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Further study of the inhibition of premature labor by indomethacin Part II double-blind study

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1 Introduction

Premature delivery is an important obstetrical complication associated with increase perinatal mortality and morbidity. There is good evidence that prostaglandins play an important role in the pathogenesis of premature labor [14]. The non-steroid anti-inflammatory agent indomethacin, is a potent inhibitor of prostaglandin biosynthesis in the body and it is also an established fact that contractions may be inhibited by indomethacin [20]. In first part of the study we have shown in a very large uncontrolled group of patients the efficacy and safety of the drug in arresting premature labor, the same as others [4, 8, 25, 29].
The purpose of the second part of the study was to test in a controlled double-blind fashion the efficacy of indomethacin in suppressing the premature labor.

2 Material and methods

Patients included in the trial were between 25–35 weeks gestation who presented with painful, regular uterine contractions occurring at intervals of two or more contractions in 10 minutes, recorded for at least 30 minutes by external tocography, or contractions accompanied by effacement and/or dilation of the cervix at least 1–2 cm, but not more than 4 cm.
The patients were informed about the aim of the investigation. All patients have had ultrasonic examination before treatment. We excluded patients with pre-eclampsia, diabetes mellitus, twins, cardiac disease, antepartum hemorrhage, ruptured membranes, intra-uterine infections or intra-uterine growth retardation. Indomethacin or placebo were allocated at random. The code key was not available to the investigators before completion of the study. The indomethacin group included 18 patients and the placebo group also included 18 patients. After an initial registration of contractions for 30 minutes, indomethacin or placebo was begun. Treatment consisted of a rectal suppository of 100 mg and then capsules of 25 mg 4 times daily for 24 hours. If uterine contractions continued after the insertion of the first suppository, the patient received an additional 100 mg suppository (from the same envelope) after 1 hour, and then the treatment was continued orally. The total dosage of indomethacin was 200–300 mg in 24 hours. If there were further indications of premature delivery and progressive dilation of the cervix 2 hours after the first suppository, this was considered as a treatment failure and other therapy for cessation of premature labor was given. The uterine activity was recorded with a cardiotocograph.
The maternal heart rate, maternal blood pressure and fetal heart rate were recorded. During hospitalization, both the indomethacin and placebo treated patients were kept at bed rest. If they had no contractions after the completion of treatment during 3 days, they were discharged from the

Tab. I. Clinical data (mean ± SEM) of the patient pupulation of the indomethacin and placebo group.

	No. of patients	Maternal age (years)	Parity	Gestational age of at start of therapy (weeks)	Dilation (cm)	Effacement %
Indomethacin	18	26.1 ± 1.6	2.5 ± 0.5	30.3 ± 0.7	1.9 ± 0.19	38.8 ± 3.7
Placebo	18	27.1 ± 1.5	2.8 ± 0.4	30.7 ± 0.8	1.8 ± 0.18	40.5 ± 2.9

hospital. The treatment was considered successful if labor was arrested and delivery was delayed for more than 7 days. It was considered to be of moderate value if labor was arrested from 48 hours to 7 days, and considered unsuccessful if delivery took place within 48 hours. The criterion for prematurity was a birth age of less than 37 week gestation confirmed at delivery using the DUBOWITZ assessment scale [6]. The pediatrician examined each newborn immediately after delivery, during hospitalization and in follow up of 6 months. There was no significant difference between the 2 groups in respect to age, parity and gestational age (Tab. I). The delay between the initiation of the indomethacin and placebo therapy and the delivery, weight and maturity of the newborn were the criteria for evaluating the differences between the two treatments.

3 Results

Effect of treatment is summarized in Tab. II.

In the indomethacin group treatment was successful (contractions stopped completely for more than 1 week) in 15 of 18 patients (83.3%), of moderate value (3–7 days) in 2 of 18 patients (11.1%) and unsuccessful (delivery within 48 hours) in 1 of 18 patients (5.6%). In the placebo group the results were successful in 3 of 18 patients (16.6%), of moderate value in 1 of 18 patients (5.6%) and unsuccessful in 14 of 18 patients (77.8%).

Among these 14 patients with unseccessful results, 8 mothers received alternative treatment (ritodrine) but 5 were delivered within 24 hours and 3 within 48 hours. The clinical outcome is presented in Tab. III. The mean duration of pregnancy for the indomethacin patients (36.4 weeks ± 0.7) was significantly greater than that for the placebo group (31.2 weeks ± 0.7) ($p < 0.001$). In the indomethacin group 3 newborns weighed less than 2500 g (mean birth weight for the group 2833 g ± 117 g) compared with 15 newborns in the placebo group (mean birth weight for the group 2028 g ± 123 g). The mean 1 minute APGAR score in the indomethacin treated group was 9.3 ± 0.2 while in the placebo treated group it was only 7.8 ± 0.5 ($p < 0.01$).

Respiratory distress syndrome was diagnosed in one infant in the indomethacin group and 4 in the placebo group. One infant in the indomethacin group (weight 1810 g) and 2 infants in the placebo group (weight 600 and 1450 g) died from respiratory distress syndrome. The autopsy showed typical pulmonary atelectasis and hyaline mem-

Tab. II. Effect of treatment.

