

Comparison of Nifedipine and Isoxsuprine to Cervical Length in Threatened Preterm Labor

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Abstract

Objective: This study aimed to determine differences in cervical length changes between administration of nifedipine and isoxsuprine.

Method: Subjects of the study were pregnant women who meet the inclusion criteria (n=16). Treatments were given for 48 hours. Parameters measured was the cervical length before and after the administration of nifedipine and isoxsuprine. This study was conducted in Dr. Hasan Sadikin General Hospital from January until April 2020.

Result: Less shortening of the cervical length after administration of tocolytic isoxsuprin for 48 hours compared with tocolytic nifedipine and statistically significant with p value of 0.0001 ($p < 0.05$) using Paired T tests.

Conclusion: Isoxsuprin is more effective to prevent shortening of the cervical length compared to nifedipine in cases of threatened preterm labor.

Key word: Nifedipine, Isoxsuprine, cervical length, threatened preterm labor

Perbandingan Efek Nifedipine dan Isoxsuprine terhadap Panjang Serviks pada Persalinan Preterm Terancam

Abstrak

Tujuan: Studi ini bertujuan untuk menelaah perbedaan perubahan panjang serviks antara pemberian nifedipine dan isoxsuprine.

Metode: Studi ini adalah sebuah uji klinis acak dengan metode randomisasi buta ganda. Partisipan studi ini adalah wanita hamil yang memenuhi kriteria inklusi (n=16). Pengobatan diberikan selama 48 jam. Parameter yang diukur adalah panjang serviks sebelum dan sesudah administrasi nifedipine dan isoxsuprine. Studi ini dilakukan di RSUP Dr. Hasan Sadikin pada Januari sampai April 2020.

Hasil: Terdapat lebih sedikit pemendekan serviks pada pemberian isoxsuprine selama 48 jam dibandingkan dengan nifedipine ($p=0.0001$).

Kesimpulan: Isoxsuprine lebih efektif untuk mencegah pemendekan serviks dibandingkan dengan nifedipine pada kasus persalinan preterm terancam.

Kata kunci: Nifedipine, Isoxsuprine, Panjang serviks, Persalinan preterm terancam

Introduction

Preterm labor is defined as babies born alive before 37 weeks of gestation or birth weight between 500 - 2499 grams.¹ Preterm labor is known to be an important cause of infant and child morbidity and mortality. Based on data from the World Health Organization (WHO) obtained in 2015 there were 1 million mortality from preterm labor.²

The mortality is caused by complications related to preterm labor. It is also called the most important cause of death in the first month of life of baby, and is associated with more than 75% of neonatal mortality in neonatal period.³

Preterm labor is caused by various factors, including maternal age, history of preterm labor, occupation, and history of smoking. Complications of pregnancy such as urinary tract infections, hypertension, asthma also increase the risk of preterm labor. Later these risk factors will trigger threatened preterm labor including uterine contraction every 10 minutes and more often, sense of pressure on the pelvis, and shortening of cervical length examined by transvaginal ultrasonography (TVS).^{4,5}

Shortening of cervical length is considered as one of the risk factors for preterm labor, especially in women without symptoms of preterm labor. Pradyuman *et al.* explained that the shorter the cervix, the greater the risk of preterm labor.⁶ Chiossi *et al.* revealed that the mean of cervical length is 3.5 cm at 24 weeks gestation. Cervical length is 2.2 cm, the risk of preterm labor is 20%. Sanin-Blair J *et al.* also proved that cervical length is less than 3.0 cm before 16 weeks gestation is associated with preterm labor.

