The Role of Local Bupivacaine Irrigation in Postoperative Pain Control After Augmentation Mammoplasty: A Systematic Review and Meta-Analysis

Le rôle de l'infiltration locale de bupivacaine pour contrôler la douleur postopératoire après une mammoplastie d'augmentation : analyse systématique et méta-analyse

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Plastic Surgery
2017, Vol. 25(1) 32-39
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sagepub.com/journalsPermissions.nav
DOI: 10.1177/2292550317693816
journals.sagepub.com/home/psg

Abstract

Background: The objective of this study is to analyze the efficacy of local bupivacaine irrigation after augmentation mammoplasty for the control of postoperative pain. **Methods:** A systematic review and meta-analysis was conducted including all randomized controlled trials (RCTs) that compared the irrigation of bupivacaine ($\pm$ ketorolac) versus normal saline or no irrigation for pain control after breast augmentation. The primary outcome was postoperative pain measured by visual analog scale. The study protocol was established a priori according to the recommendations of the Cochrane Collaboration. A bibliographical search was conducted in September 2015 in the following Cochrane Library databases: CENTRAL, MEDLINE, EMBASE, and Scielo. The strategy used for the search was ((augmentation AND ("mammoplasty"[MeSH Terms] OR "mammoplasty")) OR (("breast"[MeSH Terms] OR "breast") AND augmentation)) AND (("pain, postoperative"[MeSH Terms])). **Results:** Four RCTs with a total of 264 participants were included. Two trials compared bupivacaine alone versus placebo (normal saline or no irrigation) and 3 trials compared bupivacaine plus ketorolac versus placebo. The combined irrigation of bupivacaine and ketorolac showed a clinically significant reduction of pain in the first postoperative hour and on postoperative day 5. The irrigation with bupivacaine compared with placebo significantly reduced pain assessed on postoperative day 4. **Conclusion:** The irrigation of bupivacaine with or without ketorolac was associated with a reduction of postoperative pain compared with control groups for the first 5 postoperative days. Due to the few number of trials included, these results should be correlated further clinically.

Résumé

Historique : La présente étude vise à analyser l'efficacité de l'infiltration locale de bupivacaine pour contrôler la douleur postopératoire après une mammoplastie d'augmentation. **Méthodologie :** Les chercheurs ont procédé à une analyse systématique et à une méta-analyse incluant tous les essais aléatoires et contrôlés (EAC) qui comparaient l'infiltration de bupivacaine ($\pm$ kétorolac) à un soluté physiologique normal ou à l'absence d'infiltration pour contrôler la douleur après une augmentation mammaire. Le résultat clinique primaire était la douleur postopératoire mesurée d'après une échelle analogique visuelle. Les chercheurs ont établi le protocole de l'étude *a priori*, conformément aux recommandations de la Collaboration Cochrane. En septembre 2015, ils ont effectué une recherche bibliographique dans les bases de données suivantes de la

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Bibliothèque Cochrane : CENTRAL, MEDLINE, EMBASE et Scielo, à l'aide des termes suivants : *augmentation ET mammaplasty* (termes du MeSH) OU *mammaplasty*, OU *breast* (termes du MeSH) OU *breast ET augmentation ET pain, postoperative* (termes du MeSH). **Résultats** : Quatre EAC, totalisant 264 participants, ont été inclus dans l'étude. Deux essais comparaient la bupivacaine utilisée seule à un placebo (soluté physiologique normal ou absence d'infiltration) et trois essais, la bupivacaine associée au kétorolac à un placebo. L'infiltration combinée de bupivacaine et de kétorolac a démontré une réduction cliniquement significative de la douleur pendant l'heure suivant l'opération ainsi que le cinquième jour suivant l'opération. Par rapport à un placebo, l'infiltration de bupivacaine réduisait considérablement la douleur évaluée le quatrième jour suivant l'opération. **Conclusion** : Pendant les cinq premiers jours suivant l'opération, l'infiltration de bupivacaine, associée ou non à du kétorolac, entraînait une diminution de la douleur postopératoire par rapport à celle ressentie par les groupes témoins. Étant donné le peu d'essais en cause, il faudrait corrélérer ces résultats en clinique.

