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REVIEW

Is Forced Coughing Effective in Reducing Pain During Cervical Biopsy?

A systematic review and meta-analysis

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abstract: This review aimed to compare the potential analgesic effect of forced coughing (FC) with that of local anaesthetics (LA) or placebo during cervical biopsy. A total of 5 electronic databases—Scopus, PubMed, Web of Science, Cochrane Library and Google Scholar—were systematically searched from inception till March 2021. Data were extracted from 6 randomised controlled trials and analysed. During cervical biopsy, the overall effect favoured LA over FC (mean difference [MD] = 1.06, 95% confidence interval [CI]: 0.58 to 1.54; *P* <0.0001). 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 the LA group than in the FC group (MD = −1.94, 95% CI: −2.47 to −1.41; *P* <0.00001). FC and LA are both useful pain-lowering modalities during cervical biopsy, depending on the setting and their availability.

Keywords: Biopsy; Colposcopy; Anesthesia; Pain.

Colposcopy-guided biopsy (CGB) is an easy outpatient procedure that is generally performed to diagnose and follow-up precancerous and cancerous cervical diseases; it often requires no anaesthesia.[1] Nevertheless, procedural discomfort and pain could exacerbate patients' anxiety and fear during the procedure, especially during speculum insertion and solution application.[2] Furthermore, women with known pre-invasive cervical diseases or human papillomavirus infection have a higher risk for experiencing pain during the procedure, thus needing additional analgesia.[3]

In the past two decades, various pharmacological and non-pharmacological methods of reducing pain during CGB have been evaluated, including benzocaine gel and its spray forms, lidocaine injections, ibuprofen, topical lignocaine gel and prilocaine anaesthesia. However, the results have been inconclusive.[4–6] Injection of 1% lidocaine has shown to decrease pain during procedures compared with no anaesthetics.[7,8] However, it has several disadvantages, including painful injection; 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 has shown no benefit in reducing procedural pain.[10,11] Oral pain medications (e.g. ibuprofen) have also not shown any advantage over a placebo in decreasing pain associated with colposcopy-guided cervical biopsy.[4]

Similarly, trials of non-pharmacological methods such as coughing, simple visual distraction, hypnosis and music have been inconclusive.[12,13] Among all the non-pharmacological approaches, forced coughing (FC) has the most significant contribution to pain relief during CGB, while among the pharmacological approaches, local anaesthetic (LA) agents such as prilocaine and lidocaine have the most significant potential as pain-relieving medications. However, LA agents have adverse effects that do not exist with FC.[9]

Consequently, this systematic review and meta-analysis was performed to synthesise evidence from published randomised controlled trials (RCTs) and evaluate the efficacy and safety of FC and LA (compared with no analgesia) in reducing pain associated with CGB.

Methods

All phases of this study were performed according to the Cochrane handbook for systematic reviews of treatments. The authors also followed the PRISMA statement requirements while reporting this systematic review and meta-analysis.[14]

LITERATURE SEARCH STRATEGY

A comprehensive search was conducted on the following electronic databases from inception till March 2021: PubMed (National Library of Medicine, Maryland, USA), Cochrane Central (Cochrane, London, UK), Scopus

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(Elsevier, Amsterdam, the Netherlands), Google Scholar (Google, California, USA) and Web of Science (Clarivate, Philadelphia, USA). Several combinations of the following terms were used in the current study's 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. The authors manually screened the references of included studies to retrieve those that were not identified by the database search.

ELIGIBILITY CRITERIA AND STUDY SELECTION

Only clinical trials that met the following criteria were included in the study: (1) population: patients undergoing colposcopy-guided cervical biopsy; (2) intervention: FC; (3) comparator: LA or control (without any intervention); (4) outcomes: the authors' primary outcome was visual analogue scale (VAS) pain score during cervical biopsy, while the secondary outcomes were VAS pain score during speculum insertion as well as immediately and 5 minutes after the procedure and duration of the cervical biopsy for both groups; and (5) study design: RCT. There were no restrictions regarding age, ethnicity, location or publication date.

