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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.[4-6] 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 was performed according to the Cochrane handbook for systematic reviews of treatments.[14] We also followed the PRISMA statement requirements during reporting of this systematic review and meta-analysis.[14] 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.[14] 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).[14] 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.[15]

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 [0.58to 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, I2 = 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 = 075; 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; I2 = 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. 00001; I2 = 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. 00001; supplementary Fig.5). Pooled studies were heterogeneous under a random-effect model (p =0.0003; I2 =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.[2,5,16-19] Conversely, injecting a local anesthetic might cause tissue damage that interferes with the pathological diagnosis.[16]

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.[21,22] Several pharmacological and nonpharmacological interventions could help minimize pain sensation,[23] and FC is one of the effective pain-relieving measures.[16] Forced coughing proved effective during speculum insertion and post-procedure.[24] 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.[25-27] However, the mechanisms are not fully understood. The gate control theory of pain may explain it.[28,29] Moreover, FC results in a sudden rise in blood pressure, which could be a source of pain relief.[30,31]

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.,[5] 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.[16] 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 significantaccording 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

1. Escobar PF, Rojas-Espaillat L, Tisci S, Enerson C, Brainard J, Smith J, et al. Optical coherence tomography as a diagnostic aid to visual inspection and colposcopy for preinvasive and invasive cancer of the uterine cervix. Int J Gynecol Cancer [Internet]. 2006 Sep;16(5):1815–22. Available from: https://ijgc.bmj.com/lookup/doi/10.1111/j.1525-1438.2006.00665.x. DOI: 10.1111/j.1525-1438.2006.00665.x

2. Bogani G, Serati M, Cromi A, Di Naro E, Casarin J, Pinelli C, et al. Local anesthetic versus forced coughing at colposcopic-guided biopsy: a prospective study. Eur J Obstet Gynecol Reprod Biol [Internet]. 2014 Oct;181:15–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0301211514003947. DOI: 10.1016/j.ejogrb.2014.07.022

3. Mercier RJ, Zerden ML. Intrauterine Anesthesia for Gynecologic Procedures. Obstet Gynecol [Internet]. 2012 Sep;120(3):669–77. Available from: http://journals.lww.com/00006250-201209000-00027. DOI: 10.1097/AOG.0b013e3182639ab5

4. Church L. Analgesia for colposcopy: double-masked, randomized comparison of ibuprofen and benzocaine gel. Obstet Gynecol [Internet]. 2001 Jan;97(1):5–10. Available from: http://linkinghub.elsevier.com/retrieve/pii/S002978440001084X. DOI: 10.1016/s0029-7844(00)01084-x

5. Naki MM, Api O, Acioglu HC, Uzun MG, Kars B, Unal O. Analgesic Efficacy of Forced Coughing versus Local Anesthesia during Cervical Punch Biopsy. Gynecol Obstet Invest [Internet]. 2011;72(1):5–9. Available from: https://www.karger.com/Article/FullText/320842. DOI: 10.1159/000320842

6. Wong G, Li R, Wong T, Fan S. The effect of topical lignocaine gel in pain relief for colposcopic assessment and biopsy: is it useful? BJOG An Int J Obstet Gynaecol [Internet]. 2008 Jul;115(8):1057–60. Available from: http://doi.wiley.com/10.1111/j.1471-0528.2008.01780.xDoi: 10.1111/j.1471-0528.2008.01780.x

7. Oyama IA, Wakabayashi MT, Frattarelli LC, Kessel B. Local anesthetic reduces the pain of colposcopic biopsies: A randomized trial. Am J Obstet Gynecol [Internet]. 2003

May;188(5):1164–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002937803001200. DOI: 10.1067/mob.2003.290.

