Original Investigation

Ulus Cerrahi Derg 2016; 32: 173-177

DOI: 10.5152/UCD.2015.3138

Local bupivacaine for postoperative pain management in thyroidectomized patients: A prospective and controlled clinical study

Ersin Gürkan Dumlu[1], Mehmet Tokaç[1], Haydar Öcal[1], Doğukan Durak[1], Halil Kara[2], Mehmet Kılıç[3], Abdussamed Yalçın[3]

ABSTRACT

Objective: We aimed to evaluate the effect of bupivacaine and to compare the routes of administration of bupivacaine in the management of postoperative incision site pain after thyroidectomy.

Material and Methods: Consecutive patients who were planned for thyroidectomy surgery were randomized into three groups of 30 patients each: Group 1 (control group): standard thyroidectomy surgery without additional intervention; Group 2 (paratracheal infiltration with bupivacaine): following thyroidectomy, 0.25% bupivacaine was applied on the surgical area; Group 3 (subcutaneous infiltration with bupivacaine): following thyroidectomy, 0.25% bupivacaine was injected into the cutaneous, subcutaneous region and fascia of the surgical area. Postoperative pain was evaluated by a visual analog scale (VAS) at 1st, 4th, and 12th hours after thyroidectomy. Total daily requirement for additional analgesia was recorded.

Results: The mean age of 90 patients was 44.37±13.42 years, and the female:male ratio was 62:28. There was no difference between study groups in terms of age, thyroid volume, TSH and T4 levels. VAS score of patients in paratracheal infiltration with bupivacaine group was significantly lower than control group patients at 1st, 4th and 12th hours following thyroidectomy (p=0.030, p=0.033, p=0.039, respectively). The need for analgesics was significantly lower in both paratracheal infiltration and subcutaneous infiltration groups than the control group (86.7%, 83.0%, and 73.3%, respectively, p=0.049).

Conclusions: Intraoperative local bupivacaine application is effective in decreasing postoperative pain in patients with thyroidectomy.

Keywords: Bupivacaine, postoperative pain, thyroidectomy

INTRODUCTION

Pain in the incision site is a common complaint among patients who undergo thyroidectomy, a widely applied procedure in endocrine surgery (1-3). The postoperative pain following thyroidectomy is due to extensive tissue dissection and tension during the operation (4). Many patients with thyroidectomy suffer from incision site pain especially in the first days after surgery, which delays early discharge and causes a significant burden on both patients and healthcare teams (5-8).

Pain following thyroidectomy is commonly managed with nonsteroidal anti-inflammatory drugs (NSAIDs) or opioid analgesics (9, 10). However, NSAIDs have been reported to be associated with potential adverse events including cardiovascular events, surgical bleeding and renal impairment (11). Opioid analgesics also have side effects such as nausea and vomiting (12).

Local anesthetics have been used in surgery for a long time to reduce postoperative pain and the need for analgesics (13). The use of local anesthetics particularly in abdominal and hernia surgery has been known to effectively decrease postoperative pain (14, 15). For this purpose, long-acting local anesthetics are preferred more frequently.

Bupivacaine is a long-acting local anesthetic that effectively reduces postoperative pain (16). In practice, bupivacaine is used for infiltration anesthesia, nerve blocks, epidural, and caudal anesthesia (17). It has a more selective effect on sensory nerve fibers as compared to motor nerve fibers, therefore is preferred for epidural anesthesia in obstetrics (18). However, there are limited studies on the use of local anesthetics in neck surgery. Bupivacaine has been used for preoperative wound infiltration (19), and intraoperative bilateral superficial cervical plexus block in thyroidectomy to prevent postoperative pain (20, 21). However, there is ongoing debate on the effectiveness and the route of application of bupivacaine to control pain following thyroidectomy (17, 19, 20, 22, 23).

Based on the current knowledge, in this study, we aimed to evaluate the effect of bupivacaine and to compare the routes of administration of bupivacaine in the management of postoperative incision site pain after thyroidectomy.

