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Inhibitory effects of isradipine on uterine contractions in pregnant rats

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Abstract

Objective: To investigate the effects of isradipine, which is a calcium channel blocker, on late pregnant rats' myometrium under in vitro conditions.

Methods: Stripes were obtained from the myometriums of pregnant rats which were decapitated on the 18 days of gestation. The effects of isradipine on myometrium were investigated in four groups and four cumulative doses: 1 ng/ml, 10 ng/ml, 0.1 µg/ml, 1 µg/ml. Group 1: spontaneous myometrial contractions, Group II: myometrial contractions induced by oxytocin, Group III: myometrial contractions induced by prostaglandin, Group IV: myometrial contractions induced by oxytocin in calcium-free medium. Wilcoxon signed ranks test was used for the statistical analysis and $p<0.05$ was considered statistically significant.

Results: Group 1: compared to the control group, 10 ng/mL and 0.1 µg/mL isradipine decreased the amplitude of uterine contractions. Group II: 0.1 µg/mL isradipine decreased the frequency of contractions ($p=0.02$). Isradipine decreased the amplitudes of contractions in the doses of 10 ng/mL and 0.1 µg/mL ($p=0.02$ for each dose). Group III: 0.1 µg/mL isradipine decreased the frequency of contractions ($p=0.02$). Isradipine decreased the amplitudes of contractions in the doses of 10 ng/mL and 0.1 µg/mL ($p=0.02$ for each dose). One µg/mL isradipine completely removed all spontaneous and induced contractions. Group IV: when compared to mediums with calcium, both amplitudes and frequencies of the contractions were found lower in this group ($p<0.001$). Isradipine was only used in the dose of 1 µg/mL and it completely removed all contractions.

Conclusion: Isradipine inhibits in vitro myometrial contractions in late pregnant rats and it may be effective in preventing early labor.

Keywords: Early labor, tocolytic, calcium channel blocker, isradipine, prostaglandin, rat.

Özet: Gebe ratlarda isradipinin uterus kontraksiyonları üzerine inhibitör etkileri

Amaç: Kalsiyum kanal blokörü olan isradipinin geç gebe rat miyometriyumu üzerindeki etkilerini in vitro koşullarda araştırmaktır.

Yöntem: Gebeliğin 18. gününde dekapite edilen gebe ratların miyometriumlarından şeritler elde edildi. İsradipinin miyometrium üzerindeki etkileri dört grupta ve dört kümülatif dozda araştırıldı; 1 ng/ml, 10 ng/ml, 0.1 µg /ml, 1 µg /ml. Grup 1: Spontan, Grup II: Oksitosinle indüklenmiş, Grup III: Prostaglandin ile indüklenmiş, Grup IV: Kalsiyumsuz ortamda oksitosinle indüklenmiş miyometrial kontraksiyonlar. İstatistiksel analiz için Wilcoxon *signed ranks* testi kullanıldı ve $p<0.05$ istatistiksel olarak anlamlı kabul edildi.

Bulgular: Grup 1: Kontrol grubu ile karşılaştırıldığında 10 ng/mL ve 0.1 µg/mL isradipin, uterus kontraksiyonlarının amplitüdünü azalttı. Grup II: 0.1 µg/mL isradipin, kontraksiyonların frekansını azalttı ($p=0.02$). İsradipin 10 ng/mL ve 0.1 µg/mL dozlarda kontraksiyonların amplitüdlerini azalttı (her iki doz için $p=0.02$). Grup III: 0.1 µg/mL isradipin, kontraksiyonların frekansını azalttı ($p=0.02$). İsradipin 10 ng/mL ve 0.1 µg/mL dozlarda kontraksiyonların amplitüdlerini azalttı (her iki doz için $p=0.02$). İsradipin 1 µg/mL tüm spontan ve indüklenmiş kontraksiyonları tamamen ortadan kaldırdı. Grup IV: Kalsiyum bulunan ortamlarla karşılaştırıldığında bu grupta kontraksiyonların hem amplitüdleri hem de frekansları daha düşük bulundu ($p<0.001$). İsradipin sadece 1 µg/mL dozunda kullanıldı ve kontraksiyonları tamamen ortadan kaldırdı.