In vitro and animal studies were excluded as well as studies whose data were unreliable for extraction and analysis overlapped datasets, non-English studies and conferences, books, review articles, posters, theses, editorials, notes, letters, case series and case reports. MT and IB independently screened the titles and abstracts of the retrieved records for eligibility. In cases of disagreement, the full text of the article was retrieved and reviewed independently by a senior author (YO) for a final decision.

DATA EXTRACTION

MT and IB independently extracted the studies' data using an offline data extraction form. The extracted data included study design, population characteristics; risk of bias domains; and study outcomes. Two investigators (AAE and AKA) 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 VAS, while the secondary outcomes were VAS pain score during speculum insertion, immediately after the procedure and 5 minutes after the procedure and duration of the cervical biopsy.

RISK-OF-BIAS ASSESSMENT

Two independent reviewers (AAE and AKA) used the Cochrane risk-of-bias (ROB) assessment tool to assess the quality of the retrieved RCTs, as described in Chapter 8.5 of the Cochrane handbook of systematic reviews of interventions 5.1.0.14 The Cochrane collaboration ROB 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. Studies were classified into each domain as either having a low, high or unclear risk of bias.

DATA SYNTHESIS

Changes in VAS scores were calculated as mean differences (MD) and 95% confidence intervals (CI) in a fixed-effects model using the Mantel–Haenszel

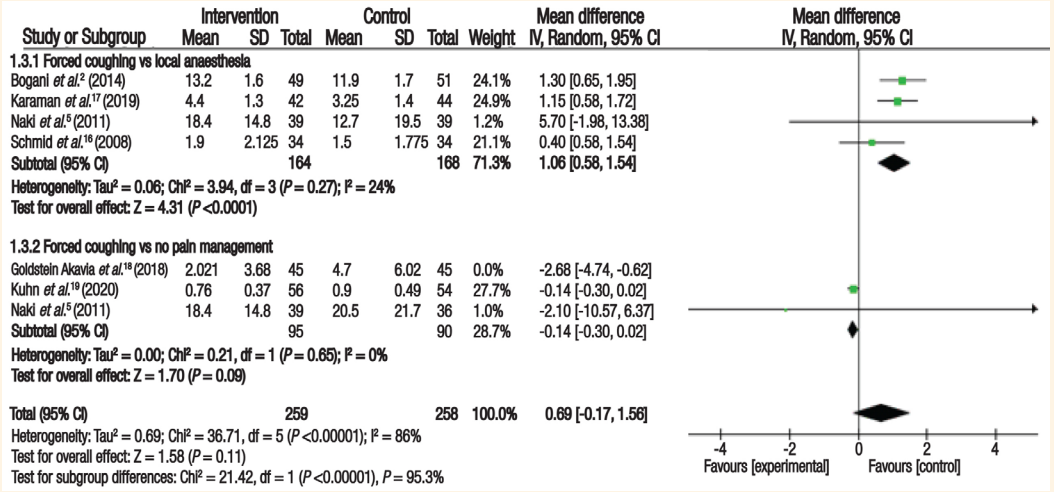

Figure 1: Visual analogue scale pain score during cervical biopsy in the forced coughing group compared with the local anaesthesia and no pain management groups after resolving the heterogeneity.

method. The fixed-effects model was used, assuming that the included studies were homogeneous and comparable in terms of their design, quality and measures of treatment effect. Review Manager 5.3 (The Cochrane Collaboration; 2014, The Nordic Cochrane Center Copenhagen, Denmark) for Windows was used during data synthesis, and a sensitivity analysis was performed to ensure that none of the included studies affected the results and to check whether the overall effect size was statistically robust. This resulted in the exclusion of two studies.

ASSESSMENT OF HETEROGENEITY

Heterogeneity was assessed by visual inspection of the forest plots and measured statistically using the I^2 statistic and Chi-squared test. The Chi-squared test measures significant heterogeneity, while the I^2 statistic quantifies the magnitude of heterogeneity in the effect size. Heterogeneity was assessed and interpreted according to the Cochrane handbook of systematic reviews and meta-analysis.[14] In this handbook, an alpha level (for Chi-squared test) below 0.1 is indicative of significant heterogeneity, and the I^2 statistic is interpreted as follows: 0–40% = might not be important; 30–60% = may represent moderate heterogeneity; and 50–90% = may represent substantial heterogeneity. In cases of significant heterogeneity, the random-effects model was used. Otherwise, the fixed-effects model was employed.