[1]Clinic of General Surgery, Atatürk Training and Research Hospital, Ankara, Turkey

[2]Department of Pharmacology, Yıldırım Beyazıt University School of Medicine, Ankara, Turkey

[3]Department of General Surgery, Yıldırım Beyazıt University School of Medicine, Ankara, Turkey

Address for Correspondence

Ersin Gürkan Dumlu
e-mail: gurkandumlu@gmail.com

Received: 12.03.2015
Accepted: 14.05.2015

MATERIAL AND METHODS

Patients and Study Design

This was a prospective, three-arm, controlled study performed in Atatürk Training and Research Hospital Department of General Surgery. The study was approved by the Institutional Ethics Committee of the Hospital for Clinical Studies (date, 19/02/2014; no, 21). The study was conducted in accordance with Helsinki Declaration, and written informed consent was obtained from all patients before participation.

Patients who were planned for a total thyroidectomy between February 2013 and October 2013 were randomized into three groups of 30 patients each. Patients who did not want to participate in the study, had undergone previous thyroid surgery, or had undergone thyroid resection in combination with neck dissection were excluded.

Study groups were as follows: Group 1 (control group): standard thyroidectomy surgery following standard anesthesia protocol without additional intervention; Group 2 (paratracheal infiltration): following standard thyroidectomy surgery, Surgicel® (Johnson and Johnson Medical, Arlington, TX, USA) impregnated with 10 mg (4 mL) 0.25% bupivacaine (Marcain 0.5%, 20 mL/flakon, Eczacıbaşı, İstanbul, Turkey) diluted with equal rate of saline was applied on the frontal aspect of the trachea in a way that it expands 1 cm laterally on each side on the surgical area; Group 3 (subcutaneous infiltration): following standard thyroidectomy surgery, local infiltration of the wound was performed by the surgeon at the end of surgery just before wound closure. A 23-gauge needle was inserted along the incision line and 10 mg of 0.25% bupivacaine was applied into the anterior group cervical muscles and subcutaneous tissue in both flaps (top and bottom).

Operation Technique

A 4–7 cm skin incision (depending on the size of the thyroid) was made. Sub-platysmal flaps were elevated, the strap muscles were separated in the midline and reflected laterally. In none of the patients the strap muscle was transected. The inferior, middle, and superior thyroid vessels were then divided. The same steps were repeated for removal of the contralateral lobe. Finally, the wound was irrigated and closed using interrupted 3-0 polyglactin sutures (Vycril, Ethicon) to approximate the strap muscles and the platysmal layer. The skin was closed subcutaneously. Suction drains were routinely used in all patients. Suction drains were removed at the first postoperative day, and no hematomas or seromas were observed in any patients.

Assessment of Postoperative Pain

Postoperative pain of the patients was evaluated by a visual analog scale (VAS) at 1, 4, and 12 hours after thyroidectomy by an investigator blinded to study groups. VAS is scored on a scale of 0 to 10 (0=no pain, 10=worst pain imaginable). For patients with a VAS score over 5, additional analgesia was provided with intramuscular 75 mg/amp diclofenac sodium. The total daily requirement for additional analgesia was recorded.

Calculation of Thyroid Gland Volume

Ellipsoid formula with correction factor, which is the most commonly used two-dimensional ultrasonographic mathematical method to estimate thyroid gland volume was used for calculation (24-26). This formula refers to width ´ depth ´ length ´ 0.524 for each lobe. For this calculation, both thyroid lobes were scanned with ultrasonography (Sonoline Ultrasonography Equipment, Siemens, Munich, Germany) individually in the transverse and longitudinal planes. Estimated error rate of this formula is approximately 15%.

