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Original Article

Efficacy of bupivacaine infiltration on pain control in standard percutaneous nephrolithotomy: a meta-analysis of randomized controlled trials

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Abstract: Introduction: The efficacy of bupivacaine infiltration to control pain for standard percutaneous nephrolithotomy remains controversial. We conduct a systematic review and meta-analysis to explore the influence of bupivacaine infiltration on pain control for standard percutaneous nephrolithotomy. Methods: We search PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases through January 2018 for randomized controlled trials (RCTs) assessing the effect of bupivacaine infiltration on pain control in standard percutaneous nephrolithotomy. Meta-analysis is performed using the random-effect model. Results: Six RCTs involving 337 patients are included in the meta-analysis. Overall, compared with control group for standard percutaneous nephrolithotomy, bupivacaine infiltration can significantly reduce VAS at postoperative 12 h (Std. MD=-0.87; 95% CI=-1.27 to -0.48; P < 0.0001) and 24 h (Std. MD=-0.78; 95% CI=-1.24 to -0.32; P=0.0008), as well as prolong the time of first an= algesic demand (Std. MD=1.02; 95% CI=0.43 to 1.62; P=0.0008), but has no remarkable influence on VAS at postoperative 6 h (Std. MD=-0.33; 95% CI=-0.81 to 0.15; P=0.18), doses of analgesic usage (Std. MD=-0.50; 95% CI=-1.24 to 0.24; P=0.18), operative time (Std. MD=0.13; 95% CI=-0.14 to 0.40; P=0.33), hospital stay (Std. MD=0.07; 95% CI=-0.30 to 0.45; P=0.70), nausea/vomiting (RR=0.52; 95% CI=0.27 to 1.00; P=0.05). Conclusions: Bupivacaine infiltration has important ability to alleviate the pain and prolong the time of first analgesic demand for standard percutaneous nephrolithotomy.

Keywords: Bupivacaine infiltration, pain control, standard percutaneous nephrolithotomy, randomized controlled trials, meta-analysis

Introduction

Percutaneous nephrolithotomy is a safe and effective approach to treat large and complex renal stones [1-3]. Percutaneous nephrolithotomy has widely accepted in clinical work because of the lower complication and morbidity rates compared to open stone surgery. However, many patients suffer from obvious pain, discomfort related to a nephrostomy tube, and distress [4, 5]. Various technical modifications have been developed for standard percutaneous nephrolithotomy in order to reduce the morbidity and postoperative pain [6-9].

The decrease in size of percutaneous nephrolithotomy tract (miniperc), tubeless percutaneous nephrolithotomy and local anesthetic infiltration are developed to make the surgery more acceptable to patients [10-13]. Especially, peritubal or tubal local anesthetic infiltration during percutaneous nephrolithotomy procedures has been reported to significantly alleviate postoperative pain [6, 14].

However, the use of bupivacaine infiltration on pain control for standard percutaneous nephrolithotomy has not been well established. Recently, several studies on the topic have been published, and the results have been conflicting [15-17]. With accumulating evidence, we therefore perform a systematic review and meta-analysis of RCTs to investigate the efficacy of bupivacaine infiltration on pain control after standard percutaneous nephrolithotomy.

Materials and methods

Ethical approval and patient consent are not required because this is a systematic review and

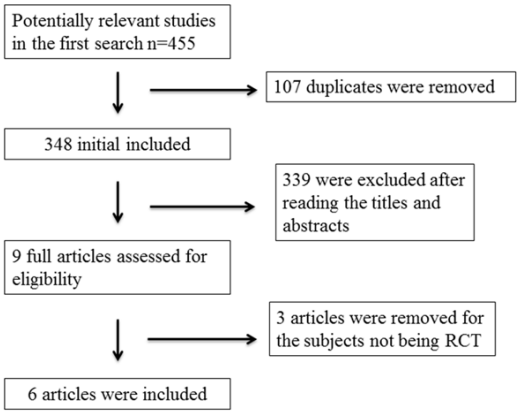

Figure 1. Flow diagram of study searching and selection process.

meta-analysis of previously published studies. The systematic review and meta-analysis are conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [18].