PUBLICATION BIAS

The number of studies included in the analysis was less than 10. Therefore, publication bias could not be assessed using the Egger test.[15]

Results

SEARCH RESULTS

A total of 501 records were identified. However, after title and abstract screening, only 12 articles were eligible for full-text screening. Of these, 6 articles (N = 532 patients) were included in the current meta-analysis, as shown in the PRISMA flow diagram [Supplementary Figure 1].

There were 3 studies that compared FC with LA (1.0–2.0 mL of 1% lidocaine); 2 studies compared FC with no pain management; and 1 study compared FC with LA and no pain treatment. The baseline characteristics of the patients and a summary of the included studies are shown in Table 1 and Supplementary Table 1, respectively.

Table 1: Baseline characteristics of the included studies

Author and year of publication	Arms	Total	Mean age ± SD	Mean BMI ± SD	n (%)						
					Obstetric history				Indication for biopsy		
					Vaginal birth	Caesarean birth	Curettage	H-SIL	L-SIL	ASCUS	Other
Bogani *et al.*[2] (2014)	Forced coughing	49	34 ± 11.25			7 (14)	2 (4)	11 (22)	32 (66)		6 (12)
	Local anaesthetic	51	38 ± 11.5			14 (27)	1 (2)	8 (16)	40 (78)		3 (6)
Goldstein Akavia *et al.*[18] (2018)	Forced coughing	45	33.02 ± 3.78					1 (2.2)	11 (24.4)	11 (24.4)	
	No pain management	45	31.23 ± 3.41					4 (8.8)	11 (24.4)	13 (30.9)	
Karaman *et al.*[17] (2019)	Forced coughing	42	41.6 ± 10.9	26.9 ± 4.2	30 (71.4)		5 (12.5)	6 (14.2)	20 (47.6)	13 (30.9)	3 (7.1)
	Lidocaine spray	44	42.1 ± 11.4	27.62 ± 3.2	32 (72.7)		6 (14.2)	6 (13.6)	20 (45.4)	14 (31.8)	2 (4.5)
Kuhn *et al.*[19] (2020)	Forced coughing	56	36.8 ± 11.1	29.1 ± 6.5	14 (25.0)	46 (82.1)					
	No pain management	54	37.9 ± 10.3	28.5 ± 4.9	22 (40.7)	40 (74.1)					
Naki *et al.*[5] (2011)	Forced coughing	39	37.3 ± 9.9								
	Local anaesthetic	39	40.4 ± 9.1								
	No pain management	36	38.9 ± 7.6								
Schmid *et al.*[16] (2008)	Forced coughing	34									
	Local anaesthetic	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.*

