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When to apply propess to provide the best activity: In the morning or evening?

En iyi propess aktivitesi için ideal uygulama zamanı nedir: Sabah mı, akşam mı?

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Abstract

Aim: Propess is a drug of choice in our daily practice for induction of labor. The dosing plan of the drugs can be idealized by arranging them according to the chronobiological model. The aim of this study is to investigate the "time of administration" suggestions on chronotherapy for propess.

Methods: Our study was conducted retrospectively by examining the records of pregnant women who were given propess at Zekai Tahir Burak Women's Health Training and Research Hospital between 2008 and 2018. A total of 2694 patients were included in the study. Two groups were allocated according to the time of drug administration. The time from application to birth was calculated.

Results: Logistic regression analysis was performed for risk factors and we found that the time of drug administration was effective on duration to labor. The time from drug administration to labor was 18.0±4.0 hours in the morning group and 19.1±3.9 hours in the evening group ($p<0.001$)

Conclusion: It appears; drugs used for labor induction in the morning may increase drug efficacy and bioavailability. At this point birth becomes compatible with body biorhythm and the time to labor can be shortened.

Keywords: Chronotherapy, Labor induction, Dinoprostone

Öz

Amaç: Propess, doğum indüksiyonu için günlük pratiğimizde sık tercih edilen bir ilaçtır. İlaçların etkinliği, uygulama zamanları kronobiyolojik modele göre düzenlenerek idealize edilebilir. Bu çalışmanın amacı, propess uygulama zamanının ilaç etkinliğine olan etkisini araştırmaktır.

Yöntemler: Çalışmamız 2008-2018 yılları arasında Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesinde doğum indüksiyonu amacıyla propess uygulanmış gebe kadınların kayıtları inceleyerek retrospektif olarak yapıldı. Çalışmaya toplam 2694 hasta dahil edildi. İlaç uygulaması zamanına göre, hastalar sabah uygulananlar ve akşam uygulananlar olarak iki gruba ayrıldı. Uygulamadan doğuma kadar geçen süre saat olarak hesaplandı.

Bulgular: Risk faktörleri için lojistik regresyon analizi yapıldı ve ilaç uygulama zamanının doğum eylemi süresi üzerinde etkili olduğu bulundu. İlaç uygulamasından doğuma kadar geçen süre sabah grubunda 18,0±4,0 saat, akşam grubunda ise 19,1±3,9 saat olarak bulundu ($p<0,001$).

Sonuç: Görünüşe göre; Sabah doğum indüksiyonu için kullanılan ilaçlar, ilaç etkinliğini ve biyoyararlanımını arttırabilir. Bu noktada doğum vücut bioritmi ile uyumlu hale gelir ve doğum zamanı kısaltılabilir.

Anahtar kelimeler: Kronoterapi, Doğum indüksiyonu, Dinoproston

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Introduction

Induction of labor; refers to the stimulation of uterine contractions by any mechanical process or pharmacological drug in the presence of ruptured or non-ruptured membranes before spontaneous birth [1].

In obstetric practice, birth induction is becoming an increasingly common medical procedure in proportion to the increased knowledge and experience in the perinatal field. Oxytocin is a safe and effective initiator of uterine contractions in labor induction but depends on the condition of the cervix. In cases where the cervix is not suitable, the start of labor is usually difficult and long, cesarean rate increases. This can lead to poor obstetric outcomes for both mother and baby [2]. By adjusting the cervix, the time from the beginning of induction to the time of birth is shortened and the need for caesarean section is reduced [3]. Various mechanical and medical methods are used to mature the cervix in term pregnancies. Medical methods; prostaglandins and relaxation, mechanical methods include finger enlargement, removal of fetal membranes and balloon catheterization [4]. Prostaglandin preparations are generally accepted for the preparation of a cervix not suitable for induction. There are different prostaglandin preparations used for this purpose. A locally administered dinoprostone formulation, PROPESS vaginal insert; cervical ripening was approved in 1995 for use. It is used to initiate cervical ripening in patients with a Bishop score of 6 or less in the absence of fetal and maternal contraindications, in the presence of a singleton cephalic condition [5].

Cervical ripening is a gradual process. Dinoprostone requires several hours of exposure. Prolonged cervical ripening times for pregnant women who require labor induction in the hospital may be a psychological distress [6]. Patients should be monitored for fetal wellbeing and uterine contractions until cervical ripening is achieved and the patient enters the travail. For this reason, it often takes more than 12 hours for hospitalized patients. Long hospitalization is not desirable as far as patients are concerned in terms of health personnel and health care institutions [7].

Propess is a drug of choice in our daily practice due to its consistently low doses of dinoprostone, controlled release, withdrawal system, which allows the end of the 12-hour dosing period or the termination of prostaglandin release during active labor [7]. Although it is a frequently used drug, studies have not yet been found in the literature on the most appropriate timing of propess administration. Chronotherapy involves the administration of medication in coordination with the body's circadian rhythms to maximize therapeutic effectiveness [8]. The dosing plan of the drugs can be idealized by arranging them according to the chronobiological model. The safety and efficacy of the drug can be brought to the peak by coordinating with the circadian rhythm [9].