		Delivery			Delivery		No. of neonates in different weight groups		
	No. of patients	within 48 hrs	3–7 days	later than 7 days	Mature	Premature	< 2500 gm	2500–2999 gm	⩾ 3000 gm
Indomethacin	18	1	2	15	15 (83.3%)	3 (16.7%)	3	10	5
Placebo	18	14	1	3	4 (22.2%)	14 (77.8%)	14	4	–
Total	36	15	3	18	19	17	17	14	5

Tab. III. Clinical outcome (mean ± SEM).

	No. of patients	Gestational week		Birth weight	APGAR score
		At therapy	At delivery*	(gm)*	(1 min)+
Indomethacin	18	30.3 ± 0.7	36.4 ± 0.7	2833 ± 117	9.3 ± 0.2
Placebo	18	30.7 ± 0.8	31.2 ± 0.7	2028 ± 123	7.8 ± 0.5

* $p < 0.001$
+ $p < 0.01$

branes in these 3 infants. There was no evidence of premature closure of the ductus arteriosus or pulmonary hypertension. The remaining children were normal at follow-up examination.

Cesarean section was performed in 1 patient in the indomethacin group because of breech presentation in the first delivery and in 1 patient in the placebo group because of prolapse of the cord. Minor side effects as nausea, vomiting and vertigo were seen in 2 mothers in the indomethacin group. In the placebo group there were no side effects. Side effects were not significantly severe to warrant discontinuance of treatment. There were no differences during and after therapy in either maternal blood pressure, or maternal and fetal heart rate.

4 Discussion

Any tocolytic agent can be used only when it needed and after its efficacy and safety to both mother and fetus has been proved. We believe that safety of indomethacin has been proved in the first part of the study comprising 297 cases. We tried to test the efficacy of the drug in the second part of the study using randomized controlled double-blind study. It was already shown that premature labor may be arrested with placebo in 48% of patients [28]. This fact can be explained by improper criteria for diagnosis of premature labor with part of the patients not being at labor, or that bed rest alone can be effective treatment in some cases. In the present study labor was arrested in 22.2% of the placebo group. The lower percentage can be explained by the strict criteria that we used for definition of premature labor. Using similar criteria, NIEBYL et al. [18] found that patients who failed to respond to placebo has a higher mean serum prostaglandin $F_2\alpha$ metabolite (PGFM) than the rest of the placebo group. The author pointed to a possible predictive value of this measurements.

Looking from the other side the patient who respond to placebo had the lower mean PGFM level which may suggest that these patients were not in true labor. It is evident that in part of the cases in which we treat what we call premature labor all we are doing is stopping the uterine contractions of a false labor. This problem, of whom to treat, will be solved only with more strict and objective criteria.

Mean duration of pregnancy, mean birth weight and the number of mature newborns in the indomethacin group was significantly greater than that in the placebo group and the incidence of respiratory distress syndrome was higher in infants of mother treated with placebo. Similar results were obtained in study conducted by NIEBYL et al. [18]. Although no conclusions can be drawn about safety from such a small number of exposed babies, considering also the first part of the study, it must be stressed that no deleterious effect on cardiovascular, renal or coagulation system could be shown to be attributed by the indomethacin. The results of this part of the study indicate that indomethacin is a potent inhibitor of premature labor.

Summary

In the etiology of premature labor prostaglandins fulfill a significant role. It is known that indomethacin is a strong inhibitor of prostaglandin synthesis. The effect of indomethacin on premature labor was studied in a prospective randomized double-blind study in 36 patients. Eighteen patients received indomethacin and eighteen

received placebo. 200–300 mg of indomethacin was the total dosage in a 24 hours period. The activity of the uterus was monitored with a cardiotocograph. The mean duration of pregnancy and the mean birth weight in indomethacin group (36.4 weeks, 2833 g) were both significantly greater ($p < 0.001$) than that in placebo group (31.2 weeks, 2028 g). In the indomethacin group 3 children weighed less than 2500 g compared with 14 in placebo group. In 15 of 18 indomethacin treated patients (83.3%) premature labor was arrested after indomethacin treatment compared with 4 of 18 in the placebo group (22.2%). The indomethacin group had a mean 1 minute APGAR score of 9.3 ± 0.2 whereas the placebo group showed a score of 7.8 ± 0.5 ($p < 0.01$). Three infants died from respiratory distress syndrome; one in the indomethacin group (1810 g) and two in the placebo group (600 and 1450 g). Autopsies in the infants demonstrated a typical picture of pulmonary atelectasis and hyaline membranes.
There was no evidence of premature closure of the ductus arteriosus or pulmonary hypertension. 2 mothers in the indomethacin group suffered minor discomfort i.e. nausea, vomiting and vertigo. In both groups, no changes were noted, either during or after therapy in maternal blood pressure or maternal and fetal heart rate. Indomethacin was shown to be significantly more effective than placebo in inhibiting premature labor.

Keywords: Indomethacin, premature labor, prostaglandin synthetase inhibitor, uterine contractions.