Sonuç: İsradipin, geç gebe ratlarda miyometrial kontraksiyonları in vitro inhibe etmektedir ve erken doğumun önlenmesinde etkili olabilir.

Anahtar sözcükler: Erken doğum, tokolitik, kalsiyum kanal blokörü, isradipin, prostaglandin, rat.

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Introduction

Early labor is the most significant reason of neonatal mortality and morbidity in the world. Although significant improvements have been made in understanding the uterine physiology and developing new agents to prevent early labor, the incidence of early labor has been at the same level.[1,2] More than half of the early labors occur either due to spontaneous contractions or early rupture of membrane. It is reported that about 75% of neonatal deaths and 50% of childhood neurological problems are associated with early labor.[3]

Today, there are various agents used as tocolytic. Magnesium sulphate, prostaglandin synthesis inhibitors (i.e. indomethacin), nitric oxide or donors (i.e. nitroglycerine), atosiban as the oxytocin antagonist and calcium channel blockers (i.e. nifedipine, nicardipine) are used as tocolytic.[4–8]

Calcium channel blockers are used quite commonly as tocolytic. In cases under early labor risk which use calcium channel blocker as tocolytic, it has been reported that less cases delivered within 7 days and under 34 weeks, the requirement to discontinue medication was less frequent, and less respiratory distress syndrome, necrotizing enterocolitis, intraventricular bleeding and jaundice were observed.[9] Despite the activities of calcium channel blockers stated above, most effective and safest doses of these medications have not been found yet. As an addition, it was reported that nifedipine and nicardipine have serious adverse effects such as pulmonary edema.[10,11] Under these conditions, new studies have been carried out to understand the most effective and safest doses of these medications and to investigate possible effects of new calcium channel blockers on the contractions of uterine myometriums.[8,12,13]

Isradipine is one of the calcium channel blockers. There are some studies on the effects of this medication on myometrium.[14,15] However, current methods are not strong enough to draw a conclusion about the effects of isradipine on myometrium and the suitability of using as a tocolytic. Under current information, this study was planned to investigate the effects of isradipine on the myometrium contractions in pregnant rats.

Methods

Experimental Animals, Tissue Preparation and Experiment Models

Approval from Local Ethics Committee of Fırat University was obtained. For the experiments, female Wistar rats (220–240 g) supplied by Biomedical Researches Unit of Fırat University were used. All of the experiments were carried out in the Physiology Laboratory of Faculty of Medicine, Fırat University. The animals were kept under controlled temperature (22±1 °C) and light (lightning between 07:00 and 19:00) conditions. Food and water were provided as ad libitum. Daily vaginal smear test was carried out on animals and rats at pro-oestrus period were kept with sexually active and experienced male rats in the nights of such days. Vaginal smear test was carried out in the next day again and the day found sperm in the smear was considered as the day zero (the inception). All rats were decapitated on the 18 days of gestation. Four myometrial strips (1 mm in thickness, 2 mm in width and 12 mm in length each) were taken from each animal.

Four groups were established to test the effect of increasing doses of isradipine. Obtained muscle strips were put in organ bath filled with Krebs solution. Organ bath was aired regularly with 95% O_2 – 5% CO_2 mixture at 37 °C. The strips were attached to a fixed metal hook on the bottom and to an symmetric force displacement transducer (MAY; Commat Ltd., Ankara, Turkey) on the top. The signals coming from the transducer were amplified by an interface (MAY; Commat Ltd., Ankara, Turkey) and the data obtained were uploaded to a computer. For recording isometric tension, the strips were kept in balance for 30 minutes in 1 g resting tension. After spontaneous contractions occurred, myometrial contractions were induced either by oxytocin (10 mU/ml bath solution) or prostaglandin PGF2α, or they were just recorded as spontaneous contractions.