The first use of chronotherapy in practice was introduced in the 1960s when morning ingestion of corticosteroid medication was adopted to reduce its adverse effects [10]. For this purpose they made a rapid release tablet formulation accompanying the cortisol release from the circulation by the adrenal cortex [11].

The aim of this study is to investigate the "time of administration" suggestions on chronotherapy for propess.

Materials and methods

Our study was conducted retrospectively by examining the records of pregnant women who were given propess at Zekai Tahir Burak Women's Health Training and Research Hospital between 2008 and 2018. Ethical committee approval was obtained in our work. A total of 3987 patient files were scanned. A total of 2694 patients were included in the study. Demographic information and antenatal information of the patients were obtained from the patient files. All patients were singleton pregnancies with occipital presentation, no vaginal delivery contraindication. Patients were between 37 and 42 weeks of gestation. All patients had a Bishop score below 5. The Bishop Score (also known as Pelvic Score) is the most commonly used method to rate the readiness of the cervix for induction of labor. The Bishop Score gives points to 5 measurements of the pelvic examination dilation, effacement of the cervix, station of the fetus, consistency of the cervix, and position of the cervix. If the Bishop score is 6 or less the chances of having a vaginal delivery are low and the cervix is said to be unfavorable or "unripe" for induction. Preterm cases, patients with additional disease (as; diabetes, thyroid disease, systemic infection) and patients with missing data were not included. Patients who underwent epidural anesthesia were also excluded. Time of drug administration and birth times of patients were recorded. The time from application to birth was calculated. Two groups were allocated according to the time of drug administration. First group; in the morning, the second group consisted of evening drug applications. Patients with caesarean section were not included in the calculation. Primer outcome measures were the time from drug administration to labor and vaginal birth rate; seconder outcomes were cesarean section birth rate, cesarean section indications, need for oxytocin, neonatal intensive care need and low APGAR score.

Statistical analysis

All data were analyzed by statistics software SPSS 19.0. Results were given as mean ± SD or percentage, time intervals were analyzed with ANOVA test, other data were analyzed with Chi-square test for qualitative and U Mann-Whitney test for quantitative variables. Logistic regression analysis was performed for risk factors effective on delivery time. All tests were two-sided, $p<0.05$ was considered statistically significant.

Results

Between 2008 and 2018, 134644 patients were delivered in our hospital. 3987 of these patients were administered propess for induction of labor. Of these patients, 287 were due to preterm, 177 due to additional disease, 246 due to epidural anesthesia and 583 were not included in the study because their records were not fully accessible. A total of 2694 patients who were able to access the data were included (Figure 1). Patients were divided into two groups according to daytime application time. First group; in the morning: 1548 (57.5%), the second group consisted of evening: 1146 (42.5%) drug applications.

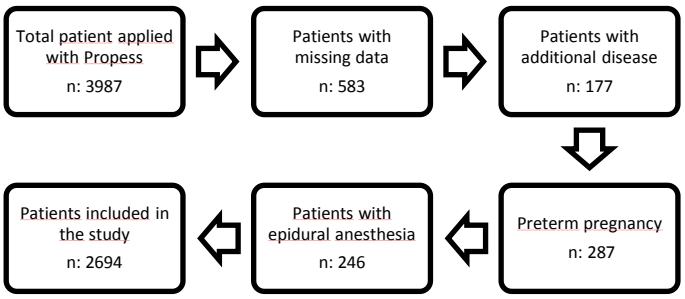

Figure 1: Patient selection flow chart

Of the patients participating in the study, 510 (18.9%) were multigravid and 2184 (81.1%) were primigravid. The ages of the patients ranged from 18 to 42 years. Pregnancy weeks were between 37 and 42 weeks. The BMI of the patients ranged from 22.6 to 34.2. The time from drug administration to labor ranged from 8 to 42 hours. The birth weight of the babies was between 2500 and 4450. Age, BMI, parity, gestational week were statistically similar in both groups. Oxytocin requirement was lower in the first group than in the second group (22.2% versus 30.6%). There was no difference between the two groups in terms of neonatal intensive care need and low Apgar score (Table 1).

A total of 262 patients were caesarean sections. Indications were as follows; 114 (43.5%) cefalopelvic disproportion, 98 (37.4%) fetal distress, 38 (14.5%) non progressive action, 7 (2.7%) placenta ablation, and 5 (1.9%) was caesarean section due to uterine rupture. There was no difference between groups in terms of cesarean rates and indications (Table 2).

Logistic regression analysis were performed for risk factors and we found that the time of drug administration was effective on duration to labor. The time from drug administration to labor was18.0±4.0 hours in the morning group and 19.1±3.9 hours in the evening group (p<0.001) (Table 3).

