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Review article

The efficacy of local anesthetics in pain relief during colposcopic-guided biopsy: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Colposcopy is an office gynecological procedure used for cervical evaluation in patients with abnormal cervical cytology. It is considered an important tool for early detection of cases of cervical cancer.

Objective: To evaluate the evidence from published randomized clinical trials (RCTs) about the efficacy of local anesthetics in pain relief during colposcopic-guided biopsy.

Data sources: Several electronic databases included MEDLINE, EMBASE, Cochrane Library, ISI and Scopus were searched using the relevant MeSH terms.

Methods of study selection: All RCTs assessing the effect of local anesthetics in relieving pain during colposcopy were considered for this meta-analysis. There were 1339 studies identified of which 11 studies deemed eligible for this review. We performed quality and risk of bias assessment for all included studies.

Data extraction: Three researchers independently extracted the data from the individual articles and entered it into RevMan software. The extracted outcomes included pain scores and the duration of the procedure.

Results: Eleven RCTs were included. Local anesthesia (LA) was associated with higher pain at speculum insertion than control (SMD = 0.23, 95% CI [0.03, 0.43]). While, LA significantly reduced biopsy pain than control (SMD= -0.57, 95% CI [-0.94, -0.20]). The overall pooled estimate showed no significant difference between LA and control regarding postprocedural pain, pain on endocervical curettage, pain expectancy, and overall pain scores.

Conclusions: This meta-analysis suggests that local anesthetics are effective in pain relief during a colposcopic-guided biopsy; however there is no strong evidence to recommend its use in current practice.

Contents

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Introduction

Colposcopy is a common gynecological procedure used to examine the cervix in women who present with abnormal cervical cytology. This helps to detect cancer or precancerous cells for the prevention of morbidity and mortality related to cervical cancer [1]. Cervical cancer is ranked as the third most common cancer worldwide for females [2], and its incidence has decreased dramatically in the United States with screening programs while it remains a problem in unscreened populations [3]. Screening helps to catch a precancerous or cancerous lesion at early stages leading to a better prognosis.

Colposcopy, as a tool for early detection and prognosis of a life-threatening neoplasm, is important to be socially accepted. Many patients know the importance of being examined colposcopically but still hesitate for fear of pain, stress, and anxiety associated with the procedure that may affect the compliance rate [4].

Analgesics, coughing, distraction and talking with the patient during the procedure may reduce the pain, anxiety, and stress experienced [5]. Few randomized controlled trials (RCTs) published later reported that local anesthesia (LA) is highly effective in reducing pain perception during colposcopy [6,7]. In 2017, Kiviharju et al. conducted an RCT comparing pain sensation during colposcopy with or without LA and found that injection of a local anesthetic significantly decreases the pain perceived [2]. Additionally, two RCTs found that LA does not provide advantages in pain relief with a comparison to forced coughing [4,5]. However, another study found that LA provides significant pain relief during cervical biopsy [7].

Consequently, we performed this systematic review and meta-analysis to synthesize evidence from published RCTs about the efficacy and safety of local anesthetics compared with other modulations or measures in reducing pain associated with colposcopic-guided biopsy.

Materials and methods

We report this review according to the Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) statement [8].

Search strategy

We performed a detailed search on MEDLINE, EMBASE, Cochrane Library, ISI web of knowledge and Scopus. We used the MeSH database and the following search terms: (Regional anesthesia OR Regional anesthetic OR Regional anesthetics OR topical anesthesia OR topical anesthetic OR local anesthesia OR local anesthetics OR local anesthetic OR Regional analgesia OR Regional analgesic OR topical analgesic OR local analgesia OR local analgesic OR lidocaine OR lignocaine OR mepivacaine OR prilocaine OR bupivacaine OR articaine OR tetracaine OR ropivacaine OR benzocaine) AND (vaginoscopy OR vaginoscopic OR colposcopy OR colposcopic or colposcopically OR colposcope OR cervical biopsy).

Eligible criteria

We included RCTs comparing any form of local anesthetic by any route of administration with different doses versus placebo or any other technique of pain relief like a forced cough in women undergoing colposcopic-guided biopsy and reported pain outcome.

We excluded non-English language studies, editorials and letters, animal and in-vitro studies, book chapters, duplicates, and overlapping dataset, conferences abstracts and studies other than clinical trials.

