Review / Derleme

DOI: 10.4274/tjod.galenos.2022.99404

Turk J Obstet Gynecol 2022;19:327-32

Efficacy of lidocaine local anesthesia on pain perception during amniocentesis: A meta-analysis of randomized controlled trials

Lidokain lokal anestezisinin amniyosentez sırasında ağrı algısı üzerindeki etkinliği: Randomize kontrollü çalışmaların bir meta-analizi

Ebraheem Albazee[1], Reem Sayad[2], Mohammad Alnifise[3], Abdulrahman Al-Anzi[4], Faisal Alshammari[5], Gheith Rasheed[3], Ahmed Samy[6], Haifa Al-Jundy[7], Marwah Ghazi Bintalib[8], Ahmed Abu-Zaid[9]

[1]*Kuwait Institute for Medical Specializations (KIMS), Kuwait City, Kuwait*
[2]*Faculty of Medicine, Assuit University, Assuit, Egypt*
[3]*Faculty of Medicine, The Hashemite University, Zarqa, Jordan*
[4]*Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan*
[5]*Department of Obstetrics and Gynecology, Jahra Hospital, Jahra, Kuwait*
[6]*Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, Cairo, Egypt*
[7]*Department of Obstetrics and Gynecology, Dr. Sulaiman Al-Habib Hospital, Riyadh, Saudi Arabia*
[8]*Department of Obstetrics and Gynecology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia*
[9]*College of Graduate Health Sciences, University of Tennessee Health Science Center, Tennessee, USA*

Abstract

To evaluate the efficacy of lidocaine local analgesia on maternal pain reduction during amniocentesis. Web of Science, Scopus, PubMed, and CENTRAL databases were screened from inception and updated in July 2022. The included randomized controlled trials (RCTs) were evaluated for the risk of bias via the Cochrane tool. The primary outcome was pain perception using the 10 cm visual analog scale, and was summarized as mean difference (MD) with 95% confidence interval (CI) in a random-effects model. Subgroup analysis was performed according to the mode of administration. Meta-analysis was done via Review Manager software. We included five RCTs totaling 1004 women (lidocaine arm n=502 patients and control arm n=502 patients). Overall, there was no significant difference between both arms [MD=-0.21, 95% CI (-0.48, 0.07), p=0.80]. The pooled analysis showed homogeneity (p=0.13, I^2=43%). Subgroup analysis according to the mode of administration showed that pain perception did not significantly differ between both arms when lidocaine was employed as injection [n=3 RCTs, MD=-0.26, 95% CI (-0.76, 0.23), p=0.29] or non-injection [n=2 RCTs, MD=-0.18, 95% CI (-0.55, 0.18), p=0.33]. The pooled analyses showed heterogeneity (p=0.05, I^2=66%) and homogeneity (p=0.27, I^2=19%), respectively. There was no noteworthy change concerning maternal pain perception between the lidocaine and control arms. Most women reported just minimal discomfort during amniocentesis. Counseling should educate patients that the pain they might experience during amniocentesis is comparable to venous blood sampling.

Keywords: Amniocentesis, local anesthesia, pain, pregnancy, analgesia

Öz

Bu çalışmada amaç, lidokain ile lokal analjezinin amniyosentez sırasında annenin ağrısının azaltılması üzerindeki etkinliğini değerlendirmektir. PubMed, Scopus, Web of Science ve CENTRAL veritabanları başlangıçtan itibaren arandı ve Temmuz 2022'de güncellendi. Dahil edilen randomize kontrollü araştırmalar (RKÇ'ler), Cochrane aracı aracılığıyla bias hatası riski açısından değerlendirildi. Primer sonlanım, 10 cm'lik görsel analog skala kullanılarak ağrı algısının ölçümü idi ve rastgele etkiler modelinde %95 güven aralığı (GA) ile ortalama fark (MD) olarak özetlendi. Uygulama şekline göre alt grup

