Is concomitant use of misoprostol and extra amniotic saline infusion more effective or safer for cervical ripening: A RCT in a tertiary center

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Abstract
Various methods have been proposed for cervical ripening. Due to conflicting results and significant heterogenisity among previous studies, we designed a randomized clinical trial to find out whether concomitant use of Misoprostol and extra-amnionic saline infusion (EASI) would lead to better outcomes or not. Ninety term pregnant women were randomly assigned to three different groups of ripening methods: vaginal misoprostol, EASI, and concomitant use of both. Time interval to reach a bishop score of five (primary outcome), time interval to amniotic membranes rupture and delivery rate, delivery route, need to oxytocin infusion, fetal distress associated cesarean delivery, meconium staining, and 1st and 5th minute Apgar scores were study outcomes. Although combined method could not reduce the time interval to a Bishop score of five (p-value=0.145) Oxytocin infusion was significantly less likely. Other outcomes were not different (p-values>0.05).

Hence, combined method could significantly reduce the Oxytocin infusion which is favorable in resource-limited countries.

Keywords: Vaginal delivery; Cervical ripening; Misoprostol; EASI (Extra Amniotic Saline Infusion); Labor induction.
Introduction

Cervical ripening agents such as mechanical methods [1-3], hyaluronidase [4], relaxin [5], and pharmacological agents [6,7] have been introduced with different safety-efficacy profile.

Numerous studies have compared Misoprostol and Foley catheter (mostly single-balloon ones) with conflicting results [8-11]. There are also scarce evidence comparing prostaglandins with EASI [12-16] and studies comparing combined methods like EASI plus Prostaglandins are lacking [17,18]. As well,, the studies population has been widely heterogenous.

Here, we designed a study to compare the effect of concomitant use of vaginal misoprostol and EASI with EASI and or Misoprostol alone. As, presence of any fetal or maternal comorbidities may affect a physician’s decision to allow labour progress or time to perform an emergent cesarean delivery, we just included pregnancies without any significant or uncontrolled comorbidity. To the best of our knowledge, it can be considered as a novelty in our study design.

Materials and methods

This randomized clinical trial was conducted on singleton term pregnant women at Taleghani Hospital labor ward (Tehran, Iran) during 2018-2020. Inclusion criteria were maternal age over 18, no contraindication for vaginal delivery, reassuring admission NST and Bishop scores less than 5 at arrival. The Ethics Committee of Shahid-Beheshti University of Medical Sciences approved the study and all participants signed an informed consent. Patients with ruptured membranes or intrauterine fetal death were excluded. Maternal co-morbidities such as preeclampsia or gestational hypertention, uncontrolled pregestational Diabetes Mellitus, significant vaginal bleeding and uterine hypertonia and serious fetal complications were also other exclusion criteria.

Patients’ demographic characteristics and obstetrical history were collected from their medical records. For randomization, each patient selected a number through 1 to 3 and they were categorized in to group 1 to 3 based on the selected number until each group reaches to 30 participants. The researchers and the person who did data analysis were blinded. The first group members received 25 micrograms Misoprostol vaginally up to 3 times or whenever at least 200-250 Monteo Video contractions were achieved, which came sooner. In the second group a 24F fully-catheter was inserted through cervical canal and the balloon was inflated by 30 cc of infusible room-temperature Normal Saline and Extra-Amniotic Salin Infusion (EASI) at the rate of 30 cc/minute was initiated. Finally, the third group received both single dose of 25 microgram vaginal Misoprostol and Foley catheter insertion with EASI concomitantly. In all arms, when the Bishop score exceeded 4 or the Foley catheter was spontaneously expluded (or otherwise after 12 hours of catheter insertion), if uterus was hypotonic, Oxytocin was infused at the rate of 4 mIU/minute and the dose was increased every 15 minutes by 4 mIU/minute till appropriate contractions were achieved. Contractions were assessed hourly and every 30 minutes in latent and active phase, respectively. Continuous FHR monitoring was applied in case of Oxytocin infusion and also during the first two hour after Misoprostol administration.