Study selection

Four of the authors independently reviewed the titles and abstracts from the electronic literature searches, and the studies that matched the eligible criteria were retrieved for full-text screening. Full-text articles of eligible abstracts were retrieved and screened for suitability for meta-analysis. Disagreements about study eligibility were resolved by consensus. All identified articles were evaluated according to a standardized format including study design, methods, participant characteristics, intervention, and results.

Data extraction and analysis

Three authors extracted the data independently using an online data extraction form. The extracted data included the following: study characteristics, participants, baseline characteristics and efficacy outcomes. Efficacy outcomes included pain scores and the duration of the procedure

Data were pooled as standardized mean difference (SMD) with 95% confidence interval (CI). Heterogeneity was assessed by visual inspection of the forest plots and measured by Q statistic and I^2 statistics [9]. Significant statistical heterogeneity was indicated by Q statistic P-value <0.1 or by $I^2 > 50\%$. In case of significant heterogeneity, a random effect model was employed for meta-analysis. Otherwise, the fixed effect model was used. We used R software version 3.4.4 (meta package) for windows during data synthesis. Subgroup analysis was conducted to compare LA versus

forcing coughing, no LA, and placebo. Furthermore, a sensitivity analysis was conducted to ensure that none of the included studies affected the results and to examine whether the overall effect size is statistically robust.

Quality of included studies and risk of bias assessment

We assessed the quality of the included studies according to the Cochrane Handbook for Systematic Reviews of Interventions using the quality assessment table provided in the same book [10].

The Cochrane risk of bias assessment tool includes the following domains: sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias. The authors' judgment is categorized as 'Low risk,' 'High risk' or 'unclear risk' of bias.

Results

Search results and characteristics of included studies

The searching process returned a total of 1339 records from the electronic databases. We removed the duplicates using Endnote software; of the remaining 1327 records screened by title/abstract, 21 records were eligible. After reading the Full-text of the 21 studies, we excluded ten studies which were ineligible according to the eligibility criteria. We searched the references of the included RCTs manually, but we did not find any more relevant records. Eleven RCTs recruiting 1405 patients underwent colposcopy for cervical biopsy were finally included (Fig. 1). The characteristics of the included studies are summarized in Tables 1 & 2 (Supplemental files no. 1& 2).

Risk of bias assessment

We used the Cochrane Collaboration's tool for assessing the risk of bias to assess the risk of bias as explained before. The results are represented in (Figs. 2 and 3).

Outcomes:

Pain score

Speculum insertion

The overall effect size showed that LA was associated with higher pain at speculum insertion than control (SMD = 0.23, 95% CI [0.03, 0.43]). This effect size was consistent with subgroup analysis that compared LA versus forcing coughing (SMD = 0.31, 95% CI [0.06, 0.56]). While, the effect size showed no significant difference between LA versus no LA (SMD = 0.34, 95% CI [−0.19, 0.87]) and placebo (SMD= −0.08, 95% CI [−0.52, 0.35]) (Fig. 4).

Pain at biopsy

The overall effect size showed that LA significantly reduced biopsy pain than control (SMD= −0.57, 95% CI [−0.94, −0.20]). This effect size was consistent with subgroup analysis that compared LA versus forced coughing (SMD= −0.46, 95% CI [−0.81, −0.12]) and no LA (SMD= -0.95, 95% CI [−1.75, -0.14]). While, no significant difference was detected between LA and placebo (SMD= −0.31, 95% CI [−0.97, 0.35]) (Fig. 5a). Significant heterogeneity was observed in subgroup analysis that compared LA versus no LA and placebo ($I^2 = 93\%$, $p < 0.01$ and $I^2 = 89\%$, $p < 0.01$, respectively) which was best resolved by excluding the studies by Duncan et al. and Wongluecha et al. (Fig. 5b).

