

PRELIMINARY REPORT

Reduction in the Cesarean Section Rate in Nulliparous Patients After Administration of Intravenous Propranolol

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Objective. A preliminary investigation to test the efficacy of intravenous propranolol in reducing the cesarean section rate in nulliparas in active labor and evaluate its effect on neonatal and maternal outcomes.

Methods. Fifty seven nulliparous patients admitted in active labor were randomly divided into two groups: a control group consisting of 23 patients, and a treatment group consisting of 34 patients given 2 mg of propranolol intravenously every 4 hours until delivery. Total length of labor, time from first administration of medication to delivery, incidence of cesarean section, APGAR scores, maternal and fetal morbidity were assessed.

Results. A total of 4 cesarean sections were performed in each group (11.7% in the treatment group and 17.3% in the control group). The rate of cesarean section due to dystocia was 6.25 and 13.6% respectively ($P = .367$). Statistical significance was not

reached due to the small number of subjects (students t test analysis). There was no increase in the incidence of low APGAR scores, intensive care unit admissions, abnormal heart rate patterns during labor, cesarean sections for fetal distress or maternal morbidity in the treated group.

Conclusions. Intravenous administration of 2 mg of propranolol every four hours is safe and not associated to increased neonatal or maternal morbidity. A 50% decrease in the incidence of cesarean sections can be documented among nulliparous patients treated with propranolol although the small numbers and overall low incidence of cesarean section in our population (14%) did not permit these differences to reach statistical significance.

Key words: Propranolol, Dystocia, Cesarean section, Dysfunctional labor

Primates, unlike many other species, give birth in a relatively unprotected environment and during labor, the mother might have to escape from predators. In order to minimize the loss of both newborn and mother under such circumstances, nature has endowed primates with rich beta-adrenergic receptors in the myometrium. This enables them to halt uterine activity, at least of the kind that leads to the expulsion of the fetus, whenever birth would endanger the mother or the newborn. The Rhesus monkeys in the University of Puerto Rico free ranging colony of Cayo Santiago, Puerto Rico,

have always timed birth at night. In the 39 year history of the colony, only one birth has been observed during the day by scientists studying primate behavior. We have never been able to see the Rhesus monkey giving birth in a cage. However, when the observer was absent, even for a brief period, upon his return birth had already occurred.

Although primitive man was less threatened by predators during labor and delivery than other primates, it is unlikely that such a basic property of uterine behavior, namely suppression of labor by the release of adrenaline, could have been lost. In this century, advantage of this concept was taken by the clinicians using epinephrine and epinephrine-like compounds as tocolytics. Specifically, beta-mimetics are the most common medication used in preterm labor prevention today. This concept is also behind the common practice of maternal sedation with narcotics during labor in order to reduce endogenous catecholamine output and "accelerate" or improve labor progression. It follows from the above well-established

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data that treatment with beta-blocking drugs could reduce the labor inhibition caused by endogenous catecholamines and therefore facilitate progression of labor. Barden and Stander (1) observed that intravenous infusion of propranolol improved uterine activity in intrapartum women at term with normal labor. This effect would be more evident in patients showing a high level of anxiety, young hypertensives or patients with a strong family history of hypertension.

In 1990 we reported that 63 patients scheduled for delivery by cesarean section because of failure of labor to progress in spite of stimulation by oxytocin achieved spontaneous vaginal delivery after intravenous administration of 1 mg of propranolol (2). The inclusion criteria required cervical dilatation of 3 or more cm and arrest of labor for two or more hours in the presence of oxytocin stimulation. Sanchez-Ramos and co-workers (3) have documented similar results in a randomized trial of women with dysfunctional labor using 2 mg of propranolol intravenously.

Because of the uniform and predictable response to propranolol of patients with arrest of labor in the absence of CPD or malpresentation, we decided that patients admitted for vaginal delivery could benefit from beta-adrenergic blockade during the intrapartum period. We proposed that the relatively high frequency of dysfunctional labor or prolonged labor of *homo sapiens* is due to the interfering effect of epinephrine upon the myometrium. Thus, all patients admitted for expected vaginal delivery, either in early labor, or active labor or admitted for induction of labor were offered propranolol 2 mg intravenously every 4 hours.

Materials and Methods

The study population consisted of 57 nulliparous patients admitted to the University of Puerto Rico University Hospital for labor and delivery between April and October 1998. Inclusion criteria included: 1) nulliparity, 2) no contraindications for vaginal delivery, 3) lack of contraindications for the use of propranolol (such as a history of bronchial asthma) and 4) willingness to participate in the study.

Subjects were assigned randomly to either a propranolol (n=34) or control group (n=23). Propranolol 2 mg was administered intravenously upon admission to the labor room after an initial period of observation revealed no evidence of abnormal fetal heart rate patterns. Recorded data included: 1) total time of labor as estimated by a history of regular uterine contractions, 2) time from administration of the first dose of propranolol to delivery, 3) incidence of cesarean sections for any reason (dystocia,

abnormal fetal heart rate patterns), 4) APGAR scores, 5) need for neonatal resuscitation or intensive care unit admission, and 6) maternal morbidity (excessive bleeding, complications arising from anesthesia).

