title/Abstract))) OR (Procedures, Cystoscopic Surgical (Title/Abstract))) OR (Surgical Procedure, Cystoscopic (Title/Abstract))) OR (Surgery, Cystoscopic (Title/Abstract)))



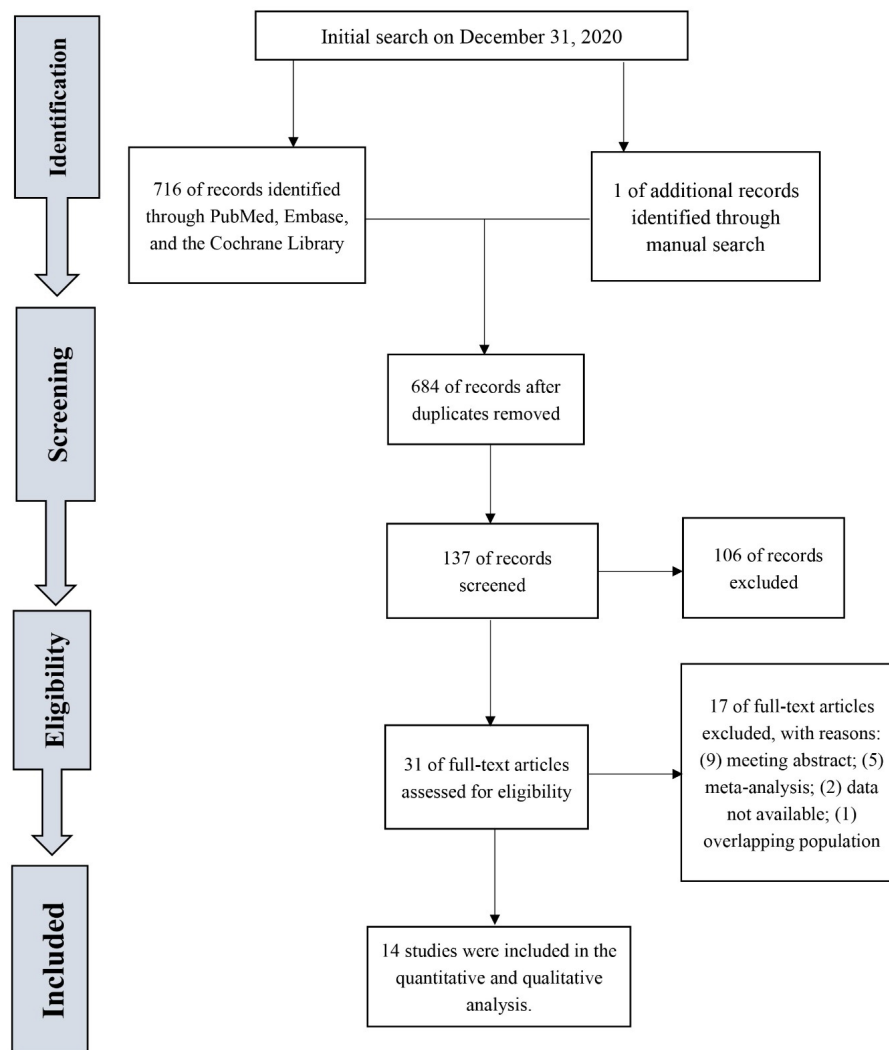


Fig. 1. The PRISMA flowchart.

OR (Surgical Procedures, Cystoscopic (Title/Abstract))) OR (Cystoscopic Surgery (Title/Abstract))) OR (Cystoscopic Surgeries (Title/Abstract))) OR (Surgeries, Cystoscopic (Title/Abstract))).