8. Duncan ID, McKinley CA, Pinion SB, Wilson SM. A Double-Blind, Randomized, Placebo-Controlled Trial of Prilocaine and Felypressin (Citanest and Octapressin) for the Relief of Pain Associated with Cervical Biopsy and Treatment with the Semm Coagulator. J Low Genit Tract Dis [Internet]. 2005 Jul;9(3):171–5. Available from: https://journals.lww.com/00128360-200507000-00008. DOI:10.1097/01.LGT.0000171663.86847.45

9. Speca SJ, Boynes SG, Cuddy MA. Allergic Reactions to Local Anesthetic Formulations. Dent Clin North Am [Internet]. 2010 Oct;54(4):655–64. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0011853210000649. Doi: 10.1016/j.cden.2010.06.006

10. Clifton PA, Shaughnessy AF, Andrews S. Ineffectiveness of topical benzocaine spray during colposcopy. J Fam Pract [Internet]. 1998 Mar;46(3):242–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9519022

11. Prefontaine M, Fung-Kee-Fung M, Moher D. Comparison of topical Xylocaine with placebo as a local anesthetic in colposcopic biopsies. Can J Surg [Internet]. 1991 Apr;34(2):163–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2025805

12. Carwile JL, Feldman S, Johnson NR. Use of a Simple Visual Distraction to Reduce Pain and Anxiety in Patients Undergoing Colposcopy. J Low Genit Tract Dis [Internet]. 2014 Oct;18(4):317–21. Available from: https://journals.lww.com/00128360-201410000-00008. DOI:10.1097/LGT.0000000000000024

13. Chan Y., Lee PW., Ng T., Ngan HY., Wong L. The use of music to reduce anxiety for patients undergoing colposcopy: a randomized trial. Gynecol Oncol [Internet]. 2003 Oct;91(1):213–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0090825803004128. DOI: 10.1016/s0090-8258(03)00412-8

14. Higgins JP, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Chichester, UK: John Wiley & Sons, Ltd; 2008.

15. Stuck AE, Rubenstein LZ, Wieland D, Vandenbroucke JP, Irwig L, Macaskill P, et al. Bias in meta-analysis detected by a simple, graphical. BMJ. 1998 Feb;316(7129):469–469.

16. Schmid BC, Pils S, Heinze G, Hefler L, Reinthaller A, Speiser P. Forced coughing versus local anesthesia and pain associated with cervical biopsy: a randomized trial. Am J Obstet Gynecol [Internet]. 2008 Dec;199(6):641.e1-641.e3. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002937808008016. DOI: 10.1016/j.ajog.2008.07.017

17. Karaman E, Kolusarı A, Alkış İ, Çetin O. Comparison of topical lidocaine spray with forced coughing in pain relief during colposcopic biopsy procedure: a randomised trial. J Obstet Gynaecol (Lahore) [Internet]. 2019 May 19;39(4):534–8. Available from: https://www.tandfonline.com/doi/full/10.1080/01443615.2018.1538329 DOI: 10.1080/01443615.2018.1538329

18. Goldstein Akavia T, Segev Y, Balan E, Siegler E. The analgesic efficacy of forced coughing during cervical punch biopsy: A prospective randomised controlled study. Aust New Zeal J Obstet Gynaecol [Internet]. 2018 Dec 7;58(6):681–5. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/ajo.12784. DOI: 10.1111/ajo.12784

19. Kuhn T, Ukazu A, Strickland PO, Roche N, Taveras Y, Kovalenko O, et al. The Effect of Forced Cough to Minimize Pain and Discomfort at the Time of Colposcopy-Guided Cervical Biopsy. J Low Genit Tract Dis [Internet]. 2020 Apr;24(2):211–4. Available from: http://journals.lww.com/10.1097/LGT.0000000000000517. DOI: 10.1097/LGT.0000000000000517

20. Stafl A. Colposcopy. Cancer [Internet]. 1976 Jul;38(1):432–5. Available from: https://onlinelibrary.wiley.com/doi/10.1002/1097-0142(197607)38:1%3C432::AID-CNCR2820380167%3E3.0.CO;2-Q

21. Linton SJ, Shaw WS. Impact of Psychological Factors in the Experience of Pain. Phys Ther [Internet]. 2011 May 1;91(5):700–11. Available from: https://academic.oup.com/ptj/article-lookup/doi/10.2522/ptj.20100330. Doi: 10.2522/ptj.20100330

22. Wandner LD, Scipio CD, Hirsh AT, Torres CA, Robinson ME. The Perception of Pain in Others: How Gender, Race, and Age Influence Pain Expectations. J Pain [Internet]. 2012 Mar;13(3):220–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S152659001100873X. Doi: 10.1016/j.jpain.2011.10.014