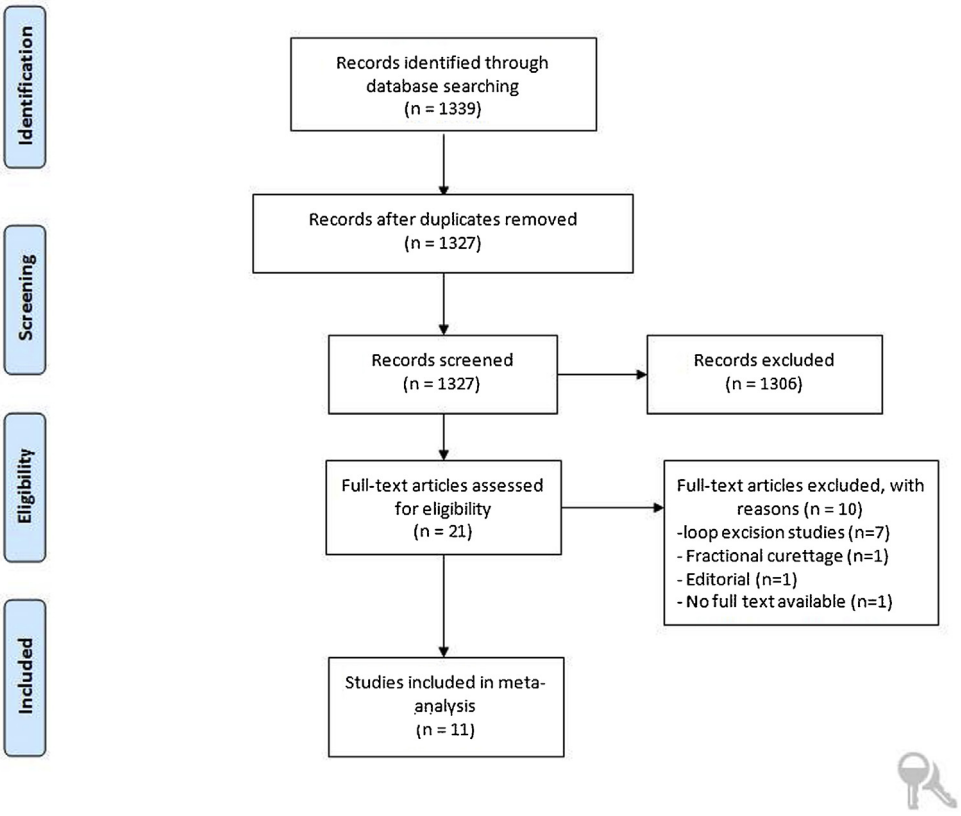

Fig. 1. PRISMA Flow Chart of the study selection process.

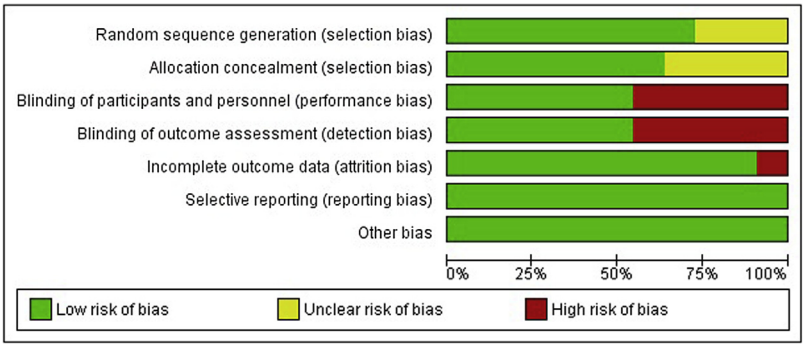

Fig. 2. Diagram of the quality of the included studies.