The effects of isradipine in increasing concentrations on myometrial contractions were investigated. Ten minutes before medication (predrug: spontaneous, preinduction by oxytocin and PGF2α) were recorded as control for each strip. Amplitudes and frequencies of contractions (number of contractions observed within 10 minutes) were recorded both before applying isradipine and in increasing doses (1 ng/mL, 10 ng/mL, 0.1 µg/mL and 1 µg/mL) every 10 minutes for each dose. Further experiments were carried out to investigate the effects of isradipine on contractions induced by oxytocin in calcium-free mediums. For that purpose, single dose (1 µg/ml) isradipine was tested on contractions induced by oxytocin in calcium-free Krebs solution. Data were recorded and analyzed by computer software (Biopac System Inc, Goleta, CA, USA).

Experiments

The experiments were planned and carried out as 4 groups. Four different strips taken from a rat were used as 4 different groups.

Group I: The contraction period for the first 10 minutes was recorded as the control of each strip. Immediately after this control period, isradipine (Dynacirc SRO; Novartis, Istanbul, Turkey) was added cumulatively in 1 ng/mL, 10 ng/mL, 0.1 µg/mL and 1 µg/mL concentrations, respectively, as with 10-minute durations for each dose. Amplitudes and frequencies of contractions and the area under the curve were recorded both before the application of isradipine at different doses between 1 ng/ml and 1 µg/ml and every 10 minutes for each dose. The records were stopped 10 minutes after the application of the last dose.

Group II: In this group, it was waited until all spontaneous contractions stopped in myometrial strips. After spontaneous contractions stopped, the contractions were induced by adding approximately 0.0004 IU/mL oxytocin (Synpitan Forte; Deva Holding A.Ş., Istanbul, Turkey). Contractions induced by oxytocin were recorded as control. Immediately after this 10-minute control period, isradipine was added to the medium as indicated in the Group I above.

Group III: Just after spontaneous contractions disappeared, 1 µM d-cloprostenol (Dalmazin; Vetaş, Istanbul, Turkey) which is a synthetic PGF2α was added to the medium. The contraction induced by PGF2α was recorded as control for 10 minutes. After this control record, isradipine was added to the medium as indicated in the Group I above, and contractions were recorded.

Group IV: This group was created to find the amplitudes and frequencies of myometrial contractions in calcium-free medium and to test the effects of oxytocin and oxytocin+isradipine combination on these strips. In this group, the effects of isradipine on contractions induced by oxytocin in calcium-free medium were investigated. Before myometrial strips were placed, calcium-free Krebs solution was added to the medium and a calcium-free medium was obtained. In calcium-free medium, a single dose (1 µg/ml) of isradipine was added on contractions induced by oxytocin. Since spontaneous contractions disappeared after a few contractions, oxytocin (0.0004 IU/mL) was added to the medium as soon as contractions disappeared. Isradipine was added once in the dose of 1 µg/mL after contractions induced by oxytocin were recorded for 5 minutes. The record was ended at 15th minute of applying isradipine.

Statistical Analysis

All the data was presented as mean±standard error (M±SE). Non-parametric Wilcoxon signed ranks test was used for the analysis of the data. All statistical analyses of the data were done by using SPSS software, version 13.0 (SPSS, Inc., Chicago, IL, USA). A p-value <0.05 was considered as significant.

Results

Group I: The frequency of spontaneous contractions was calculated as 11.2±0.6/10 minutes. This value was measured as 11.0±0.6/10 minutes after 1 ng/mL isradipine was added and when contraction frequency was compared to the control group, the difference was not significant (p=0.317). After 10 ng/mL and 0.1 µg isradipine was added, the contraction frequency was measured as 10.7±0.5/10 and 6.3±2.0/10 minutes, respectively; these values was also not different than the control group (p=0.180 and p=0.68, respectively). By adding 1 µg isradipine, the spontaneous contractions disappeared completely (**Figs. 1a** and **b**).