Address for Correspondence/Yazışma Adresi: Ahmed Abu-Zaid, MD,
College of Graduate Health Sciences, University of Tennessee Health Science Center, Tennessee, USA
Phone: +19012834596 **E-mail:** aabuzaid@live.com **ORCID ID:** orcid.org/0000-0003-2286-2181
Received/Geliş Tarihi: 13.09.2022 **Accepted/Kabul Tarihi:** 14.11.2022

analizi yapıldı. Meta-analiz, Review Manager yazılımı aracılığıyla yapıldı. Toplam 1.004 kadını kapsayan beş RKÇ'yi dahil ettik. Bunlardan 502 hasta lidokain grubuna, 502 hasta ise kontrol grubuna ayrıldı. Genel olarak, her iki grup arasında anlamlı bir fark yoktu [n=5 RKÇ, MD=-0,21, %95 GA (-0,48, 0,07), p=0,80]. Birleştirilmiş analiz homojendi (ki-kare p=0,13, I^2=%43). Uygulama şekline göre alt grup analizi yapıldığında, lidokainin enjeksiyon olarak kullanması ile [n=3 RKÇ, MD=-0,26, %95 GA (-0,76, 0,23), p=0,29] enjeksiyon olarak kullanılmaması [n=2 RKÇ, MD=-0,18, %95 GA (-0,55, 0,18), p=0,33] durumlarında ağrı algısının her iki grup arasında anlamlı bir şekilde farklı olmadığı gösterilmiştir. Birleştirilmiş analizler sırasıyla heterojen (ki-kare p=0,05, I^2=%66) ve homojendi (ki-kare p=0,27, I^2=%19). Lidokain lokal anestezi grubu ile kontrol grubu arasında ağrı algısı açısından anlamlı fark yoktu. Kadınların çoğu, amniyosentez sırasında çok az rahatsızlık bildirdi. Danışmanlık ile hastaların amniyosentez sırasında yaşayabilecekleri ağrının venöz kan örneklemesi ile benzer olduğu konusunda eğitim verilmelidir.

Anahtar Kelimeler: Amniyosentez, lokal anestezi, ağrı, gebelik, analjezi

Introduction

Amniocentesis is an invasive procedure employed primarily in prenatal diagnosis[1]. Pain is a common concern among pregnant women undergoing amniocentesis[2]. The most popular approach for evaluating pain perception with high reliability during and after procedures is the visual analog scale (VAS)[2,3].

Currently, there are two main approaches for pain relief during amniocentesis, namely, pharmacological agents and non-pharmacological methods[2]. Among the pharmacological agents, lidocaine is a common local anesthetic agent for pain relief[4].

Several randomized controlled trials (RCTs) explored the capacity of lidocaine-mediated pain relief among pregnant women undergoing amniocentesis[5-9]. However, the findings of these RCTs were limited by various shortcomings, such as small sample sizes, relatively poor quality of studies, different routes of administration, and inconsistent reported results. All in all, the analgesic efficacy of lidocaine among pregnant women undergoing amniocentesis remains poorly delineated. Moreover, no meta-analysis report has been published to assess the clinical utility of lidocaine during amniocentesis. Such research is enormously imperative to generate evidence-based recommendations that will inform obstetric practice.

Therefore, the purpose of this contemporary investigation is to determine whether lidocaine administration has any analgesic effect on reducing maternal pain during amniocentesis when contrasted with a control treatment. The hypothesis is that the lidocaine administration will correlate with better maternal analgesia than the control treatment during amniocentesis.

In this study, we followed the steps of the Cochrane Handbook for Systematic Reviews of Interventions[10] as well as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[11]. Ethical approval was exempted.

Search Approach

Web of Science, Scopus, PubMed and Cochrane Central Register of Controlled Trials were searched until July 2022. The search approach comprised (amniocentesis OR amniocenteses) AND (anesthesia OR "local anesthesia" OR lidocaine OR xylocaine OR EMLA OR "lidocaine-prilocaine" OR lignocaine OR prilocaine OR dalcaine OR xylocitin OR xylesthesin OR xyloneural OR "2-2EtN-2MePhAcN" OR otocaine).

Inclusion and Exclusion Criteria

The inclusion criteria comprised (*a*) patients: Females undergoing amniocentesis, (*b*) intervention: Local analgesia using lidocaine, (*c*) comparison: Placebo or no treatment, (*d*) outcome: Pain perception, (*e*) study design: RCTs. The exclusion criteria comprised non-RCT study designs and studies published in languages other than English.

Screening and Study Selection

The retrieved citations were sequentially subjected to removal of duplicates, title/abstract examination, and lastly full-text inspection to determine final eligibility. Two independent authors completed the task and resolved the conflicts.

