Received: 1 November 2020 | Accepted: 21 December 2020

DOI: 10.1111/ijcp.13969

ORIGINAL PAPER

UROLOGY

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

An effective treatment option for pain caused by urolithiasis: A randomised-controlled trial of local active warming with heat-patch

Huseyin Mutlu[1] | Kasim Ertas[2] | Kamil Kokulu[1] | Ekrem Taha Sert[1] | Mehmet Akif Diri[3] | Murat Gul[4]

[1]Department of Emergency Medicine, Aksaray University School of Medicine, Aksaray, Turkey

[2]Department of Urology, Van Yüzüncü Yil University School of Medicine, Van, Turkey

[3]Department of Urology, Aksaray University School of Medicine, Konya, Turkey

[4]Department of Urology, Selcuk University School of Medicine, Konya, Turkey

Correspondence
Huseyin Mutlu, Department of Emergency Medicine, Aksaray University Medical School, 68100 Aksaray, Turkey.
Email: hmutlu70@hotmail.com

Abstract

Background: There is growing interest in physical medicine treatment options for renal colic. In this study, we aimed to determine whether or not heat-patch treatment with no drug was effective in relieving renal colic.

Methods: For this purpose, patients who were diagnosed with renal colic in the emergency department were randomised to have either heat-patch or sham treatment. The Visual Analogue Scale (VAS) scores of renal colic, body temperature (Btemp), and sub-patch skin temperature (Stemp) values were measured at 0, 15, 30, 45, and 60 minutes. In addition, the salvage treatment needs of the groups were compared.

Results: The average age of the study group was 30.5 ± 8.3 years and that of the sham group was 31.0 ± 8.2 years ($P = .75$). According to the baseline VAS score of the patients, 15, 30, 45, and 60 minutes VAS scores significantly decreased in the heat-patch group ($P < .001$). The Btemp values did not differ significantly between the heat-patch and sham groups. In addition, no statistically significant difference was found between the two groups in terms of Stemp values at 0 and 15 minutes ($P = .39$ and $P = .10$, respectively). However, there was a significant difference in the heat-patch group in terms of Stemp values at 30, 45, and 60 minutes compared with the sham group ($P < .001$). The salvage treatment rates for the heat-patch and sham groups were 11.5% and 31.4%, respectively ($P = .01$).

Conclusion: As non-pharmaceutical treatment, the heat-patch has been shown to be a possible candidate for pain relief in patients with urolithiasis. Further research should concentrate on multicentre and large scale randomised studies.

1 | INTRODUCTION

For centuries, urolithiasis has been known for being one of the most painful diseases and its prevalence is increasing.[1] It is estimated that 8%-15% of people around the world would face renal colic some time in their lives. In total, urolithiasis has been diagnosed in about 12% of the US population, and every year, there are approximately 2 million treatment visits at outpatient clinics for the disease.[2] In the United States, renal colic accounts for 1% of all visits to the emergency department. However, for 50% of all patients with a history of renal calculi, this portion will rise to 50% after10 years.[1,3]

Renal colic occurs as a result of spasm because of the obstruction and distension caused by calculus in the ureter.[1] As recommended by the European Association of Urology, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are first-line treatments for renal colic.[4] However, they may cause renal injury by reducing renal blood circulation.[5,6] In addition, NSAIDs can cause gastrointestinal complications (such as ulcers and reflux).[7,8] Their use is also limited

in patients with hepatic failure and chronic obstructive pulmonary disease.[5] Opioids the other analgesic option have a wide range of side effects, including nausea, vomiting, hypotension, sedation, dizziness, and even respiratory depression.[9,10]

In addition to these pharmaceutical agents, there are non-pharmaceutical alternative treatment methods that are used in relieving renal colic, including acupuncture, descending or ascending ladder, trigger point injection, Turkish bath, and local heating with a blanket.[11,12]

Heat-patch is an effective physical medicine treatment option designed to alleviate muscle pain by applying heat and is frequently used as physical therapy. The heat patch is quickly activated upon contact with air after being removed from its sheath. It contains no drugs, but iron powder, activated carbon, and water. Heat is generated when the iron particles inside the patch come in contact with air. The patch starts dissipating natural heat (long-term, 8 hours) several minutes after being targeted on the projective area of the pain. Patient satisfaction is high because it has an odourless and thin-dimension design.