Search strategy and study selection

Two investigators have independently searched the following databases (inception to January 2018): PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases. The electronic search strategy is conducted using the following keywords: bupivacaine, and nephrolithotomy. We also check the reference lists of the screened full-text studies to identify other potentially eligible trials.

The inclusive selection criteria are as follows: (i) population: patients undergoing standard percutaneous nephrolithotomy; (ii) intervention: peritubal bupivacaine infiltration; (iii) comparison: no infiltration or normal saline infiltration; (iv) study design: RCT. Patients with tubeless percutaneous nephrolithotomy are excluded.

Data extraction and outcome measures

We have extracted the following information: author, number of patients, age, body mass index or weight, female, and detail methods in each group etc. Data have been extracted independently by two investigators, and discrepancies are resolved by consensus. We also contact the corresponding author to obtain the data when necessary. No simplifications and assumptions are made. The primary outcomes are visual analogue score (VAS) at postoperative 6 h, 12 h, and 24 h. Secondary outcomes include first analgesic demand, doses of analgesic usage, operative time, hospital stay, and nausea/vomiting.

Quality assessment in individual studies

Methodological quality of the included studies is independently evaluated using the modified Jadad scale [19]. There are 3 items for Jadad scale: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points). The score of Jadad Scale varies from 0 to 5 points. An article with Jadad score ≤ 2 is considered to be of low quality. If the Jadad score ≥ 3, the study is thought to be of high quality [20].

Statistical analysis

We estimate the standard mean difference (Std. MD) with 95% confidence interval (CI) for continuous outcomes (VAS at postoperative 6 h, 12 h and 24 h, first analgesic demand, doses of analgesic usage, operative time, and hospital stay) and (risk ratio) RR with 95% CIs for dichotomous outcomes (nausea/vomiting). A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the I^2 statistic, and $I^2 > 50\%$ indicates significant heterogeneity [21]. Whenever significant heterogeneity is present, we search for potential sources of heterogeneity via omitting one study in turn for the meta-analysis or performing subgroup analysis. Publication bias is not evaluated because of the limited number (< 10) of included studies. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

Results

Literature search, study characteristics and quality assessment

A detailed flowchart of the search and selection results is shown in **Figure 1**. 455 potentially relevant articles are identified initially. Finally, six RCTs that meet our inclusion criteria are included in the meta-analysis [14-17, 22, 23].

The baseline characteristics of the six eligible RCTs in the meta-analysis are summarized in **Table 1**. The six studies are published between 2007 and 2015, and sample sizes range from 22 to 105 with a total of 337. Peritubal infiltra-

Table 1. Characteristics of included studies

NO.	Author	Bupivacaine group						Control group						Jada scores
		Number	Age (years)	Female (n)	Body mass index (kg/m^2) or weight (kg)	Stone size (mm)	Methods	Number	Age (years)	Female (n)	Body mass index (kg/m^2) or weight (kg)	Stone size (mm)	Methods	
1	Lojanapiwat 2015	53	56.64 ± 11.34	18	22.54 ± 3.46 kg/m^2	40.0 ± 18.3	Peritubal injection with 10 mL of 0.25% bupivacaine	52	53.84 ± 10.65	16	23.81 ± 3.97 kg/m^2	40.5 ± 18.8	No infiltration	4
2	Sharifi 2014	20	39.6 ± 12.1	7	76.6 ± 11.12 kg	39.3 ± 8.3	Peritubal infiltration with 5 ml of 0.25% bupivacaine	20	40.65 ± 10.2	7	75.8 ± 8.7 kg	38.2 ± 8.6	Normal saline	5
3	Kirac 2013	36	42.5 ± 13.2	14	-	30.5 ± 10.1	Peritubal 20 mL infiltration of 0.25% bupivacaine	34	41.6 ± 13.8	15	-	26.3 ± 8.5	No infiltration	4
4	Parikh 2011	30	40	3	60.73 kg	-	Peritubal 10 ml of 0.25% bupivacaine	30	41.2	8	62.1 kg	-	Normal saline infiltration	3
5	Jonnavithula 2009	20	41.8	12	59.4 kg	-	Peritubal 20 mL of 0.25% bupivacaine	20	45.7	13	58.9 kg	-	No infiltration	4
6	Haleblian 2007	10	45.7	-	94.1 kg	-	Peritubal 1.5 mg/kg of 0.25% bupivacaine	12	44.9	-	89.5 kg	-	Normal saline infiltration	3