All patients were surveyed during labor by electronic monitors and labor patterns were compared between the treated and control groups.

Statistical analysis was performed using a standard student's t test with a $P < .05$ considered statistically significant.

Results

During the study period, 57 subjects were enrolled based on willingness to participate in the study, presence of inclusion criteria and availability of investigators to be present during the complete labor and delivery period. Management of labor, administration of oxytocin and sedation were performed according to standard criteria provided by the American College of Obstetricians and Gynecologists (4).

Among the treatment group (n=34) a total of 4 cesarean sections were performed. In two of these, the indication for cesarean delivery was dystocia while in the other two, abnormal (non-reassuring) fetal heart rate patterns required surgical intervention. The overall cesarean section rate in this group was 11.7% and the cesarean section rate for dystocia was 6.25%. In the control group (n=23), 4 cesarean sections were performed (3 for dystocia and 1 for non-reassuring fetal heart rate patterns). The overall cesarean section incidence in this group was 17.4% and the cesarean section rate for dystocia was 13.6%. T test analysis of this data showed a P value of .367 (not statistically significant).

The total time of labor for the treatment group was 7.92 hrs (range 2.25 – 11.0 hrs) and 6 hrs in the control group (range 2.0 – 11.25 hrs). These differences were not statistically significant. The average time from administration of the first dose of propranolol to delivery was 2.5 hours (range 10 min to 5 hrs and 55 min). Analysis of recorded uterine contractions by electronic monitoring techniques showed no differences in the frequency or intensity of uterine contractions among the treated and control groups.

There were no cases of low APGAR scores, neonatal complications, postpartum bleeding or anesthesia-related morbidity in either group.

Discussion

Reflecting upon the abnormal environment in which *homo sapiens* labors and delivers, particularly after the

relocation of the birth from home to hospitals and the intensification of the surveillance techniques of the parturient and the fetus, it is surprising that no attention has been paid to the fact that the extraordinary long labor in man in comparison to other primates might be simply due to the reduced efficiency of uterine contractions brought about by the action of epinephrine.

The interest of the clinician in the duration of labor has been vanishing during the second half of this century. In the tenth edition of Williams, published in 1950, two pages are devoted to this subject (5). Mean duration of labor in primigravidas is given as 18 hours, including 1.75 hours to 2.00 hours of second stage, and 0.25 hours to 0.5 hours of third stage. The publication by Foederl (6) gives, for patients with normal a pelvis, and fetal weight not exceeding 3500g, a mean duration of labor for primigravidas of 14 hours, and multiparas of 8 hours. Busby (7), reviewing medical records of 14,775 Caucasian parturients at the Johns Hopkins Hospital found a mean duration of labor for primigravidas. of 15.4 hours, and a median of 10.6 hours. In contrast to the detailed examination of the subject of duration of labor in 1950, the 16th edition of Williams of 1980 has allocated only one sentence to the duration of labor (8). The attention is given only to the duration of the second stage of labor, (50 minutes in primigravidas and 20 minutes in multiparas). In the more recent literature like the 7th edition of Danforth (9) we find that emphasis is placed on the limits of normal labor (not more than 21 hours in primigravidas, and not more than 14 hours in multiparas) without much importance given to the mean.

Perhaps the interest in studying the normal duration of labor in man was lost because of the more aggressive attitude to the conduct of labor during the last decades. Stimulation of the uterus with oxytocin became popular, as became the induction of labor with prostaglandins. Concern about duration of labor was further attenuated by the acceptance of "failure of labor to progress" as a reasonable indications for termination of labor by cesarean section.

What had escaped the attention of the clinician is the extraordinary discrepancy between duration of labor in man compared to other primates. Another observation, which should have puzzled the clinician, is that duration of labor in primigravidas was as much as 5 to 6 hours longer than in multiparas. Considering the physical properties of the cervix of the multipara (greater wall thickness, and greater collagen content), the cervix of the multipara should be more difficult to dilate than that of the primigravida. It is evident that there was something wrong with the explanation regarding the compliance of the multiparas' cervix. It should have been noted already

from the publication by Harris in 1922 (10), in which he noted that some young (according to the standards of that time) primigravidas (16 to 19 years) sometimes completed the entire labor in a few hours. He could not provide an explanation why in other patients of the same age, labor lasted as long as 36 hours. Perhaps a contact between primatologists and clinicians would have enabled the obstetrician to explain these seemingly contradictory observations, and to recognize that the duration of labor in man has been extraordinarily prolonged by the endogenous release of epinephrine, which through stimulation of myometrial beta-adrenergic receptors attenuates uterine contractions.