Keywords

breast augmentation, bupivacaine, postoperative pain

Introduction

Breast augmentation is estimated to be one of the most common procedures performed by plastic surgeons. For this reason, multiple studies have been done in order to improve the technique and the postoperative complications and management of these patients.¹

Retropectoral breast augmentation requires dissection beneath the pectoralis major muscle to create a pocket suitable for implant placement. During the dissection, some muscular fibres of the costal and sternal heads of the pectoralis major will be detached, resulting in significant postoperative pain. It is imperative to search for methods that could relieve this pain, especially since augmentation mammaplasty is often performed in an ambulatory setting. An ideal postoperative pain control regimen should provide adequate analgesia while minimizing or eliminating side effects in patients. Narcotic medications usually provide relatively rapid and adequate alleviation of pain. Unfortunately, these medications can also cause a wide array of untoward side effects.² Many attempted to reduce narcotic use in the postoperative period using different modalities. Adding celecoxib^{3,4} and methocarbamol^{5,6} to narcotics may reduce the requirement of the latter. Many authors used topical local anesthetics at the surgical field either by continuous infusion,⁷ intermittent bolus, sustained release,⁸ pain pumps,⁹ or indwelling catheters.¹⁰⁻¹² Topical local anesthetics have been shown to significantly lengthen the pain-free period after surgery.¹³ Bupivacaine is a common choice, with a pKa of 8.1, a relatively long half-life of 2.7 hours, and is comparatively inexpensive. Bupivacaine liposome injectable suspension¹⁴ and DepoFoam (Pacira Pharmaceuticals, Inc) bupivacaine tumescent infiltration in addition to bupivacaine injection are some examples of its use.^{15,16} The question arises as to whether there is a role for placing irrigation containing local anesthetics with additional nonsteroidal anti-inflammatory drugs, into the implant pocket. Although this procedure has been used several years ago, its effectiveness has not been proved.

The lack of prior appropriate evidence leads us to assess the effectiveness of irrigating the pocket of breast augmentation with local anesthetics and analgesic drugs. We conducted a systematic review and meta-analysis of randomized controlled

trials (RCTs) that compared the irrigation of bupivacaine with or without analgesic drugs in comparison to irrigation with normal saline or no irrigation into the retropectoral pocket for postoperative pain relief in patients who underwent augmentation mammaplasty.

Methods

A study protocol for the systematic review was established in advance, prespecifying the review's objectives, inclusion and exclusion criteria, primary and secondary outcomes, and methods of synthesis. The review included all relevant RCTs regardless of publication status, country, date, or language of publication. Participants in the trials were patients who underwent primary breast augmentation by means of an inframammary, periareolar, or transaxillary incision with retropectoral placement of implants. All the studies included in the present meta-analysis stated the retropectoral placement of the implants without mentioning the access. We did not place restrictions on the type of the implants used for augmentation.

The comparisons of interest were the irrigation of the pocket with bupivacaine (with or without analgesic drug) versus normal saline or no irrigation. The irrigation could be performed by means of a pain pump or directly into the pocket before implant insertion. The solution contained saline alone, bupivacaine, or bupivacaine plus ketorolac. The primary outcome was the pain score measured by the visual analog scale (VAS) at different time intervals.¹⁷

Literature Search and Selection of Studies

The electronic search was conducted in September 2015. Two authors (Y.C.C. and S.S.Q.) independently performed a systematic literature search and reviewed the titles and abstracts of the references retrieved and selected all potentially relevant studies. The systematic literature search was done on electronic databases in the Cochrane Library, including CENTRAL, MEDLINE, EMBASE, and Scielo—which is one of the largest Spanish databases. The search was done using the following strategic terms: ((augmentation AND (“mammaplasty”[MeSH Terms] OR “mammaplasty”)) OR (“breast”[MeSH Terms]

OR “breast”) AND augmentation)) AND (“pain, postoperative”[MeSH Terms] OR (“pain” AND “postoperative”) OR “postoperative pain” OR (“postoperative” AND “pain”)).