Considering the success of heat-patch treatment amongst other non-pharmaceutical alternative treatment methods.[12-15] The aim of this study was to evaluate the efficacy of a heat-patch in relieving renal colic and to investigate its usability in daily treatment plans.

What's known

- The use of heat therapy in several diseases showed promising results. However, the use of heat therapy in the treatment of renal colic is scarce.

What's new

- The use of heat-band therapy for acute renal colic might be used in emergency services as a first-line treatment.

2 | MATERIALS AND METHODS

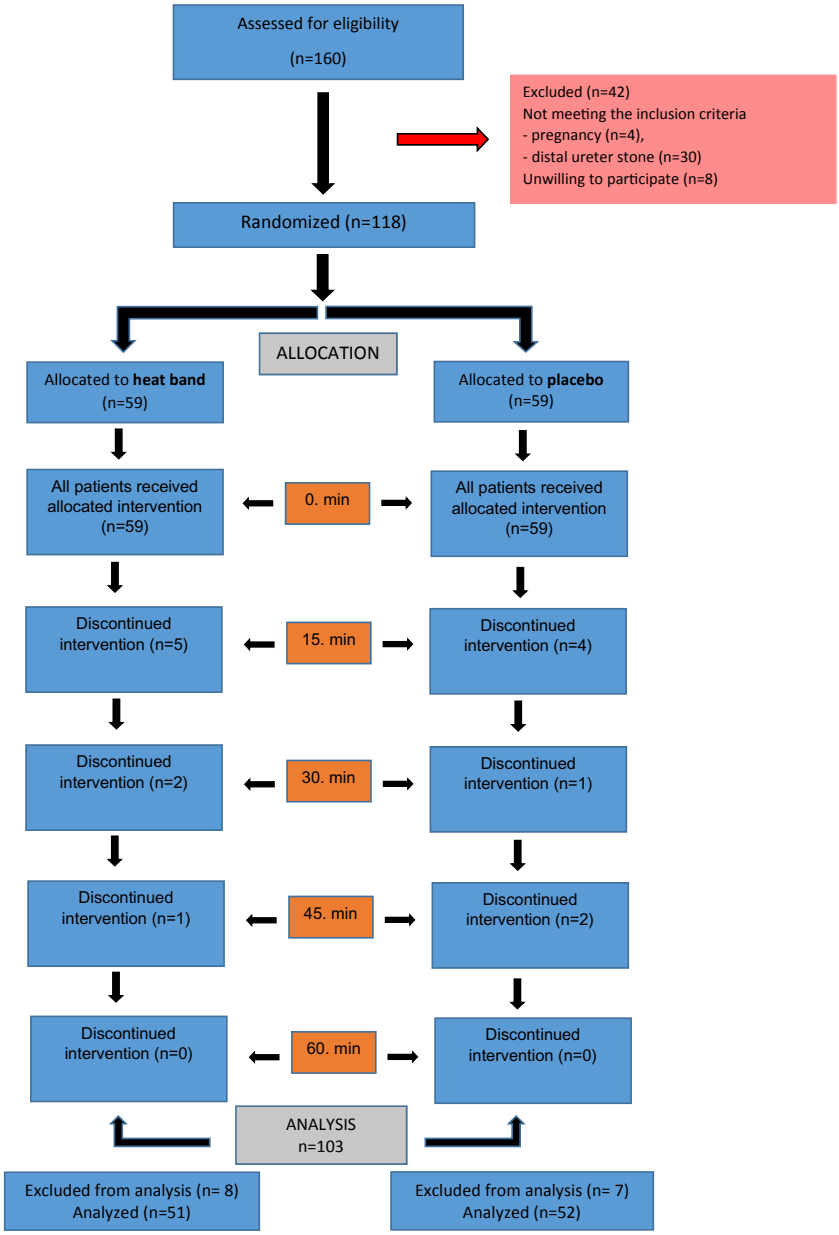
This prospective study was designed as a randomised controlled, patient blind, single-centre clinical study held in Aksaray University Hospital between November 2018 and March 2019. The patients were provided detailed information about the study and the informed consent form was signed. A total of 160 patients aged between 18 and 50 years and diagnosed with ureter stones by radiological imaging techniques (kidney–bladder–ureter radiography, ultrasonography, or computed tomography) were subsequently registered for the study. Patients who had distal ureter stones(one-third of the last part of the ureter), were pregnant, had known previous allergy to skin patches, or had difficulty comprehending the Visual Analogue Scale (VAS) were excluded from the study. In addition, patients who could not with stand pain and wanted analgesic agents were excluded. Out of 160, 42 patients failed to meet the inclusion criteria, and the remaining 118 patients who fulfilled the criteria for this study were offered participation by written information, and randomisation was performed to receive either heat-patch or sham treatment (Figure 1). Randomisation was conducted with a closed-envelope method. On the basis of the envelope selection, for patients who chose the letter S, a heat patch (9.5 × 13.0 cm)containing iron powder, activated carbon, and water (VoltaPatch;Glaxo Smith Kline Pharmaceuticals) was administered to the most painful region as indicated by the patients. For those who chose the letter C, a sham-patch a cotton pad wrapped with gauze and designed to have the same size, weight, colour, and temperature (room temperature) as that of a heat patch was applied in a similar base. The patients in both groups did not receive any medical treatment outside the patch, but analgesic treatment (3 mL of diclofenac sodium 75 mg) was initiated if the patient requested it during any period of the study. If the pain persisted, opioids (fentanyl 1.5 mcg/kg, iv) were the second option.