2.2 Study selection

The PICOS method was used to identify eligible studies. Patients (P): male patients aged >18 years who underwent FC; intervention (I): nonpharmacologic interventions to alleviate pain and anxiety during cystoscopy; comparison (C): publications comparing nonpharmacologic treatments to a control group; outcomes (O): postprocedural pain perception, measured using a visual analog scale (VAS) ranging from 0 to 10 [11]. A high score on the scale indicates high pain intensity. Study design (S): randomized controlled trials (RCTs). Exclusion criteria included the following items: (1) meeting abstracts and reviews including meta-analysis; (2) no systemic sedation or analgesia before cystoscopy; (3) current urinary infection; (4) current pain in the pelvic area, such as bladder pain syndrome and in-

terstitial cystitis; (5) pregnancy; (6) prior urethral surgery; (7) cystoscopy with other procedures, like ureteral stent removal or insertion and biopsy; or, (8) no available data. The study selection process is shown in a flowchart (Fig. 1).

2.3 Data extraction and quality assessment

After removing duplicate publications, the authors independently screened the titles, viewed the abstracts and read the final full texts to determine the eligibility of the retrieved studies. Any disagreements among authors were resolved through discussion. Data from the included studies were extracted using a preformulated table. Two independent reviewers extracted the following data using forms prepared in advance: the first author's name, publication year, age, country, period, sample size, interventions, local anesthesia, and cystoscopy type.

Two authors used the tool of the Cochrane Collaboration's Risk of Bias (RoB) in RevMan software to independently evaluate the methodological quality of the studies. This tool primarily contains seven items covering five types

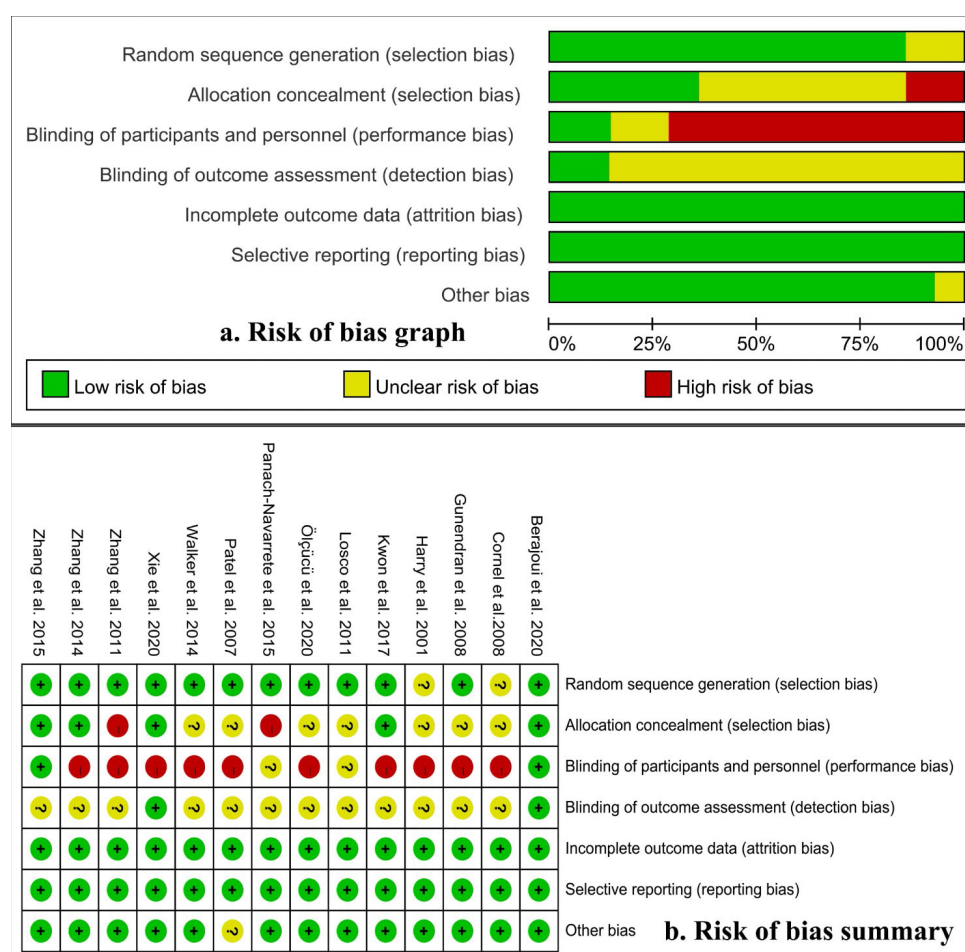


Fig. 2. The evaluated result of methodological quality of enrolled studies in this study. (a) The risk of bias graph. (b) The risk of bias summary.

