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Review Article

Benefits of ropivacaine infiltration for reducing postoperative pain after thyroid surgery: a meta-analysis of randomized controlled trials

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Abstract: Introduction: The effect of ropivacaine infiltration on postoperative pain after thyroid surgery remains controversial. Here, a systematic review and meta-analysis was conducted to explore the influence of ropivacaine infiltration versus placebo on postoperative pain after thyroid surgery. Methods: PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases were searched through November 2018 for randomized controlled trials (RCTs) assessing the effect of ropivacaine infiltration versus placebo on postoperative pain after thyroid surgery. This meta-analysis is performed using the random-effect model. Results: Four RCTs involving 335 patients are included in the meta-analysis. Overall, compared with control group for thyroid surgery, ropivacaine infiltration shows significantly positive effect on (Std. MD=-0.87; 95% CI=-1.69 to -0.04; P=0.04), and postoperative analgesic consumption (Std. MD=-1.71; 95% CI=-2.94 to -0.47; P=0.0007), but has no special influence on surgical duration (Std. MD=0.12; 95% CI=-0.21 to 0.44; P=0.49), hospital stay (Std. MD=0; 95% CI=-0.34 to 0.34; P=1.00), nausea and vomiting (RR=0.58; 95% CI=0.19 to 1.75; P=0.33). Conclusions: Ropivacaine infiltration produces favorable impact on pain management for thyroid surgery.

Keywords: Ropivacaine infiltration, postoperative pain, thyroid surgery, randomized controlled trials, meta-analysis

Introduction

Minimally invasive operation has been widely developed for the surgery [1-3]. In particular, the advantages of minimally invasive thyroidectomy are improved in terms of superior postoperative cosmetic outcomes, lower complication rates, and faster recovery after incorporation of the Robot System compared to conventional open thyroidectomy [4-8]. However, immediate postoperative pain still commonly occurs after minimally invasive thyroidectomy due to the flap dissection that is required to establish an adequate operative field [9-12].

Various methods have been developed to alleviate the pain after minimally invasive thyroid surgery, and they mainly include thyroidectomy with the bilateral axillo-breast approach, and local infiltration of the flap site with the anesthetic agent levobupivacaine and ropivacaine which are were administered by spray or subcutaneous injection [13-17]. Local infiltration with anesthetic agents is found to have important potential in reducing postoperative pain. Ropivacaine has the advantage of long block duration, better safety and lower toxicity than levobupivacaine [18]. Its low lipophilic profile enables to reduce the possibility to induce cardio- and central nervous system toxicity [19, 20].

However, the benefit of ropivacaine infiltration versus placebo for pain control after thyroid surgery has not been well established. Recently, several studies on the topic have been published, and the results have been conflicting [14, 21, 22]. With accumulating evidence, a systematic review and meta-analysis of RCTs was performed here to explore the efficacy of ropivacaine infiltration versus placebo for pain control after thyroid surgery.

Materials and methods

Ethics approval and patient consent were not required because this is a systematic review

and 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) [23].

Search strategy and study selection

Two investigators independently searched the following databases (inception to November 2018): PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases. The electronic search strategy was conducted using the following keywords: ropivacaine, and thyroid surgery or thyroidectomy. Reference lists of the screened full-text studies were also checked to identify other potentially eligible trials.

The inclusive selection criteria are as follows: (i) population: patients undergoing thyroid surgery; (ii) intervention: ropivacaine infiltration; (iii) comparison: matched placebo; (iv) study design: RCT.

Data extraction and outcome measures

The following information was extracted: author, number of patients, age, female, body mass index, the number of total thyroid surgery and detail methods in each group etc. Data have been extracted independently by two investigators, and discrepancies are resolved by consensus. The corresponding author was also contacted to obtain the data when necessary.

The primary outcome was pain scores. Secondary outcomes included analgesic consumption, surgical duration, hospital stay, nausea, and vomiting.

Quality assessment in individual studies

Methodological quality of the included studies was independently evaluated using the modified Jadad scale [24]. 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 [25].