All the patients enrolled in the study were evaluated with a detailed medical history and physical examination. Patches were attached to the locations with most pain. The VAS scores were evaluated for both groups at 0, 15, 30, 45, and 60 minutes after patch application. All the patients were monitored and their vital findings were checked. Their body temperature (Btemp) values were measured with a tympanic thermometer (Braun ThermoScan IRT4520; Braun GmbH, Kronberg, Germany; range 34.0°-42.2°). The skin temperature (Stemp) values were measured using a thermometer (Nihon Kohden YSI-409A;Nihon Kohden, Tokyo, Japan) placed underneath the patch application site. At the end of this period, those who did not want to wait until the end and those who could not withstand pain and were given analgesic treatment (3 mL of diclofenac sodium 75 mg, im) were also excluded.

2.1 | Statistical analysis

Statistical Package for the Social Sciences (SPSS) Statistics (v.15.0; SPSS Inc, Chicago, IL, USA) was used to perform statistical analyses. Numerical data were presented as means ± standard deviation and medians (interquartile range). Frequency data were presented as n and %. The normal distribution of data was determined by the Kolmogorov–Smirnov test. The Mann–Whitney *U* test and Student *t* test were used to analyse comparisons between the two groups for numerical data. Homogeneity of the variance was tested using the Levene test. The mean and median differences were presented in a 95% confidence interval. The study was planned as a superiority trial and all the analyses were performed according to the principle of intention to treat. All the hypotheses were constructed as two-tailed and an alpha critical value of 0.05 was accepted as significant. For this study, the sample size was calculated using the G*power software(v.3.1). In a similar study conducted earlier, it was found that the average VAS scores for pre and post-treatment were 82.7 and

FIGURE 1 Study flow diagram



36.3, respectively, achieving an effect size of greater than one.[13] In this study, we aimed to reach at least 45 people in each group and 90 people in total in order to obtain a moderate effect size ($d = 0.50$) by predicting a smaller effect size.