Zusammenfassung

Weitere Untersuchungen zur Hemmung vorzeitiger Wehen durch Indometacin – Teil II – Doppelblindstudie
In der Ätiologie vorzeitiger Wehen spielen Prostaglandine eine bedeutende Rolle. Es ist bekannt, daß Indometacin ein starker Hemmstoff der Prostaglandinsynthese ist. Wir untersuchten die Wirksamkeit von Indometacin bei vorzeitigen Wehen in einer prospektiven, randomisierten Doppelblindstudie bei 36 Patientinnen. 18 Frauen erhielten Indometacin und 18 ein Placebo. Die Gesamtdosis betrug 200–300 mg Indometacin über 24 Stunden. Die Uteruskontraktionen wurden mit einem Kardiotokographen aufgezeichnet. In der Indometacin-Gruppe lag die durchschnittliche Schwangerschaftsdauer und das durchschnittliche Geburtsgewicht signifikant höher als in der Placebo-Gruppe (36,4 Wochen, 2833 g bzw. 31,2 Wochen, 2028 g; $p < 0{,}001$). In der Indometacin-Gruppe wogen 3 Neugeborene unter 2500 g im Vergleich zu 14 Kindern in der Placebo-Gruppe. Bei 15 der 18 mit Indometacin behandelten Patientinnen (83,3%) konnten die Wehen gehemmt werden; in der Placebo-Gruppe sistierten die Wehen in 4 Fällen (22,2%). In der Indometacin-Gruppe betrug der APGAR-Score 1 Minute pp. durchschnittlich $9{,}3 \pm 0{,}2$, während er in der Placebo-Gruppe bei $7{,}8 \pm 0{,}5$ lag ($p < 0{,}01$). 3 Kinder starben an einem RDS: 1 aus der Indometacin-Gruppe (1810 g) und 2 aus der Placebo-Gruppe (600 g bzw. 1450 g). Bei der Sektion dieser Kinder zeigte sich das typische Bild pulmonaler Atelektasen und hyaliner Membranen. Es fanden sich keine Hinweise auf einen vorzeitigen Verschluß des Ductus arteriosus oder auf eine pulmonale Hypertension. Zwei Frauen in der Indometacin-Gruppe hatten Beschwerden wie Übelkeit, Erbrechen und Schwindelgefühle. In beiden Gruppen konnten weder während noch nach der Therapie Veränderungen hinsichtlich des Blutdrucks und der Herzfrequenz bei der Patientin beobachtet werden; auch die fetale Herzfrequenz blieb unverändert. Wir konnten zeigen, daß Indometacin bei der Hemmung vorzeitiger Wehen signifikant effektiver wirkt als ein Placebo.

Schlüsselwörter: Indometacin, Prostaglandinsynthetase-Hemmstoff, Uteruskontraktionen, vorzeitige Wehen.

Résumé

Etude complémentaire du blocage de l'accouchement prématuré par l'indométacine – II. – Etude en double aveugle
Les prostaglandines revêtent un rôle significatif dans l'étiologie de l'accouchement prématuré. Il est connu que l'indométacine est un inhibiteur puissant de la synthèse des prostaglandines. L'effet de l'indométacine sur l'accouchement prématuré a été étudié dans une étude prospective randomisée en double aveugle portant sur 36 patientes. 18 patientes ont reçu de l'indométacine et 18 ont reçu un placebo. La dose totale quotidienne d'indométacine a été de 200 à 300 mg. L'activité utérine a été surveillée à l'aide d'un cardiotocographe. La durée moyenne de la grossesse et le poids de naissance moyen (36,4 semaines, 2833 g) ont été de façon significative ($p < 0{,}001$) plus grands dans le groupe indométacine que dans le groupe placebo (31,2 semaines, 2028 g). 3 enfants pesaient moins de 2500 g dans le groupe indométacine contre 14 dans le groupe placebo. Le travail prématuré a été stoppé chez 15 des 18 patientes traitées par indométacine (83,3%) contre 4 sur 18 dans le groupe placebo (22,2%). Le score d'APGAR à 1 minute dans le groupe indométacine était de $9{,}3 \pm 0{,}2$, alors que dans le groupe placebo il était de $7{,}8 \pm 0{,}5$ ($p < 0{,}01$). Trois sont morts d'un syndrome de détresse respiratoire; l'un dans le groupe indométacine (1810 g) et deux dans le groupe placebo (600 et 1450 g). L'autopsie de ces enfants a montré un tableau typique d'atelectasie pulmonaire et de membranes hyalines.
Il n'y a pas eu de fermeture prématurée du canal artériel ni d'hypertension pulmonaire. Deux mères dans le groupe indométacine ont présenté des troubles minimes à savoir nausées, vomissements et vertiges. Dans les 2 groupes, on n'a pas observé de modification de la pression artérielle maternelle ou du rythme cardiaque fœtal ni pendant ni après le traitement. Il est montré que l'indométacine est de façon significative plus efficace qu'un placebo dans l'inhibition de l'accouchement prématuré.

Mots-clés: Accouchement prématuré, contractions utérines, indométacine, inhibiteur de la synthèse des prostaglandines.

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