



The use of a heating pad to reduce anxiety, pain, and distress during cystoscopy in female patients

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Abstract

Introduction and hypothesis This study evaluated the effects of using a heating pad during cystoscopy on anxiety, pain, and distress in female patients.

Methods Seventy-four female patients who underwent rigid cystoscopy between January 2017 and August 2017 were randomized to either the experimental group using a heating pad ($n = 37$) or the control group using a pad without heat ($n = 37$). In the experimental group, a heating pad was applied to the patient's sacrum during cystoscopy. All patients completed the State-Trait Anxiety Inventory-S (STAI-S, 20-80) before and after the procedure and assessed their degree of pain and distress after the procedure using a visual analog scale (0–10). Systolic and diastolic blood pressure and pulse rate were also measured before and after the procedure.

Results Demographic characteristics, mean age, procedure duration, and pre- and post-procedural systolic and diastolic blood pressures and pulse rate were statistically similar between the experimental and control groups. The mean STAI-S score of the experimental group was significantly lower than that in the control group (33.1 ± 10.1 vs 48.2 ± 11.1 , $p < 0.001$). The experimental group had significantly lower pain and distress scores (visual analog scale, 3.8 ± 1.6 and 3.8 ± 1.8 respectively,) than the control group (6.4 ± 1.9 and 6.3 ± 2.1 respectively, both $p < 0.001$).

Conclusions Using a heating pad during cystoscopy significantly reduced female patients' anxiety, pain, and distress. We found this to be a safe, simple, and effective tool to use during cystoscopy.

Keywords Heating pad · Cystoscopy · Anxiety · Pain · Distress

Introduction

Cystoscopy is a commonly performed urological procedure for investigating lower urinary tract symptoms in addition to various pathological conditions of the urethra, prostate, and bladder. It is the gold standard for bladder cancer detection, which is the most common malignancy of the urinary tract. Currently, approximately 200,000 bladder tumors occur worldwide annually, with an increased risk for tumors in certain geographic areas. Although the prevalence of this disease is relatively low in some countries, cystoscopy is considered an essential procedure

[1]. The procedure is performed by inserting an optical instrument through the urethra and into the bladder [2–4].

The cystoscope may be metal and rigid or flexible, and its insertion may be associated with patient discomfort, pain or anxiety [5, 6]. Although flexible cystoscopy is more commonly used for diagnostic purposes in developed nations, rigid cystoscopy continues to be widely used in the developing world because of cost and availability [7, 8]. Diagnostic rigid cystoscopy is frequently associated with considerable anxiety and discomfort, and local anesthesia is required to make the procedure more tolerable. Seklehner et al. [4] have reported that 22% of patients feel moderate to severe pain associated with rigid cystoscopy.

Therefore, physicians are sometimes reluctant to refer patients for cystoscopy, and patients may refuse to undergo this necessary urological evaluation. Moreover, anxiety, physical distress, and other aspects of the patient's experience have an impact on future compliance.

Although rigid cystoscopy is generally well tolerated, most patients regard it as an unpleasant and stressful procedure [5]. Additionally, pain-specific anxiety, physical injury, and isolation can cause patient stress during cystoscopy. These stressors affect

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the sympatho-adreno-medullary system, increasing the heart rate and blood pressure, which could cause hyperglycemia or peripheral vasoconstriction [9]. Accordingly, Wong et al. [10] suggested that as respiratory rate and BP are closely related to the respiratory and cardiovascular systems, these physiological responses are important indicators for assessing anxiety.

Using a heating pad has become an established complementary modality in some invasive procedures [11, 12], and an effective tool for decreasing pain and anxiety [13]. Therefore, we sought to assess the impact of using a heating pad on patients' perceptions of anxiety, distress, and pain during cystoscopy.

Materials and methods

Patients and cystoscopy procedure

Seventy-four female patients who underwent rigid cystoscopy between January 2017 and August 2017 were classified into two groups: 37 patients in the experimental group, who had a heating pad applied during the procedure, and 37 patients in the control group, who had a heating pad applied without heat. The study was prospective, and randomization was performed using a random allocation table. Once patient consent had been obtained, a random allocation table was used to assign each patient to one of the two arms of the study.

Rigid cystoscopy was performed on an outpatient basis before any treatment was initiated. Information collected included demographic characteristics such as age, weight, height, and reason for cystoscopy.