The bibliographies and all potentially relevant articles were then retrieved through the consensus of both authors. Their reference lists were cross-referenced to identify additional relevant articles. Study titles, abstracts, and full texts were analyzed for the study design, and they were stratified into groups of case reports, retrospective studies, observational studies, and randomized trials. Copies of these full articles were obtained and reviewed independently by the same authors.

Data Extraction and Management

Two authors (Y.C.C. and S.S.Q.) independently extracted data concerning the details of patient characteristics, study methods, interventions, and outcomes using a standardized data extraction method. The data extraction method was developed by one author and was checked by the other. Missing data were sought by contacting the authors of the primary studies when necessary. Two authors (Y.C.C. and S.S.Q.) recorded all the data.

Assessment of Risk of Bias in the Included Studies

Two authors (Y.C.C. and S.S.Q.) independently assessed the methodological quality of the considered studies, assessing their risk of bias regarding allocation concealment, method of randomization, blinding of participants and health-care personnel, incomplete outcome data, and selective outcome reporting. The assessment was based on the recommendations in the *Cochrane Handbook*, version 5.1.0. Any discrepancies were resolved by discussion among all authors.

Data Synthesis

The treatment effect on pain score was assessed using the mean differences with its 95% confidence interval (CI). Pooled estimates of effect on pain were computed under a fixed effects model for the pain score on each postoperative day. Statistical analyses were conducted with the Review Manager (RevMan) software, version 5.2 (Cochrane collaboration, Oxford, United Kingdom).

Assessment of Heterogeneity

Statistical heterogeneity between trials was evaluated using the I^2 statistic and Q statistic (χ^2 test) for heterogeneity. The significance level of the χ^2 test was set at 0.10. To explore potential sources of clinical heterogeneity, we estimated the effect on pain of irrigating a solution of bupivacaine with or without ketorolac separately.

Sensitivity Analysis

To assess the robustness of the results, 2 sensitivity analyses were performed: (1) applying a random effects method and (2) excluding studies with high or unclear risk

Figure 1. Flow diagram of the literature search according to PRISMA statement.

of bias. If the results did not change significantly after excluding the low-quality studies, then they were considered to be robust. Publication bias could not be explored either statistically or through inspection of funnel plots, due to the very small number of included trials in the review, for each comparison.¹⁸

Results

Our search strategy yielded 194 articles. The full text was reviewed for 38 articles and 4 RCTs, which included a total of 264 patients in the analysis.^{19–22} Figure 1 shows an overview of the literature search according to the PRISMA statement.

Three trials were excluded from the present meta-analysis due to their discrepancy with those included in the type of administration and control group. The study of Pacik 2004⁷ was excluded not because of the use of a catheter but because the solution administered to the patients was unlimited, whereas in the study of Kazmier et al,²² the reservoirs were filled preoperatively with a predetermined volume of 200 cc. The other 2 studies by Minkowitz et al¹⁵ and Smoot et al²³ compared 2 different doses of bupivacaine administered by DepoFoam. Due to this unique way of administration and the absence of placebo or control group, they were excluded from the quantitative analysis.

Study Characteristics and Quality Assessment

Study characteristics are summarized in Table 1. Table 2 presents the results of the assessment of the risk of bias in the included studies according to the *Cochrane Handbook*, version

Table 1. Included Study Characteristics.