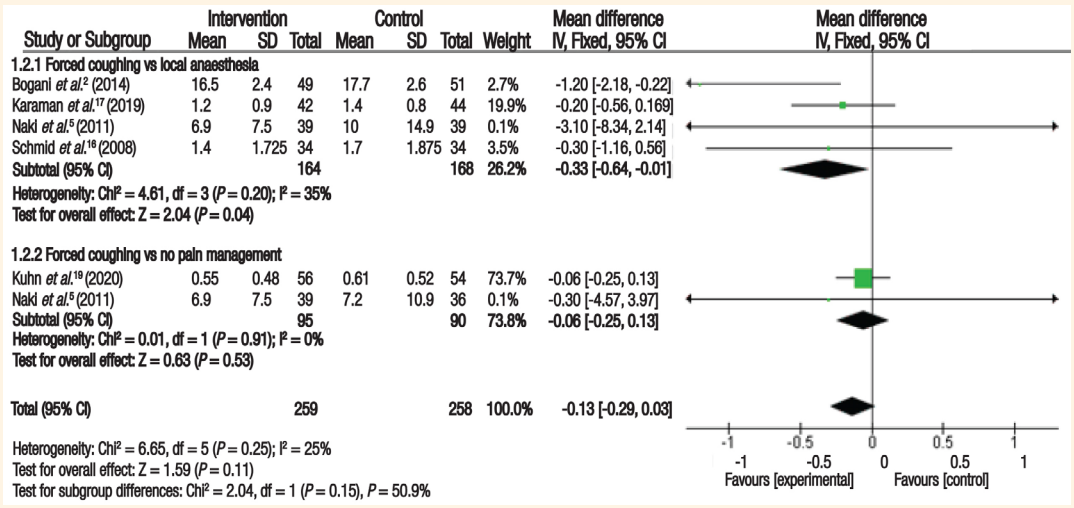

Figure 2: Visual analogue scale pain score during speculum insertion in the forced coughing group compared with the local anaesthesia and no pain management groups.

RISK-OF-BIAS ASSESSMENT

Using ROB 2, it was found that the quality of the included studies was low in most domains except for the 'bias due to missing outcome data' and 'bias in the selection of reported results' domains [Supplementary Figure 2].

PAIN DURING CERVICAL BIOPSY

Pooled data from 4 studies involving 378 patients showed a lower pain score in the LA group compared with the FC group (MD = 1.06, 95% CI: 0.58 to 1.54; *P* <0.0001).[2,5,16,17] The pooled studies were homogenous (*P* = 0.27) [Supplementary Figure 3].

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). Significant heterogeneity was observed in a subgroup analysis that compared FC with no pain management (I^2 = 67%; *P* = 0.05); this heterogeneity was best resolved by excluding the study by Goldstein Akavia *et al.*[18] [Figure 1].

PAIN DURING SPECULUM INSERTION

Pooled data from 4 studies showed a statistically significant difference between the FC and LA groups, with a reduction in the pain score of the FC group (MD = −0.33, 95% CI: −0.64 to −0.01; *P* = 0.04).[2,5,16,17] The pooled studies were homogenous (*P* = 0.2). In contrast, the overall effect from studies by Kuhn *et al.* and Naki *et al.* showed no statistically significant difference in pain score during speculum insertion between the FC and no pain management groups (MD = −0.06, 95% CI: −0.25 to 0.13; *P* = 0.53).5,19 The pooled studies were homogenous (*P* = 0.91) [Figure 2].

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 the overall pain score immediately post-procedure between the FC and no pain management groups (MD = −2.10, 95% CI: −5.81 to 1.61; *P* = 0.27). The pooled studies were heterogeneous (I^2 = 90%; *P* <0.0001). The heterogeneity was best resolved by excluding the study by Goldstein Akavia *et al.*[18] [Figure 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). The results were heterogeneous under a random-effects model (I^2 = 96%; *P* <0.00001) [Supplementary Figure 4].

DURATION OF PROCEDURE

Pooled data from 4 studies showed a statistically significant difference between FC and LA, with a longer procedure duration in the LA group compared to the FC group (MD = −1.94, 95% CI: −2.47 to −1.41; *P* <0.00001).2,5,16,17 The pooled studies were heterogeneous under a random-effects model (I^2 = 84%; *P* = 0.0003). The heterogeneity was best resolved by excluding the study by Naki *et al.*[5] [Supplementary Figure 5].