We define labor as uterine contractions in which the post contraction length is shorter than the pre-contraction length. This distinguishes uterine contractions occurring in general from those of true labor. Surprisingly, such definition is missing in our textbooks, and even in the review articles dealing with uterine contractions during labor. Without a post contraction shortening, the uterine cavity will not diminish in size and the myometrium will not expel the uterine contents. Incomplete post-contraction relaxation of a contractile protein is a rare phenomenon, and it appears to exist only in the uterine musculature.

We are proposing that epinephrine (adrenaline) can affect the myometrium through two different mechanisms:

1. By attenuation or complete elimination of uterine contractions (as seen after the administration of tocolytic agents such as terbutaline).
2. By prevention of the post contraction shortening of the myometrial fiber leading to contractions which do not change the dilatation of the cervix, nor do they advance the presenting part of the fetus. Examples here are patients in the so-called "arrest of labor", during which the uterus continues to contract.

By blocking the beta-adrenergic receptors in the myometrium the clinician would have eliminated the interference brought about by epinephrine, to ensure that the myometrial activity would expel the uterine contents before the exhaustion of the myometrium.

Our first experience with beta-adrenergic blockade using propranolol (Inderal) 1 mg I.V. was obtained in 1990 when we decided to treat with I.V. propranolol those patients in arrested labor, refractory to oxytocin, and who had been scheduled for delivery by cesarean section for "failure of labor to progress". In our presentation to the Society of Gynecologic Investigation in 1991 (2), we reported that 67% of the patients, some of whom had been arrested for five hours, accomplished vaginal delivery after administration of 1 mg of propranolol I.V. To the

present day we continue the use of propranolol for dysfunctional labor with encouraging results. This lead us to consider routine use of propranolol in all our patients admitted in early labor, but particularly in primigravidas.

Since propranolol is not an oxytocic, but a substance that prevents the myometrial inhibition by epinephrine, neither the frequency nor the amplitude of uterine contractions should be altered by propranolol.

We have been able to evaluate 57 patients with intrapartum use of propranolol. All our initial impressions have been confirmed. The principal observations are:

- Propranolol does not increase uterine contractions or decrease the interval between the contractions as evidenced by similar patterns of uterine contractions recorded by electronic monitoring among treated and control subjects.
- The rapid progression in cervical dilatation, and in the descent of the fetus is due to an increase in post contraction shortening of the myometrial cell.
- Maximal shortening of labor is seen on patients in whom propranolol is administered shortly after onset of labor. Our documented shortest labor was in a primigravida age 16 in which the treatment to delivery interval was 10 minutes.
- There have been no cases of post-partum uterine atony and it is our impression that the normal intrapartum blood loss has been less. This, however, needs to be yet quantified.

Our data points to a 50% reduction in the incidence of cesarean section due to dystocia in nulliparas in active labor receiving propranolol on admission for labor and delivery at our institution. These results did not reach statistical significance mainly due to the small number of subjects in each group and the overall low incidence of cesarean sections in our population. Statistical analysis would have required at least 50 patients in each group in order to show a significant 50% reduction in the cesarean section rates. This preliminary study has prompted us to start a double-blinded, placebo controlled trial of propranolol in labor at our institution.

We are proposing that without the inhibitory effects of epinephrine on the uterine muscle, the expulsion of the uterine contents of a pregnancy at or near term should not require more than 30 to 50 contractions. Because of the rapidity in which labor can progress after propranolol we do not recommend that administration of propranolol I.V. before the obstetrician is present in the Labor Room. Since propranolol is not an oxytocic, there are no potential adverse events affecting the perfusion of the inter-villous space and hence the oxygenation of the fetus. If the patient is a candidate for vaginal delivery, we can not identify

any contraindication for routine use of propranolol to significantly reduce the duration of labor not only in primigravidas but also in multiparas.

Resumen

Se llevó a cabo este estudio preliminar con el propósito de determinar la eficacia de propranolol en reducir la incidencia de cesáreas. Cincuenta y siete nulíparas de parto fueron divididas en un grupo control (n=23) y de tratamiento (n=34) que recibió 2 mg de propranolol intravenoso cada 4 horas. Se evaluó la duración del parto, el intervalo desde la administración del medicamento al alumbramiento, la incidencia de cesáreas, los valores de Apgar y la morbilidad. Se efectuaron 4 cesáreas en cada grupo (11.7% en tratados, 17.3% en controles). La incidencia de cesáreas por distocia fue 6.25 y 13.6% respectivamente, (P=.367). No hubo aumento en valores de Apgar bajos, admisiones a la unidad de cuidado intensivo neonatal, patrones cardiacos anormales, cesáreas por angustia fetal o morbilidad materna. Concluimos que el uso de propranolol no se asocia a un aumento en la morbilidad materna o neonatal. La reducción de un 50% en la incidencia de cesáreas documentada no logró significado estadístico debido al número limitado de sujetos y la baja incidencia de cesáreas en nuestra población.

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