Study	Type	Population	Intervention	Control	Outcomes
Mahabir et al 2004 ¹⁹	Double-blind RCT	Retropectoral implants, n = 100	Locally administered intraoperatively Group 1: 29 mL NS + 1 mL ketorolac (30 mg/mL) Group 2: 15 mL NS + 15 mL bupivacaine (0.5% with epinephrine) Group 3: 14 mL NS + 1 mL ketorolac (30 mg/mL) + 15 mL bupivacaine (0.5% with epinephrine)	Saline	1. VAS after surgery at 30 minutes, 60 minutes, and before discharge 2. Time spent in recovery room
Mahabir et al 2008 ²⁰	Double-blind RCT	Retropectoral implants, n = 94	Locally administered intraoperatively Group 1: 29 mL NS + 1 mL ketorolac (30 mg/mL) Group 2: 15 mL NS + 15 mL bupivacaine (0.5% with epinephrine) Group 3: 14 mL NS + 1 mL ketorolac (30 mg/mL) + 15 mL bupivacaine (0.5% with epinephrine)	Saline	VAS at 6 and 12 hours postoperative on POD 1, 2, 3, 4, 5, 10
Kazmier et al 2008 ²²	RCT	Retropectoral implants, n = 20	Infusion using catheter into the pockets Bupivacaine 0.5% 240 mg/d, 2 cc/h	Saline (contralateral side)	Pain questionnaire on POD 1, 2, 3, 4, 7
McCarthy et al 2009 ²¹	Double-blind RCT	Retropectoral implants, n = 50	Locally administered intraoperatively 1 mL ketorolac (30 mg/mL) + 15 mL bupivacaine 0.5% + 14 mL NS	No irrigation	1. VAS at 1, 3, and 6 hours postoperatively and daily until POD 6 2. Narcotic use

Abbreviations: NS, normal saline; POD, postoperative day; RCT, randomized controlled trial; VAS, visual analog scale.

Table 2. Risk of Bias According to Cochrane Risk of Bias Criteria.^a

Author	Adequate Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data Addressed	Free of Selective Outcome Reporting
Mahabir et al 2004 ¹⁹	No	No	No	No	Unclear
Kazmier et al 2008 ²²	Unclear	Unclear	No	Yes	Unclear
Mahabir et al 2008 ²⁰	No	No	No	Yes	Unclear
McCarthy et al 2009 ²¹	No	No	No	No	Unclear

^a The level of bias was determined as "Yes," indicating risk of bias; "Unclear," indicating an uncertain risk of bias; and "No," indicating no risk of bias.

5.0.2. All the studies included were randomized and had adequate sequence generation and allocation concealment except one,²² where a surgical technician allocated patients to the intervention groups without using any randomization system. Incomplete outcome data were found in 2 studies. The total number of participants included in the trial of Kazmier et al²² was 20 (5 of 25 patients included did not return the questionnaire), 94 of 100 in the study of Mahabir et al²⁰ (6 of the 100 patients did not respond to the questionnaire; 3 from bupivacaine plus ketorolac group and 3 from normal saline irrigation group), and 50 in the trial of McCarthy et al.²¹ The study of Mahabir et al (2008) originally had 50 patients distributed into 2 groups, normal saline irrigation and bupivacaine plus ketorolac irrigation. However, when the authors were requested to send more detailed information regarding their study, they added 2 more groups of 25 patients in each group, which were not included in the publication. Data were provided from both the bupivacaine and ketorolac groups.

Outcomes Assessed

The efficacy for bupivacaine alone and bupivacaine plus ketorolac solution was analyzed independently (Figures 2 and 3).

Bupivacaine Plus Ketorolac Versus Placebo

Figure 2 presents the results of pooled analysis for bupivacaine plus ketorolac versus placebo or no treatment. The result favored bupivacaine plus ketorolac over the placebo or no treatment group for pain relief during the first postoperative hour, with statistical differences of MD = -2.39 and 95% CI = -3.23 to -1.54, and similar results were yielded for postoperative day 5 (MD = -0.63; 95% CI = -1.24 to -0.02).

Bupivacaine Versus Placebo

In Figure 3, the results for bupivacaine versus placebo yielded statistically significant differences for postoperative day 3

Figure 2. Forest plot for bupivacaine plus ketorolac versus placebo. Three trials were included. POD indicates postoperative day.

(MD = -0.68; 95% CI = -1.31 to -0.05) and postoperative day 4 (MD = -0.82; 95% CI = -1.48 to -0.16).

Discussion

This study revealed 2 important findings. First, irrigation in the retropectoral pocket with bupivacaine plus ketorolac is related to a mean reduction of 2.39 points in the VAS during the first immediate hour after breast augmentation, whereas irrigation with bupivacaine alone did not show a beneficial effect. Second, the effect on the pain of irrigating with a bupivacaine solution (either alone or plus ketorolac) was significant during the first 5 postoperative days, although the effect on the clinical significance remained unclear. Due to the small number of included trials, the evidence obtained in the current study may not be strong enough. However, according to the available

studies regarding this issue, the former might provide the most solid evidence to date.