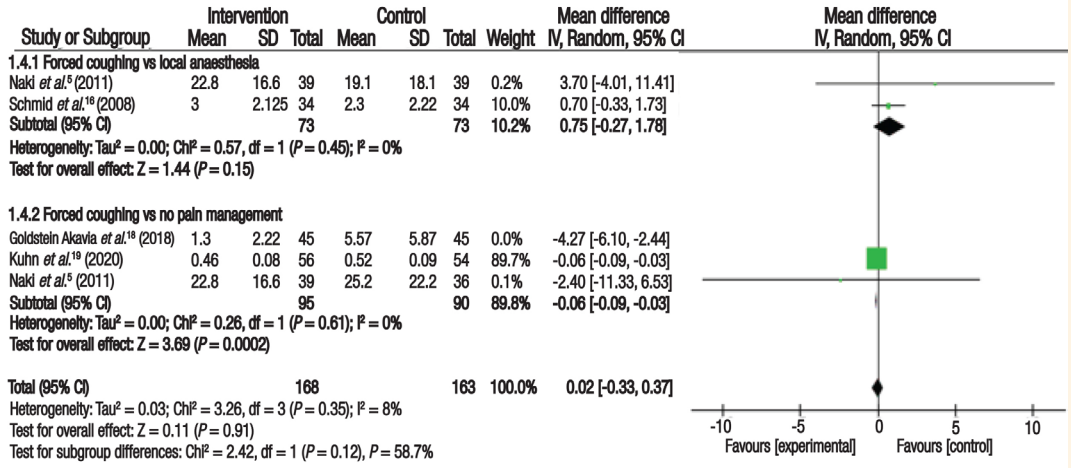

Figure 3: Overall visual analogue scale pain score immediately after the procedure in the forced coughing group compared with the local anaesthesia and no pain management groups after resolving heterogeneity.

Discussion

To the best of the authors' knowledge, following a literature search, this is the first systematic review and meta-analysis to investigate the efficacy of FC in relieving pain during CGB. The current systematic review and meta-analysis showed that FC was better than LA in reducing pain during speculum insertion; however, no significant differences were found when FC was compared with non-pain management. In contrast, the current analysis found that the LA group had lesser pain scores during cervical biopsy compared to the FC group; however, the pain scores were comparable in the LA and no pain management groups. There was no significant difference in the overall pain score post-procedure in the FC group compared to the LA and no pain management groups. Moreover, the duration of the procedure was shorter in the FC group than in the LA group, in which time was spent injecting the drug; however, this did not affect the amount of tissue obtained.

CGB has great value in modern gynaecology; it is used to examine patients with abnormal cytology and can be used to diagnose changes in the cervical and vaginal epithelium. However, many patients are reluctant to undergo a CGB due to the procedure-related pain, anxiety and discomfort. The fear of pain seems to be the main obstacle to proper gynaecological examination.[20] LA injections, such as lidocaine injections, are painful, and many women are afraid of needles and refuse to have these injections. An alternative non-pharmacological pain management technique is FC, which can replace LA injection.[18] The literature has reported no adverse effects or reactions and no additional costs in the FC group.[2,5,16–19] Conversely, injecting an LA might cause tissue damage that will interfere 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 non-pharmacological interventions could help minimise pain, and FC is one of the effective pain-relieving measures.[16,23] FC proved effective during speculum insertion and post-procedure.[24] Based on the current analysis, the procedure duration was shorter in the FC group than in the LA group; the latter might be more time-consuming because of the need for an injection, which adds an extra step to the surgical procedure.

FC and other methods, such as cognitive tasks, music cartoons for children, humour and imagining pleasant scenes, are effective as distraction methods and could reduce procedural pain.[25–27] However, the mechanisms underlying how these methods bring about pain relief are not yet fully understood. The gate control theory of pain may be a possible explanation.[28,29] Moreover, FC results in a sudden rise in blood pressure, which could be the source of pain relief.[30,31]

In terms of cervical biopsies, LA is more effective than FC in reducing pain. This was also demonstrated in a recent randomised study by Naki *et al.*, in which local lidocaine injection was compared to FC as a distracting method.[5] They found that the FC method may not be a potent distractor and that LA provided significant pain relief during cervical biopsy. In contrast, a study by Schmid *et al.* reported that FC, during cervical biopsies, reduced patients' discomfort to an extent comparable to that of LA.[16] These conflicting results were evaluated in the current analysis, and the present study found no differences in the overall pain score post-procedure between the two methods. Pain associated with injection is absent

during FC; however, this advantage does not reduce pain sensation during CGB.

Colposcopy is performed as an outpatient clinical procedure, and physicians are careful to perform this procedure at an appropriate time. Indeed, FC cuts down the cost associated with cervical biopsy, and it has been shown here that FC is more time-saving than LA, which should be an important aspect to consider for clinics with low resources and a high volume of patients when choosing pain relief methods.

Nevertheless, the use of LA is encouraged because of its significant effect in reducing pain during cervical biopsy compared with the non-pharmacological FC method.