Statistical analysis

The standard mean difference (Std. MD) with 95% confidence interval (CI) for continuous outcomes (pain scores, analgesic consumption, surgical duration, hospital stay) and risk ratios (RRs) with 95% CIs for dichotomous outcomes (nausea and vomiting) was used for analysis. A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the I^2 statistic, and $I^2 > 50\%$ indicates significant heterogeneity [26]. Whenever significant heterogeneity was present, potential sources of heterogeneity were searched via omitting one study in turn for the meta-analysis or performing subgroup analysis. 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**. A total of 309 potentially relevant articles were identified initially. Finally, four RCTs that met the inclusion criteria were included in the meta-analysis [14, 21, 22, 27].

The baseline characteristics of the four eligible RCTs in the meta-analysis are summarized in **Table 1**. The four studies were published between 2007 and 2017, and sample sizes range from 34 to 148 with a total of 335. The concentrations of ropivacaine infiltration ranged from 0.1% to 2%.

Among the four studies included here, two studies reported pain scores [22, 27], three studies reported analgesic consumption [14, 22, 27], four studies reported surgical duration [14, 21, 22, 27], two studies reported hospital stay [14, 22], three studies reported nausea and vomiting [14, 22, 27]. Jadad scores of the four included studies vary from 4 to 5, and all four studies are considered to be high-quality ones according to quality assessment.

Primary outcome: pain scores

This outcome data is analyzed with the random-effects model, and compared to control group for thyroid surgery and ropivacaine infiltration resulted in significant pain scores (Std. MD=-0.87; 95% CI=-1.69 to -0.04; P=0.04) with significant heterogeneity among the studies (I^2=81%, heterogeneity P=0.02) (**Figure 2**).

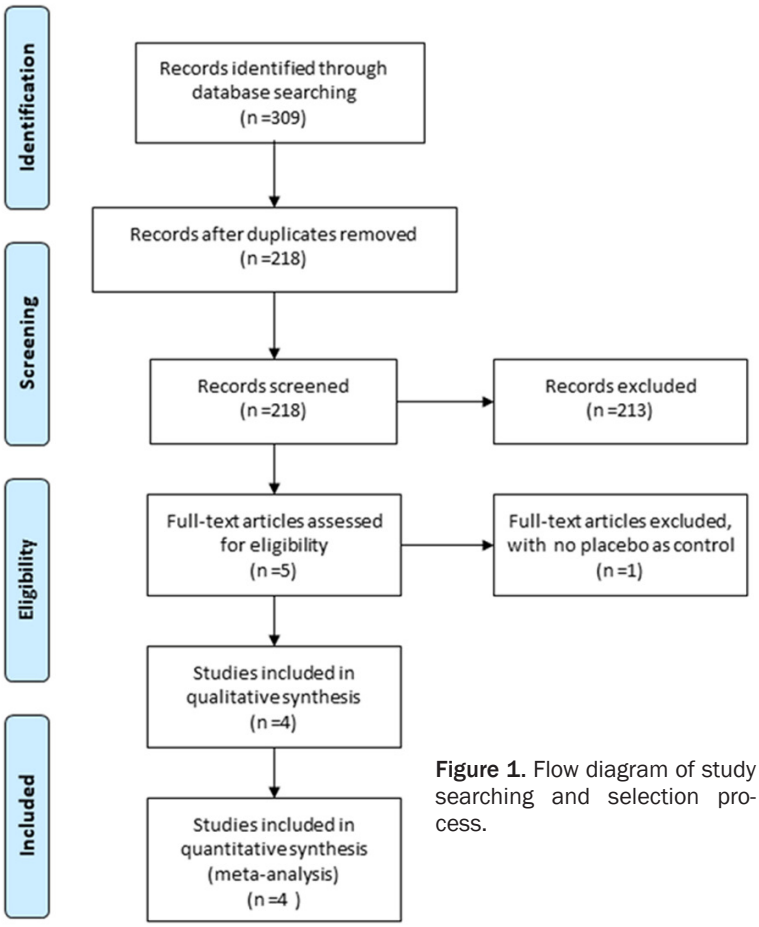

Figure 1. Flow diagram of study searching and selection process.

Sensitivity analysis

Significant heterogeneity was observed among the included studies for pain scores, but there are just two RCTs, and it was not available to perform sensitivity analysis via omitting one study in turn.