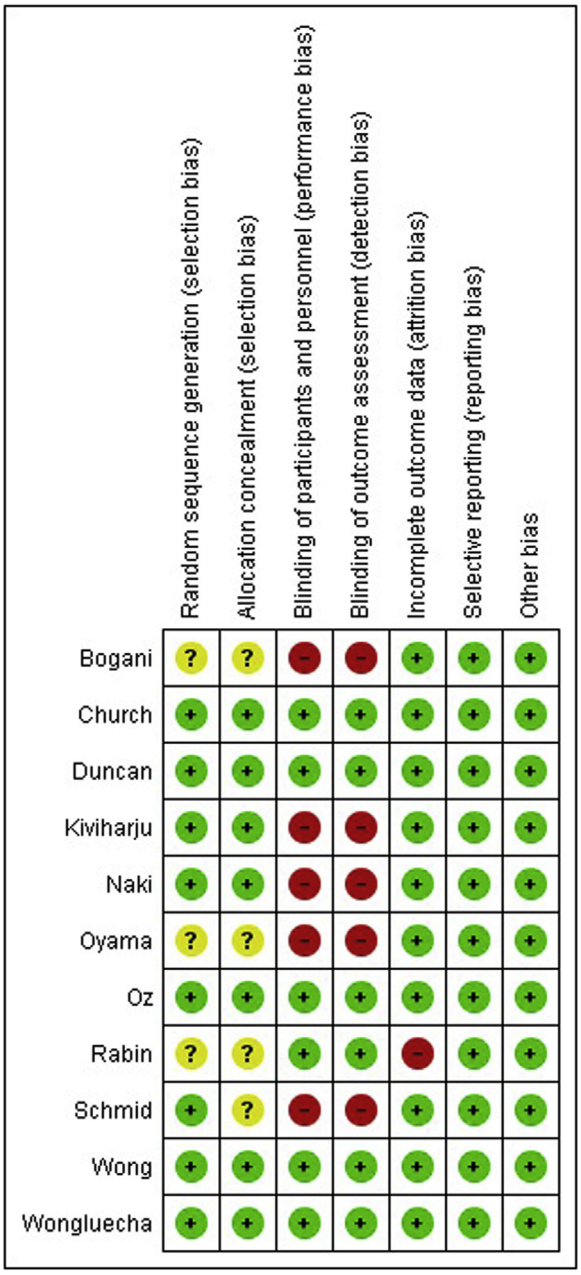

Fig. 3. Risk of bias summary graph.

Post-procedural pain

The overall effect size showed no significant difference between LA and control (SMD = 0.42, 95% CI [−0.85, 1.69]). This effect size was consistent with subgroup analysis that compared LA versus no LA (SMD= −0.22, 95% CI [−0.49, 0.06]). While, subgroup analysis showed that LA significantly increased post-procedural pain than forcing coughing (SMD = 1.08, 95% CI [0.66, 1.50]) (Fig. 6).

Pain on endocervical curettage (ECC)

The effect size showed that LA significantly reduced pain on ECC than no local anesthesia (MD= −1.59, 95% CI [−2.12, −1.07]). The overall effect size showed no significant difference between LA and control (SMD= -0.34, 95% CI [−0.83, 0.16]). This effect size was consistent with subgroup analysis that compared LA versus placebo (SMD = 0.05, 95% CI [−0.19, 0.29]). While, subgroup analysis showed that LA significantly reduced pain on ECC than no LA (SMD= −0.73, 95% CI [−0.99, −0.48]) (Fig. 7).

Pain expectancy

The effect size showed that LA significantly reduced pain expectancy than forcing coughing (MD= -4.80, 95% CI [−5.78, −3.82]). The overall effect size showed no significant difference between LA and control (SMD= −0.49, 95% CI [−1.83, 0.84]). This effect size was consistent with subgroup analysis that compared LA versus placebo (SMD = 0.19, 95% CI [−0.16, 0.54]). While, subgroup analysis showed that LA significantly reduced pain on ECC than no LA (SMD= −1.91, 95% CI [−2.38, −1.43]) (Fig. 8).

Overall pain score

The effect size showed that LA significantly reduced overall pain score than no local anesthesia (MD= −1.77, 95% CI [−2.78, −0.75]). The overall effect size showed no significant difference between LA and control (SMD= −0.25, 95% CI [−0.64, 0.13]). This effect estimate was consistent with subgroup analysis that compared LA versus forced coughing (SMD= −0.15, 95% CI [−0.48, 0.17]) and placebo (SMD = 0.08, 95% CI [−0.36, 0.51]). While, LA significantly reduced overall pain score compared to no LA (SMD= −0.89, 95% CI [−1.44, −0.34]) (Fig. 9).

Operative duration

The effect size showed that LA was associated with longer operative time than forcing cough (MD=2.06 min, 95% CI [1.15, 2.96],