23. Bukola IM, Paula D. The Effectiveness of Distraction as Procedural Pain Management Technique in Pediatric Oncology Patients: A Meta-analysis and Systematic Review. J Pain Symptom Manage [Internet]. 2017 Oct;54(4):589-600.e1. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0885392417302695. Doi: 10.1016/j.jpainsymman.2017.07.006

24. Kiviharju M, Kalliala I, Nieminen P, Dyba T, Riska A, Jakobsson M. Pain Sensation During Colposcopy and Cervical Biopsy, With or Without Local Anesthesia: A Randomized Trial. J Low Genit Tract Dis [Internet]. 2017 Apr;21(2):102–7. Available from: https://journals.lww.com/00128360-201704000- 00004. DOI: 10.1097/LGT.0000000000000292

25. Tsao JCI, Fanurik D, Zeltzer LK. Long-Term Effects of a Brief Distraction Intervention on Children's Laboratory Pain Reactivity. Behav Modif [Internet]. 2003 Apr 26;27(2):217–32. Available from: http://journals.sagepub.com/doi/10.1177/0145445503251583. Doi.org/10.1177/0145445503251583

26. Fowler-Kerry S, Lander JR. Management of injection pain in children. Pain [Internet]. 1987 Aug;30(2):169–75. Available from: https://journals.lww.com/00006396-198708000-00003. Doi: 10.1016/0304-3959(87)91072-4.

27. Weisenberg M, Tepper I, Schwarzwald J. Humor as a cognitive technique for increasing pain tolerance. Pain [Internet]. 1995 Nov;63(2):207–12. Available from: https://journals.lww.com/00006396-199511000-00009. Doi: 10.1016/0304-3959(95)00046-U

28. Melzack R, Wall PD. Pain Mechanisms: A New Theory. Science (80-) [Internet]. 1965 Nov 19;150(3699):971–8. Available from: https://www.sciencemag.org/lookup/doi/10.1126/science.150.3699.971. DOI: 10.1126/science.150.3699.971

29. Bruehl S, Chung OY, Ward P, Johnson B, McCubbin JA. The relationship between resting blood pressure and acute pain sensitivity in healthy normotensives and chronic back pain sufferers: the effects of opioid blockade. Pain [Internet]. 2002 Nov;100(1):191–201. Available from: https://journals.lww.com/00006396- 200211000-00020. DOI: 10.1016/S0304-3959(02)00295-6

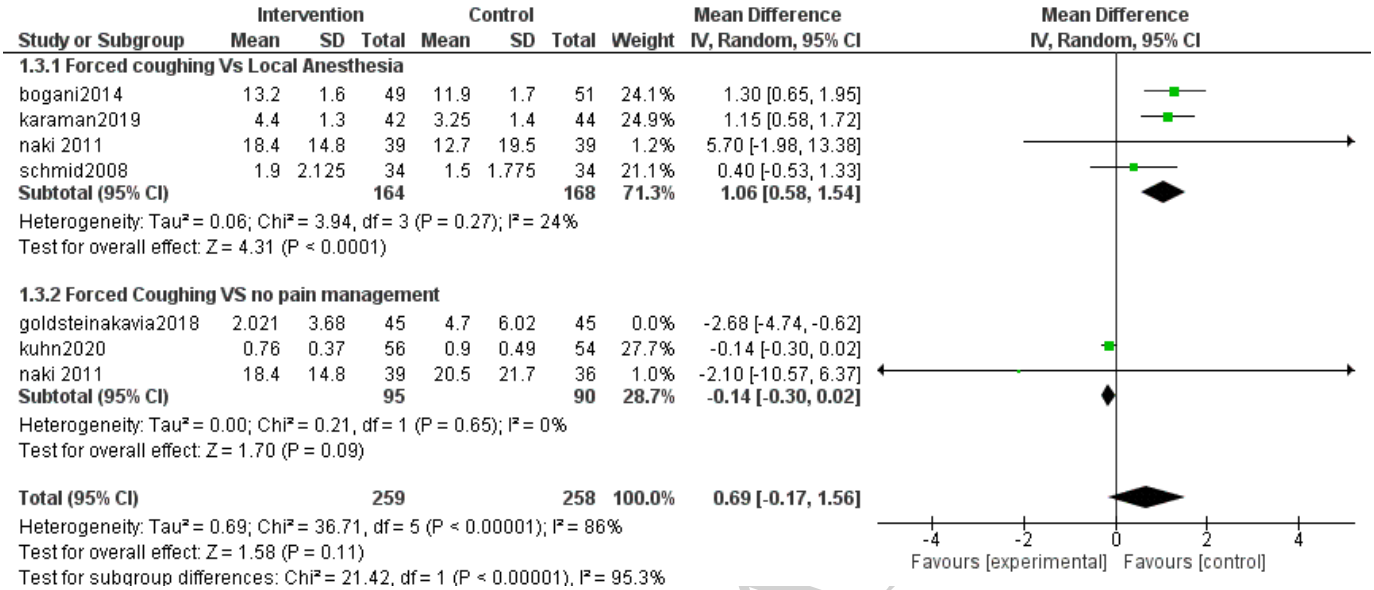
30. Kern MJ, Gudipati C, Tatineni S, Aguirre F, Serota H, Deligonul U. Effect of abruptly increased intrathoracic pressure on coronary blood flow velocity in patients. Am Heart J [Internet]. 1990 Apr;119(4):863–70. Available from:

https://linkinghub.elsevier.com/retrieve/pii/S0002870305803242. DOI: 10.1016/S0002-8703(05)80324-2

Table 1: Baseline characteristics of included studies

Study ID	Arms	Total number	Age M±SD	BMI M±SD	Obstetric history			Indicat	
					Vaginal birth number (%)	Cesarean birth number (%)	Curettage number (%)	H-SIL number (%)	L-SIL numbe (%)
Bogani 2014 (2)	Forced coughing	49	34±11.25			7 (14%)	2 (4%)	11 (22%)	32(66%
	Local anesthetic	51	38±11.5			14 (27%)	1(2%)	8 (16%)	40 (78%
Goldstein akavia 2018 (17)	Forced coughing	45	33.02±3.78					1 (2.2%)	11 (24.4%
	no pain management	45	31.23±3.41					4 (8.8%)	11 (24.4%
Karaman 2019 (20)	Forced coughing	42	41.6± 10.9	26.9 ± 4.2	30 (71.4%)		5 (12.5%)	6 (14.2%)	20 (47.6%
	Lidocaine spray	44	42.1 ± 11.4	27.62 ± 3.2	32 (72.7%)		6 (14.2%)	6 (13.6%)	20(45.4
Kuhn 2020 (18)	Forced coughing	56	36.8± 11.1	29.1 (6.5)	14 (25)	46 (82.1)			
	no pain management	54	37.9±10.3	28.5 (4.9)	22 (40.7)	40 (74.1)			
Naki 2011 (5)	Forced coughing	39	37.3±9.9						
	Local anesthetic	39	40.4±9.1						
	no pain management	36	38.9±7.6						
Schmid 2008 (21)	Forced coughing	34							
	Local anesthetic	34							

***** *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.*



406 **Figure 1:** VAS pain score during cervical biopsy in the forced coughing group compared with
407 LA and no pain management group respectively after resolving heterogeneity.