Secondary outcomes

In comparison with control group for thyroid surgery, ropivacaine infiltration is able to reduce the postoperative analgesic consumption (Std. MD=-1.71; 95% CI=-2.94 to -0.47; P= 0.0007; **Figure 3**), but exhibits no obvious impact on surgical duration (Std. MD=0.12; 95% CI=-0.21 to 0.44; P=0.49; **Figure 4**), hospital stay (Std. MD=0; 95% CI=-0.34 to 0.34; P= 1.00; **Figure 5**), nausea and vomiting (RR= 0.58; 95% CI=0.19 to 1.75; P=0.33; **Figure 6**).

Discussion

One meta-analysis aims to investigate five types of analgesic interventions for acute postoperative pain management, and they include epidural analgesia, local anesthetic wound infiltration, systemic N-methyl-d-aspartic acid (NMDA) receptor antagonists, systemic nonsteroidal anti-inflammatory drugs (NSAIDs), and systemic opioids. The results find that preemptive epidural analgesia resulted in consistent improvements in postoperative pain scores, analgesic consumption and time to first rescue analgesic request, while local anesthetic wound infiltration and NSAID administration can significantly reduce analgesic consumption and time to first rescue analgesic request, but not postoperative pain scores [28]. Thyroidectomies are not included in that meta-analysis. Our meta-analysis include four RCTs involving ropivacaine infiltration after thyroid surgery.

A previous study reveals that preoperative surgical site injection with local anesthetics is effective to reduce the pain intensity after conventional open thyroidectomy [29]. In that study, 0.25% levobupivacaine spray on the flap site after thyroid surgery in 58 patients results in the reduction in pain scores and analgesic consumption at 1, 6, 24, and 48 hours after surgery [15]. One RCT involved 34 women, and preoperative ropivacaine injection of the flap site reduced the pain score, analgesic consumption, and additional analgesic requirement at 2, 6, 18, 30, 42, and 66 hours after surgery [14]. Pain scores and analgesic consumption are remarkably reduced after ropivacaine for thyroid surgery in our meta-analysis, but there is no statistical difference of surgical duration, hospital stay, nausea and vomiting between ropivacaine group and control group.

In addition, preoperative local infiltration may be more effective for pain control than postoperative spray, because most of the spray tends to drain out postoperatively [14, 30]. A mixture of ropivacaine and epinephrine is reported to significantly and safely alleviate postoperative

Table 1. Characteristics of included studies

NO.	Author	Ropivacaine group						Control group						Jada scores
		Number	Age (years)	Female (n)	Body mass index (kg/m^2)	Total thyroid surgery	Methods	Number	Age (years)	Female (n)	Body mass index (kg/m^2)	Total thyroid surgery	Methods	
1	Lee 2017	74	35.5±8.8	66	23.3±4.0	21	225 mg of ropivacaine and epinephrine 1 mg/1 mL diluted by 1:100,000 with 100 mL of normal saline injected into the subcutaneous layer of the flap site for hydrodissection	74	38.0±9.3	69	22.9±2.5	20	Matched placebo	4
2	Bae 2016	53	40.5±9.4	49	22.2±3.5	49	40 mL of 0.25% ropivacaine was instilled into the skin flap	50	39.9±11.1	47	22.4±2.7	43	Matched placebo	5
3	Kang 2015	17	38.0±10.1	-	22.1±2.3	14	0.1% ropivacaine with saline (3 mg/kg) injection prior to skin incision	17	34.7±7.6	-	21.8±2.7	13	Matched placebo	4
4	Motamed 2007	25	41±6	18	-	12	Wound infiltration with 15 ml of ropivacaine 2% at end-of-surgery	25	43±8	20	-	14	Matched placebo	5

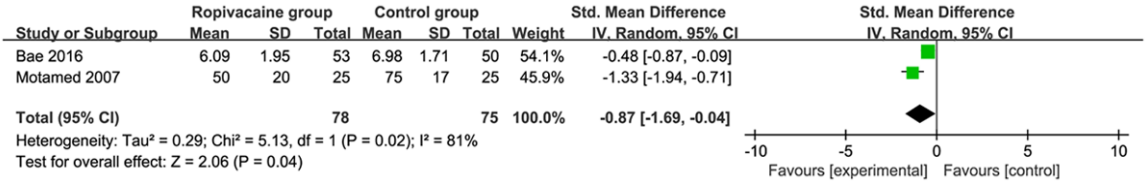

Figure 2. Forest plot for the meta-analysis of pain scores.