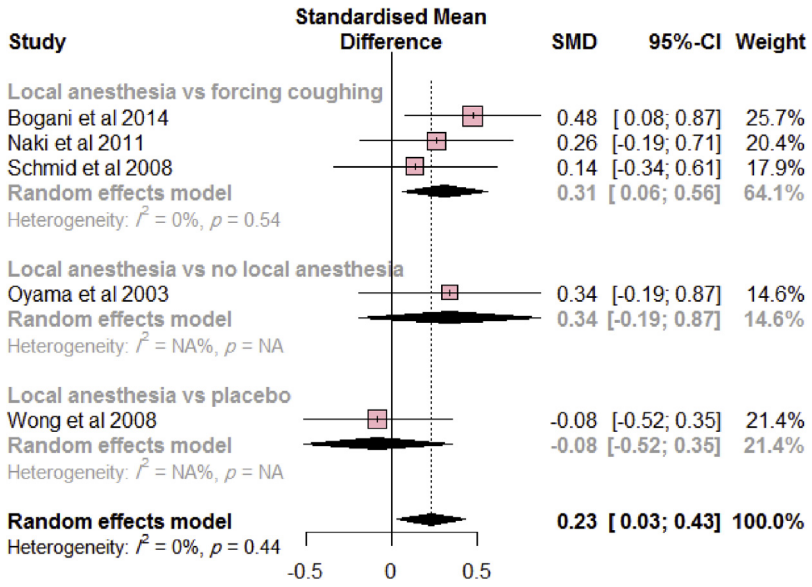

Fig. 4. Forest plot for pain score during speculum insertion favors control group.

$p < 0.0001$). The effect size showed that local anesthetics were associated with longer operative time than control (SMD = 3.58, 95% CI [1.59, 5.57]). This effect estimate was consistent with subgroup analysis that compared LA versus forcing coughing and no LA (SMD = 5.06, 95% CI [1.61, 8.51] and SMD = 0.33, 95% CI [0.05, 0.61], respectively) (Fig. 10a). Significant heterogeneity was observed in subgroup analysis that compared LA versus forcing coughing ($I^2 = 99\%$, $p < 0.01$) which was best resolved by excluding the study by Bogani et al. (Fig. 10b).

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to investigate the efficacy of local anesthetics in pain relief during colposcopic-guided biopsy.

Colposcopy is widely used in the examination of abnormal cervical cytology; however, many patients remain reluctant due to its pain effect. In the current review, we assessed the local anesthetics used to reduce the pain, compared to placebo, no treatment or forced coughing. When compared to no treatment, LA was superior in terms of pain reduction while obtaining a biopsy, ECC, and overall pain. However, compared to placebo, there was no significant difference, and that could be attributed to the effect of psychological state on pain perception. That was inconsistent with forced coughing; LA was more effective during the biopsy, while forced coughing was favored in speculum insertion.

The operative time was longer with LA, which was linked to the waiting time for the anesthetics to be effective. It is also deemed to be a waste of time and lead to patients' discomfort [4,7]. The injection of LA also has other disadvantages due to being an invasive, painful procedure, and may cause tissue damage interfering with the pathological diagnosis [5]. The intracervical injection can also cause additional bleeding, which is not the case with the topical administration; gel and spray. On the other hand, topical anesthetics may not be as effective as injections due to lack of strong evidence suggests which is better, and that is most likely the reason behind the heterogeneity in the biopsy results.

There were some differences between the included trials, one of which was that Rabin et al. reported the pain associated with biopsy and tenaculum together as one outcome [11]. Thus, the data for this outcome were excluded from the analysis since pain associated with tenaculum is out of our scope and could head to misleading results if we added it to the biopsy pain. Another difference was in the methods used in pain assessment. Out of 11 included studies, seven used the Visual Analog Scale (VAS). Another three trials used the Numerical Rating Scale (NRS), and one study used the Wong-Baker Faces Pain Rating Scale. In terms of practicality, VAS is more difficult, and the graphic orientation affects the data distribution, yet VAS and NRS are significantly correlated with a strong level of agreement [12,13].

Pain is very subjective and complex; its perception can be affected by intra-personal and interpersonal factors as age, previous experience, number of vaginal births, and psychological state as in anticipation of biopsy result. These factors can also result in anxiety [14–16]. Therefore, a large number of trials have been done to reach the most appropriate modality to handle pain. One of these modalities is the forced coughing which was compared to LA in this review. However it is safer and more effective in speculum insertion, and post-procedural pain, the instability of coughing carries the risk of obtaining the wrong biopsy [2]. Oral NSAIDs are one of the commonly used drugs clinically, and Rodney et al. found them to be significantly effective in pain reduction when compared to no treatment [17]. On the contrary, Church et al. found no significant difference when compared to benzocaine and placebo [18].

In the included studies there was no difference between pain score reported at speculum insertion with LA, forced coughing or placebo. However, higher pain scores were reported in the current meta-analysis at speculum insertion with LA. This could be explained by two points: first; forced coughing distract the patient attention to speculum insertion so they reported lower pain scores. Second; application of LA in most of studies was after speculum insertion; therefore it was a subjective variation in reporting the pain among the study participants and this is one of the drawbacks of using VAS or NRS scores in pain assessment.