All patients received information about the procedure and provided informed consent to undergo the procedure. Rigid cystoscopy was performed according to a standard protocol by the same surgeon in an aseptic manner with all procedures being identical [2].

We used a commercially available instant heating pad. The 39 × 26 cm heating pad (Loess Fomentation Pack; MDPrime, Yangju, Korea) was warmed to 40–45 °C. Each patient in the experimental group had the heating pad applied to her sacrum for 10 min, whereas patients in the control group had an unheated pad similarly applied during rigid cystoscopy.

Analysis of anxiety, pain, and distress

Before the procedure, we measured systolic and diastolic BP and pulse rate (PR) after sufficient rest. We measured anxiety levels using the State-Trait Anxiety Inventory (STAI), a self-assessed anxiety inventory comprising two subscales of 20 multiple choice questions each. The STAI was established by Spielberger [14], and has been translated into Korean. The Korean version of the STAI has been validated and shown to exhibit excellent psychometric properties. Its internal

consistency was reported to be Cronbach $\alpha = 0.91$. The STAI-S is scored between 20 and 80 points, with larger scores indicating greater anxiety levels. The anxiety ranges were defined as follows: 0–19, no anxiety; 20–39, minor anxiety; 40–59, moderate anxiety; 60–79, high anxiety; and ≥ 80 , panic [15].

Within 5 min of the procedure, we repeated STAI, BP, and PR measurements, and the patients self-reported their pain, distress, and ability to tolerate a rigid cystoscopy according to the visual analog scale (VAS, scored 0–10) [16]. The patients were given information about the results of the cystoscopy after each patient's BP and pulse were measured and on completion of the questionnaire.

Continuous variables are expressed as percentages and mean \pm standard deviation, and statistical significance was determined using the Mann–Whitney test and Wilcoxon signed rank tests. All analyses were performed using SPSS software (version 22.0; IBM Corp, Armonk, NY, USA). *p*-values < 0.05 were considered statistically significant. The institutional review board of our hospital reviewed and approved the study protocol.

Results

The mean age of the patients in both the experimental group and the control group were similar (61.1 ± 11.5 and 61.1 ± 12.1 years respectively; $p = 0.758$). No significant differences were noted between the two groups regarding demographic characteristics, reasons for cystoscopic examination, or pre-procedural parameters, including systolic and diastolic BP and PR ($p = 0.198, 0.341, 0.592, \text{ and } 0.452$ respectively; Table 1).

The procedure duration was also statistically similar for both the experimental (8.3 ± 2.1 min) and the control (8.6 ± 2.8 min, $p = 0.64$) group. After rigid cystoscopy, mean anxiety scores according to the STAI-S in the experimental and control groups differed significantly (33.1 ± 10.1 , and 48.2 ± 11.1 respectively; $p < 0.001$, Fig. 1), and the degree of the decrease of anxiety levels according to the STAI (δ) (pre-score minus post-score) in the experimental group and control group differed significantly (21.1 ± 12.4 and 6.4 ± 12.6 respectively; $p < 0.001$). The mean pain scores for the experimental group (3.8 ± 1.6) were significantly lower than those for the control group (6.4 ± 1.9 , $p < 0.001$). The mean distress scores for the experimental group (3.8 ± 1.8) were significantly lower than those for the control group (6.3 ± 2.1 , $p < 0.001$). No significant differences were detected between the two groups regarding post-procedural parameters, including systolic and diastolic BP and PR ($p = 0.103, 0.185, \text{ and } 0.82$ respectively). However, there were significant differences in the amount of change in systolic and diastolic BP and PR ($p = 0.003, 0.012, \text{ and } 0.006$ respectively; Table 2).

Table 1 Summary of patient characteristics and pre-procedural status

Parameter	Experimental (<i>n</i> = 37) Mean ± SD/median	Control (<i>n</i> = 37) Mean ± SD/median	<i>p</i> value
Patient characteristics			
Age (years)	61.1 ± 11.5/62	61.1 ± 12.1/64	0.758
Body weight (kg)	56.9 ± 8.6/55	54.4 ± 8.7/54	0.270
Height (cm)	156.0 ± 5.2/157	155.1 ± 4.8/155	0.278
Reason for cystoscopy, <i>n</i> (%)			
BN obstruction	5(13.5)	6 (16.2)	0.198
IC/BPS	9 (24.3)	9 (24.3)	
Bladder tumor	1 (2.7)	3 (8.1)	
Hematuria	22(59.5)	19(51.4)	
Pre-procedural parameter			
Systolic BP (mmHg)	133.2 ± 17.2/130	129.2 ± 17.1/130	0.341
Diastolic BP (mmHg)	81.6 ± 10.1/80	80.3 ± 11.7/80	0.493
Pulse rate (beats/min)	80.3 ± 12.6/79	80.9 ± 10.3/80	0.592
STAI-S	57.2 ± 9.4/59	54.6 ± 12.8/58	0.452