Based on these two studies, the cervical length shortens at first and second trimesters increase the risk of preterm labor.^{7,8} The length of the cervix shortens due to changes in collagen and proteoglycans made up the structure of the cervix as a result of continuous

uterine contractions. Prostaglandin, relaxin, and cytokines also play a role in the process of shortening of the cervix. Administering tocolytic can be done to all women as primary prevention, reducing the risk of preterm labor, to minimize the risk in high-risk of pregnant women.^{9,10}

Tocolytic drugs are expected to extend the pregnancy so that the fetus can reach maximum of maturity. The effective use of tocolytic drugs is expected to prevent a reduction of cervical length in threatened preterm labor.^{11,12}

Nifedipine is a calcium antagonist or calcium channel blocker that is widely used as a tocolytic drug. Many studies have concluded that nifedipine can be used as a first-line tocolytic drug. Nifedipine (and other calcium antagonists) can reduce the risk of labor during the seven days of initiation and delivery before 34 weeks gestation by improving clinical neonates outcomes, such as respiratory failure syndrome, intraventricular hemorrhage, necrotizing enterocolitis and neonatal jaundice.

However, the 2005 Cochrane review concluded that nifedipine did not prevent preterm labor or improve neonatal outcomes. The review is constrained by the lack of a study population, so the conclusion is still doubtful.^{13,14}

Isoxsuprine is an adrenergic receptor agonist class β_2 . A study studying Isoxsuprine and compared with Terbutalin sulfate found that Isoxsuprine and Terbutalin were effective in prolonging pregnancy, but Terbutalin was proven to be more effective than Isoxsuprine in prolonging labor.⁸

The results of the study presented by Giorgino *et al.*, also found that Isoxsuprine was a drug which is superior and should be the drug of choice in preventing preterm labor, the risk of abortion, and the potential for relapse.¹⁵

Nifedipine and Isoxsuprine are both effective tocolytics but the administration

protocol in some centers still varies. Studies conducted to compare effects on cervical length, which are one predictor of preterm labor, have not been done much. This study aimed to determine differences in cervical length changes between administration of nifedipine and isoxsuprine.

Method

This study was a randomized controlled trial (RCT) with a double blind randomization method. Subjects of the study were pregnant women who meet the inclusion criteria (n=16). Treatments were given for 48 hours, parameters measured was the cervical length before and after the administration of nifedipine and isoxsuprine. This study was conducted in Dr. Hasan Sadikin General Hospital from January until April 2020. Sampling was done by consecutive sampling, and the allocation of subjects into one group was carried out randomly by permutation block. The results of subsequent studies will be analyzed statistically. The study was approved by the Research Ethics Committee and the Director of Hasan Sadikin Hospital.

Before the study conducted, the conference among clinical doctors in obstetric ward and fetomaternal policlinic of Hasan Sadikin hospital was done.

Administering Nifedipine

Nifedipine was given at an initial dose of 20 mg orally which can be repeated until the uterine contractions disappear with a maximum dose of 160 mg/24 hours, and followed by a dose of 20 mg orally every six hours for two days.

Administering Isoxsuprine

Isoxsuprine was given by infusion at an initial dose of 0.25-0.5 mg/minute and can be increased to 1 mg/minute until the uterine

contractions disappear, then followed by administration of 10 mg orally every six hours for two days.

Examination of Cervical Length

Patients who presented with threatened preterm labor would have transvaginal ultrasound examination to measure the cervical length before the intervention. The patients were asked to empty the bladder.

The cervix was measured in the longitudinal axis by measuring the length of the cervical canal from *ostium uteri internum* (OUI) to *ostium uteri externum* (OUE). The results of cervical length before the intervention and after 48 hours of intervention were recorded. Transvaginal ultrasonography is performed by an operator to minimize bias.

Result

Table 1 shows the characteristics of the study subjects and explains the categories based on age, occupation, education, gravida, and gestational age of each treatment group by giving Nifedipine and Isoxsuprine.

Table 2 explains the comparison of cervical lengths on threatened preterm labor before and after intervention in the group of patients given nifedipine. In the group of patients given nifedipine, the mean of cervical length before the intervention was 3.16 ± 0.502 cm, while the mean of cervical length after the intervention was 1.85 ± 0.341 cm.