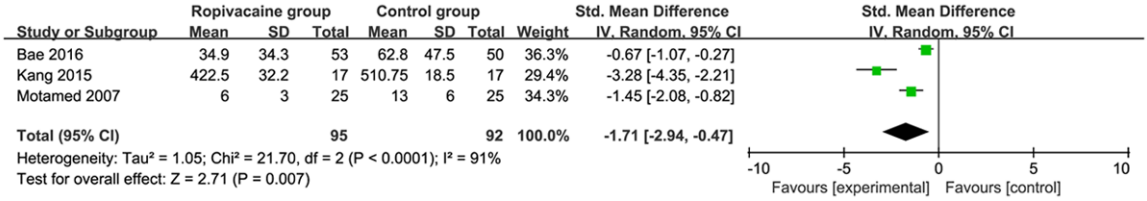

Figure 3. Forest plot for the meta-analysis of analgesic consumption.

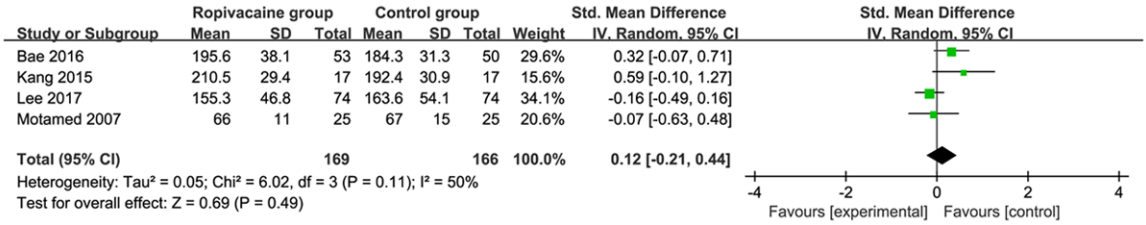

Figure 4. Forest plot for the meta-analysis of surgical duration (min).

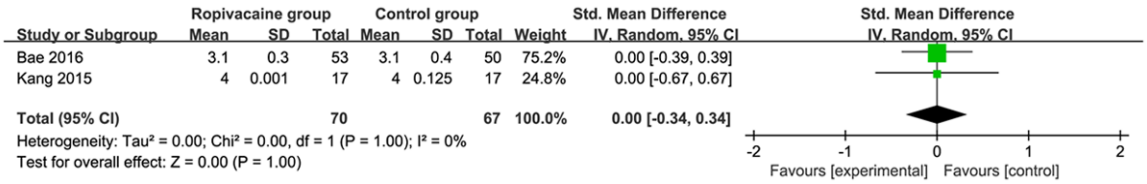

Figure 5. Forest plot for the meta-analysis of hospital stay (day).

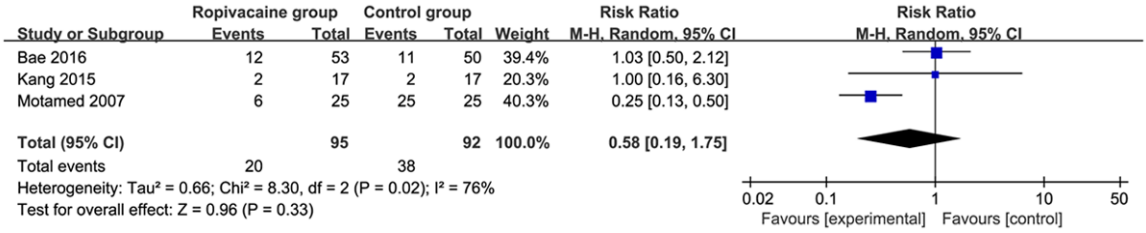

Figure 6. Forest plot for the meta-analysis of nausea and vomiting.

pain in cesarean section patients [31]. Epinephrine is frequently used in hydro-dissection during bilateral axillo-breast approach to reduce bleeding during flap formation due to its ability to induce peripheral vasoconstriction and yield a spotless flap. The use of epinephrine can decrease the estimated blood loss (18.0 vs 30 mL) and operation time (155.3 vs 163.6 minutes) in the ropivacaine-epinephrine group compared to control group [21]. Regar-

ding the sensitivity analysis, there is significant heterogeneity which may be caused by different concentration, combination and administration time of ropivacaine, various pain intensity scales due to different operation methods and procedures.