In this group, mean amplitude of control contractions was measured as 3416.3±560.3 mg. When isradipine was added in the dose of 1 ng/mL, this value was measured as 3281.5±494.3 mg and statistically no significant difference was found between these values (p=0.08). Adding 10 ng/mL and 0.1 µg isradipine caused a statistical significant decrease in the contractions (2834.8±324.2 mg and 1188.8±271.7 mg, respectively) (p=0.02 for both). Adding isradipine in the dose of 1 µg/mL caused spontaneous contractions disappear completely (**Figs. 1a** and **c**).

Group II: After oxytocin application, the frequency of contractions was measured as 14.3±0.3/10 minutes. Adding isradipine in the doses of 1 ng/mL and 10 ng/mL did not cause any significant change in contraction frequencies (14.3±0.3/10 and 13.3±1/10 minutes, respectively; p=1 and p=0.1). While isradipine in the dose of 0.1 µg/mL caused statistically a significant decrease to 1.50±1.50/10 minutes in the contraction frequency (p=0.02), isradipine in the dose of 1 µg/mL caused oxytocin-induced contractions to disappear completely (**Figs. 2a** and **b**).

Mean contraction amplitude in the control group was calculated as 2892.3±165.7 mg. By adding 1 ng/mL isradipine, this value reached 2894.7±176.0 mg and the difference was statistically not significant (p<0.05). By adding 10 ng/mL and 0.1 µg/mL isradipine, amplitude decreased to 2168.5±100.0 mg and 100.3±100.3 mg, respectively, and when these values were compared to the control group, the difference was statistically significant (p=0.02 for both). One µg/mL isradipine caused spontaneous contractions to disappear completely (**Figs. 2a** and **c**).

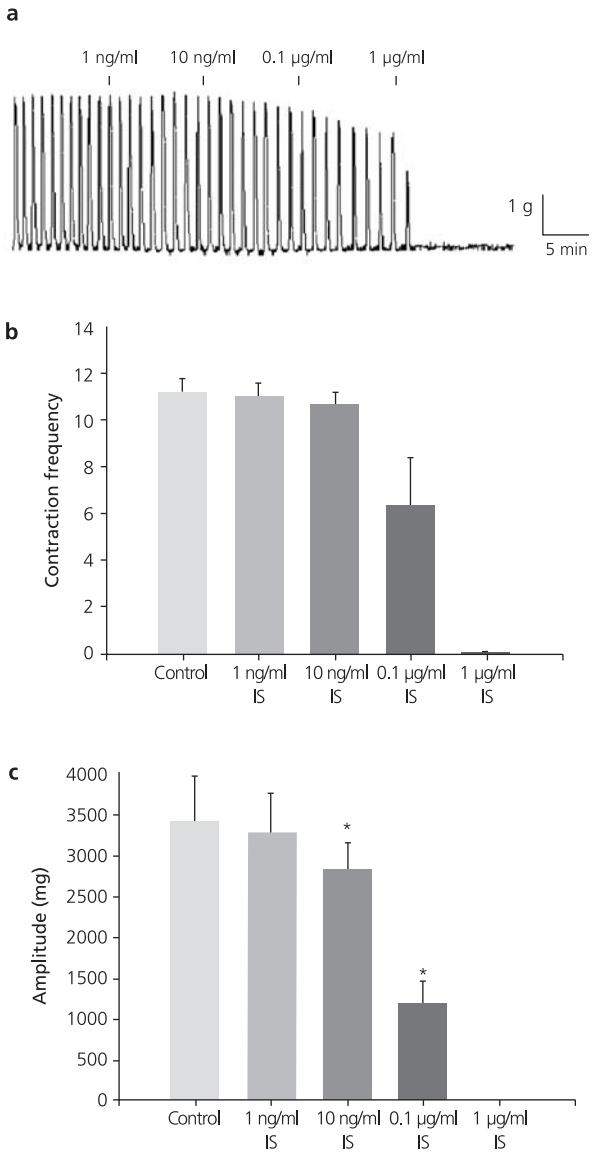

Fig. 1. The effects of isradipine (**IS**) with increasing concentrations on spontaneous myometrial contractions in late pregnant rats. Isradipine's (**a**) peak frequency (number of contractions observed within 10 minutes), (**b**) peak amplitude level, (**c**) effects on spontaneous contractions. *p<0.05 when compared to the control group, Wilcoxon signed ranks test.