The results of the bibliographical search conducted in this review highlighted the scarcity of studies with strong evidence on the management of postoperative pain using irrigation in patients undergoing augmentation mammoplasty. Although many studies related to postoperative pain control in breast augmentation were performed, most of them were done on a large series of patients,^{10,11} or bupivacaine placement was not performed by a single irrigation, or with more sophisticated devices, such as DepoFoam bupivacaine.^{15,23} In order to limit our study, we included only those RCTs that studied the role of the irrigation of bupivacaine with or without analgesic in the control of postoperative pain in breast augmentation measured by VAS.

Another limitation of the review is the subjective nature of the perception of pain and the need for complementary data on

Figure 3. Forest plot for bupivacaine versus placebo. Two trials were included. POD indicates postoperative day.

other parameters of pain assessment such as the amount of narcotics required. Visual analog scale is, among validated pain scores, one of the most widely used response scale either in clinical practice or in therapeutic trials. In order to determine whether a pain decrease in the VAS had clinical correlation, Grilo et al²⁴ conducted a meaningful study. In 50 patients, they found that VAS score changes correlated linearly with clinical pain relief. A 20-mm decrease was the minimum value to have some impact on clinical symptoms.

According to the results obtained in the present study, significant pain reduction was achieved only for the first postoperative hour and for postoperative day 5 with placing bupivacaine in addition to ketorolac irrigation at the retropectoral pocket. With bupivacaine alone, this reduction was found for postoperative days 3 and 4. These results were similar to those obtained by the 2 trials of Mahabir et al^{19,20} and the study by McCarthy et al.²¹ However, in the latter, a higher requirement of oral narcotic use was found in the first postoperative days in addition with a significant improvement of VAS score. The use of narcotic was only included in this trial and thus comparison with the other trials could not be performed. Other authors found that when using bupivacaine irrigation at the surgical bed either after laparoscopic cholecystectomy or after cesarean delivery,^{25,26} narcotic requirement decreased in the group of bupivacaine irrigation in spite of the absence of

significant results in pain relief achieved by irrigation. The difference in time interval used by these authors may probably influence the narcotic used, since in the Mahabir study the pain was measured at the first 48 hours after surgery, whereas in the McCarthy trial, the study was prolonged until postoperative day 6. Similar results were obtained using intraoperative irrigation of the diaphragm with bupivacaine for a management of shoulder tip pain following laparoscopy.²⁷ They obtained significant results for the time interval between 4 and 24 hours postoperatively in comparison with irrigation with normal saline. In addition, the requirement of postoperative analgesics was also reduced in the treatment group. Although clinical pain relief was achieved in all the aforementioned time intervals, the largest change was observed during the first postoperative hour. The addition of ketorolac to bupivacaine may be partially responsible because of its strong and remarkable anti-inflammatory effect.²⁸ Additionally, its topical administration avoided its systemic side effect, making this route of administration a most suitable choice.

Augmentation mammoplasty is a common surgical procedure in our field. Implant placements are mainly done through 3 different incisions: inframammary fold, periareolar, and transaxillary approaches. Whichever incision location is chosen, access to the breast must be sufficient to allow accurate dissection of the pocket for the easy insertion of the implant

and for precise hemostasis. Each approach presents both advantages and disadvantages, and several reports were conducted in order to determine the differences in scar visibility,²⁹ the incidence of capsule contracture,³⁰ nipple-areola complex sensitivity,^{31,32} and the occurrence of hematoma.¹ Roughly, 90% of breast augmentation was done through the inframammary approach. In all the patients included in the present study, retropectoral plane was chosen for implant placement. Adding the size of implants would have provided more information to the present study, but it was not available in every included trial. The site of incision might not be an essential factor determining postoperative pain since very few studies showed its impact. However, the influence of other variables on pain such as the plane of implant placement, the extension of pocket dissection, and the size of breast implants have been extensively described.³³ Moreover, during preoperative planning, factors taken into account for the scar choice did not address postoperative pain but patient preference, physical examination, and surgeon comfort while performing the procedure.