Statistical Analysis

Study data were summarized using descriptive statistics (e.g., mean, median, standard deviation, range, frequency, percentage). Kolmogorov-Smirnov test was used to test whether continuous variables were distributed normally or not. Data of the three study groups were compared with analysis of variance (ANOVA) test, and secondary comparisons between two groups were performed with post-hoc Tukey test. For the comparison of data at different time points, repeated measured ANOVA test was applied. For comparison of categorical variables, chi-square and Fisher's exact tests were used. Statistical analysis was performed using Statistical Package for the Social Sciences version 16.0 (SPSS Inc; Chicago, IL, USA). Statistical significance was set to $p<0.05$.

RESULTS

Clinical and Demographic Characteristics of Study Patients

The mean age of 90 patients included in the study was 44.37±13.42 years (range 18-67 years), and the female:male ratio was 62:28 (females, 68.9%; males, 31.1%). The indication for thyroidectomy was a significantly large nodule (n=26, 28.9%), toxic goiter (n=20, 22.2%), malignancy (n=14, 15.6%), suspicion of malignancy (n=8, 8.9%), atypia of undetermined significance (n=8, 8.9%), insufficient thyroid fine needle aspiration biopsy (n=6, 6.7%), follicular lesion of undetermined significance (n=4, 4.4%), and difficulty in swallowing (n=4, 4.4%).

The mean thyroid volume calculated by the ellipsoid volume formula was 37.16±23.59 cm^3. There was no difference between study groups in terms of age, thyroid volume, TSH and T4 levels ($p>0.05$). T3 level was significantly lower in the control group than subcutaneous bupivacaine infiltration group ($p=0.006$) (Table 1). Considering TSH, T4 and T3 levels together, study groups were not different in terms of hyperthyroidism that may interfere with the duration of surgery, amount of intraoperative bleeding, and postoperative pain by increasing vascularization in the surgical area. In each group one patient developed transient hypocalcemia, no additional complication was observed.

VAS Score

VAS score of all study patients decreased significantly after the thyroidectomy operation at all time points ($p<0.001$ for all groups) (Table 2). VAS score of patients in the paratracheal infiltration with bupivacaine was significantly lower than control group patients at 1, 4, and 12 hours following the thyroidectomy operation ($p=0.030$, $p=0.033$, $p=0.039$, respectively) (Table 2).

Analgesic Requirement

Of all study patients (n=90), 72 (66.7%) required analgesics in addition to bupivacaine application. The need for analgesics was significantly lower in both the paratracheal infiltration and subcutaneous infiltration groups as compared to the control group (86.7%, 83.0%, and 73.3%, respectively, $p=0.049$) (Table 3).

DISCUSSION

The elimination or reduction of postoperative pain following thyroidectomy enhances patients' quality of life and allows patients to quickly return to normal daily activities. For the management of postoperative pain following throidectomy, NSAIDs and/or opioid analgesics are used commonly in practice. To decrease the postoperative pain and reduce the need for analgesics following thyroidectomy surgery, preoperative oral controlled-release analgesia with opioids and alternative regional techniques such as incisional local anesthesia, intraoperative bilateral superficial and/or deep cervical plexus block, local wound infiltration with local analgesia have also been suggested recently (20, 21, 23, 27-29). Performing thyroidectomy under local or regional anesthesia rather than general anesthesia has also been suggested to control postoperative pain (30).

In the present study, we evaluated whether bupivacaine is effective in postoperative pain control in thyroidectomy surgery, and compared the two administration ways of bupivacaine: paratracheal infiltration and subcutaneous infiltration. Bupivacaine is a local anesthetic with minimum effect on motor nerve conduction (16). Since postoperative pain following thyroid surgery is related to increased excitability of the dorsal horn neurons, blocking superficial branches of the cervical plexus was proposed in order to prevent postoperative pain. Local injection of bupivacaine may provide blockage of superficial branches of the cervical plexus. Bilateral superficial cervical plexus block with bupivacaine has been shown to significantly reduce pain intensity in the postoperative period after thyroid surgery, but did not provide optimal pain relief alone (31). We found that paratracheal infiltration with bupivacaine is effective in decreasing postoperative pain as assessed by VAS score. On the other hand, the need for analgesia with diclofenac sodium, an NSAID, was lowest in subcutaneous infiltration with bupivacaine group. In previous studies on the effect of bupivacaine on the control of postoperative pain, various dose intervals and routes were implemented with conflicting results. Sardar et al. (23) applied bilateral superficial cervical plexus block with 0.25% bupivacaine intraoperatively to decrease pain after thyroid surgery, but did not find decrease in postoperative analgesic requirement. In a prospective controlled study, Ayman et al. (19) compared preoperative incision site infiltration of bupivacaine 0.5% and ropivacaine 0.75% to decrease postoperative pain in total thyroidectomy, and concluded that wound infiltration with local analgesia