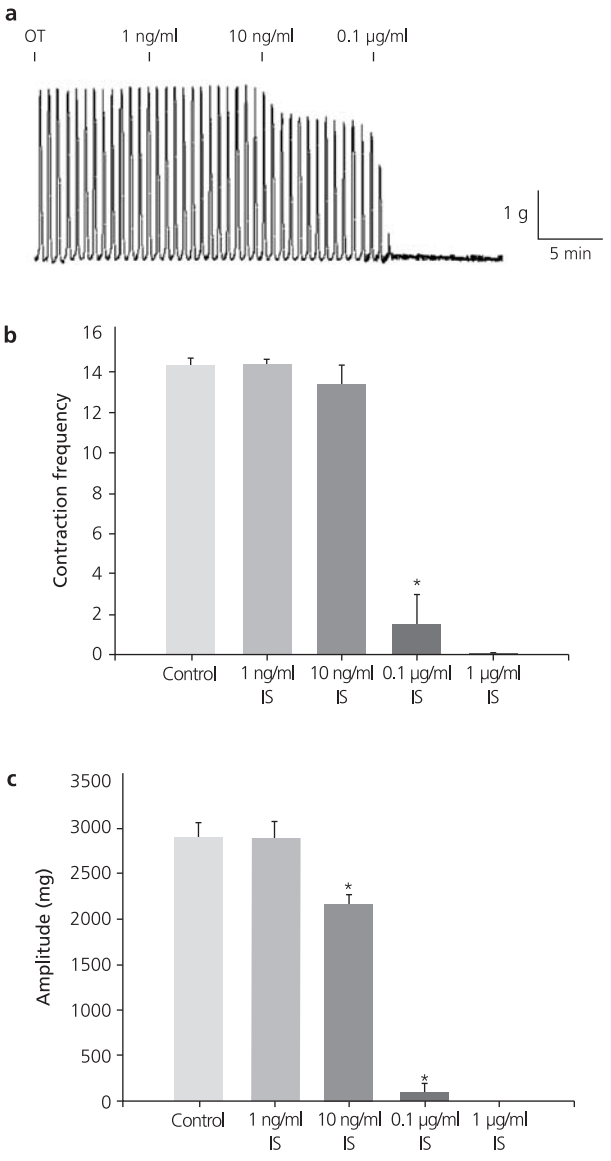

Fig. 2. The effects of isradipine (**IS**) with increasing concentrations on myometrial contractions induced by oxytocin in late pregnant rats. Isradipine's (**a**) peak frequency (number of contractions observed within 10 minutes), (**b**) peak amplitude level, (**c**) effects on oxytocin-induced contractions. *p<0.05 when compared to the control group, Wilcoxon signed ranks test. **OT:** oxytocin.

Group III: In the control group induced by PGF2α, mean contraction frequency was calculated as 12.7±0.3/10 minutes. Adding isradipine in the doses of 1 ng/mL and 10 ng/mL did not cause any significant decrease in contraction frequencies (12.7±0.3/10 and 11.7±0.8/10 minutes, respectively; p=1 and p=0.1). Isradipine in the dose of 0.1 µg/mL caused a significant decrease in the frequency of contractions (5.2±1.7/10 minutes, p=0.02). The contractions induced by PGF2α disappeared completely by adding 1 µg/mL isradipine (**Figs. 3a** and **b**).