This study summarized the results of independent trials regarding the role of bupivacaine (with or without analgesic) irrigation into the pocket for postoperative pain control in augmentation mammoplasty. To the best of our knowledge, there was no similar study that has ever been performed on this topic, and the evidence provided in this review is the best available to date. Due to a scarce number of RCTs on this issue, only 4 trials met the inclusion criteria. Further well-designed RCTs including the requirement of postoperative narcotics in both irrigation and placebo groups are needed since a reduction of their intake would reduce the side effects produced by the former trials.

Local irrigation of bupivacaine with or without ketorolac was associated with reduced postoperative pain after augmentation mammoplasty for the first 5 postoperative days. Due to the limited number of trials included in the current study, the strength of the results should be correlated with clinical pain relief. The use of irrigation with local anesthetic might alleviate postoperative pain, but further studies are warranted to investigate the effect of bupivacaine irrigation in decreasing the need of additional analgesics rather than its use as a treatment alone.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Stutman RL, Codner M, Mahoney A, Amei A. Comparison of breast augmentation incisions and common complications. *Aesthetic Plast Surg*. 2012;36(5):1096-1104.
2. Papanastasiou S, Evans J. Postoperative analgesia in augmentation mammoplasty. *Plast Reconstr Surg*. 2000;105(3):1241.
3. Freedman BM, Balakrishnan TP, O'Hara EL. Celecoxib reduces narcotic use and pain following augmentation mammoplasty. *Aesthet Surg J*. 2006;26(1):24-28.
4. Parsa AA, Soon CWM, Parsa FD. The use of celecoxib for reduction of pain after subpectoral breast augmentation. *Aesthetic Plast Surg*. 2005;29:441-444.
5. Schneider MS. Pain reduction in breast augmentation using methocarbamol. *Aesthetic Plast Surg*. 1997;21(1):23-24.
6. Schneider MS. Methocarbamol: adjunct therapy for pain management in breast augmentation. *Aesthet Surg J*. 2002;22(4):380-381.
7. Pacik PT. Pain management in augmentation mammoplasty: a randomized, comparative study of the use of a continuous infusion versus self-administration intermittent bolus of a local anesthetic. *Aesthet Surg J*. 2004;24(6):523-530.
8. Zhibo X, Miaobo Z. Effect of sustained-release lidocaine on reduction of pain after subpectoral breast augmentation. *Aesthet Surg J*. 2009;29(1):32-34.
9. Paul MD. Breast augmentation and abdominoplasty: postoperative management with pain pumps. *Aesthet Surg J*. 2005;25(1):69-71.
10. Tebbetts JB. Pain control in augmentation mammoplasty: the use of indwelling catheters in 200 consecutive patients. *Plast Reconstr Surg*. 2004;113(2):784-785.
11. Pacik PT, Nelson CE, Werner C. Pain control in augmentation mammoplasty using indwelling catheters in 687 consecutive patients: data analysis. *Aesthet Surg J*. 2008;28(6):631-641.
12. Pacik PT, Werner C. Pain control in augmentation mammoplasty: the use of indwelling catheters in 350 consecutive patients. *Plast Reconstr Surg*. 2005;115(2):575-577.
13. Swerdlow M, Jones R. The duration of action of bupivacaine, prilocaine and lignocaine. *Br J Anaesth*. 1970;42(4):335-339.
14. Dasta J, Ramamoorthy S, Patou G, Sinatra R. Bupivacaine liposome injectable suspension compared with bupivacaine HCl for the reduction of opioid burden in the postsurgical setting. *Curr Med Res Opin*. 2012;28(10):1609-1615.
15. Minkowitz HS, Onel E, Patronella CK, Smoot JD. A two-year observational study assessing the safety of DepoFoam bupivacaine after augmentation mammoplasty. *Aesthet Surg J*. 2012;32(2):186-193.
16. Jabs D, Richards BG, Richards FD. Quantitative effects of tumescent infiltration and bupivacaine injection in decreasing postoperative pain in submuscular breast augmentation. *Aesthet Surg J*. 2008;28(5):528-533.
17. Huskisson EC. Measurement of pain. *Lancet*. 1974;2(7889):1127-1131.
18. Higgins JPH, Green S, eds. Addressing reporting biases. Cochrane Handbook for systematic reviews of intervention. Version 5.1.0. The Cochrane Collaboration. 2011. Available from www.handbook.cochrane.org.
19. Mahabir RC, Peterson BD, Williamson JS, Valnicek SM, Williamson DG, East WE. Locally administered ketorolac and bupivacaine for control of postoperative pain in breast augmentation patients. *Plast Reconstr Surg*. 2004;114(7):1910-1916.
20. Mahabir RC, Peterson BD, Williamson JS, Valnicek SM, Williamson DG, East WE. Locally administered ketorolac and bupivacaine for control of postoperative pain in breast augmentation patients: part II. 10-day follow-up. *Plast Reconstr Surg*. 2008;121(2):638-643.