This meta-analysis has several potential limitations. First, the analysis is based on four RCTs, and two of them have a relatively small sample size ($n < 100$). Overestimation of the treatment effect was more likely in smaller trials compared with larger samples. Next, there was significant heterogeneity which may be derived from different concentration, combination and administration time of ropivacaine, various operation methods, and procedures. Finally, it was not available to perform the meta-analysis of some important index such as the first time for analgesic requirement based on current RCTs.

Conclusions

Ropivacaine infiltration can provide improved pain control after thyroid therapy.

Disclosure of conflict of interest

None.

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References

[1] Miccoli P, Berti P, Raffaelli M, Conte M, Materazzi G, Galleri D. Minimally invasive video-assisted thyroidectomy. Am J Surg 2001; 181: 567-70.

[2] Chung YS, Choe JH, Kang KH, Kim SW, Chung KW, Park KS, Han W, Noh DY, Oh SK, Youn YK. Endoscopic thyroidectomy for thyroid malignancies: comparison with conventional open thyroidectomy. World J Surg 2007; 31: 2302-6.

[3] Zhao J, Zhang S, Li X, He B, Ou Y, Jiang D. Comparison of minimally invasive and open transforaminal lumbar interbody fusion for lumbar disc herniation: a retrospective cohort study. Med Sci Monit 2018; 24: 8693-8.

[4] Chai YJ, Song J, Kang J, Woo JW, Song RY, Kwon H, Kim SJ, Choi JY, Lee KE. A comparative study of postoperative pain for open thyroidectomy versus bilateral axillo-breast approach robotic thyroidectomy using a self-reporting application for iPad. Ann Surg Treat Res 2016; 90: 239-45.

[5] Son SK, Kim JH, Bae JS, Lee SH. Surgical safety and oncologic effectiveness in robotic versus conventional open thyroidectomy in thyroid cancer: a systematic review and metaanalysis. Ann Surg Oncol 2015; 22: 3022-32.

[6] Sun GH, Peress L, Pynnonen MA. Systematic review and meta-analysis of robotic vs conventional thyroidectomy approaches for thyroid disease. Otolaryngol Head Neck Surg 2014; 150: 520-32.

[7] Alkan U, Zarchi O, Rabinovics N, Nachalon Y, Feinmesser R, Bachar G. The cause of brachial plexopathy in robot-assisted transaxillary thyroidectomy-a neurophysiological investigation. Laryngoscope 2016; 126: 2187-93.

[8] Materazzi G, Fregoli L, Manzini G, Baggiani A, Miccoli M, Miccoli P. Cosmetic result and overall satisfaction after minimally invasive video-assisted thyroidectomy (MIVAT) versus robot-assisted transaxillary thyroidectomy (RATT): a prospective randomized study. World J Surg 2014; 38: 1282-8.

[9] Tae K, Ji YB, Jeong JH, Lee SH, Jeong MA, Park CW. Robotic thyroidectomy by a gasless unilateral axillo-breast or axillary approach: our early experiences. Surg Endosc 2011; 25: 221-8.

[10] Tae K, Kim KY, Yun BR, Ji YB, Park CW, Kim DS, Kim TW. Functional voice and swallowing outcomes after robotic thyroidectomy by a gasless unilateral axillo-breast approach: comparison with open thyroidectomy. Surg Endosc 2012; 26: 1871-7.

[11] Choi KW, Nam KH, Lee JR, Chung WY, Kang SW, Joe YE, Lee JH. The effects of intravenous lidocaine infusions on the quality of recovery and chronic pain after robotic thyroidectomy: a randomized, double-blinded, controlled study. World J Surg 2017; 41: 1305-12.

[12] Fregoli L, Materazzi G, Miccoli M, Papini P, Guarino G, Wu HS, Miccoli P. Postoperative pain evaluation after robotic transaxillary thyroidectomy versus conventional thyroidectomy: a prospective study. J Laparoendosc Adv Surg Tech A 2017; 27: 146-50.

