Is Forced Coughing Effective in Reducing Pain During Cervical Biopsy?

A systematic review and meta-analysis

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Abstract

Our objective was to compare potential analgesic effect of forced coughing (FC) technique versus local anesthetics (LA) or placebo during cervical biopsy. We systematically searched five electronic databases from inception till March 2021; Scopus, PubMed, Web of Science, Cochrane Library, Google Scholar. The data was extracted from six RCTs and analyzed them using Review Manager Software. During cervical biopsy, the overall effect estimate favored LA over FC group (MD = 1.06; 95% CI [0.58 to 1.54]; p < 0.0001). On the other hand, when compared to no pain management pooled data were comparable between the two groups (MD = -1.2; 95% CI [-3.35 to 0.94]; p = 0.27). Procedure duration was significantly longer in LA than FC group (MD = -1.94; 95% CI [-2.47 to -1.41]; p < 0.00001). FC and LA seemed to useful pain-lowering modalities during the cervical biopsy according to settings and availability.

Further studies are recommended.
Keywords: Cervical Biopsy; Colposcopy; Forced Coughing; Pain.

Introduction

Colposcopic-guided biopsy (CGB) is an easily performed outpatient procedure and is generally done without anesthesia to diagnose and follow up precancerous and cancerous cervical diseases.\(^1\) Nevertheless, procedural discomfort and pain could exacerbate patients' anxiety and fear during the procedure, the speculum insertion, or solution application.\(^2\) Furthermore, women with known with pre-invasive cervical disease or human papillomavirus (HPV) infection have a higher risk for experiencing pain during the procedures thus needing additional analgesia.\(^3\)

In the past two decades, various pharmacological and nonpharmacological methods have been evaluated to reduce pain with CGB. These include benzocaine gel and its spray forms, lidocaine injections, ibuprofen, topical lignocaine gel, and prilocaine anesthesia; however, their results were mixed and non-conclusive.\(^4\) Injection of 1% lidocaine decreased pain during procedures compared with no anesthetics.\(^7,8\) However, it has several disadvantages, such as painful injections, difficulty accessing the injection site, the possibility of tissue damage by needles, thus interfering with the pathological diagnosis, risk of accidental intravascular injection, and allergic reactions.\(^9\) In addition, the use of benzocaine spray or topical xylocaine before cervical biopsy showed no benefit in reducing procedural pain.\(^10,11\) Oral delivery of pain medication, e.g., ibuprofen, also did not provide an advantage over a placebo in decreasing pain associated with colposcopic-guided cervical biopsy.\(^4\)

Similarly, trials of nonpharmacological methods such as coughing, simple visual distraction, hypnosis, and music reported non-conclusive results.\(^12,13\) Among all nonpharmacological approaches, forced coughing (FC) has the most significant contribution to pain relief during CGBs, while among pharmacological approaches, local anesthetic agents such as prilocaine and lidocaine have the most significant potential as pain-relieving medication. However, local anesthetic agents have adverse effects that do not exist with forced coughing.\(^9\)

Consequently, this systematic review and meta-analysis was performed to synthesize evidence from published RCTs and compare the efficacy and safety of forced coughing versus local
anesthetics compared with no analgesia in reducing pain associated with colposcopic-guided biopsy.

Methods
All phases of this study were performed according to the Cochrane handbook for systematic reviews of treatments. We also followed the PRISMA statement requirements during reporting of this systematic review and meta-analysis. Because this study was a systematic review and meta-analysis, formal ethical approval was not required.

Literature Search Strategy
A comprehensive search was conducted including the following electronic databases: PubMed, Cochrane Central, Scopus, and Web of Science from inception till March 2021. The combination of the following terms were used in our search strategy; (forced and cough or coughing and cervical or cone or cervix and biopsy or colposcopic). No restrictions by language or publication period were employed. We manually screened the references of included studies to retrieve those not identified by database searching.

Eligibility criteria and study selection
All clinical trials that met the following criteria were included in the study:(1) population: patients undergoing colposcopic-guided cervical biopsy; (2) intervention: forced coughing; (3) comparator: local anesthetics or control (without any intervention); (4) outcomes: our primary outcome was VAS pain score during cervical biopsy while secondary outcomes were VAS pain score during speculum insertion, immediately and five minutes after the procedure, and duration of the cervical biopsy for both the groups; (5) study design: randomized controlled trials. There was no restriction regarding age, ethnicity, location, and publication date.