In a recent Cochrane review assessing the different pharmacological interventions to reduce colposcopy pain, the combination of local anesthetics and vasoconstrictors were reported to be the best choice so far. They are also considered safe with minimal adverse effects; dizziness, shaking, abdominal cramps, weakness, and moderate, transient hypertension [19]. The published Cochrane review by Gajjar et al., 2016 is different from the present

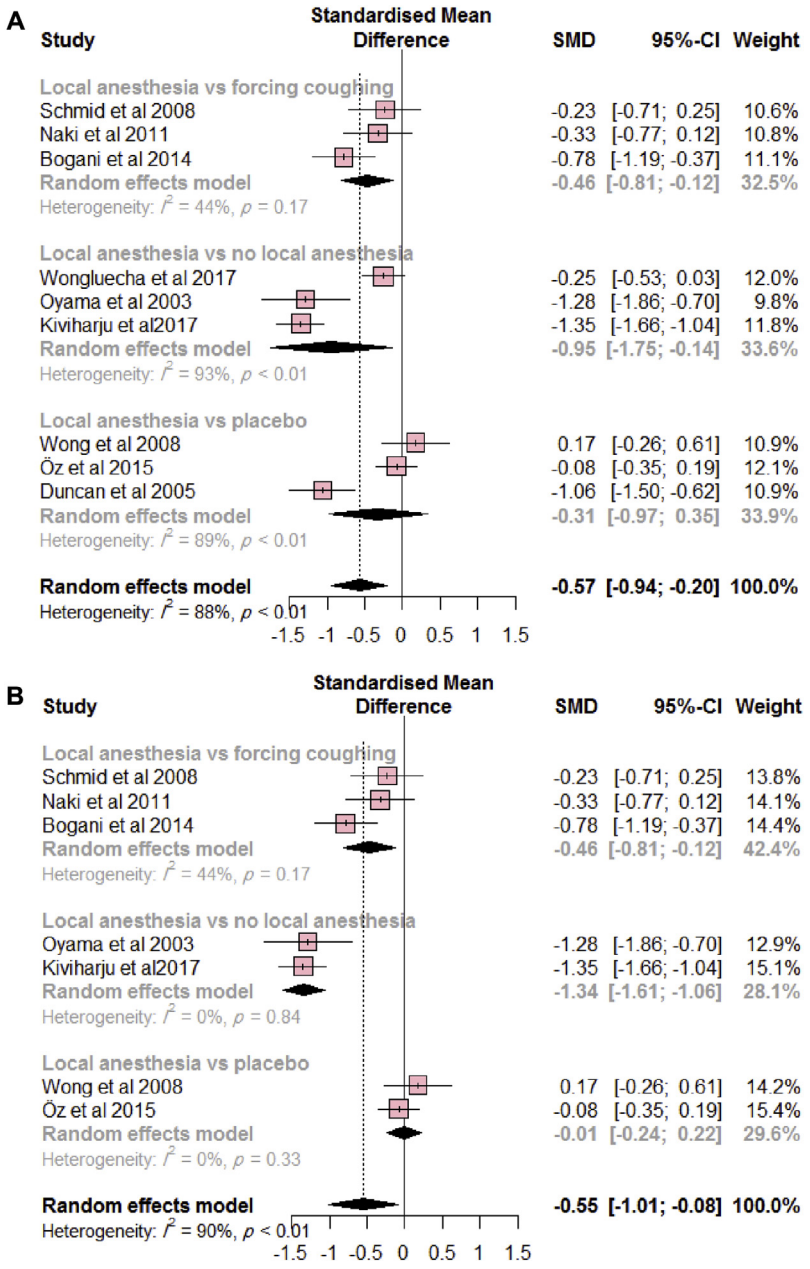

Fig. 5. (a) Forest plot for pain score at biopsy favors local anesthesia group. (b) Forest plot for subgroup analysis of pain score at biopsy.