Quality Assessment

Quality assessment was completed using the revised version of the Cochrane Risk of Bias assessment tool[12]. Two authors performed the quality assessment independently for all RCTs to assess the risk of bias of the included studies according to the second version of the Cochrane Risk of Bias assessment tool[12]. "Low," "some concerns," or "high" risk of bias judgments were assigned to each domain. Two independent authors completed the task and resolved the conflicts.

Data Extraction and Outcome

Data extraction of studies comprised country, trial period, total number of patients, the intervention arm, the control arm, and type of administration. Data extraction of patients comprised the number of patients per arm, age, gestational age (weeks), parity, body mass index (kg/m^2), weight (kg), and height (in). The primary outcome included pain perception by using the 10 cm VAS. Two independent authors completed the task and resolved the conflicts.

Meta-analysis

The primary outcome was analyzed via the Inverse-Variance method and reported as mean difference (MD) with 95% confidence interval (CI). The random-effects model of statistical analysis was employed. I^2 values of more than 50% and the chi-square test ($p<0.1$) were indicative of high heterogeneity. Forest plots were generated through the Review Manager software, version 5.4.

Results

Literature Search

Overall, 203 citations were retrieved after the omission of duplicates. Additionally, nine articles progressed to full-text screening, of which five studies met the eligibility criteria and were included in the quantitative synthesis (Figure 1)[5-9].

Summary of the Included Studies

We included five RCTs[5-9] with 1004 patients (lidocaine arm n=502 patients and control arm n=502 patients). Three RCTs used lidocaine as injection[5-7] and two RCTs used it as non-injection [spray[8] and cream[9]]. Table 1 and Table 2, respectively, summarize the major features of the included studies and participants.

Quality Assessment

Three RCTs achieved an overall low risk of bias[6,8,9]. One RCT[7] was evaluated as "some concerns" in the domain of randomization because it provided no information about the randomization process and allocation concealment. Lastly, one RCT[5] was judged as high risk of bias in the domain of randomization because it provided no information about the randomization process and allocation concealment, and baseline imbalance suggested a problem in the randomization process (Figure 2).

Meta-Analysis of Pain Perception (VAS)

All RCTs reported pain perception[5-9]. Overall, there was no significant difference between both arms [MD=-0.21, 95% CI (-0.48, 0.07), p=0.80]. The pooled analysis showed homogeneity (p=0.13, I^2=43%). Subgroup analysis according to the mode of administration showed that pain perception did not significantly differ between both arms when lidocaine was employed as injection [n=3 RCTs, MD=-0.26, 95% CI (-0.76, 0.23), p=0.29] or non-injection [n=2 RCTs, MD=-0.18, 95% CI (-0.55, 0.18), p=0.33]. The pooled analyses showed heterogeneity (p=0.05, I^2=66%) and homogeneity (p=0.27, I^2=19%), respectively (Figure 3).

Discussion

Summary of the Main Findings

During amniocentesis, this meta-analysis of five RCTs showed no significant difference concerning maternal pain perception between the local analgesia group with lidocaine and the control group.