We excluded in vitro and animal studies; studies whose data were unreliable for extraction and analysis overlapped datasets; non-English studies; and conferences, books, review articles, posters, thesis, editorial, notes, letters, case series, and case reports. Two authors independently screened the titles and abstracts of retrieved records for eligibility. In case of disagreement, the full text was retrieved and reviewed independently by a senior author for a final decision.
Data extraction
Two authors extracted the studies data independently using an offline data extraction form. The extracted data were study design, population characteristics; risk of bias domains; and study outcomes. Two investigators scored the studies and collected the information independently. In case of discrepancies in scoring, a consensus was reached after discussion. The primary outcome was pain score during cervical biopsy measured by visual analog scale (VAS), while secondary outcomes were VAS pain score during speculum insertion, immediately after the procedure, Five minutes after the procedure, and duration of the cervical biopsy.

Risk of bias assessment
Two independent reviewers used the Cochrane risk of bias (ROB) assessment tool to assess the quality of retrieved RCTs, as described in Chap. 8.5 of the Cochrane handbook of systematic reviews of interventions 5.1.0. The Cochrane collaboration risk of bias tool includes six domains, namely random 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 classified studies in each domain as low, high, or unclear risk of bias.

Data synthesis
Changes in VAS scores were calculated as mean difference (MD) and 95% confidence interval (CI) in a fixed-effect model using the Mantel–Haenszel (M–H) method. The fixed-effect model was used, assuming that the included studies were homogeneous and comparable in terms of study design, quality, and measures of treatment effect. Review Manager 5.3 was used for windows during data synthesis and a sensitivity analysis was performed to ensure that none of the included studies affected the results and whether the overall effect size was statistically robust. This resulted in excluding two studies.

Assessment of heterogeneity
Heterogeneity was assessed by visual inspection of the forest plots and measured statistically by I2 statistics and chi-square tests. The chi-square test measures significant heterogeneity, while the I2 statistics quantify the magnitude of heterogeneity in the effect size. We assessed and interpreted heterogeneity according to the Cochrane handbook of systematic reviews and meta-analysis (chapter 9). In this handbook, an alpha level (for chi-square test) below 0.1 is indicative of significant heterogeneity, and the I2 statistic is interpreted as follows: 0–40 %: might not be important; 30–60 %: may represent moderate heterogeneity; 50–90 %: may represent substantial heterogeneity). In the case of significant heterogeneity, the random-effects model was used. Otherwise, the fixed-effect model was employed.

Publication bias
The number of included studies in the analysis was less than 10. Therefore, we cannot assess the publication bias using the Egger test.

Results
Search results
We searched databases for randomized controlled trials matching our eligibility criteria and found a total of 501 records. Only 12 articles were eligible for full-text screening after the title and abstract screening. Of them, only six articles (N=532 patients) were included in our meta-analysis, as shown in the PRISMA flow diagram (supplementary fig.1); three studies compared FC with LA (1.0–2.0 mL of 1% lidocaine), two studies compared FC with no pain management, and only one study reported the results of FC compared with LA and no pain treatment. The baseline characteristics of patients and a summary of included studies are shown in Table 1 and supplementary Table 1.

Risk of bias assessment
Using the Cochrane risk-of-bias tool (Version 2) for randomized trials (ROB 2), we found that the quality of included studies was low in most criteria except for bias due to missing outcome data and bias in the selection of reported results. The summary of quality bias assessment domains of included studies is shown in (supplementary fig.2).
**Pain during cervical biopsy**

Pooled data from four studies\(^2,5,16,17\) with 378 patients showed a lower pain score in LA group than FC group (MD = 1.06; 95% CI [0.58 to 1.54]; p < 0.0001; supplementary fig.3). Pooled studies were homogenous (p = 0.27).

The effect size of a subgroup analysis that compared FC and no pain management showed no statistically significant difference between the two groups (MD = -1.2; 95% CI [-3.35 to 0.94]; p = 0.27; Fig.1). Significant heterogeneity was observed in subgroup analysis that compared FC versus no pain management (p = 0.05, I\(^2\) = 67%), best resolved by excluding Goldesteinakavia et al. study,\(^18\) as shown in Fig.1.

**Pain during speculum insertion**

Pooled data from four studies\(^2,5,16,17\) showed a statistically significant difference between the FC and LA groups with a reduction in the pain score in the FC group (MD = -0.33; 95% CI [-0.64 to -0.01]; p = 0.04; Fig.2). Pooled studies were homogenous (p = 0.2).