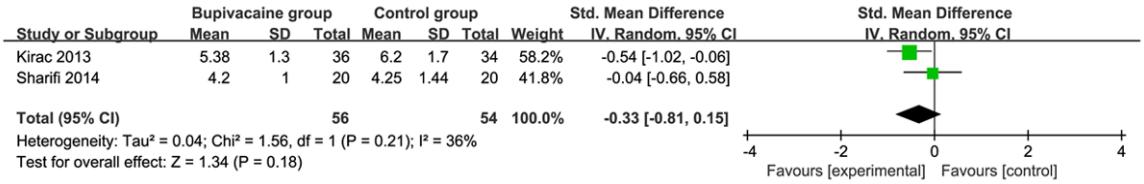

Figure 2. Forest plot for the meta-analysis of VAS at postoperative 6 h.

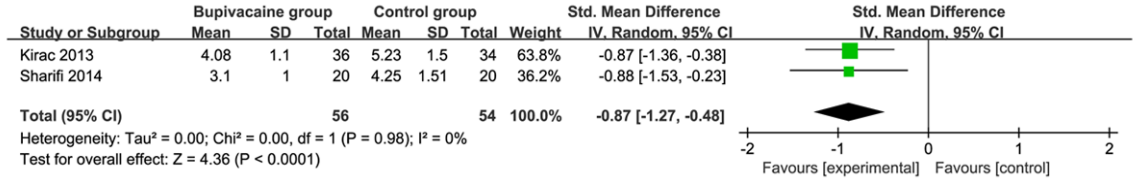

Figure 3. Forest plot for the meta-analysis of VAS at postoperative 12 h.

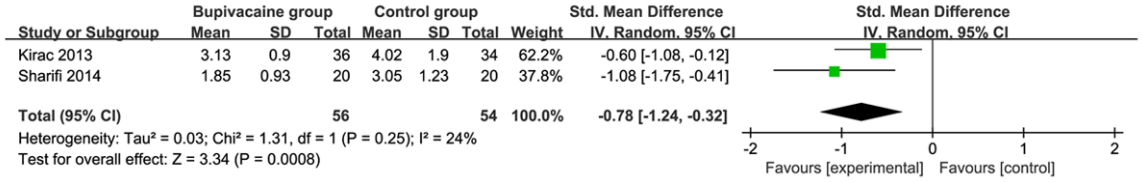

Figure 4. Forest plot for the meta-analysis of VAS at postoperative 24 h.

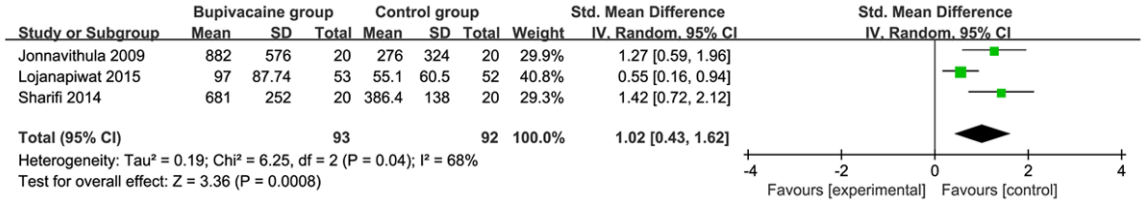

Figure 5. Forest plot for the meta-analysis of first analgesic demand (min).