Table 1. Clinical and demographic characteristics of study patients

	Total (n=90)	Control (n=30)	Paratracheal infiltration of bupivacaine (n=30)	Subcutaneous infiltration of bupivacaine (n=30)	p
Age	44.37±13.42	47.1±12.79	45.37±13.88	44.38±13.43	0.159
Thyroid volume (cm^3)	37.16±23.59	30.07±17.61	40.71±24.61	37.17±23.6	0.130
TSH (U/mL)	1.03±1.00	1.2±1.1	0.74±0.66	1.04±1.01	0.137
T3 (pg/mL)	3.50±1.87	2.74±0.64	3.59±2.05	3.51±1.88	0.009[a]
T4 (ng/dL)	2.15±5.31	1.44±0.88	1.45±0.65	2.16±5.32	0.197

TSH: Thyroid stimulating hormone; T3: triiodothyronine; T4: thyroxine
[a]p=0.163 for Control vs. paratracheal infiltration; p=0.006 for Control vs. subcutaneous infiltration; p=0.400 for Paratracheal infiltration vs. subcutaneous infiltration groups.

Table 2. VAS scores (mean±standard deviation) of study groups at 1, 4, and 12 hours after the thyroidectomy operation

VAS scoring time	Control (n=30)	Paratracheal infiltration of bupivacaine (n=30)	Subcutaneous infiltration of bupivacaine (n=30)	p
1st hour	6.64±1.76	5.37±2.42	5.4±1.36	0.026[a]
4th hour	4.14±2.12	2.93±1.60	3.33±1.71	0.038[b]
12th hour	1.94±0.95	1.6±0.9	1.78±0.63	0.048[c]
p	0.001	0.001	0.001	

VAS Score: Visual Analog Scale Score
[a]p=0.030 for Control vs. paratracheal infiltration; p=0.882 for Control vs. subcutaneous infiltration; p=0.092 for Paratracheal infiltration vs. subcutaneous infiltration groups.
[b]p=0.033 for Control vs. paratracheal infiltration; p=0.210 for Control vs. subcutaneous infiltration; p=0.672 for Paratracheal infiltration vs. subcutaneous infiltration groups.
[c]p=0.039 for Control vs. paratracheal infiltration; p=0.272 for Control vs. subcutaneous infiltration; p=0.622 for paratracheal infiltration vs. subcutaneous infiltration.

Table 3. Patients who required analgesia in study groups

	Control (n=30)	Paratracheal infiltration of bupivacaine (n=30)	Subcutaneous infiltration of bupivacaine (n=30)	p
Requirement for analgesics	26 (86.7%)	25 (83.0%)	20 (73.3%)	0.049[a]
No requirement for analgesics	4 (13.3%)	5 (17.0%)	10 (26.7%)	

[a]p=0.037 for Control vs. paratracheal infiltration; p=0.020 for Control vs. subcutaneous infiltration; p=0.0791 for paratracheal infiltration vs. subcutaneous infiltration groups.