In the control group induced by PGF2α, mean amplitude of the contractions was calculated as 2787.2±471.9 mg. Adding 1 ng/mL isradipine did not cause a significant decrease in the amplitude of contractions (2756.2±469.3 mg, p=0.08). Isradipine in the doses of 10 ng/mL and 0.1 µg/mL decreased the amplitudes of the contractions to 2474.8±535.7 and 695.7±306.1 mg, and the decrease was considered statistically significant compared to the control group (p=0.02 for both). The contractions induced by PGF2α disappeared completely by adding 1 µg/mL isradipine (**Figs. 3a** and **c**).

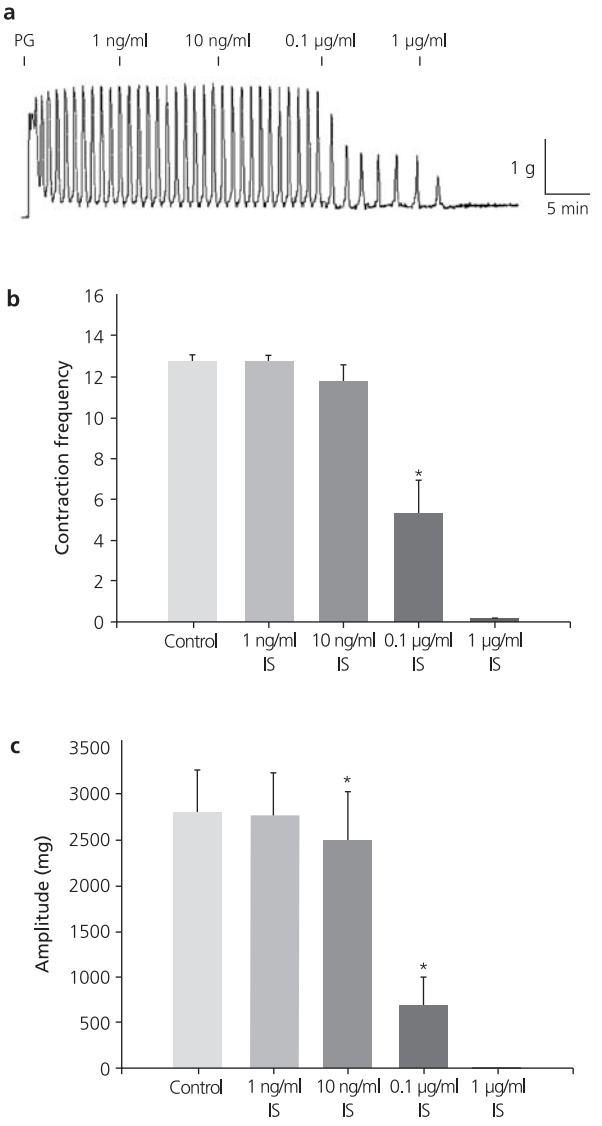

Fig. 3. The effects of isradipine (**IS**) with increasing concentrations on myometrial contractions induced by prostaglandin (**PG**) F2α in late pregnant rats. Isradipine's (**a**) peak frequency (number of contractions observed within 10 minutes), (**b**) peak amplitude level, (**c**) effects on contractions induced by PGF2α. *p<0.05 when compared to the control group, Wilcoxon signed ranks test.

Group IV: In this group, contraction experiments carried out in calcium-free Krebs solution. It was observed that the contractions induced by oxytocin in the calcium-free medium continued at least for 30 minutes (records were not presented). After the contractions were induced by oxytocin, 1 µg/mL isradipine was added to the medium (at the 7th minute of oxytocin addition). By adding isradipine, all contractions disappeared (**Fig. 4**). Since the contractions did not continue as in the mediums including calcium, cumulative doses of isradipine were not applied in this group.