SD standard deviation, *BP* blood pressure, *BN* bladder neck, *IC/BPS* interstitial cystitis/bladder pain syndrome, *STAI-S* State-Trait Anxiety Inventory-S

Discussion

Cystoscopy is invasive and somewhat painful for patients and often causes feelings of anxiety and distress [5, 6, 17, 18]. Yerlikaya et al. [18] reported that patients find cystoscopy to be more painful than urodynamic studies, and Greenstein et al. [6] reported that pain levels during a patient's first cystoscopy were higher than those for repeated tests. Biardeau et al. [17] reported that most patients were likely to have anxiety, pain, or embarrassment during cystoscopy.

A flexible cystoscope is more commonly used in developed nations, but rigid cystoscopy continues to be widely used in the developing world because it is less expensive, easier to

perform, and has a better visual field. Diagnostic rigid cystoscopy is frequently associated with considerable anxiety and discomfort, and local anesthesia is required to make it somewhat tolerable [7, 8]. However, some physicians perform rigid cystoscopy in female patients without any anesthesia because they believe that the cystoscope will pass more easily through the shorter female urethra and because female patients have overall better pain tolerance [19]. In addition, most studies on pain and patient morbidity during cystoscopy have focused on male patients [4, 20, 21]. Few data exist regarding the tolerance of cystoscopy in female patients [22, 23].

Therefore, various techniques and treatments to reduce pain, anxiety, and distress in female patients who undergo

Fig. 1 Comparison of the mean anxiety scores between the two groups according to the State-Trait Anxiety Inventory-S