2.1.1 | Ethical approval

All the procedures performed in this study involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the Declaration of Helsinki,1964,and its later amendments or comparable ethical standards. Approval from the Institutional Review Board of Van Training and Research Hospital, Van, Turkey, was obtained prior to the execution of the study (2018/16). Written informed consent was obtained from all the patients. The study was reported in accordance with the Consolidated Standards of Reporting Trials statement and the trial was registered at clinicaltrials.gov (NCT03790514).

3 | RESULTS

A total of 103 patients (51 treated with a heat-patch and 52 sham) with renal colic were included in the study. The baseline characteristics between the two groups did not differ significantly (Table 1). The dropout rates for the two groups were n = 8 (13.5%) and n = 7 (11.9%) patients, respectively (Figure 1).

On admission, both groups had similar VAS scores. The changes in VAS scores over time for the two groups are presented in Figure 2. In the heat-patch group, 15, 30, 45, and 60 minutes VAS scores

TABLE 1 Demographics and baseline characteristics of the study population

Characteristics	Heat band n = 51	Placebo n = 52	*P*
Age (years), mean ± SD	30.5 ± 8.3	31.0 ± 8.5	.75[a]
Gender			.94[b]
Male, n (%)	34 (65.4%)	33 (64.7%)	
Female, n (%)	18 (34.6%)	18 (35.3%)	
Initial systolic arterial pressure (mm Hg), median (IQR)	111.5 (107-132)	112 (110-130)	.84[c]
Initial diastolic arterial pressure (mm Hg), median (IQR)	72 (65-80)	69 (65-78)	.44[c]
Initial BTemp (°C)	36.8 (36.2-37.1)	36.7 (36.2-37.0)	.17[c]
Initial STemp (°C)	36.3 (35.5-36.3)	36.1 (35.5-36.3)	.39[c]
Baseline heart rate (bpm)	73 (68-79)	73 (68-79)	.85[c]

Note: Data are expressed as mean ± standard deviation (SD), as number (percentage), or as median (interquartile range).

[a]Independent sample *t*-test.

[b]Pearson's chi-squared test.

[c]Mann–Whitney *U* test.

Abbreviations: BTemp, body temperature; STemp, skin temperature.