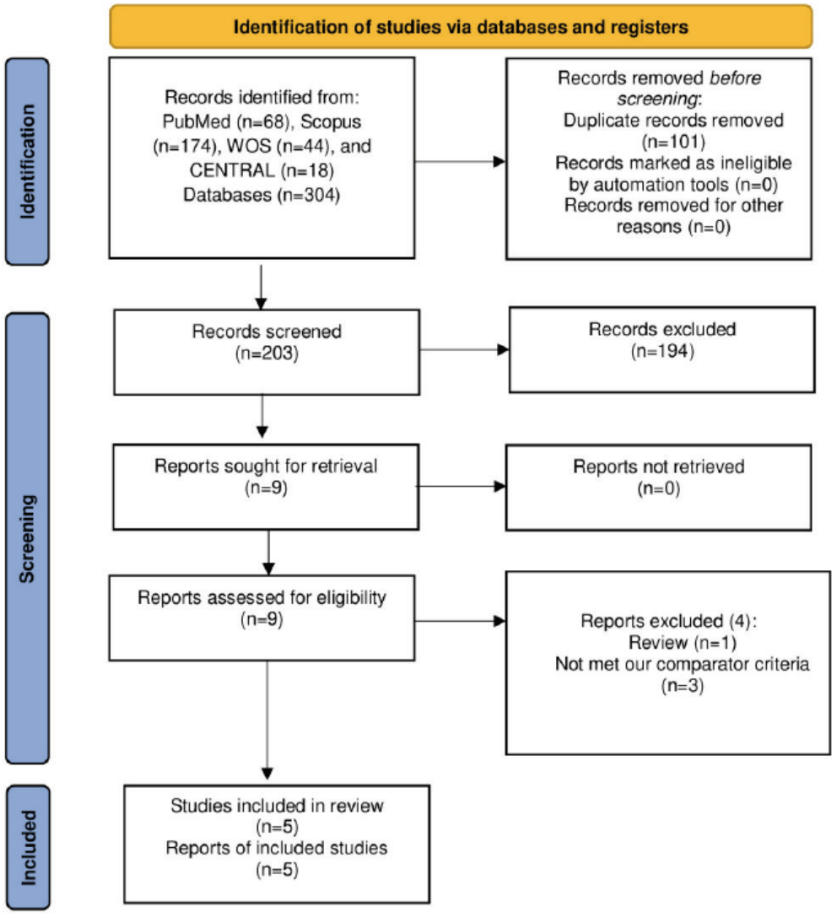

Figure 1. The preferred reporting items for systematic reviews and meta-analyses flowchart for literature search

Interpretation of Findings

Lidocaine is among the most potent anesthetic substances frequently used in medical procedures[4]. Lidocaine spray is a practical approach that is simple to employ in clinical practice for relieving pain in the skin or mucosa. A previous study showed that women who received lidocaine spray experienced less pain than those who received a placebo[8]. Women who are highly fearful of the procedure or have low pain tolerance may be given the option of lidocaine spray[8]. Some restrictions apply to this investigation; although the lidocaine spray starts immediately, the one-minute wait before the procedure may not have been long enough to provide the required anesthetic effect[8]. However, waiting for just a minute would prevent any intervening fetal movement that would change the targeted puncture site on the mother's abdomen[8].

In another trial on lidocaine cream[9], the results showed that patients' perceptions of worry and pain were mild before amniocentesis. There were no discernible variations in the VAS values between the two arms for anxiety (before procedure), anticipated pain, and pain (after procedure). Based on the distinction between the VAS pain levels before and after the procedure, the findings showed that lidocaine-prilocaine cream did not significantly reduce amniocentesis-related pain[8]. The local anesthetic effect can explain this result as it lowers cutaneous pain but not peritoneal discomfort. The peritoneum and uterus are the primary sources of pain during the procedure[8].

According to data from a previous study by Van Schoubroeck and Verhaeghe[5], most patients (59%) believed that the pain induced by amniocentesis was analogous to that induced by venipuncture. After injecting a local anesthetic into the dermis and subcutaneous tissues, they noticed no variance

Table 1. The summary of the included studies

Study ID	Country	Trial duration	Total sample size, n	Trial arms		Type of administration
				Lidocaine	Control	
Van Schoubroeck and Verhaeghe[5] 2000	Belgium	Between April 1998 and November 1998	n=220	Lignocaine (1%)	Nothing	Injection
Gordon et al.[6] 2007	USA	Between January 1995 and March 2001	n=204	Lidocaine (1%)	Nothing	Injection
Pongrojpaw et al.[8] 2007	Thailand	Between October 2006 and April 2007	n=120	Lidocaine-prilocaine	Placebo	Cream
Elimian et al.[7] 2013	USA	Between October 2007 and September 2009	n=76	Lidocaine (1%)	Placebo	Injection
Homkrun et al.[9] 2019	Thailand	Between June 2017 and January 2018	n=384	Lidocaine (10%)	Placebo	Spray

Table 2. The baseline characteristics of the included studies

Study ID	Group	Sample size, n	Age (years)	Gestational age (weeks)	Parity	BMI (kg/m²)	Weight (kg)	Height (in)
Van Schoubroeck and Verhaeghe[5] 2000	Lidocaine	n=114	34.1	15.9	1.1	NA	62.7	NA
	Control	n=106	33	15.8	1.1	NA	67.7	NA
Gordon et al.[6] 2007	Lidocaine	n=101	33.7±5.7	19.6±6.1	1.2±1	26.4±3.8	71.4±11.3	64.8±2.7
	Control	n=103	33.3±5.9	19.3±5.5	1.2±1.1	27.3±5.1	72.5±15.4	64.0±2.7
Pongrojpaw et al.[8] 2007	Lidocaine	n=60	36.8±3.79	17.6±1.6	0.7±0.8	24.4±4.2	NA	NA
	Control	n=60	36.9±3.41	19.9±6.6	0.6±0.7	24.1±3.6	NA	NA
Elimian et al.[7] 2013	Lidocaine	n=36	31.3±6.5	19.8±2.6	NA	NA	167.1±30.7 (Ibs)	64.9±2.6
	Control	n=40	30.1±7.5	20.1±2.4	NA	NA	170.2±37.7 (Ibs)	65.6±3.1
Homkrun et al.[9] 2019	Lidocaine	n=191	36±3	17±1	NA	NA	NA	NA
	Control	n=193	36±3	17±2	NA	NA	NA	NA