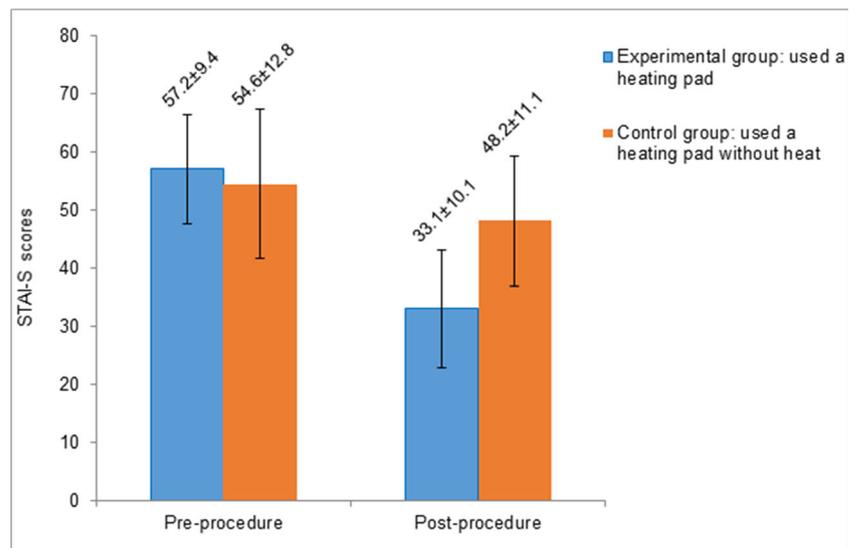


Table 2 Anxiety, pain, and distress during and after cystoscopy

Parameter	Experimental (<i>n</i> = 37) Mean ± SD/median	Control (<i>n</i> = 37) Mean ± SD/median	<i>p</i> value
Duration of procedure (min)	8.3 ± 2.1/10	8.6 ± 2.8/9	0.641
Post-procedural parameters			
Pain (VAS)	3.8 ± 1.6/3	6.4 ± 1.9/6	< 0.001*
Distress (VAS)	3.8 ± 1.8/4	6.3 ± 2.1/6	< 0.001*
STAI-S	33.1 ± 10.1/33	48.2 ± 11.1/48	< 0.001*
STAI-S (δ)	21.1 ± 12.4/23	6.4 ± 12.6/8	< 0.001*
Systolic BP (mmHg)	130.5 ± 14.9/130	135.7 ± 16.4/140	0.103
Systolic BP (δ)	2.7 ± 13.3/0	−6.5 ± 13.4/−10	0.003*
Diastolic BP (mmHg)	82.4 ± 11.4/80	86.0 ± 10.4/90	0.185
Diastolic BP (δ)	−0.8 ± 8.0/0	−5.7 ± 10.1/−10	0.012*
Pulse rate (beats/min)	78.7 ± 11.7/78	83.0 ± 10.3/81	0.82
Pulse rate (δ)	1.6 ± 5.7/2	−2.1 ± 7.0/−4	0.006*

SD standard deviation, *STAI-S* anxiety scores with the State-Trait Anxiety Inventory-S, *STAI-S (δ)* degree of decrease of anxiety levels with the State-Trait Anxiety Inventory-S, *VAS* visual analog scale (0–10), *BP* blood pressure, *systolic BP (δ)* degree of decrease of systolic BP, *diastolic BP (δ)* degree of decrease of diastolic BP, *pulse rate (δ)* degree of decrease of pulse rate

* *p* < 0.05

rigid cystoscopy are needed. Various anesthetic techniques and nonpharmacological alternative treatments are used during cystoscopy for the relief of anxiety, pain, and distress, including urethral lubrication [24], intra-urethral lidocaine injection [19, 25], or pretreatment with intramuscular narcotics [26], providing a detailed explanation [27], hand-holding [28], listening to music [7, 21], and virtual reality distraction [29]. Goldfischer et al. [24] stated that adequate amounts of lidocaine jelly placed in the urethra for 20 min before cystoscopy can significantly decrease pain in male patients. Song et al. [26] reported that midazolam anesthesia may relieve pain during rigid and flexible cystoscopy. Kwon et al. [28] reported that hand-holding during cystoscopy significantly reduced patients' feelings of anxiety, pain, discomfort, and dissatisfaction. Yeo et al. [7] and Zhang et al. [21] also stated that listening to music during rigid cystoscopy decreased anxiety, pain, and dissatisfaction in male patients. However, Stein et al. [25] found no decrease in pain perception in male or female patients following lidocaine gel instillation with a 5- or 10-min indwelling time compared with instillation of a plain lubricant. Walker et al. [29] reported that virtual reality distraction treatments during cystoscopy did not mitigate pain in male patients. Therefore, these approaches may be suboptimal for alleviating patient pain, fear, and anxiety during the procedure. Other effective, nonpharmacological alternative treatment modalities should be considered.

Heating treatments are inexpensive, readily available, and commonly used in the treatment of musculoskeletal disorders. As an alternative treatment modality, heat is often used to relieve pain and muscle spasms, to increase blood flow through vasodilatation, to facilitate tissue healing, and to decrease

distress [30, 31]. Heat may also stimulate certain areas of the brain, exerting a psychosomatic effect [32]. Several studies suggested that heating treatments improve psychological and physiological parameters. Heating treatments also have anxiolytic effects and have previously been applied to ameliorate stressful interventions. Using a heating pad is an established complementary treatment for several diseases and invasive procedures [33, 34]. Nuhr et al. [33] reported that active warming relieved acute low back pain in a clinical setting. Denegar et al. [34] stated that female patients were more likely to report clinically meaningful improvement in pain and symptoms of knee osteoarthritis using heat, cold, and a heating pad.

Importantly, the present study showed remarkable and statistically significant beneficial effects of using a heating pad to reduce female patients' anxiety, pain, and distress during rigid cystoscopy. To our knowledge, no previous study has investigated whether using a heating pad on a patient's sacrum would decrease female patients' anxiety, pain, and distress during cystoscopy.

This study showed that systolic and diastolic BP and PR were slightly elevated after cystoscopy in the control group. These effects were statistically significant, but clinically insignificant as the changes were small and there were no other symptoms. However, it may be meaningful that there was no change in BP and PR in the heating pad group whereas there was a slight increase in the control group after cystoscopy. Although we hypothesized that we could assess anxiety or distress quantitatively by measuring vital signs, multiple environmental variables affect changes in BP and PR.