STRENGTHS AND LIMITATIONS

A total of 6 RCTs were included in this quantitative analysis, constituting a strong evidence level. The included studies had moderate to high quality. The main limitation of this study was the evaluation of pain with VAS, which was not an objective method and can be influenced by several factors, such as social and cultural status.

Conclusion

Forced coughing technique and local anaesthetics are useful as pain-lowering modalities during colposcopy-guided biopsy; however, LA seemed to be more beneficial, although this was not statistically significant according to settings and availability. The use of LA is recommended as a potentially effective pain-lowering modality during colposcopy and cervical biopsy. If not available, the FC technique is an appropriate, simple and practical alternative for lowering pain during colposcopy. Further studies with larger sample sizes are recommended.

AUTHORS' CONTRIBUTION

AS conceptualised 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 analysed 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 2006; 16:1815–22. https://doi.org/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 2014; 181:15–19. https://doi.org/10.1016/j.ejogrb.2014.07.022.
3. Mercier RJ, Zerden ML. Intrauterine anesthesia for gynecologic procedures. Obstet Gynecol 2012; 120:669–77. https://doi.org/10.1097/AOG.0b013e3182639ab5.
4. Church L. Analgesia for colposcopy: Double-masked, randomized comparison of ibuprofen and benzocaine gel. Obstet Gynecol 2001; 97:5–10. https://doi.org/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 2011; 72:5–9. https://doi.org/10.1159/000320842.
6. Wong GC, Li RH, Wong TS, Fan SY. The effect of topical lignocaine gel in pain relief for colposcopic assessment and biopsy: Is it useful? BJOG 2008; 115:1057–60. https://doi.org/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 2003; 188:1164–5. https://doi.org/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 2005; 9:171–5. https://doi.org/10.1097/01.LGT.0000171663.86847.45.
9. Speca SJ, Boynes SG, Cuddy MA. Allergic reactions to local anesthetic formulations. Dent Clin North Am 2010; 54:655–64. https://doi.org/10.1016/j.cden.2010.06.006.
10. Clifton PA, Shaughnessy AF, Andrews S. Ineffectiveness of topical benzocaine spray during colposcopy. J Fam Pract 1998; 46:242–6.
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 1991; 34:163–5.
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 2014; 18:317–21. https://doi.org/10.1097/LGT.0000000000000024.
13. Chan YM, Lee PW, Ng TY, Ngan HY, Wong LC. The use of music to reduce anxiety for patients undergoing colposcopy: A randomized trial. Gynecol Oncol 2003; 91:213–17. https://doi.org/10.1016/s0090-8258(03)00412-8.
14. Higgins JP, Green S, Eds. 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 test. BMJ 1998; 316:469. https://doi.org/10.1136/bmj.315.7109.629.

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 2008; 199:641.e1–3. https://doi.org/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 2019; 39:534–8. https://doi.org/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 2018; 58:681–5. https://doi.org/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 2020; 24:211–14. https://doi.org/10.1097/LGT.0000000000000517.

20. Stafl A. Colposcopy. Cancer 1976; 38:432–5. https://doi.org/10.1002/1097-0142(197607)38:1<432::aid-cncr2820380167>3.0.co;2-q.

21. Linton SJ, Shaw WS. Impact of psychological factors in the experience of pain. Phys Ther 2011; 91:700–11. https://doi.org/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 2012; 13:220–7. https://doi.org/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 2017; 54:589-600.e1. https://doi.org/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 2017; 21:102–7. https://doi.org/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 2003; 27:217–32. https://doi.org/10.1177/0145445503251583.

26. Fowler-Kerry S, Lander JR. Management of injection pain in children. Pain 1987; 30:169–75. https://doi.org/10.1016/0304-3959(87)91072-4.

27. Weisenberg M, Tepper I, Schwarzwald J. Humor as a cognitive technique for increasing pain tolerance. Pain 1995; 63:207–12. https://doi.org/10.1016/0304-3959(95)00046-U.

28. Melzack R, Wall PD. Pain mechanisms: A new theory. Science 1965; 150:971–8. https://doi.org/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 2002; 100:191–201. https://doi.org/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 1990; 119:863–70. https://doi.org/10.1016/S0002-8703(05)80324-2.