Table 1: Demographic and clinical characteristics of the subjects

Variables	Morning (n:1548)	Evening (n:1176)	p value
Age(yrs)	27.0±6.1	26.9±6.2	0.387*
BMI (kg/m2)	27.5±3.0	27.7±3.4	0.311
Primipar	1245(80.4%)	939(81.9%)	0.322¶
Birthweight(gr)	3293±319	3273±344	0.163*
Gestationalage (wks)	39.8±1.3	39.9±1.2	0.084*
Delivery route			0.075¶
Vaginal	1411(91.1%)	1021(89.1%)	
C-section	137(8.9%)	125(10.9%)	
Delivery time (hrs)	18.0±4.0	19.1±3.9	<0.001*
Oxytocin	344 (22.2%)	351(30.6%)	<0.001¶
Nicuadmission	57(3.7%)	44(3.8%)	0.832¶
5th minuteApgar<7	62(4.0%)	57(5.0%)	0.226¶

Mean ± standard deviation and number (percentage).*Mann Whitney-U test, ¶ Chisquare test. A p value<0.05 is considered statistically significant

Table 2: Comparison of the group saccording to the delivery route

Variables	C-section (n:262)	Vaginal birth (n:2434)	p value
Age(yrs)	33.2±7.0	26.3±5.6	<0.001*
Primipar	211(80.5%)	1973(81.1%)	0.816¶
Birthweight(gr)	3363±416	3276±318	<0.001*
Gestationalage (wks)	39.8±1.3	39.9±1.3	0.506*
Day time			0.075
Morning	137(52.3%)	1411(58%)	
Evening	125(47.7%)	1021(42%)	
Delivery time (hrs)	19.3±4.0	18.4±4.0	0.001*
Oxytocin	61(23.3%)	634 (26.1%)	0.327¶
Nicuadmission	21(8.1)	80(3.3%)	<0.001¶
5th minuteApgar<7	29(11.1%)	90(3.7%)	<0.001¶

Mean ± standard deviation and number (percentage).*Mann Whitney-U test, ¶ Chisquare test. A p value<0.05 is considered statistically significant.

Table 3: Multivariate logistic regression analysis of risk factors effective on delivery time

Variable	Wald	p value	Odds ratio	95% CI
Daytime	-0.124	<0.001	-1.004	-1.299-0.710
Parity	-0.266	<0.001	-2.709	-3.154-2.265
Oxytocin	-0.017	0.370	-0.153	-0.486-0.181
Gestationalweek	-0.004	0.828	-0.013	-0.126-0.101
Birthweight	-0.018	0.341	0.000	-0.001-0.000
Age	0.036	0.098	0.023	-0.004-0.051
BMI	-0.011	0.629	-0.013	-0.068-0.041

BMI: body mass index, CI: confidence interval. A p value<0.05 is considered as statistically significant

Discussion

The main objective of obstetrics is to provide a healthy fetal birth with minimal trauma to the mother. Sometimes it may be necessary to terminate the pregnancy because of maternal or fetal reasons [12]. Although induction of labor is necessary for a variety of obstetric and medical reasons, inability to cervical ripeness is often a negative factor affecting the success of labor induction [13]. Many agents are used to prepare the cervix for breeding and for inducing uterine changes that can respond to induction with oxytocin. Among these agents, prostaglandin analogs have an important place [14].

The use of prostaglandin E2 (dinoprostone) increases the likelihood of successful induction, reduces the incidence of prolonged labor and reduces maximum oxytocin doses. Propess; is the drug of choice in our daily practice due to its ability to provide continuous low dose dinoprostone, controlled release, withdrawal system that allows it to stop prostaglandin release at the end of the 12-hour dosing period or during active labor [15].

Various investigations have been made to keep the drug activity and bioavailability at the optimum level. As a result of the chronotherapy, the safety and efficacy of the drug can be brought to the peak by coordinating with the circadian rhythm. The first use of chronotherapy in practice was introduced in the 1960s when morning ingestion of corticosteroid medication was adopted to reduce its adverse effects. For this purpose they made a rapid release tablet formulation accompanying the cortisol release from the circulation by the adrenal cortex [10].

At the beginning of a normal term birth, the function of the hormones is great. This process provides the fetus fundamentally through the placenta, fetal membranes and the endocrine system of the mother. In the case of chronic stress, the hypothalamic axle is stimulated and pathological corticotropin releasing hormone (CRH) begins to be released. Pathological CRH stimulates uterine contractions and causes birth to start [16]. CRH plays the most basic role in determining the duration of pregnancy or the time of birth in term or preterm labor. The increase in levels of cortisol released from the adrenal glands causes an increase in placental oxytocin, Prostaglandin E2, Prostaglandin F2 and placental CRH. Following these changes, contraction of the uterus and maturation of the cervix are ensured. As a result of all this, labor starts [17].

In this study we found that the time from drug administration to labor were 18.0±4.0 hours in the morning group and 19.1±3.9 hours in the evening group. This situation looks like the time of drug administration was effective on duration to labor. A few hours' difference in time of delivery due to high cortisol levels in the morning. Starting induction of labor while high cortisol levels may be causing the shortening of the labor until birth.

Conclusion

Drugs used for labor induction in the morning may increase drug efficacy and bioavailability. At this point birth becomes compatible with body biorhythm and the time to labor can be shortened.

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