had limited efficacy in decreasing postoperative pain in the short period up to 4 hours after surgery, and ropivacaine was more effective than bupivacaine in this manner. In contrast, Herbland et al. (32) found that bilateral superficial cervical plexus block with ropivacaine did not prevent postoperative pain after total thyroidectomy. However, Karthikeyan et al. (20) reported that intraoperative bilateral superficial cervical plexus block with bupivacaine was effective in reducing postoperative pain and analgesic requirements in thyroidectomy. In a study comparing preoperative oral controlled release morphine, postoperative sublingual buprenorphine and intraoperative wound infiltration with 0.25% bupivacaine, sublingual buprenorphine was found to provide better analgesia after thyroidectomy than the other interventions (22). Gozal et al. (27) reported that bupivacaine 0.5% wound infiltration at the end of surgery reduced postoperative pain and opioid demand. In a recent study by Ryu et al. (33), spraying 0.25% levobupivacaine on the dissection area after robotic thyroidectomy reduced postoperative pain and patient-controlled analgesia consumption without adverse events. We determined that VAS score of patients with paratracheal infiltration of bupivacaine was significantly lower at 1, 4 and 12 hours following thyroidectomy, which indicates that paratracheal infiltration with bupivacaine is effective in decreasing postoperative pain in both the short and long term. The need for analgesics decreased in both paratracheal infiltration and subcutaneous infiltration groups. We think that our overall findings suggest the efficacy of bupivacaine by paratracheal infiltration in the management of postoperative pain following thyroidectomy; however, further studies are required to determine the most appropriate route of administration. Since total thyroidectomy was applied on all patients, we do not think that the difference between preoperative T3 values of the groups is a factor that may affect postoperative pain. We believe this to be pure coincidence (34).

Our findings along with previous reports indicate that bupivacaine application may be promising for control of postoperative pain following thyroidectomy. Recently, the advent of a liposomal formulation of bupivacaine has provided more favorable pharmacokinetics that reduces the risk of amide-related toxicity and provides long-lasting postoperative analgesia (13, 18, 35, 36). Potential risks and benefits of liposomal bupivacaine, a very recently approved formulation of bupivacaine, need to be elucidated for postoperative pain control (36, 37). It is obvious that bupivacaine is used in high doses for motor and sensory blockade in both spinal anesthesia and peripheral nerve block. However, there were no signs of motor blockage in any of our operations (38).

In spite of our findings in favor of the analgesic efficacy of bupivacaine, the main limitation of our study is the small sample size precludes us from reaching a definite conclusion. Further studies with a larger sample size and those comparing different application routes are required to conclude on the efficacy of and the most efficient application route of bupivacaine for postoperative pain control.

In addition, the absence of data on operation durations, the volume of pathologic specimens, and comparison with the ultrasonographic volume measurements may be considered as other limitations of our study.

CONCLUSION

Intraoperative local bupivacaine application is effective in decreasing postoperative pain in patients undergoing thyroidectomy. Effective pain management following thyroidectomy should be implemented in order to increase the quality of postoperative care, to reduce both opioid consumption and subsequent dose-related complications.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Yıldırım Beyazıt University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.G.D., M.T.; Design – E.G.D., H.K.; Supervision – A.Y., M.K.; Resources – D.D.; Materials – D.D., H.Ö.; Data Collection and/or Processing – D.D.; Analysis and/or Interpretation – E.G.D., M.T.; Literature Search – E.G.D., M.T.; Writing Manuscript – E.G.D.; Critical Review – M.K., A.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Sosa JA, Udelsman R. Total thyroidectomy for differentiated thyroid cancer. J Surg Oncol 2006; 94: 701-707. [CrossRef]
2. Dionigi G, Dionigi R, Bartalena L, Tanda ML, Piantanida E, Castano P, et al. Current indications for thyroidectomy. Minerva Chir 2007; 62: 359-372.
3. Christou N, Mathonnet M. Complications after total thyroidectomy. J Visc Surg 2013; 150: 249-256. [CrossRef]
4. Wheeler MH. The technique of thyroidectomy. J R Soc Med 1998; 91(Suppl 33): 12-16.
5. Kumrow D, Dahlen R. Thyroidectomy: understanding the potential for complications. Medsurg Nurs 2002; 11: 228-235.
6. Rutledge J, Siegel E, Belcher R, Bodenner D, Stack BC Jr. Barriers to same-day discharge of patients undergoing total and completion thyroidectomy. Otolaryngol Head Neck Surg 2014; 150: 770-774. [CrossRef]
7. Giddings AE. Surgical treatment of thyroid disease, thyroidectomy and parathyroidectomy: a medical guide for doctors and nurses. J R Soc Med 1998; 91(Suppl 33): 36-41.
8. Giddings AE. Thyroidectomy and parathyroidectomy: a guide for patients. J R Soc Med 1998; 91(Suppl 33): 33-35.
9. Abdulla S, Eckhardt R, Netter U, Abdulla W. Efficacy of three IV non-opioid-analgesics on opioid consumption for postoperative pain relief after total thyroidectomy: a randomised, double-blind trial. Middle East J Anesthesiol 2012; 21: 543-552.
10. Fourcade O, Sanchez P, Kern D, Mazoit JX, Minville V, Samii K. Propacetamol and ketoprofen after thyroidectomy. Eur J Anaesthesiol 2005; 22: 373-377. [CrossRef]
11. Mathiesen O, Wetterslev J, Kontinen VK, Pommergaard HC, Nikolajsen L, Rosenberg J, et al. Adverse perioperative paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: a topical review. Acta Anaesthesiol Scand 2014; 58: 1182-1198. [CrossRef]
12. Porreca F, Ossipov MH. Nausea and vomiting side effects with opioid analgesics during treatment of chronic pain: mechanisms, implications, and management options. Pain Med 2009; 10: 654-662. [CrossRef]