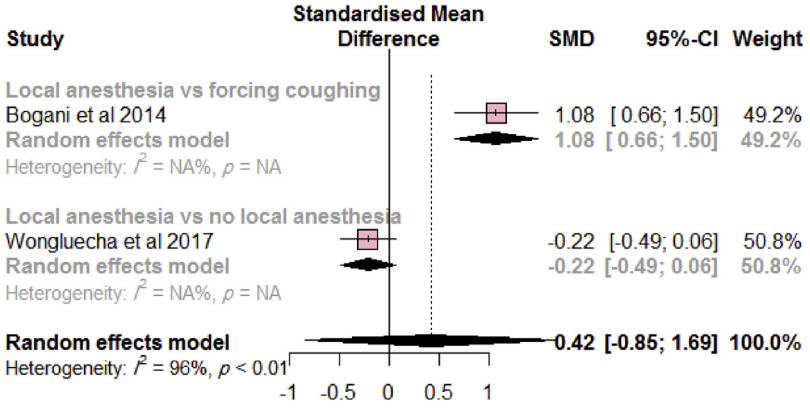

Fig. 6. Forest plot for post-procedural pain score with no difference between groups.

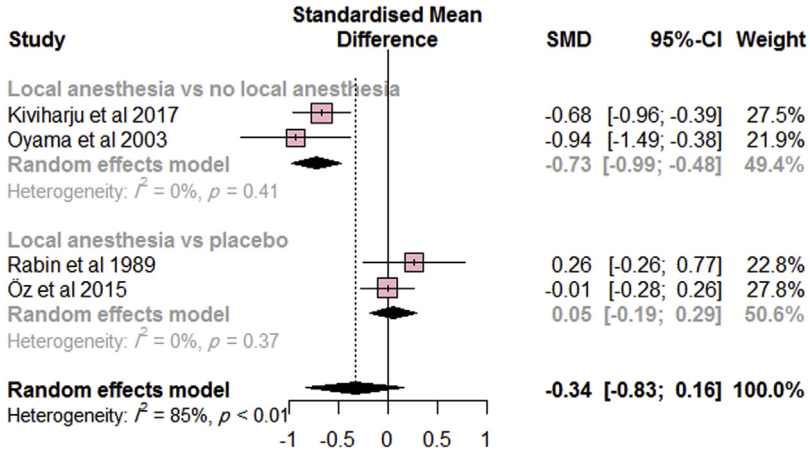

Fig. 7. Forest plot for pain score at endocervical curettage with no difference between groups.

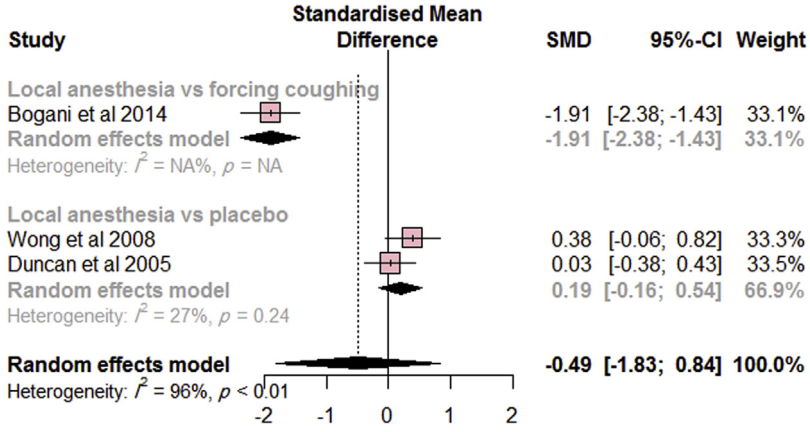

Fig. 8. Forest plot for pain expectancy with no difference between groups.