The primary outcome was time interval to reach a Bishop Score of at least five. Time interval to membranes rupture and delivery, delivery mode, need for Oxytocin infusion, onset of intrapartum fetal distress, meconium staining, umbilical cord PH, and Apgar scores were considered as secondary outcomes. Moreover patients’and physicians’ satisfaction regarding the applied method was assessed by a 1-10 Linkert scale. SPSS software version 23(EBM,USA) was used for data analysis.

Results

90 patients were included for final analysis, 30 patients in each group. Demographic features and obstetrical history did not differ between the groups (Table 1).

Bishop score of three was the most common score on admission time among study population (55 cases (61.5%)). Scores of 4, 2, and 1 were observed in 19(21.1%), 12(13.4%), and 4 women (4.4%), respectively. As well, Bishop score of three was the most prevalent score in each group. Dilatation of one centimeter was the most prevalent dilatation in each group (57.1%, 63.3%, and 36.7%, respectively) followed by Cervical dilation in excess of tip finger.

The mean time interval to reach a Bishop score of five or more, to the amniotic membranes rupture and to delivery did not differ significantly between three groups (Kruskal-Wallis test, p-values>0.05) (Table 2).

In respect to other secondary outcomes, it should be said that in the third group, in 6(25%) participants Oxytocin was infused while, in the first and second group, in 14(60.9%) and 13(41.9%) pregnant women infusion was indicated (p-value=0.04). In fact, combined use of EASI and Misoprostol could reduce the chance of Oxytocin infusion by 36% (OR:0.64, CI: 0.1-4.15).

Regarding fetal distress rate, 11 cases were seen, 8 cases in the first and 3 in the third group, but Kruskal-Wallis test showed no association between the cervical ripening method and fetal distress occurrence (P-value=0.12, Chi²=0.423).

The umbilical cord blood pH mean values(±std.) were 7.27(±0.04), 7.28(±0.05), and 7.26(±0.05) in group 1 to 3, respectively (P-value = 0.708, Chi² =0.691).

The mean Apgar scores at the 1st minute were 8.86±0.62, 8.96±0.17, and 9±0.00 in group 1 to 3 in order (p-value=0.42, Chi²=0.97). Regarding to 5th minute Apgar Score one neonate in group 1 and 3 had scores less than 10 but no newborn had scores less than 10 in EASI group; However, the difference was not significant too.

Ten cases of meconium staining were seen during study. In other words, its occurrence was 7.8%, 9.7%, and 20.8% in group 1 to 3, in order but the difference was not significant (p-value=0.37, Chi² =1.97).

Regarding to delivery mode, 18(78.3%), 22(71%), and 14(58.3%) cases delivered vaginally in group 1 to 3, respectively but the difference was not statistically significant (p-value=0.32, Chi²=2.23).

Finally, 56.7%, 36.78%, and 40% of Patients delivered vaginally (p-value=0.91, chi²=0.19).
The physicians’s satisfaction did not differ between groups neither (p-value=0.45, chi2=1.58, respectively).

Conclusion
Concomitant use of Misoprostol and EASI could reduce the need for Oxytocin infusion while not affecting other perinatal outcomes. So, it seems this method could be an appropriate alternative for cervical ripening, especially when medical staff resources or facilities are limited.

Plain language summary: There are different cervical ripening methods which could be used to increase vaginal delivery rate during labor induction, including mechanical or pharmacological agents. In each category variation exists regarding these comorbidities may affect a physician’ desire for iatrogenic interventions. In contrast a small sample size is a main limitation which could resulted in statistically non-significant associations. Hence, larger sample size studies are essential.
and also safety and efficacy profile. According to this significant heterogeneity in literature, even in one single method, pulling the results together and making a conclusion seems impossible. Studies which have compared combined use of misoprostol and Foley catheter insertion with EASI are sparse. Here, in this randomized clinical trial we compared vaginal Misoprostol, Foley catheter insertion with EASI and combined method. No significant difference was seen regarding time to reach a Bishop Score of 5, time to delivery, delivery mode, meconium staining and cord blood gas status; However, need for Oxytocin infusion was less among combined group patients. Hence, the combined method may be an appropriate alternative for cervical ripening specially in resource-limited countries.

Declarations

Acknowledgement: The authors highly appreciate our patients for their kind cooperation. We also thank medical staff in delivery ward of Taleghani Hospital for their assistance.

Conflicts of interests: The authors declare no conflicts.

References