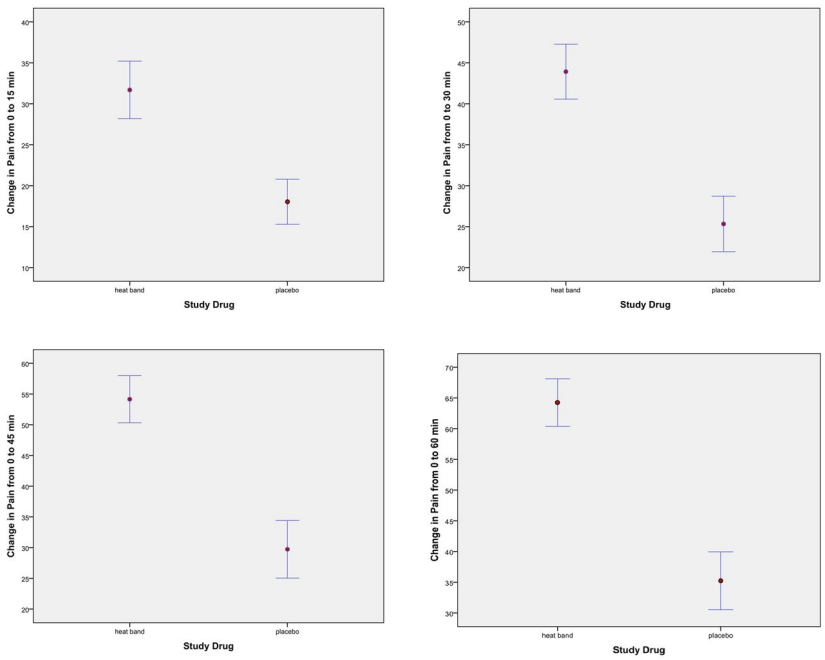


FIGURE 2 Pain improvement at 15, 30, 45, and 60 minutes in study and sham group

were significantly lower than those in the sham group. In addition, according to the baseline VAS score, the decrease in pain level in the heat-patch group at 15, 30, 45, and 60 minutes was statistically significantly higher than that in the sham group. For both groups, 15, 30, 45, and 60 minutes VAS scores and changes in pain severity are provided in Table 2. Fourteen and six patients in the sham and heat-patch groups, respectively, needed pain salvage treatment ($P = .01$).

There was no statistically significant difference between the two groups in terms of 15, 30, 45, and 60 minutes Btemp values ($P = .17$, =0.21, =23, =0.37, and = 0.23, respectively).In addition, there was no statistical difference found at 0 and 15 minutes Stemp values of the two groups ($P = .39$ and $P = .10$, respectively). However, when Stemp was analysed between the heat-patch and place groups at 30, 45, and 60 minutes, a statistically significant difference was found (Table 3).

4 | DISCUSSION

Nowadays, NSAIDs, paracetamol, and opioids are considered first-line treatments for renal colic; however, these drugs have many side effects. Besides, patients cannot directly access these medicines when the pain starts. Therefore, a simple and safe analgesic method during the prehospital phase could be useful for patients

TABLE 2 VAS scores at certain time points and change in pain intensity at 15, 30, 45, and 60 minutes for each study arm

VAS scores	Heat band n = 51	Placebo n = 52	Difference of medians or means (95% CI)	*P*
Baseline VAS score, median (IQR)	90.5 (81.3-95)	86 (78-92)	2.0 (−6.0 to 1.0)	.16[a]
VAS score at 15th minutes, median (IQR)	58 (51-64.8)	68 (59-77)	−10.0 (−15.0 to −5.0)	<.001[a]
VAS score at 30th minutes, median (IQR)	45.5 (36-54.8)	58 (49-70)	−14.0 (−20.0 to −9.0)	<.001[a]
VAS score at 45th minutes, mean ± SD	34 ± 11.4	56 ± 18.9	−21.98 (−28.12 to −15.84)	<.001[b]
VAS score at 60th minutes, median (IQR)	24 (20.3-31.8)	49 (34-65)	−25.0 (−33.0 to −18.0)	<.001[a]
Difference between baseline and 15th minutes, median (IQR)	30.5 (23.3-39)	17 (10-27)	13.0 (9.0 to 18.0)	<.001[a]
Difference between baseline and 30th minutes, mean ± SD	43.9 ± 12.1	25.3 ± 12.1	18.59 (13.88 to 23.3)	<.001[b]
Difference between baseline and 45th minutes, median (IQR)	57 (48.5-62)	31 (15-42)	25.0 (18.0 to 32.0)	<.001[a]
Difference between baseline and 60th minutes, mean ± SD	64.3 ± 13.9	35.2 ± 16.7	29.01 (22.99 to 35.03)	<.001[b]

Note: Data are expressed as mean ± standard deviation (SD) or median (interquartile range), as appropriate.

[a]Mann–Whitney *U* test.

[b]Independent sample *t*-test

Abbreviation: CI, confidence interval.

with renal colic. In this study, heat-patch treatment performed as a local warming method was shown to be superior to sham as an alternative treatment method for the treatment of renal colic. The changes in VAS scores were statistically significant and clinically relevant.