of bias: selection bias (random sequence generation; allocation concealment); performance bias (blinding of participants and personnel); detection bias (blinding of outcome assessment); attrition bias (incomplete outcome data); reporting bias (selective reporting) and other bias (such as funding sources). Moreover, the two reviewers independently assessed the level of evidence of the included articles using the Oxford Centre for Evidence-Based Medicine criteria [12]. The strength of evidence was graded from level 1 (strongest) to level 5 (weakest) based on research design and data quality.

The RoB summary of the fourteen RCTs [13–26] is shown in Fig. 2. Overall, the risks of selection bias (random sequence generation), attrition bias and reporting bias were low, but the risk of performance bias was high. The risk of detection bias was indeterminate because descriptions of the blinding during outcome assessment were lacking.

2.4 Statistical analysis

Continuous variables are presented as means \pm standard deviation (SD). The median and range were also converted to the mean and SD [27]. The percentiles were trans-

formed to SD using the relevant formula [28]. Continuous variables were calculated using the weighted mean difference (WMD) or standard mean difference (SMD). When there was heterogeneity ($I^2 > 50\%$, $p < 0.1$), a random effect model was used. Otherwise, we used a fixed effect model. Statistical significance was considered as $p < 0.05$. The meta-analysis was completed using STATA 14.2 (StataCorp, College Station, TX, USA).

3. Meta-analysis results

3.1 Search results

Overall, 717 records were initially identified, and fourteen RCTs [13–26] were included in the final analysis. Our study enrolled 1684 male patients who were from the United Kingdom, China, Canada, New Zealand, Spain, USA, Netherlands, Turkey, or South Korea. All flexible cystoscopies included in this study were performed under local anesthesia. Table 1 summarizes the main features of the studies that were included in this meta-analysis.

Table 1. The baseline characteristics of studies included in this study.