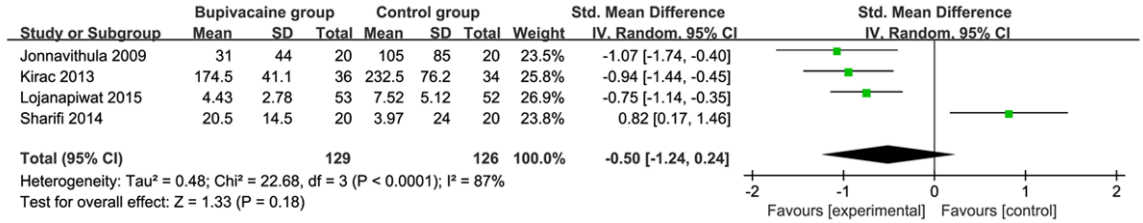

Figure 6. Forest plot for the meta-analysis of doses of analgesic usage (mg).

tion is performed with 5-20 ml of 0.25% bupivacaine or 1.5 mg/kg of 0.25% bupivacaine.

Among the six studies included here, two studies report VAS at postoperative 6 h, 12 h and 24 h [16, 17], three studies report first analgesic demand [15, 16, 23], four studies report doses of analgesic usage [15-17, 23], three studies report operative time [15-17], two studies report hospital stay [16, 17], and two stud-

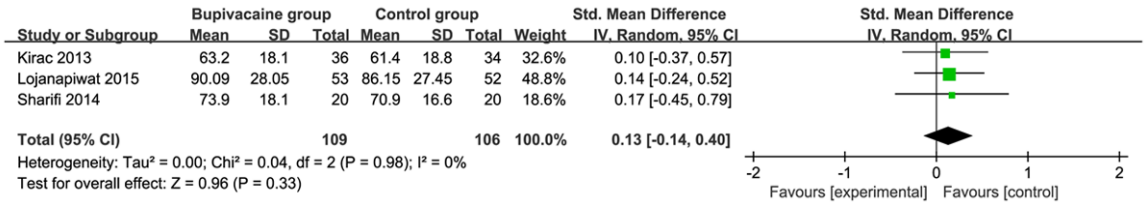

Figure 7. Forest plot for the meta-analysis of operative time (min).

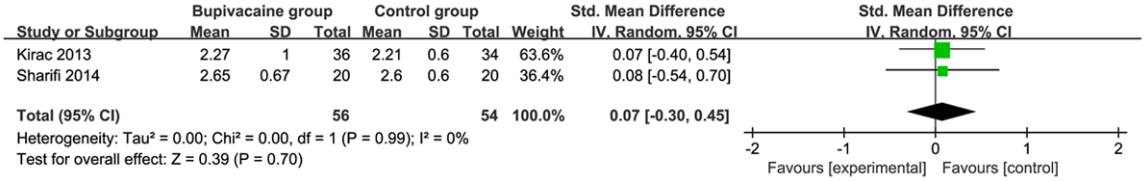

Figure 8. Forest plot for the meta-analysis of hospital stay (days).

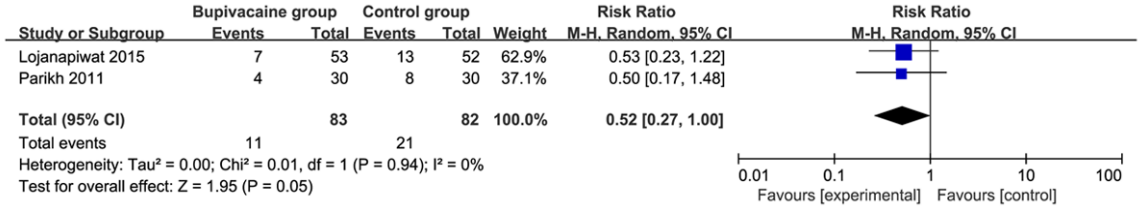

Figure 9. Forest plot for the meta-analysis of nausea/vomiting.

ies report nausea/vomiting [15, 22]. Jadad scores of the six included studies vary from 3 to 5, and all six studies are considered to be high-quality ones according to quality assessment.

Primary outcomes: VAS at postoperative 6 h, 12 h and 24 h

These outcome data are analyzed with the random-effects model, and the pooled estimate of the two included RCTs suggested that compared to control group for standard percutaneous nephrolithotomy, bupivacaine infiltration has no remarkable influence on VAS at postoperative 6 h (Std. MD=-0.33; 95% CI=-0.81 to 0.15; P=0.18), with low heterogeneity among the studies (I^2=36%, heterogeneity P=0.21) (**Figure 2**), but is associated with significantly reduced VAS at postoperative 12 h (Std. MD=-0.87; 95% CI=-1.27 to -0.48; P < 0.0001), with no heterogeneity among the studies (I^2=0%, heterogeneity P=0.98) (**Figure 3**). In addition, VAS at postoperative 24 h is found to be substantially decreased after bupivacaine infiltration (Std. MD=-0.78; 95% CI=-1.24 to-0.32; P=0.0008), with no heterogeneity among the studies (I^2=24%, heterogeneity P=0.25) (**Figure 4**).