Discussion

Spontaneous preterm contractions are observed more frequently in multiple pregnancies and polyhydramnios cases. It is considered that extreme stress of uterine triggers the myometrial contractions. In vitro stud-

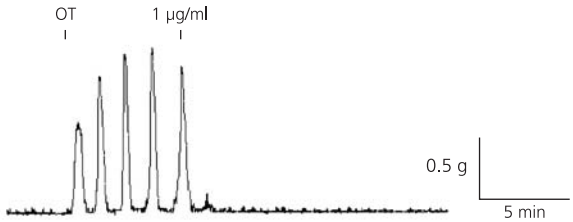

Fig. 4. The effects of isradipine in the dose of 1 µg/mL on oxytocin-induced contractions in myometrium strips of late pregnant rats within calcium-free medium. **OT:** oxytocin.

ies show that the stress of myometrial strips may also induce contractions similar to the extreme stress of uterine. It was reported that myometrial stress increased activator proteins (AP-1), connexin-26 and connexin-43 expressions, and decreased membrane potential.[16,17] The distinct result of this stress is the increase in intracellular calcium ion concentration and in the stimulability of myometrium.

In the current study, it was observed that isradipine inhibited the spontaneous myometrial contractions in myometrium of late pregnant rats depending on the dose. This observation seems consistent with the recommendations of Kantas et al.[18] It is considered that isradipine inhibits myometrium contractions by inhibiting L-type calcium channels, decreasing calcium release from intracellular repositories and facilitating intracellular calcium to move into extracellular area.[19,20]

Although it has been shown that isradipine inhibited myometrial contractions effectively in vitro, there is no study carried on pregnant women except the study presented by Wide-Swensson et al.[21] In this study, isradipine was used during the active phase of delivery and no inhibitory activity on uterine contractions was reported. We think that the active phase of delivery is resistant relatively to tocolytic agents and isradipine requires further studies to investigate its potential tocolytic effect.

It was observed in Group II of the study that isradipine inhibited oxytocin-induced myometrial contractions dose-dependently and removed completely in the highest dose. Çetin et al. reported that isradipine inhibited myometrial contractions in rat myometrium in vitro.[22] While it was observed in our study that isradipine removed contractions completely, this effect was not seen in the study of Çetin et al. It was thought that the highest dose used in this study was not strong enough to remove the contractions completely. The highest dose used in this study was 10^{-4} mol/L, and it was lower than the dose we used in our study.

It is known that oxytocin activates inositol triphosphate pathway by connecting to its own receptor to release calcium from intracellular repositories and hydrolyzes membrane phospholipids. Calcium release from intracellular repositories causes an increase in the calcium flow towards cytosol.[23] It is also known that oxytocin causes the depolarization of membranes by opening activated cation channels.[24] In this way, the use of isradipine inhibits calcium entrance into intracellular distance and calcium release from intracellular repository as in L-type calcium channel blockers[19,20] and therefore inhibits myometrium contractions induced by oxytocin.

In this study, it was shown for the first time that isradipine inhibits PGF2α-induced myometrial contractions in vitro. This is the first study investigating the effects of isradipine on PGF2α-induced myometrial contractions. Also, inhibitory effect of isradipine is dose-dependent and the highest dose caused PGF2α-induced myometrial contractions to disappear completely. Prostaglandins have a critical role in the inflammatory process of labor. Their effects were shown not only on myometrium but also on cervix and fetal membranes. They display their effects by increasing the number of gap-junctions between myocytes, the number of oxytocin receptors and by connecting to their own receptors.[25] Infections being the reason of 30–40% of early labors[26] and showing the distinct role of infections in early labor and suppression of PGF2α-induced myometrial contractions by isradipine make us think that isradipine may have an effect on the treatment of early labor.

Myometrial contractions in calcium-free medium had lower amplitude and frequency rates than those in the mediums with calcium. Isradipine in the dose of 1 μg/mL removed all myometrial contractions in calcium-free medium. This finding may indicate that our results are consistent with the study of Kaya et al.[27] and that isradipine in calcium-free medium displays activity by inhibiting calcium release from intracellular repositories.

Conclusion

In conclusion, the findings of this study show that in vitro isradipine inhibits dose-dependently the myometrial contractions occurring spontaneously, induced by oxytocin and induced by PGF2α. The results indicate that isradipine may have a tocolytic effect in spontaneous and infection-associated early labor cases. Further studies are required to establish the activity and safety of the medication.

Conflicts of Interest: No conflicts declared.

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