Study	Country	Period	Sample size	Age (years)	Interventions	Local anesthesia	FC	LoE
Gunendran <i>et al.</i> 2008	United Kingdom	Not reported	151	Mean (range) EG: 65.8 (35–88) CG: 66.6 (29–89)	Bag squeeze	10 mL of 2% lidocaine gel beforehand	14F (Olympus CYF-4)	2b
Zhang <i>et al.</i> 2015	China	2011.3–2012.12	112	Mean (SD) EG: 65.0 (12.5) CG: 62.3 (13.4)	EG: 150 cm (height from the bag to the bed) CG: 80 cm	10 mL 2% lidocaine gel for 3 minutes before cystoscopy	16F (Olympus CYF-5A)	2b
Berajoui <i>et al.</i> 2020	Canada	2019.9–2019.11	190	Mean (SD) EG: 70.7 (9.7) CG: 69.9 (13)	Bag squeeze	10 mL, lidocaine 2% gel prior to the procedure	Not reported	2b
Harry <i>et al.</i> 2001	USA	Not reported	100	Rang: 45–83	10 mL 2% lidocaine gel retained in the urethra for at least 10 to 15 minutes	10 mL, lidocaine 2% gel prior to the procedure	15F	2b
Losco <i>et al.</i> 2011	New Zealand	2010.8–2010.11	50	Mean EG: 71.44 CG: 66.92	10 mL local anesthesia in the urethra for 3 minutes. After that, a further 10 mL was instilled into the urethra	20 mL of lignocaine 2% gel with chlorhexidine 0.05% (Pfizer (Perth) Pty Limited, Australia)	15F	2b
Panach-Navarrete <i>et al.</i> 2015	Spain	5 months	242	Not reported	12.5 g Cathejell lubricant with lidocaine retained in the urethra for 5 minutes	12.5 g Cathejell lubricant with lidocaine beforehand	15.5F	2b
Patel <i>et al.</i> 2007	USA	Not reported	100	Mean EG: 66.3 CG: 69.5	Visualizing the cystoscopy on a real-time video monitor along with the urologist.	10 cc 2% viscous lidocaine intraurethral before cystoscopy.	16.2F (Olympus CYF-5)	2b
Cornel <i>et al.</i> 2008	Netherlands	2007.6–2007.9	154	Mean (range) EG: 70 (32–88) CG: 70 (31–91)	Watching the video screen together with the urologist during the procedure	water, 2 mL of Instillagel® (Farco-pharma GmbH, Köln, Germany)	16.2F (CYF-5, Olympus Keymed, UK)	2b
Zhang <i>et al.</i> 2011	China	2010.1–2011.1	86	Mean (range) EG: 62.9 (28–84) CG: 64.5 (30–91)	Watching the video screen together with the urologist during the procedure	10 mL 2% viscous lidocaine administrated intraurethrally for 3 minutes before FC	16F (Olympus CYF-5A)	2b
Zhang <i>et al.</i> 2014	China	2013.1–2013.9	124	Mean (SD) EG: 64.8 (11.2) CG: 62.0 (12.7)	Classical music, Chinese folk music, popular music, and foreign music ready for patient selection	10 mL 2% lidocaine jelly administrated intraurethrally for 3 minutes before FC	16F (Olympus CYF-5A)	2b
Ölçücü <i>et al.</i> 2020	Turkey	2019.7–2020.3	148	Mean (SD) EG: 57.89 (12.71) CG: 55.56 (16.41)	Classical music	10 mL 2% lidocaine jelly administrated intraurethrally for 5 minutes before FC	17F (Hawk GmbH, China)	2b
Kwon <i>et al.</i> 2017	South Korea	2015.11–2017.3	86	Mean (SD) EG: 56.1 (7.9) CG: 53.9 (8.8)	Holding the nurse's hand during cystoscopy;	10 mL 2% lidocaine jelly administrated intraurethrally over 3 minutes before FC	15.6F (Olympus CYF-4)	2b
Xie <i>et al.</i> 2020	China	2017.4–2018.4	96	Mean (SD) EG: 53.35 (15.87) CG: 54.10 (15.48)	Urinating during FC	10 mL 2% lidocaine jelly administrated intraurethrally for 10 minutes before FC	16F (Olympus CYF-5A)	2b
Walker <i>et al.</i> 2014	USA	Not reported	45	Rang: 18–70	Virtual reality	2% lidocaine jelly before FC	Not reported	2b

Note: FC, flexible cystoscopy; EG, experimental group; CG, control group; SD, standard deviation; LoE, level of evidence.

3.2 Pressure makes pleasure

Irrigation pressure can be increased by squeezing the irrigation bag or by increasing the height of the irrigation bag during flexible cystoscopy. A pooled analysis of three studies [13–15] including a total of 453 male patients demonstrated that patients in the higher irrigation pressure group had significantly lower VAS scores than their counterparts during FC (WMD: -1.43 ; 95% confidence interval (CI): -1.72 to -1.14 ; Fig. 3) with no between-study heterogeneity ($p = 0.661$).

3.3 Immediate versus delayed FC

The effect of the time interval between application of local anesthetics and FC insertion on patient discomfort remains controversial. Three trials [16–18] containing a total of 392 male patients evaluated the pain with immediate versus delayed FC after the administration of local anesthetics. The results of the meta-analysis showed that there was no significant difference in pain perception between the immediate or delayed insertion groups treated with the same local anesthetic (SMD: -0.19 ; 95% CI: -0.39 to 0.01 ; Fig. 3).

3.4 Patient observation of FC

A pooled analysis of three articles [19–21] including a total of 340 male patients showed that men who watched the cystoscopy on a monitor experienced significantly lower pain compared to those who did not watch the operation (SMD: -0.64 ; 95% CI: -1.14 to -0.15 ; Fig. 3).