Sensitivity analysis

No or low heterogeneity is observed among the included studies for the primary outcomes, and thus we do not perform sensitivity analysis by omitting one study in each turn to detect the source of heterogeneity.

Secondary outcomes

Compared to control group for standard percutaneous nephrolithotomy, bupivacaine infiltration can substantially increase the time of first analgesic demand (Std. MD=1.02; 95% CI= 0.43 to 1.62; P=0.0008; **Figure 5**), but shows no significant impact on doses of analgesic usage (Std. MD=-0.50; 95% CI=-1.24 to 0.24; P=0.18; **Figure 6**), operative time (Std. MD= 0.13; 95% CI=-0.14 to 0.40; P=0.33; **Figure 7**), hospital stay (Std. MD=0.07; 95% CI=-0.30 to 0.45; P=0.70; **Figure 8**), nausea/vomiting (RR= 0.52; 95% CI=0.27 to 1.00; P=0.05; **Figure 9**).

Discussion

Postoperative pain has emerged as an important problem for percutaneous nephrolithotomy, and can result in poor life quality, anxiety, delayed mobilization, increased postoperative complications and prolonged hospitalization [24-26]. With better understanding of acute pain physiology, new analgesic agents, better analgesia delivery procedures and better local anesthetic infiltration techniques are used to alleviate postoperative pain [22, 23, 27]. Several techniques have been developed for percutaneous nephrolithotomy, including multimodal analgesic regimens, the use of small nephrostomy tube, tubeless percutaneous nephrolithotomy, mini- percutaneous nephrolithotomy, local analgesic infiltration and renal capsule analgesic infiltration [28-30].

Peritubal local infiltration of bupivacaine demonstrates important ability to relief the pain after percutaneous nephrolithotomy [14, 22]. Our meta-analysis suggests that peritubal local infiltration of bupivacaine is able to substantially reduce the pain intensity at postoperative 12 h and 24 h, as well as improve the time of first analgesic demand after percutaneous nephrolithotomy, but has no import influence on VAS at postoperative 6 h, doses of analgesic usage, operative time and hospital stay.

Traditional opioid analgesics (e.g. meperidine and morphine) are used in postoperative pain management, and they can cause various side effects including postoperative nausea and vomiting, drowsiness, respiratory depression, ileus, urinary retention and constipation [31-33]. The local anesthesia can effectively reduce the systemic response of drugs, which is revealed in general surgery, gynecology, cesarean sections, hysterectomy, thyroid surgery, mastectomy, total-hip arthroplasty, and cervical spine surgery [34-36]. No increase in nausea/vomiting is observed after percutaneous nephrolithotomy in our meta-analysis. Postoperative pain is caused by the dilatation of renal capsule and parenchyma of access tract with local inflammation reaction, and renal capsule and parenchyma are richly innervated of pain-conductive neurons [22, 23]. These theoretically support the results of our meta-analysis.

This meta-analysis has several potential limitations that should be taken into account. Firstly, our analysis is based on only six RCTs and five of them have a relatively small sample size ($n < 100$). More RCTs with large samples should be conducted to confirm this issue. Next, although there is no significant heterogeneity when performing sensitivity analysis, different doses of 0.25% bupivacaine may have an influence on the pooling results. Finally, some unpublished and missing data may lead bias to the pooled effect.

Conclusions

Peritubal local infiltration of bupivacaine is effective and safety to control the pain after standard percutaneous nephrolithotomy, and should be recommended to be administrated in clinical work with caution.

Disclosure of conflict of interest

None.

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References

[1] Chien TM, Lu YM, Chou YH, Wu WJ and Huang CN. Percutaneous nephrolithotomy increases the risk of new-onset hypertension: a nationwide 6-Year follow-up study. Urology 2016; 97: 61-65.