Mechanosensitive receptors that are stimulated by mechanical induction, such as lithiasis, are the receptors that innervate the kidney and ureter mainly.[16] However, unlike somatic pain, visceral pain is generally diffuse and poorly localised. It is also referred to as the body wall, where viscerosomatic convergence is the key in the central pain pathways. Visceral afferents are placed in only a few of the afferent inflows of the dorsal horn and viscerosomatic convergence in the dorsal horn, and supraspinal centres are very well documented. Therefore, visceral mechanosensitive receptors converge with heat afferents, raising from the body wall, and may change the central viscerosensory response in the dorsal column.[16,17] This hypothesis may explain the pain relieving the impact of body heating in this study. Another hypothesis that plays a role in reducing pain with the effect of heat may involve increased intravascular prostaglandins, bradykinin, and histamine secretion as a result of the increased blood flow to the region led by heat-patch treatment.[12-15]

In a preclinical trial, sympathetic blockading was found to be associated with attenuated visceral nociceptive responses. Pertovaara et al demonstrated that following sympathectomy, visceral nociceptive responses decreased in rats.[18] In addition, Kober et al treated patients with renal colic by active warming of the lower back region and showed high sympathetic activity in patients with pain and

TABLE 3 Skin temperature alterations over time

Stemp	Heat-band, n = 51	Placebo, n = 52	*P* value
Stemp at 0th minutes, median (IQR)	36.3 (35.5-36.3)	36.1 (35.5-36.3)	.39[a]
Stemp at 15th minutes, median (IQR)	36.5 (35.9-36.6)	36.0 (35.6-36.5)	.10[a]
Stemp at 30th minutes, median (IQR)	36.8 (36.5-36.9)	36.1 (35.8-36.5)	<.001[a]
Stemp at 45th minutes, median (IQR)	37.1 (36.8-37.3)	36.1 (35.9-36.5)	<.001[a]
Stemp at 60th minutes, median (IQR)	37.5 (37.0-37.8)	36.2 (35.9-36.6)	<.001[a]

[a]Mann–Whitney *U* test.

urolithiasis.[13] These findings highlight the role of the sympathetic nervous system in the perception of visceral pain.

Outside any situation of urolithiasis, local heat was recommended as a way of reducing the pain of trauma patients in the emergency department. In a study conducted by Bertalanffy et al on patients with acute pelvic pain, where the other reasons for pelvic pain excluded gynaecological causes, active heat treatment (electric blanket) was found to be a significantly effective method in reducing pelvic pain.[19] Similarly, in a study conducted by Nuhr et al on patients with acute back pain, the pain was found to be reduced more in active heat treatment areas compared with passive heat treatment areas.[15] In a randomised controlled study performed by Kober et al on patients with renal colic, it was shown that VAS scores were statistically decreased in patients receiving active heat treatment compared with those receiving passive heat treatment.[13] Similar to these studies, in our study, we also showed that in the heat-patch group, Stemp values increased statistically, and the decrease in VAS scores was higher in the heat-patch group than in the sham group.

There are some inherent limitations in this study. The major limitation is the absence of a comparison of heat-patch treatment and an analgesic agent. In addition, the fact that the patients received their actual treatment late could be considered a limitation; however, we were able to protect them from the possible side effects of the medications to be given. Another limitation that must be noted is that although we used patches that waited at room temperature for at least 24 hours before the application in the sham group, we were aware that these patches would never reach the Stemp values of the study groups. However, no patient reported any heat-related complaints during the study. Last but not least, we did not include distal ureter stones, as the pain referred from these stones is mediated by the ilioinguinal and genitofemoral nerves, which radiate the pain to the groin, testicle, or labia majora.

5 | CONCLUSIONS

Heat-patch treatment appears to be an ideal candidate to reduce pain in patients with urolithiasis, especially during the prehospital phase. As it does not contain any drug and has no side effects, health care professionals are not required for the application. We recommend that heat-patches be used at least as the primary treatment option for patients with urolithiasis before the actual treatment (if needed).