3.5 Music intervention

Two studies [22,23] including a total of 272 patients assessed the impact of listening to music on pain and anxiety in male patients undergoing FC. Our meta-analysis found that music significantly improved patient pain (WMD: -0.92 ; 95% CI: -1.29 to -0.54 ; Fig. 3).

3.6 Other interventions

Kwon *et al.* [24] found that hand-holding during FC resulted in a remarkable reduction in pain experienced by male patients (2.9 ± 1.0 in hand-holding group versus 3.7 ± 1.2 in control group). In addition, anxiety was also reduced by hand-holding (41.4 ± 7.8 in hand-holding group versus 48.4 ± 10.8 in control group), and patient satisfaction was improved (8.5 ± 1.8 in hand-holding group versus 6.7 ± 2.4 in control group). Xie *et al.* [25] investigated the effects of urination during FC on urethral pain in male patients, and they observed that the urination group showed significantly lower pain scores 2 (IQR 1-3) during cystoscopy insertion compared to the control group 3 (IQR 2-3), ($p = 0.001$). In addition, Walker *et al.* [26] assessed the ability of virtual reality distraction to relieve pain and anxiety during FC; however, virtual reality distraction did not reduce pain or anxiety in men during cystoscopy.

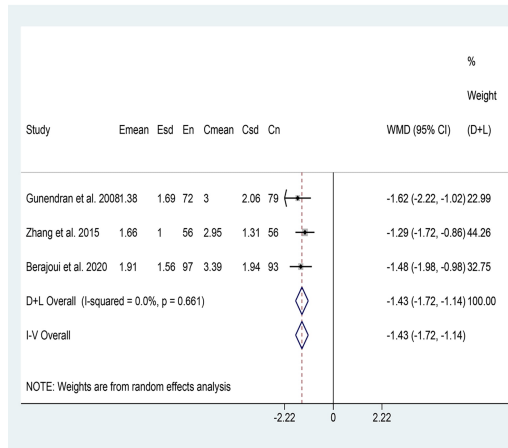
4. Discussion

Flexible cystoscopy has well established advantages, and, thus, it is a common outpatient procedure in urology practice [3–6]. Most studies regarding pain relief during the FC procedure have focused on the instillation of local anesthetics, and previous meta-analyses concluded that intraurethral lidocaine instillation is associated with significantly improved patient pain during FC [7–9]. Other pharmacologic interventions included use of intrarectal diclofenac suppositories [29] and nitrous oxide inhalation [30]. Male patients frequently suffer more discomfort during FC than females because of anatomical differences between males and females [22,23,31]. To date, investigators have conducted many trials to identify potential adjuvant therapies to alleviate pain associated with FC, especially for male patients. The nonpharmacological methods investigated include: increasing irrigation pressure [13–15], delaying the instillation time of topical anesthetics in the urethra [16–18], allowing patients to watch the procedure process [19–21], listening to music [22,23], hand-holding [24], urinating during FC [25], and virtual reality distraction [26]. All of these interventions are practical, inexpensive, and harmless.

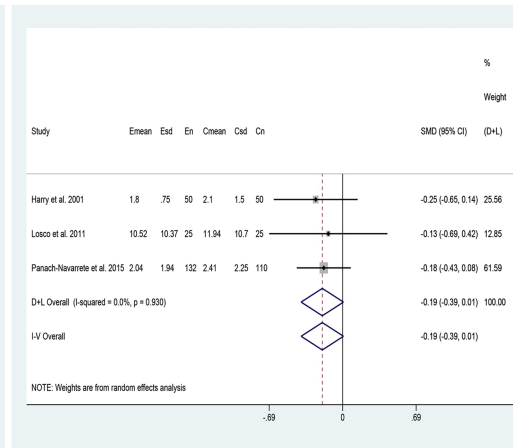
The friction between the cystoscope and the urethral mucosa leads to bleeding and causes pain. Several studies found that the membranous urethra of the external sphincter is the most painful anatomical region during FC [22,32]. Higher irrigation pressures might dilate the FC pathway, improving endoscopic vision and facilitating movement through the urethra. The present study showed that increased irrigation pressure reduced pain during FC. In contrast, delayed cystoscopy after administration of anesthetics had no effect on patient pain. Insufficient volume and action time might contribute to this result. Holmes *et al.* [33] demonstrated a significant reduction in pain during FC in patients administered 20 mL of gel containing lidocaine. In addition, distraction methods were associated with reduced pain during FC. Our study indicated that patient observation of the procedure on the video monitor with the urologist was associated with lower pain ratings. Similarly, listening to music improved pain in men undergoing FC. Other interventions, such as hand-holding or urination, had promising effects on pain reduction during FC. Gooran *et al.* [34] also found that the combination of intraurethral lidocaine gel and lidocaine injection into the glans penis significantly reduced pain during cystoscopy.