13. Lonner J. Role of liposomal bupivacaine in pain management after total joint arthroplasty. J Surg Orthop Adv 2014; 23: 37-41. [CrossRef]
14. Barreveld A, Witte J, Chahal H, Durieux ME, Strichartz G. Preventive analgesia by local anesthetics: the reduction of postoperative pain by peripheral nerve blocks and intravenous drugs. Anesth Analg 2013; 116: 1141-1161. [CrossRef]
15. Stuhldreher JM, Adamina M, Konopacka A, Brady K, Delaney CP. Effect of local anesthetics on postoperative pain and opioid consumption in laparoscopic colorectal surgery. Surg Endosc 2012; 26: 1617-1623. [CrossRef]
16. Chapman PJ. Review: bupivacaine--a long-acting local anaesthetic. Aust Dent J 1987; 32: 288-291. [CrossRef]
17. Sun J, Wu X, Meng Y, Jin L. Bupivacaine versus normal saline for relief of post-adenotonsillectomy pain in children: a meta-analysis. Int J Pediatr Otorhinolaryngol 2010; 74: 369-373. [CrossRef]
18. Ilfeld BM. Liposome bupivacaine in peripheral nerve blocks and epidural injections to manage postoperative pain. Expert Opin Pharmacother 2013; 14: 2421-2431. [CrossRef]
19. Ayman M, Materazzi G, Bericotti M, Rago R, Nidal Y, Miccoli P. Bupivacaine 0.5% versus ropivacaine 0.75% wound infiltration to decrease postoperative pain in total thyroidectomy, a prospective controlled study. Minerva Chir 2012; 67: 511-516.
20. Karthikeyan VS, Sistla SC, Badhe AS, Mahalakshmy T, Rajkumar N, Ali SM, et al. Randomized controlled trial on the efficacy of bilateral superficial cervical plexus block in thyroidectomy. Pain Pract 2013; 13: 539-546. [CrossRef]
21. Shin ML, Duh QY, Hsieh CB, Liu YC, Lu CH, Wong CS. Bilateral superficial cervical plexus block combined with general anesthesia administered in thyroid operations. World J Surg 2010; 34: 2338-2343. [CrossRef]
22. Lacoste L, Thomas D, Kraimps JL, Chabin M, Ingrand P, Barbier J, et al. Postthyroidectomy analgesia: morphine, buprenorphine, or bupivacaine? J Clin Anesth 1997; 9: 189-193. [CrossRef]
23. Sardar K, Rahman SH, Khandoker MR, Amin ZA, Pathan FH, Rahman MK. The analgesic requirement after thyroid surgery under general anaesthesia with bilateral superficial cervical plexus block. Mymensingh Med J 2013; 22: 49-52.
24. Ruggieri M, Fumarola A, Straniero A, Maiuolo A, Coletta I, Veltri A, et al. The estimation of the thyroid volume before surgery: an important prerequisite for minimally invasive thyroidectomy. Langenbecks Arch Surg 2008; 393: 721-724. [CrossRef]
25. Van Isselt JW, de Klerk JM, van Rijk PP, van Gils AP, Polman LJ, Kamphuis C, et al. Comparison of methods for thyroid volume estimation in patients with Graves' disease. Eur Nucl Med Mol Imaging 2003; 30: 525-531. [CrossRef]