Table 3 explainsthe comparison of cervical lengths on threatened preterm labor before and after intervention in the group of patients given Isoxsuprine. In the group of patients given Isoxsuprine, the mean of cervical length before the intervention was 2.29 ± 0.615 cm, while the mean of cervical length after the intervention was 1.94 ± 0.510 cm.

Table 4 explains the changes in cervical

Table 1 The Comparison Between Characteristics of Subjects

Variable	Group		P value
	Nifedipine n=16	Isoxsuprine n=16	
Maternal Age (years)			0.142
<20	3 (18.8%)	3 (18.8%)	
20-35	9 (56.3%)	13 (81.3%)	
>35	4 (25.0%)	0 (0.0%)	
Occupation			0.633
Housewife	8 (50.0%)	5 (31.3%)	
Employee	6 (37.5%)	9 (56.3%)	
Entrepreneur	2 (12.5%)	2(12.5%)	
Education			0.376
Elementary school	2 (12.5%)	2 (12.5%)	
Junior high school	6 (37.5%)	7 (43.8%)	
Senior high school	7 (43.8%)	3 (18.8%)	
Undergraduate	1 (6.3%)	4 (25.0%)	
Gravid			0.404
Gravid 1	8 (50.0%)	7 (43.8%)	
Gravid 2	2 (12.5%)	5 (31.3%)	
Gravid 3	4 (25.0%)	4 (25.0%)	
Gravid >4	2 (12.5%)	0 (0.0%)	
Gestational age (weeks)			0.799
30 – 31	2 (12.5%)	2 (12.5%)	
31 – 32	5 (31.3%)	3 (18.8%)	
32 – 33	4 (25.0%)	7 (43.8%)	
33 – 34	5 (31.3%)	4 (25.0%)	

Baessed on Fisher's exact analysis. *significant if p value <0.05.

Table 2 The Comparison of Cervical Lengths on Threatened Preterm Labor Before and After Administering Nifedipine

Variable	Administering Nifedipine		P value
	Before N=16	After N=16	
Cervical length (cm)			<0.001**
Mean ± SD	3.16 ± 0.502	1.85 ± 0.341	
Median	3.11	1.86	
Range (min-max)	2.49 – 4.17	1.29 – 2.39	

Note: The results of the normality test using Shapiro-Wilk, data are normally distributed. Different test using paired T test. *significant if p value <0.05.

Table 3 The Comparison of Cervical Lengths on Threatened Preterm Labor Before and After Administering Isoxsuprine

Variable	Administering Isoxsuprine		P value
	Before N=16	After N=16	
Cervical length (cm)			<0.001**
Mean ± SD	2.29 ± 0.615	1.94 ± 0.510	
Median	2.39	2.05	
Range (min-max)	0.83 – 3.11	0.79 – 2.91	

Note: The results of the normality test using Shapiro-Wilk, data are normally distributed. Different test using paired T test. *significant if p value <0.05.

Table 4 Comparison of the Change of Cervical Lengths on Threatened Preterm Labor in Isoxsuprine and Nifedipine Groups

Variable	Group		P value
	Nifedipine N=16	Isoxsuprine N=16	
The change of cervical lengths (cm)			<0.001**
Mean ± SD	1.31 ± 0.459	0.35 ± 0.296	
Median	1.29	0.32	
Range (min-max)	0.60 – 2.48	0.04 – 1.02	

Note: The results of the normality test using Shapiro-Wilk, data are normally distributed. Different test using paired T test. *significant if p value <0.05.

length after and before intervention recorded shorter in the group treated with Isoxsuprine (0.36 ± 0.296 cm) compared to Nifedipine group (1.32 ± 0.459 cm). The difference in changes of cervical length after intervention in the 2 study groups was statistically significant, p value <0.001.