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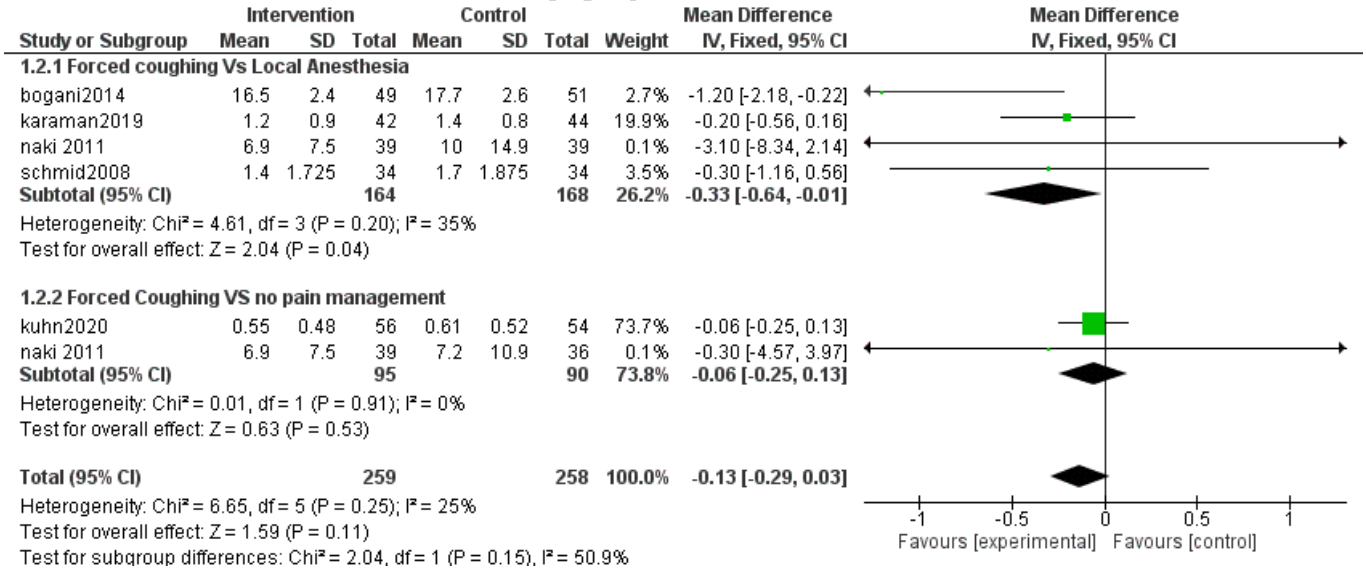

410 **Figure 2:** VAS pain score during speculum insertion in forced coughing group compared with
411 LA and no pain management group respectively

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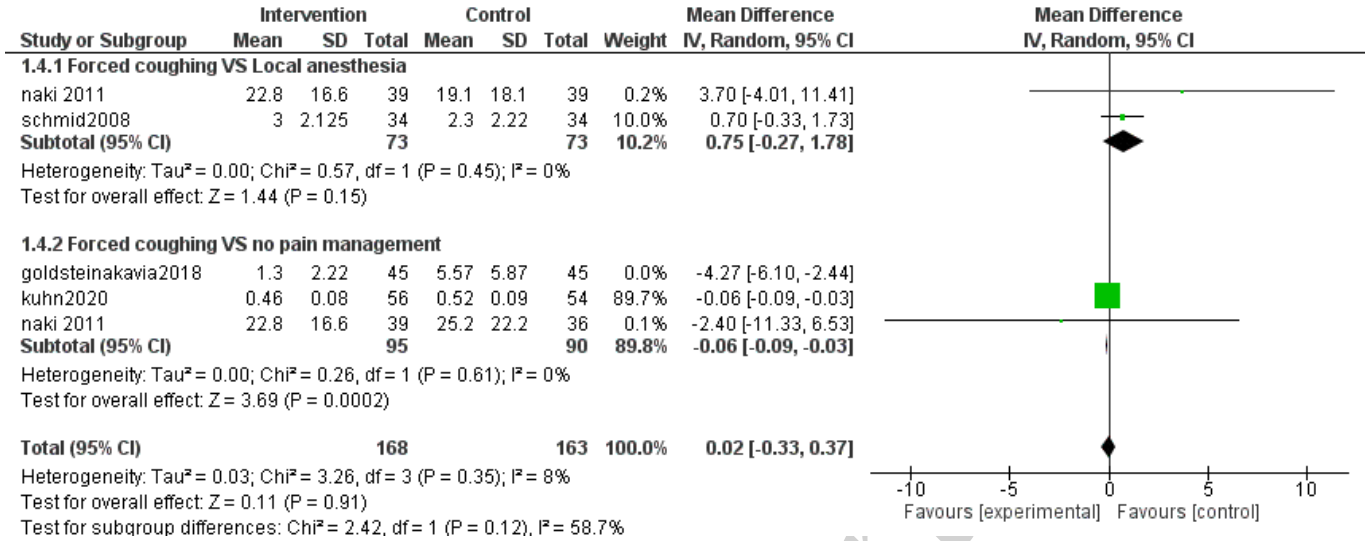

Figure 3: Overall VAS pain score immediately after the procedure in the forced coughing group compared with LA and no pain management group respectively, after removing heterogeneity.