BMI: Body mass index, NA: Not available

in pain or distress during amniocentesis[5]. This finding is crucial since skipping local anesthetics saves both time and money. It takes time to aspirate the local anesthesia, slowly inject it and wait for it to take effect. Also, it is possible to avoid paying 3.26 EUR ($3.41) for each patient for a single syringe, two needles, and local anesthesia material (lidocaine)[5].

In the investigations by Van Schoubroeck and Verhaeghe[5] and Gordon et al.[6], lidocaine was locally injected before amniocentesis, but neither group reported that this technique reduced pain. The verbal rating scale of 1 to 4 was employed in the study by Van Schoubroeck and Verhaeghe[5], however without blinding. In the study by Gordon et al.[6], 66% of the local anesthetic arm and 53% of the control arm had the procedure performed by maternal-fetal medicine staff. They also discovered that women felt less discomfort when staff members performed the procedure. This result might be confusing since the women experienced pain due to local penetration. Although the study by Van Schoubroeck and Verhaeghe[5] was a quasi-randomized trial, the results of the investigation by Gordon et al.[6] showed no evidence of considerable heterogeneity. The amniocentesis procedures were not wholly carried out by doctors with the exact clinical expertise. Still, because in the Gordon et al.[6] study, maternal-fetal medicine staff carried out more operations involving an anesthetic, this might have influenced the study in favor of an affirmative conclusion regarding the utility of local anesthesia.

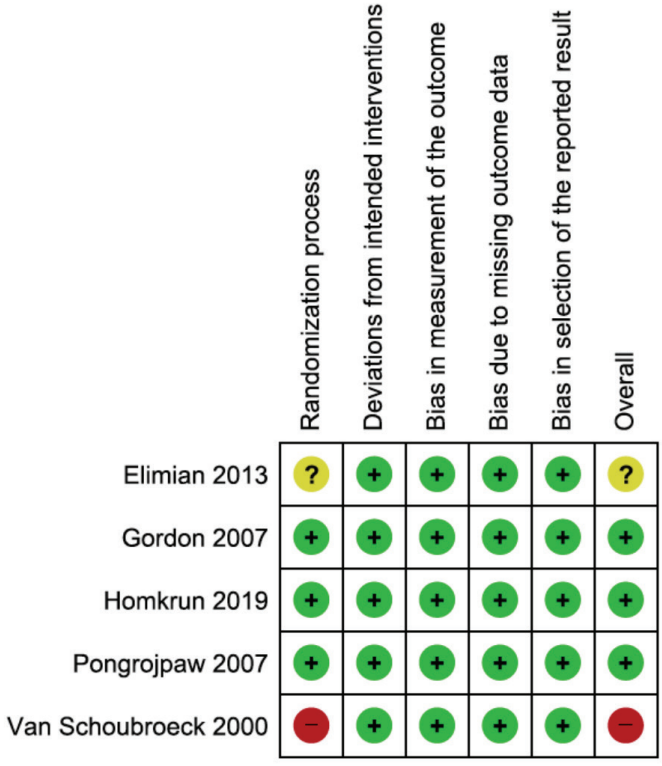

Figure 2. The summary of risk of bias assessment of the included randomized controlled trials

Study Limitations

The usage of LA for pain management is not yet supported by sufficient evidence (i.e., small number of trials and sample sizes). Our study only evaluated post-procedural pain and did not analyze post-procedural anxiety. Also, publication bias was not explored secondary to the few studies included.

Conclusion

There was no noteworthy change concerning maternal pain perception between the lidocaine and control arms. Most women reported just minimal discomfort during amniocentesis. Counseling should educate patients that the pain they might experience throughout the procedure is comparable to discomfort during venipuncture.