21. McCarthy CM, Pusic AL, Hidalgo DA. Efficacy of pocket irrigation with bupivacaine and ketorolac in breast augmentation: a randomized controlled trial. *Ann Plast Surg.* 2009;62(1):15-17.
22. Kazmier FR, Henry SL, Christiansen D, Puckett CL. A prospective, randomized, double-blind, controlled trial of continuous local anesthetic infusion in cosmetic breast augmentation. *Plast Reconstr Surg.* 2008;121:711-715.
23. Smoot JD, Bergese SD, Onel E, Williams HT, Hedden W. The efficacy and safety of DepoFoam bupivacaine in patients undergoing bilateral, cosmetic, submuscular augmentation mammoplasty: a randomized, double-blind, active-control study. *Aesthet Surg J.* 2012;32(1):69-76.
24. Grilo RM, Treves R, Preux PM, Vergne-Salle P, Bertin P. Clinically relevant VAS pain score change in patients with acute rheumatic conditions. *Jt Bone Spine.* 2007;74(4):358-361.
25. Castillo-Garza G, Díaz-Elizondo JA, Cuello-García CA, Villegas-Cabello O. Irrigation with bupivacaine at the surgical bed for postoperative pain relief after laparoscopic cholecystectomy. *JSLs.* 2012;16(1):105-111.
26. Givens VA, Lipscomb GH, Meyer NL. A randomized trial of postoperative wound irrigation with local anesthetic for pain after cesarean delivery. *Am J Obstet Gynecol.* 2002;186(6):1188-1191.
27. Cunniffe MG, McAnena OJ, Dar MA, Callearly J, Flynn N. A prospective randomized trial of intraoperative bupivacaine irrigation for management of shoulder-tip pain following laparoscopy. *Am J Surg.* 1998;176(3):258-261.
28. Rainer TH, Jacobs P, Ng YC, et al. Cost effectiveness analysis of intravenous ketorolac and morphine for treating pain after limb injury: double blind randomised controlled trial. *BMJ.* 2000;321(7271):1247-1251.
29. Niechajev I. Improvements in transaxillary breast augmentation. *Aesthetic Plast Surg.* 2010;34(3):322-329.
30. Wiener TC. Relationship of incision choice to capsular contracture. *Aesthetic Plast Surg.* 2008;32(2):303-306.
31. Pitanguy I, Vaena M, Radwanski HN, Nunes D, Vargas AF. Relative implant volume and sensibility alterations after breast augmentation. *Aesthetic Plast Surg.* 2007;31(3):238-243.
32. Araco A, Araco F, Sorge R, Gravante G. Sensitivity of the nipple-areola complex and areolar pain following aesthetic breast augmentation in a retrospective series of 1200 patients: periareolar versus submammary incision. *Plast Reconstr Surg.* 2011;128(4):984-989.
33. Lista F, Ahmad J. Evidence-based medicine: augmentation mammoplasty. *Plast Reconstr Surg.* 2013;132(6):1684-1696.