On the other hand, the overall effect from Kuhn et al.\(^19\) and Nakiet al.\(^5\) showed no statistically significant difference in pain score during speculum insertion between FC and no pain management group (MD = -0.06; 95% CI [-0.25 to 0.13]; p = 0.53; Fig.2). Pooled studies were homogenous (p = 0.91).

**Overall pain score immediately post-procedure**

The overall effect size showed no significant difference between FC and LA (MD = 0.75; 95% CI [-0.27 to 1.78]; p = 0.15). Pooled data were homogenous (P = 0.45).

There was no significant difference in overall pain score immediately post-procedure between FC and no pain management group (MD = -2.10; 95% CI [-5.81 to 1.61]; p = 0.27) (Fig.3). Pooled studies were heterogeneous (p < 0.0001; I\(^2\) = 90%). Heterogeneity was best resolved by excluding Goldesteinakavia et al. study,\(^18\) as shown in Fig.3.

**Overall score 5 minutes post procedure**
The overall effect size showed no significant difference between FC and LA (MD = - 0.20; 95% CI [-0.89 to -0.58]; p = 0.62; supplementary Fig.4). The results were heterogeneous under a random effect model (p < 0.0001; I^2 = 96%).

**Duration of procedure**

Pooled data from four studies\(^2,5,16,17\) showed a statistically significant difference between FC and LA with longer procedure duration in LA group than FC group (MD= -1.94; 95% CI [-2.47 to -1.41]; p < 0.0001; supplementary Fig.5). Pooled studies were heterogeneous under a random-effect model (p =0.0003; I^2 =84 %; supplementary Fig.5). Heterogeneity was best resolved by excluding Naki et al. study,\(^5\) as shown in supplementary Fig.5.

**Discussion**

To the best of our knowledge and based on a literature search, this is the first systematic review and meta-analysis to investigate the efficacy of FC in relieving pain during the colposcopic-guided biopsy. Our systematic review and meta-analysis showed that FC was better than local anesthesia in reducing pain during speculum insertion; however, no significant differences were found compared to the non-pain management. On the other hand, our analysis favored the LA group with more reduction in pain scores during cervical biopsy compared to the FC group; however, pain scores were comparable in the LA group compared with the non-pain management group. There was no significant difference in the overall pain score post-procedure in the FC group compared to the LA and no pain management. Moreover, the duration of the procedure was shorter in the FC group than in the LA group due to time spent to inject the drug, however this did not affect the amount of tissue obtained.

Colposcopic-guided biopsy (CGB) has great value in modern gynecology; it is used to examine patients with abnormal cytology and can be used to diagnose changes in cervical or vaginal epithelium. However, many patients remain reluctant to undergo a CGB due to procedure-related pain, anxiety, and discomfort. The fear of pain seems to be the main obstacle to proper gynecological examination.\(^20\) The LA injection, such as lidocaine, was painful, and many women were afraid of needles and refused to have those injections. An alternative nonpharmacological pain management technique is FC which can replace LA injections.\(^18\) The published literature
reported no adverse effects or other reactions or costs in the FC group. Conversely, injecting a local anesthetic might cause tissue damage that interferes with the pathological diagnosis.

Pain is a highly subjective, complex phenomenon, and its perception can be influenced by several factors such as race/ethnicity, gender, previous experience, number of vaginal births, and psychological state. Several pharmacological and nonpharmacological interventions could help minimize pain sensation, and FC is one of the effective pain-relieving measures. Forced coughing proved effective during speculum insertion and post-procedure. Based on our analysis, the procedure duration in the FC group was shorter than the LA group; the latter might be considered time-consuming due to the inclusion of injection as an additional step in the entire surgical procedure.

In numerous cases, FC and other methods such as cognitive tasks, music cartoons in children, humor, and imagining pleasant scenes work as distraction methods and could reduce procedural pain. However, the mechanisms are not fully understood. The gate control theory of pain may explain it. Moreover, FC results in a sudden rise in blood pressure, which could be a source of pain relief.

In terms of cervical biopsies, LA was more effective in reducing pain than FC. This was also demonstrated in a recent study by Naki et al., in which they conducted a randomized study comparing local lidocaine injection vs. FC as a distracting method. They found that the FC method may not be a potent distractor, and LA provided significant pain relief during the cervical biopsy. On the other hand, another study by Schmid et al. reported that FC during cervical biopsies reduced patients' discomfort to a comparable extent to local anesthesia. So, these conflicting results were evaluated in our analysis, and we also found no differences between the two methods in the overall pain score post-procedure. Pain associated with the injection is missing during forced coughing; however, this advantage did not reduce pain sensation during CGB.
The colposcopic procedure is performed as an outpatient clinical practice, and physicians give attention to doing this procedure at an appropriate time. FC cuts down the costs associated with the biopsy, and we show here that FC is time-saving compared with LA, in which its use would be an important issue for clinics with low resources and a high volume of patients when choosing their pain relief methods.