Discussion

Maternal age, occupation, education, gravid status, gestational age could influence the incidence of prematurity.¹⁶ Maternal age is an important factor in threatened preterm labor. According to Astolfi *et al.* described that maternal age >40 years is closely related to incidence of preterm labor. Group of 30-34 years is included in low incidence of preterm labor. Study by Cavazos-Relg *et al.* showed that the incidence of preterm labor increased

at age <20 years and >35 years, decreased at age 20-30 years.^{17,18} In this study, preterm labor was most common in the age group of 20-35 years.

A retrospective study conducted by Dudenhausen JW *et al.* Found that the incidence of preterm labor increased significantly in multiparous women and gestational age more than 30 weeks.¹⁶

However in this study, preterm labor was most common in nullipara group of the two intervention groups. The incidence of threatened preterm labor is most common in 33-34 weeks for the Nifedipine group and 32-33 weeks for the Isoxsuprine group.

Nifedipine is a tocolytic of calcium channel blockers inhibiting uterine contractions. The decrease in frequency and strength of uterine contraction after administering Nifedipine is caused by

direct inhibition of electrical activity in myometrial cells, by inhibiting calcium ions from entering the cell membrane and also preventing calcium from being released from the sarcoplasmic reticulum. Thus, a decrease in free calcium occurs in cells and prevents phosphorylation of *Myosin Light Chain Kinase* (MLCK) from occurring and causes relaxation of myometrial cells.^{19,20}

Isoxsuprine has an effect acting on β_1 or β_2 receptors. This agent induces peripheral vasodilation directly affects the smooth muscle of blood vessels, especially in skeletal muscle and uterine relaxation with low effect on blood flow in the skin because Isoxsuprine works in intracellular contractility. β -agonists attach to the receptors in membrane, and this complex will activate *adenyl cyclase* then c-AMP increased, causes directly inhibiting MLCK and decreasing intracellular calcium, which in turn can prevent uterine contraction. In general, β -agonists effectively stop uterine contractions within 48 hours in 80-90% of pregnant women with premature contractions. In uterine relaxation, lower uterine segment does not stretch so that the cervix is not pulled.^{15, 21, 22}

The tocolytic agent described previously has a role in influencing uterine contractions. Indirectly contracted uterine contractions will prevent shortening of cervical length as a marker of threatened preterm labor. Many studies reported the mean of cervical length in pregnant women with gestational age of 14-30 weeks ranging between 35-40 mm.²³ In threatened preterm labor, shortening of cervical length occurs. Measurement of cervical length could be assessed using transvaginal ultrasound (TVS). A meta-analysis found that women with cervical length <15 mm has a high risk of developing preterm labor within 7 days.^{23, 24}

This study found that administration of Isoxsuprine is better than Nifedipine in preventing the shortening of cervical length in threatened preterm labor. This is consistent

with study by Jaju *et al.*

Who found that administration of Isoxsuprine could significantly prevent preterm labor for >48 hours. This is also supported by an observational study conducted by Oktavia Nur *et al.* Who examined 17 patients with threatened preterm labor. The study found that the use of Isoxsuprine is more effective than nifedipine.^{6, 15} Raymajhi *et al.* concluded that Nifedipine is safer and more effective as a tocolytic compared to Isoxsuprine. The mean of pregnancy could be extended by 25 days after using Nifedipine, whereas with Isoxsuprine only 19 days.²⁵

Nisha Singh *et al.* showed that nifedipine has a better effect than other tocolytics, especially if given at the onset of symptoms of preterm labor.²¹ Nifedipine is effective in preventing preterm labor in the cervical length of less than 3 cm.¹¹ Several studies comparing tocolytic, the beta-sympathomimetic agents are believed to be the most effective agents for inhibiting uterine contractions, prevent shortening of cervical length, and prolonging pregnancy, in high-risk preterm labor and abortion. Tocolytic agent reduces the chance of preterm labor with an active effect in the range of 24-48 hours to 1 week post-treatment.

Conclusion

Isoxsuprin is more effective to prevent shortening of the cervical length compared to nifedipine against the threatened preterm labor.

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