The present study had several limitations. First, this study was not blinded for the patients or physicians, possibly resulting in some bias in data interpretation or patients' reporting of

anxiety, pain, and distress levels. Owing to the nature of the intervention, it was not possible to completely blind the patient and physician to the treatment allocation. Second, although the sample size was estimated based on data from a previous study, our sample size was small and from a single center. Third, the timing of BP and pulse measurement could be a potential limitation. Finally, STAI-S and VAS scores are partially subjective, but objective parameters were not investigated because these tools are widely used for such studies.

Despite these limitations, this study demonstrated that female patients using a heating pad on the sacrum experienced less anxiety, pain, and distress during invasive rigid cystoscopy. Using a heating pad on the sacrum of female patients during cystoscopy is a non-invasive, nonpharmacological, safe, simple, and effective intervention that could be clinically beneficial in patients undergoing urological procedures under local anesthesia. Using a heating pad on the sacrum of female patients during cystoscopy also resulted in increased patient comfort, and satisfaction, which could contribute to the long-term success of the procedure. We recommend using a heating pad as an effective adjunct to other pain and anxiety-reducing treatments used during cystoscopy. In addition, applying a heating pad is a possible complementary modality for improving patients' comfort during invasive procedures in general.

Compliance with ethical standards

Conflicts of interest None.

References

- Lodde M, Mian C, Comploj E, Palermo S, Longhi E, Marberger M, et al. uCyt+ test: alternative to cystoscopy for less-invasive follow-up of patients with low risk of urothelial carcinoma. *Urology*. 2006;67:950–4.
- Babjuk M, Bohle A, Burger M, Capoun O, Cohen D, Comperat EM, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. *Eur Urol*. 2017;71:447–61.
- Burger M, Catto JW, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, et al. Epidemiology and risk factors of urothelial bladder cancer. *Eur Urol*. 2013;63:234–41.
- Seklehner S, Remzi M, Fajkovic H, Saratlija-Novakovic Z, Skopek M, Resch I, et al. Prospective multi-institutional study analyzing pain perception of flexible and rigid cystoscopy in men. *Urology*. 2015;85:737–41.
- Seklehner S, Engelhardt PF, Remzi M, Fajkovic H, Saratlija-Novakovic Z, Skopek M, et al. Anxiety and depression analyses of patients undergoing diagnostic cystoscopy. *Qual Life Res*. 2016;25:2307–14.
- Greenstein A, Greenstein I, Senderovich S, Mabeesh NJ. Is diagnostic cystoscopy painful? Analysis of 1,320 consecutive procedures. *Int Braz J Urol*. 2014;40:533–8.
- Yeo JK, Cho DY, Oh MM, Park SS, Park MG. Listening to music during cystoscopy decreases anxiety, pain, and dissatisfaction in patients: a pilot randomized controlled trial. *J Endourol*. 2013;27:459–62.
- Vasudeva P, Kumar A, Kumar N, Jha SK, Kumar R, Mohanty A, et al. Effect of intraurethral dwell time of local anesthetic jelly on pain perception in men undergoing outpatient rigid cystoscopy: a randomized prospective study. *J Endourol*. 2014;28:846–9.
- Robinson L. Stress and anxiety. *Nurs Clin N Am*. 1990;25:935–43.
- Wong HL, Lopez-Nahas V, Molassiotis A. Effects of music therapy on anxiety in ventilator-dependent patients. *Heart Lung*. 2001;30:376–87.
- Ng V, Lai A, Ho V. Comparison of forced-air warming and electric heating pad for maintenance of body temperature during total knee replacement. *Anaesthesia*. 2006;61:1100–4.
- Weerasekara RM, Tennakoon SU, Suraweera HJ. Contrast therapy and heat therapy in subacute stage of grade I and II lateral ankle sprains. *Foot Ankle Spec*. 2016;9:307–23.
- Kim JW, Kim HJ, Park YJ, Kang SG, Park JY, Bae JH, et al. The effects of a heating pad on anxiety, pain, and distress during urodynamic study in the female patients with stress urinary incontinence. *Neurourol Urodyn*. 2018;37:997–1001.
- Julian LJ. Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). *Arthritis Care Res*. 2011;63(Suppl 11):S467–72.
- Wu PY, Huang ML, Lee WP, Wang C, Shih WM. Effects of music listening on anxiety and physiological responses in patients undergoing awake craniotomy. *Complement Ther Med*. 2017;32:56–60.
- Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres? *Pain*. 1997;72:95–7.
- Biardeau X, Lam O, Ba V, Campeau L, Corcos J. Prospective evaluation of anxiety, pain, and embarrassment associated with cystoscopy and urodynamic testing in clinical practice. *Can Urol Assoc J*. 2017;11:104–10.
- Yerlikaya G, Laml T, Elenskaia K, Hanzal E, Kolbl H, Umek W. Pain perception during outpatient cystoscopy: a prospective controlled study. *Eur J Obstet Gynecol Reprod Biol*. 2014;173:101–5.
- Choe JH, Kwak KW, Hong JH, Lee HM. Efficacy of lidocaine spray as topical anesthesia for outpatient rigid cystoscopy in women: a prospective, randomized, double-blind trial. *Urology*. 2008;71:561–6.
- Patel AR, Jones JS, Angie S, Babineau D. Office based flexible cystoscopy may be less painful for men allowed to view the procedure. *J Urol*. 2007;177:1843–5.
- Zhang ZS, Wang XL, Xu CL, Zhang C, Cao Z, Xu WD, et al. Music reduces panic: an initial study of listening to preferred music improves male patient discomfort and anxiety during flexible cystoscopy. *J Endourol*. 2014;28:739–44.
- Seklehner S, Saratlija-Novakovic Z, Skopek M, Fajkovic H, Remzi M, Duvnjak M, et al. Prospective, multi-institutional pain assessment of 150 women undergoing diagnostic cystoscopy. *Minerva Urol Nefrol*. 2016;68:417–23.
- Patel AR, Jones JS, Babineau D. Impact of real-time visualization of cystoscopy findings on procedural pain in female patients. *J Endourol*. 2008;22:2695–8.
- Goldfischer ER, Cromie WJ, Karrison TG, Naszkiewicz L, Gerber GS. Randomized, prospective, double-blind study of the effects on pain perception of lidocaine jelly versus plain lubricant during outpatient rigid cystoscopy. *J Urol*. 1997;157:90–4.
- Stein M, Lubetkin D, Taub HC, Skinner WK, Haberman J, Kreutzer ER. The effects of intraurethral lidocaine anesthetic and patient anxiety on pain perception during cystoscopy. *J Urol*. 1994;151:1518–21.
- Song YS, Song ES, Kim KJ, Park YH, Ku JH. Midazolam anesthesia during rigid and flexible cystoscopy. *Urol Res*. 2007;35:139–42.
- Kesari D, Kovisman V, Cytron S, Benjamin J. Effects on pain and anxiety of patients viewing their cystoscopy in addition to a detailed explanation: a controlled study. *BJU Int*. 2003;92:751–2.
- Kwon WA, Lee JW, Seo HK, Oh TH, Park SC, Jeong HJ, et al. Hand-holding during cystoscopy decreases patient anxiety, pain, and dissatisfaction: a pilot randomized controlled trial. *Urol Int*. 2017;100:222–7.