However, the use of LA is encouraged due to its significant effect in reducing pain sensation during cervical biopsy compared with the nonpharmacological forced coughing method.

**Strengths and weaknesses**

We included six RCTs in the quantitative analysis constituting a strong evidence level. The included studies range from moderate to high quality. The main limitation of our study is related to the evaluation of pain with a VAS score which is not an objective method and can be influenced by several factors, such as social and cultural status.

**Conclusion**

The forced coughing technique and local anesthetics are useful as pain-lowering modalities during the colposcopy-guided biopsy, however local anesthetics seemed to be more beneficial but this was not statistically significant according to settings and availability. We advise using local anesthetics as potentially effective pain lowering modality during colposcopy and cervical biopsy. If not available, forced coughing technique would be an appropriate, simple and practical alternative to lower pain during colposcopy. Further studies with larger sample size are recommended to support this recommendation.

**Conflict of Interest**

The authors have no conflicts of interest.

**Authors’ Contribution**

AS conceptualized the idea. YO validated the idea and formulated the search strategy. YO, AAE, IB, MT and AKA collected the data. AAE, IB, MT and AKA assessed the quality of the data and prepared the graphs. IB prepared the summary and baseline tables. YO and AAE analyzed the
data. YO, AAE, MT and AKA drafted the manuscript. NAR and AS reviewed and edited the manuscript. All authors approved the final version of the manuscript.

References


Table 1: Baseline characteristics of included studies

<table>
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<tr>
<th>Study ID</th>
<th>Arms</th>
<th>Total number</th>
<th>Age M±SD</th>
<th>BMI M±SD</th>
<th>Obstetric history</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vaginal birth number (%)</td>
<td>Cesarean birth number (%)</td>
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<tr>
<td>Bogani 2014</td>
<td>Forced coughing</td>
<td>49</td>
<td>34±11.25</td>
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<td>7 (14%)</td>
<td>2 (4%)</td>
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<tr>
<td></td>
<td>Local anesthetic</td>
<td>51</td>
<td>38±11.5</td>
<td></td>
<td>14 (27%)</td>
<td>1 (2%)</td>
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<tr>
<td>Goldstein akavia 2018</td>
<td>Forced coughing</td>
<td>45</td>
<td>33.02±3.7</td>
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<tr>
<td></td>
<td>no pain management</td>
<td>45</td>
<td>31.23±3.4</td>
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<tr>
<td>Karaman 2019</td>
<td>Forced coughing</td>
<td>42</td>
<td>41.6± 10.9</td>
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<td>26.9 ± 4.2</td>
<td>30 (71.4%)</td>
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<td></td>
<td>Lidocaine spray</td>
<td>44</td>
<td>42.1 ± 11.4</td>
<td></td>
<td>27.62 ± 3.2</td>
<td>32 (72.7%)</td>
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<tr>
<td>Kuhn 2020</td>
<td>Forced coughing</td>
<td>56</td>
<td>36.8± 11.1</td>
<td></td>
<td>29.1 ± 6.5</td>
<td>14 (25)</td>
</tr>
<tr>
<td></td>
<td>no pain management</td>
<td>54</td>
<td>37.9±10.3</td>
<td></td>
<td>28.5 (4.9)</td>
<td>22 (40.7)</td>
</tr>
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<td>Naki 2011</td>
<td>Forced coughing</td>
<td>39</td>
<td>37.3±9.9</td>
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<tr>
<td></td>
<td>Local anesthetic</td>
<td>39</td>
<td>40.4±9.1</td>
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<td></td>
<td>Local anesthetic</td>
<td>34</td>
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* SD: Standard deviation; BMI: body mass index; H-SIL: high grade squamous intraepithelial lesion; L-SIL: low grade squamous intraepithelial lesion; ASCUS: atypical squamous cell of undetermined significance.
Figure 1: VAS pain score during cervical biopsy in the forced coughing group compared with LA and no pain management group respectively after resolving heterogeneity.

Figure 2: VAS pain score during speculum insertion in forced coughing group compared with LA and no pain management group respectively.
Figure 3: Overall VAS pain score immediately after the procedure in the forced coughing group compared with LA and no pain management group respectively, after removing heterogeneity.