[2] Borofsky MS, Wollin DA, Reddy T, Shah O, Assimos DG and Lingeman JE. Salvage percutaneous nephrolithotomy: analysis of outcomes following initial treatment failure. J Urol 2016; 195: 977-81.

[3] Trudeau V, Karakiewicz PI, Boehm K, Dell'Oglio P, Tian Z, Briganti A, Shariat SF, Valiquette L and Bhojani N. The effect of obesity on perioperative outcomes following percutaneous nephrolithotomy. J Endourol 2016; 30: 864-70.

[4] Nouralizadeh A, Basiri A, Ziaee SA, Tabibi A, Sharifiaghdas F, Narouie B, Sarhangnejad R, Valipour R, Sotoudeh M, Shemshaki H, Ketabi N and Movahed S. Efficacy and safety of percutaneous nephrolithotomy with adult standard size instruments in children under 3 years of age: a 10 years single-center experience. Urologia 2016; 83: 190-193.

[5] Ganpule AP, Vijayakumar M, Malpani A and Desai MR. Percutaneous nephrolithotomy (PCNL) a critical review. Int J Surg 2016; 36: 660-664.

[6] Shah HN, Shah RH, Sodha HS, Khandkar AA and Gokhale A. A randomized control trial evaluating efficacy of nephrostomy tract infiltration with bupivacaine after tubeless percutaneous nephrolithotomy. J Endourol 2012; 26: 478-83.
[7] Clayman RV. Pain after percutaneous nephrolithotomy: impact of nephrostomy tube size. J Urol 2005; 173: 1199-200.
[8] Resorlu B, Kara C, Sahin E and Unsal A. Comparison of nephrostomy drainage types following percutaneous nephrolithotomy requiring multiple tracts: single tube versus multiple tubes versus tubeless. Urol Int 2011; 87: 23-27.
[9] Sepulveda F, Aliaga A, Fleck D, Fernandez M, Mercado A, Vilches R, Moya F, Ledezma R, Reyes D and Marchant F. Hemostatic agents for access tract in tubeless percutaneous nephrolithotomy: is it worth? Urol Ann 2016; 8: 208-12.
[10] Mishra S, Sharma R, Garg C, Kurien A, Sabnis R and Desai M. Prospective comparative study of miniperc and standard PNL for treatment of 1 to 2 cm size renal stone. BJU Int 2011; 108: 896-899; discussion 899-900.
[11] Resorlu B, Kara C and Unsal A. Prospective comparative study of miniperc and standard PNL for treatment of 1 to 2 cm size renal stone. BJU Int 2011; 108: E160; author reply E160-2.
[12] Maheshwari PN, Andankar MG and Bansal M. Nephrostomy tube after percutaneous nephrolithotomy: large-bore or pigtail catheter? J Endourol 2000; 14: 735-737; discussion 737-738.
[13] Moosanejad N, Firouzian A, Hashemi SA, Bahari M and Fazli M. Comparison of totally tubeless percutaneous nephrolithotomy and standard percutaneous nephrolithotomy for kidney stones: a randomized, clinical trial. Braz J Med Biol Res 2016; 49: e4878.
[14] Haleblian GE, Sur RL, Albala DM and Preminger GM. Subcutaneous bupivacaine infiltration and postoperative pain perception after percutaneous nephrolithotomy. J Urol 2007; 178: 925-8.
[15] Lojanapiwat B, Chureemas T and Kittirattarakarn P. The efficacy of peritubal analgesic infiltration in postoperative pain following percutaneous nephrolithotomy - a prospective randomized controlled study. Int Braz J Urol 2015; 41: 945-52.
[16] Sharifi SH, Soltani MH, Rezaeetalab GH, Sharif RY, Khaledi F, Lashay A and Sharifiaghdas F. Intermittent perirenal instillation of bupivacaine after tubeless percutaneous nephrolithotomy under spinal anesthesia: a double-blind, placebo-controlled clinical trial. J Endourol 2014; 28: 1299-303.
[17] Kirac M, Tepeler A, Bozkurt OF, Elbir F, Ozluk C, Armagan A, Unsal A and Biri H. The efficacy of bupivacaine infiltration on the nephrostomy tract in tubeless and standard percutaneous nephrolithotomy: a prospective, randomized, multicenter study. Urology 2013; 82: 526-31.
[18] Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009; 62: 1006-12.
[19] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ and McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17: 1-12.
[20] Kjaergard LL, Villumsen J and Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Ann Intern Med 2001; 135: 982-9.
[21] Higgins JP and Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-58.
[22] Parikh GP, Shah VR, Modi MP and Chauhan NC. The analgesic efficacy of peritubal infiltration of 0.25% bupivacaine in percutaneous nephrolithotomy - a prospective randomized study. J Anaesthesiol Clin Pharmacol 2011; 27: 481-4.
[23] Jonnavithula N, Pisapati MV, Durga P, Krishnamurthy V, Chilumu R and Reddy B. Efficacy of peritubal local anesthetic infiltration in alleviating postoperative pain in percutaneous nephrolithotomy. J Endourol 2009; 23: 857-60.
[24] Remy C, Marret E and Bonnet F. Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. Br J Anaesth 2005; 94: 505-13.
[25] Sinatra RS, Jahr JS, Reynolds LW, Viscusi ER, Groudine SB and Payen-Champenois C. Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. Anesthesiology 2005; 102: 822-31.
[26] Liu Y, Yu X, Sun X, Ling Q, Wang S, Liu J, Luo A, Tian Y and Mei W. Paravertebral block for surgical anesthesia of percutaneous nephrolithotomy: care-compliant 3 case reports. Medicine (Baltimore) 2016; 95: e4156.
[27] Schug SA and Manopas A. Update on the role of non-opioids for postoperative pain treatment. Best Pract Res Clin Anaesthesiol 2007; 21: 15-30.
[28] Ugras MY, Toprak HI, Gunen H, Yucel A and Gunes A. Instillation of skin, nephrostomy tract, and renal puncture site with ropivacaine decreases pain and improves ventilatory function after percutaneous nephrolithotomy. J Endourol 2007; 21: 499-503.
[29] Desai MR, Kukreja RA, Desai MM, Mhaskar SS, Wani KA, Patel SH and Bapat SD. A prospective randomized comparison of type of