DISCLOSURES

None of the authors declare conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

ORCID

Huseyin Mutlu https://orcid.org/0000-0002-1930-3293

REFERENCES

1. Raheem OA, Khandwala YS, Sur RL, Ghani KR, Denstedt JD. Burden of urolithiasis: trends in prevalence, treatments, and costs. *Eur Urol Focus*. 2017;3(1):18-26.
2. Golzari SEJ, Soleimanpour H, Rahmani F, et al. Therapeutic approaches for renal colic in the emergency department: a review article. *Anesth Pain Med*. 2014;4(1):e16222.
3. Bultitude M. Urolithiasis around the world. *BJU Int*. 2017;120(5):601.
4. Türk C, Neisius A, Petřík A, Seitz C, Thomas K, Skolarikos A. EAU Guidelines on Urolithiasis 2020. *European Association of Urology Guidelines. 2020 Edition*. Vol presented at the EAU Annual Congress Amsterdam 2020. Arnhem, The Netherlands: The European Association of Urology Guidelines Office; 2020. https://uroweb.org/guideline/urolithiasis
5. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med*. 2011;8(9):e1001098.
6. Lafrance JP, Miller DR. Selective and non-selective non-steroidal anti-inflammatory drugs and the risk of acute kidney injury. *Pharmacoepidemiol Drug Saf*. 2009;18(10):923-931.
7. Davenport K, Timoney AG, Keeley FX. Conventional and alternative methods for providing analgesia in renal colic. *BJU Int*. 2005;95(3):297-300.
8. Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet*. 2013;382(9894):769-779.
9. Pathan SA, Mitra B, Romero L, Cameron PA. What is the best analgesic option for patients presenting with renal colic to the emergency department? Protocol for a systematic review and meta-analysis. *BMJ Open*. 2017;7(4):e015002.
10. Pathan SA, Mitra B, Straney LD, et al. Delivering safe and effective analgesia for management of renal colic in the emergency department: a double-blind, multigroup, randomised controlled trial. *Lancet*. 2016;387(10032):1999-2007.
11. Kaynar M, Koyuncu F, Buldu İ, et al. Comparison of the efficacy of diclofenac, acupuncture, and acetaminophen in the treatment of renal colic. *Am J Emerg Med*. 2015;33(6):749-753.

12. Gul A, Gul M. Intracutaneous sterile water injection for pain relief during extracorporeal shock wave lithotripsy: comparison with diclofenac sodium. *Urolithiasis*. 2020;48(2):103-108.
13. Kober A, Dobrovits M, Djavan B, et al. Local active warming: an effective treatment for pain, anxiety and nausea caused by renal colic. *J Urol*. 2003;170(3):741-744.
14. Kober A, Scheck T, FüLesdi B, et al. Effectiveness of resistive heating compared with passive warming in treating hypothermia associated with minor trauma: a randomized trial. *Mayo Clin Proc*. 2001;76(4):369-375.
15. Nuhr M, Hoerauf K, Bertalanffy A, et al. Active warming during emergency transport relieves acute low back pain. *Spine (Phila Pa 1976)*. 2004;29(14):1499-1503.
16. CerveroF,LairdJM.Visceralpain.*Lancet*.1999;353(9170):2145-2148.
17. Al-Chaer ED, Traub RJ. Biological basis of visceral pain: recent developments. *Pain*. 2002;96(3):221-225.
18. Pertovaara A, Kalmari J. Neuropathy reduces viscero-somatic inhibition via segmental mechanisms in rats. *NeuroReport*. 2002;13(8):1047-1050.
19. Bertalanffy P, Kober A, Andel H, Hahn R, Frickey N, Hoerauf K. Active warming as emergency interventional care for the treatment of pelvic pain. *BJOG*. 2006;113(9):1031-1034.

How to cite this article: Mutlu H, Ertas K, Kokulu K, Sert ET, Diri MA, Gul M. An effective treatment option for pain caused by urolithiasis: A randomised-controlled trial of local active warming with heat-patch. *Int J Clin Pract*. 2021;75:e13969. https://doi.org/10.1111/ijcp.13969