26. Vurdem ÜE, Acer N, Ertekin T, Savranlar A, Topuz Ö, Keceli M. Comparison of three volumetric techniques for estimating thyroid gland volume. Turk J Med Sci 2012; 42 (Suppl 1): 1299-1306.
27. Gozal Y, Shapira SC, Gozal D, Magora F. Bupivacaine wound infiltration in thyroid surgery reduces postoperative pain and opioid demand. Acta Anaesthesiol Scand 1994; 38: 813-815. [CrossRef]
28. Egan RJ, Hopkins JC, Beamish AJ, Shah R, Edwards AG, Morgan JD. Randomized clinical trial of intraoperative superficial cervical plexus block versus incisional local anaesthesia in thyroid and parathyroid surgery. Br J Surg 2013; 100: 1732-1738. [CrossRef]
29. Kim SY, Kim EM, Nam KH, Chang DJ, Nam SH, Kim KJ. Postoperative intravenous patient-controlled analgesia in thyroid surgery: comparison of fentanyl and ondansetron regimens with and without the nonsteriodal anti-inflammatory drug ketorolac. Thyroid 2008; 18: 1285-1290. [CrossRef]
30. Arora N, Dhar P, Fahey TJ 3rd. Seminars: local and regional anesthesia for thyroid surgery. J Surg Oncol 2006; 94: 708-713. [CrossRef]
31. Dieudonne N, Gomola A, Bonnichon P, Ozier YM. Prevention of postoperative pain after thyroid surgery: a double-blind randomized study of bilateral superficial cervical plexus blocks. Anesth Analg 2001; 92: 1538-1542. [CrossRef]
32. Herbland A, Cantini O, Reynier P, Valat P, Jougon J, Arimone Y, et al. The bilateral superficial cervical plexus block with 0.75% ropivacaine administered before or after surgery does not prevent postoperative pain after total thyroidectomy. Reg Anesth Pain Med 2006; 31: 34-39. [CrossRef]
33. Ryu JH, Yom CK, Kwon H, Kim KH, Choi JY, Jung JW, et al. 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: 163-169. [CrossRef]
34. Sugita M, Harada H, Yamamoto T. Perioperative management of a patient with thyroid hormone resistance who underwent total thyroidectomy for thyroid cancer. J Anesth. 2012; 26: 595-597. [CrossRef]
35. Hu D, Onel E, Singla N, Kramer WG, Hadzic A. Pharmacokinetic profile of liposome bupivacaine injection following a single administration at the surgical site. Clin Drug Investig 2013; 33: 109-115. [CrossRef]
36. Lambrechts M, O'Brien MJ, Savoie FH, You Z. Liposomal extended-release bupivacaine for postsurgical analgesia. Patient Prefer Adherence 2013; 6: 885-890.
37. Portillo J, Kamar N, Melibary S, Quevedo E, Bergese S. Safety of liposome extended-release bupivacaine for postoperative pain control. Front Pharmacol 2014; 30: 90. [CrossRef]
38. Bedder MD, Kozody R, Craig DB. Comparison of bupivacaine and alkalinized bupivacaine in brachial plexus anesthesia. Anesth Analg 1988; 67: 48-52. [CrossRef]