nephrostomy drainage following percutaneous nephrostolithotomy: large bore versus small bore versus tubeless. J Urol 2004; 172: 565-7.
[30] Verma R, Agarwal A, Singh PK, Gupta D and Shamim R. Evaluation of efficacy of amikacin for attenuation of catheter-related bladder discomfort in patients undergoing percutaneous nephrolithotomy: a prospective, randomized, placebo-controlled, double-blind study. Anesth Essays Res 2016; 10: 613-617.
[31] Bektas F, Eken C, Karadeniz O, Goksu E, Cubuk M and Cete Y. Intravenous paracetamol or morphine for the treatment of renal colic: a randomized, placebo-controlled trial. Ann Emerg Med 2009; 54: 568-74.
[32] Memis D, Inal MT, Kavalci G, Sezer A and Sut N. Intravenous paracetamol reduced the use of opioids, extubation time, and opioid-related adverse effects after major surgery in intensive care unit. J Crit Care 2010; 25: 458-62.
[33] Sangesland A, Storen C and Vaegter HB. Are preoperative experimental pain assessments correlated with clinical pain outcomes after surgery? A systematic review. Scand J Pain 2017; 15: 44-52.
[34] Ng A, Swami A, Smith G, Davidson AC and Emembolu J. The analgesic effects of intraperitoneal and incisional bupivacaine with epinephrine after total abdominal hysterectomy. Anesth Analg 2002; 95: 158-62, table of contents.
[35] Pobereskin LH and Sneyd JR. Wound infiltration with bupivacaine after surgery to the cervical spine using a posterior approach. Br J Anaesth 2000; 84: 87-8.
[36] Hsu GL, Ling PY, Hsieh CH, Wang CJ, Chen CW, Wen HS, Huang HM, Einhorn EF and Tseng GF. Outpatient varicocelectomy performed under local anesthesia. Asian J Androl 2005; 7: 439-44.