29. Walker MR, Kallingal GJ, Musser JE, Folen R, Stetz MC, Clark JY. Treatment efficacy of virtual reality distraction in the reduction of pain and anxiety during cystoscopy. *Mil Med.* 2014;179:891–6.
30. Wang Y, Feng J, You G, Kan X, Qiu L, Chen G, et al. Heating pad for the bleeding: external warming during hemorrhage improves survival. *J Trauma.* 2011;71:1915–9.
31. Nadler SF, Steiner DJ, Erasala GN, Hengehold DA, Abeln SB, Weingand KW. Continuous low-level heatwrap therapy for treating acute nonspecific low back pain. *Arch Phys Med Rehabil.* 2003;84:329–34.
32. Garra G, Singer AJ, Leno R, Taira BR, Gupta N, Mathaikutty B, et al. Heat or cold packs for neck and back strain: a randomized controlled trial of efficacy. *Acad Emerg Med.* 2010;17:484–9.
33. Nuhr M, Hoerauf K, Bertalanffy A, Bertalanffy P, Frickey N, Gore C, et al. Active warming during emergency transport relieves acute low back pain. *Spine (Phila Pa 1976).* 2004;29:1499–503.
34. Denegar CR, Schimizzi ME, Dougherty DR, Friedman JE, Clark JE, Comstock BA, et al. Responses to superficial heating and cooling differ in men and women with knee osteoarthritis. *Physiother Theory Pract.* 2012;28:198–205.