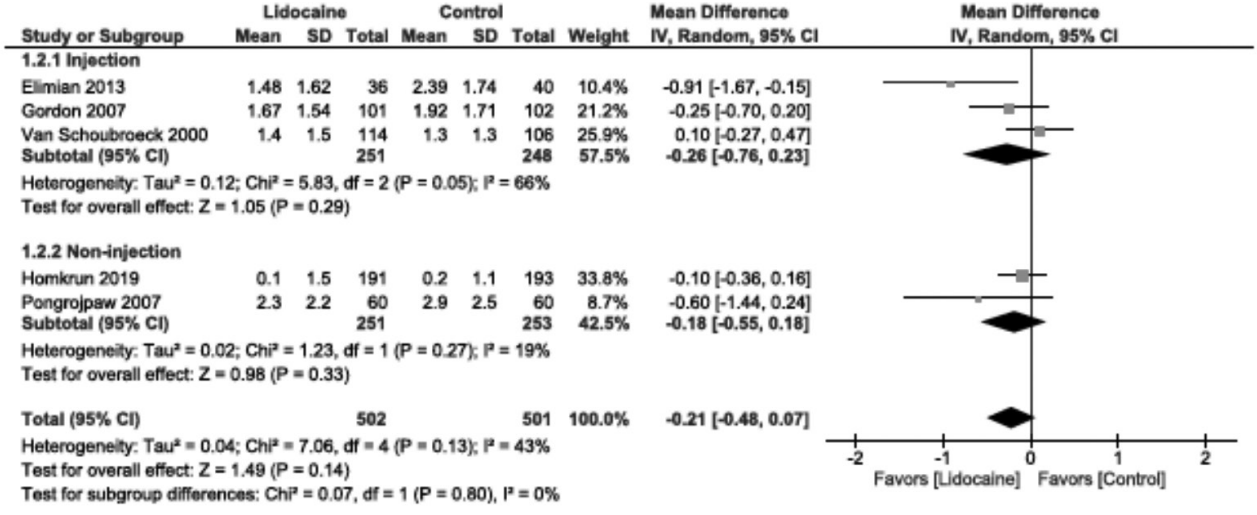

Figure 3. Meta-analysis of the post-procedural pain of amniocentesis

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.A., A.S., A.A., Design: E.A., A.S., A.A., Data Collection or Processing: E.A., R.S., M.A., Ab.A., F.A., G.R., H.A., Analysis or Interpretation: E.A., R.S., A.S., Literature Search: E.A., R.S., M.A., Ab.A., F.A., G.R., H.A., M.G.B., A.A., Writing: E.A., R.S., M.G.B., A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Alfirevic Z, Navaratnam K, Mujezinovic F. Amniocentesis and chorionic villus sampling for prenatal diagnosis. Cochrane Database Syst Rev 2017;9:Cd003252.
2. Mujezinovic F, Alfirevic Z. Analgesia for amniocentesis or chorionic villus sampling. Cochrane Database Syst Rev 2011:Cd008580.
3. Heller GZ, Manuguerra M, Chow R. How to analyze the Visual Analogue Scale: Myths, truths and clinical relevance. Scand J Pain 2016;13:67-75.
4. Beecham GB, Nessel TA, Goyal A. Lidocaine. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing; 2022.
5. Van Schoubroeck D, Verhaeghe J. Does local anesthesia at mid-trimester amniocentesis decrease pain experience? A randomized trial in 220 patients. Ultrasound Obstet Gynecol 2000;16:536-8.
6. Gordon MC, Ventura-Braswell A, Higby K, Ward JA. Does local anesthesia decrease pain perception in women undergoing amniocentesis? Am J Obstet Gynecol 2007;196:55.e1-4.
7. Elimian A, Goodman JR, Knudtson E, Wagner A, Wilson P, Williams M. Local anesthesia and pain perception during amniocentesis: a randomized double blind placebo-controlled trial. Prenat Diagn 2013;33:1158-61.
8. Pongrojpaw D, Somprasit C, Chanthasenanont A. The efficacy of lidocaine-prilocaine cream to reduce pain in genetic amniocentesis. J Med Assoc Thai 2007;90:1992-6.
9. Homkrun P, Tongsong T, Srisupundit K. Effect of Xylocaine spray for analgesia during amniocentesis: a randomized controlled trial. Prenat Diagn 2019;39:1179-83.
10. Higgins J GS, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [Internet]. [updated March 2011]. The Cochrane Collaboration, www.handbook.cochrane.org AAf.
11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
12. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.