[13] Shin S, Chung WY, Jeong JJ, Kang SW, Oh YJ. Analgesic efficacy of bilateral superficial cervical plexus block in robot-assisted endoscopic thyroidectomy using a transaxillary approach. World J Surg 2012; 36: 2831-7.

[14] Kang KH, Kim BS, Kang H. The benefits of preincision ropivacaine infiltration for reducing postoperative pain after robotic bilateral axillo-breast approach thyroidectomy: a prospective, randomized, double-blind, placebo-controlled study. Ann Surg Treat Res 2015; 88: 193-9.

[15] Ryu JH, Yom CK, Kwon H, Kim KH, Choi JY, Jung JW, Kim SW, Oh AY. A prospective, randomized, controlled trial of the postoperative analgesic effects of spraying 0.25% levobupivacaine after bilateral axillo-breast approach robotic thyroidectomy. Surg Endosc 2015; 29: 163-9.

[16] Sanfilippo F, Conticello C, Santonocito C, Minardi C, Palermo F, Bernardini R, Gullo A, Astuto M. Remifentanil and worse patient-reported outcomes regarding postoperative pain management after thyroidectomy. J Clin Anesth 2016; 31: 27-33.
[17] Yucel A, Yazici A, Muderris T, Gul F. Comparison of lornoxicam and low-dose tramadol for management of post-thyroidectomy pain. Agri 2016; 28: 183-9.
[18] Leone S, Di Cianni S, Casati A, Fanelli G. Pharmacology, toxicology, and clinical use of new long acting local anesthetics, ropivacaine and levobupivacaine. Acta Biomed 2008; 79: 92-105.
[19] Lepner U, Goroshina J, Samarutel J. Postoperative pain relief after laparoscopic cholecystectomy: a randomised prospective double-blind clinical trial. Scand J Surg 2003; 92: 121-4.
[20] Zink W, Graf BM. Benefit-risk assessment of ropivacaine in the management of postoperative pain. Drug Saf 2004; 27: 1093-114.
[21] Lee JH, Suh YJ, Song RY, Yi JW, Yu HW, Kwon H, Choi JY, Lee KE. Preoperative flap-site injection with ropivacaine and epinephrine in BABA robotic and endoscopic thyroidectomy safely reduces postoperative pain: a CONSORT-compliant double-blinded randomized controlled study (PAIN-BREKOR trial). Medicine (Baltimore) 2017; 96: e6896.
[22] Bae DS, Kim SJ, Koo do H, Paek SH, Kwon H, Chai YJ, Choi JY, Lee KE, Youn YK. Prospective, randomized controlled trial on use of ropivacaine after robotic thyroid surgery: effects on postoperative pain. Head Neck 2016; 38 Suppl 1: E588-E93.
[23] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Medicine 2009; 62: 1006-12.
[24] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996; 17: 1-12.
[25] Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Ann Intern Med 2001; 135: 982-9.
[26] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-58.
[27] Motamed C, Merle JC, Combes X, Yahkou L, Saidi NE, Degranges P, Dhonneur G. Postthyroidectomy pain control using ropivacaine wound infiltration after intraoperative remifentanil: a prospective double blind randomized controlled study. Acute Pain 2007; 9: 119-23.
[28] Ong CK, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. Anesth Analg 2005; 100: 757-73.
[29] Fontseré N, Salinas I, Bonal J, Bayés B, Riba J, Torres F, Rios J, Sanmartí A, Romero R. Are prediction equations for glomerular filtration rate useful for the long-term monitoring of type 2 diabetic patients? Nephrol Dial Transplant 2006; 21: 2152-8.
[30] Bagul A, Taha R, Metcalfe MS, Brook NR, Nicholson ML. Pre-incision infiltration of local anesthetic reduces postoperative pain with no effects on bruising and wound cosmesis after thyroid surgery. Thyroid 2005; 15: 1245-8.
[31] Cohen S, Chhokra R, Stein MH, Denny JT, Shah S, Mohiuddin A, Naftalovich R, Zhao R, Pashkova A, Rolleri N, Patel AG, Hunter-Fratzola CW. Ropivacaine 0.025% mixed with fentanyl 3.0 mug/ml and epinephrine 0.5 mug/ml is effective for epidural patient-controlled analgesia after cesarean section. J Anaesthesiol Clin Pharmacol 2015; 31: 471-7.