There are some limitations in the present study. First, the limited number of studies, the sample sizes, study population, surgeon's experience, and the definition of outcome measures make it difficult to draw definitive conclusions. In addition, ethnic differences in penis size and FC diameters might affect the results. Second, the surgeons were not blinded during the procedure, so it is possible that the FC procedure might have been performed with greater care in patients in the intervention group compared with those in the control group. Finally, VAS scores are patients' self-

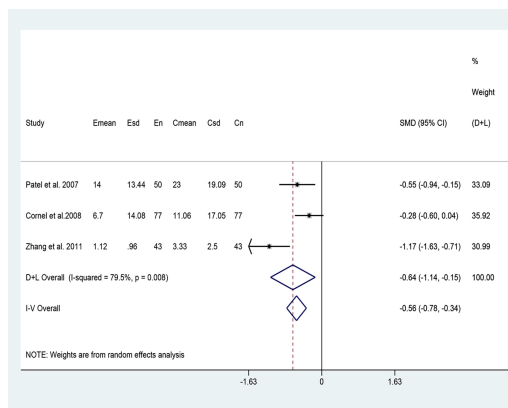
A. Pressure makes pleasure



B. Immediate versus delayed cystoscopy



C. Patient's self-viewing of cystoscopy



D. Music intervention

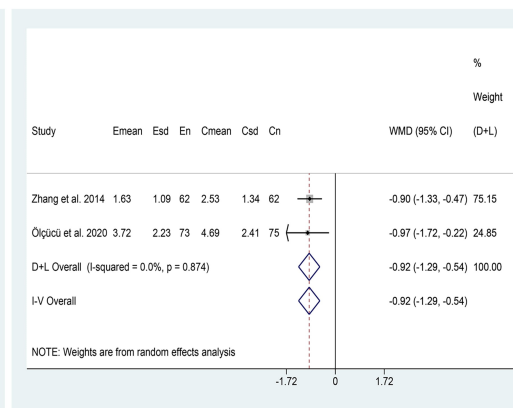


Fig. 3. The results of evaluated outcomes in this meta-analysis. (A) The result of increasing irrigation pressure versus the control group. (B) The result of immediate versus delayed flexible cystoscopy. (C) The result of watching the monitor versus control group. (D) The result of listening to music versus control group.

reported perceptions of pain, which are partly subjective. Objective parameters related to pain remain to be developed.

5. Conclusions

We observed that increased irrigation pressure, real-time visualization of the procedure, and music therapy alleviated pain in male patients undergoing FC. Well-designed trials are needed to confirm these promising, but preliminary, findings.

Author contributions

Conception and design: ZHW; Administrative support: WRW; Provision of study materials or patients: ZHW; Collection and assembly of data: ZHW; Data analysis and interpretation: ZHW; Manuscript drafting: ZHW; Final approval of manuscript: All authors.

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and re-solved.

Acknowledgment

We would like to express our gratitude to all those who helped us during the writing of this manuscript. Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This work was supported by Department of Science and Technology of Sichuan Province (2020YFH0099). The funders had no role in study design, data collection or analysis, preparation of the manuscript, or the decision to publish.

Conflict of interest

The authors declare no conflict of interest.

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