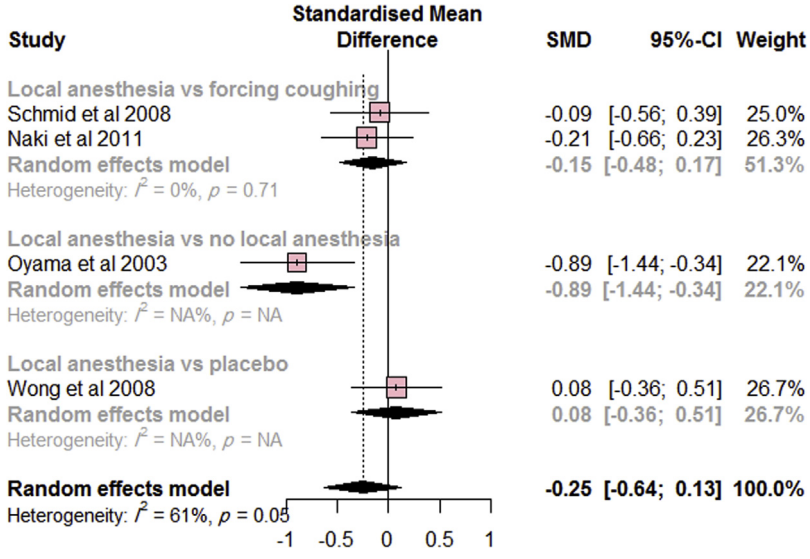

Fig. 9. Forest plot for overall pain score with no difference between groups.

review as it included women with cervical intraepithelial neoplasia (CIN) undergoing colposcopy treatment as LLETZ or Laser therapy. Unlike the current one, it is regarding the use of a colposcopic guided biopsy. The two procedures are different regarding the duration, baseline characteristics of included women, pain scores, blood loss, and other complications. Similarly, non-pharmacological approaches, as music and visual distraction with images were found to be effective in reducing pain perception [20,21].

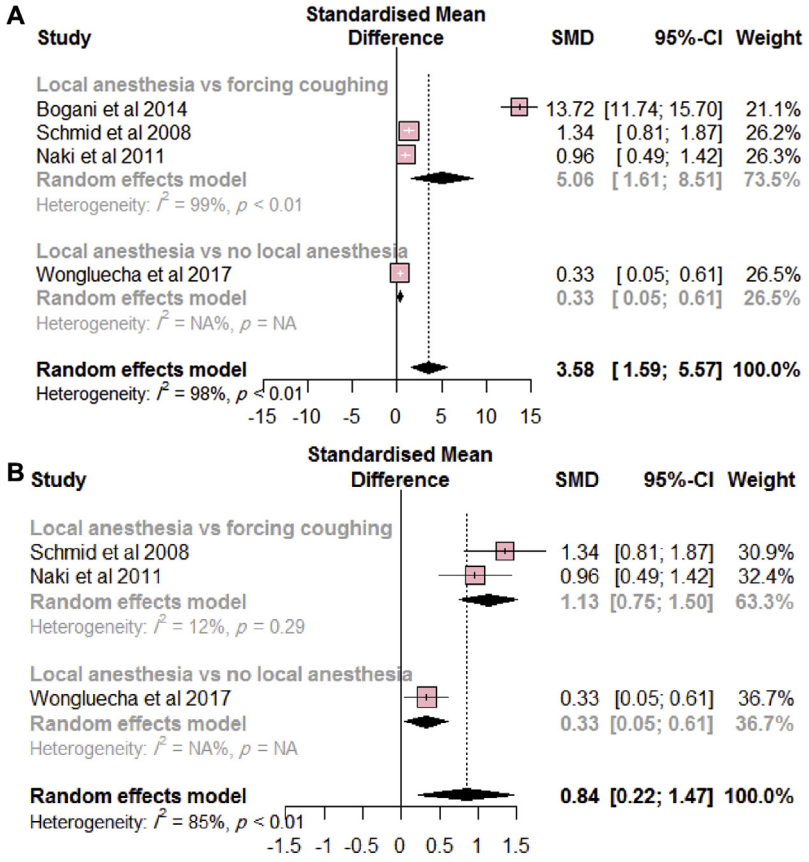

Fig. 10. (a) Forest plot for the operative duration favors control group. (b) Forest plot for subgroup analysis of operative duration.

The main limitation is, although pain is complex and multifactorial; none of the included trials assessed any of these factors. Therefore, it is hard to attribute these results solely to the medications. Moreover, there is no evidence on the clinically significant change of pain in gynecology, unlike other areas where it is considered effective with a minimum change of 13 on 100-mm VAS [22,23]. Therefore, further high-quality trials are needed to determine the clinically significant level of pain, and also the optimum route of administration and dose of local anesthetics.

Conclusion

In summary, the use of LA is effective in pain control during colposcopic-guided biopsy, yet the current evidence is insufficient to confirm their optimum route of administration and dose. We recommend the use of LA in minor rapid procedures during colposcopic-guided biopsy as punch biopsy, but patients at risk of painful procedures as loop, wedge biopsy and endocervical curettage need more effective method of pain relief.

Conflict of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2019.04.047.

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