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Have we achieved progress in tocolytic treatment? – results of a retrospective cohort study in a tertiary university hospital

Czy osiągnęliśmy postęp w leczeniu tokolitycznym? Wyniki retrospektywnego badania kohortowego przeprowadzonego w szpitalu III stopnia referencyjności

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Abstract

Objectives: *Beta-agonists play an important role in tocolytic treatment. In light of recent changes in the Polish medical care system, we decided to assess the effectiveness of oral continuous treatment (in 2012) and compare it with a 3-day intravenous administration of fenoterol (in 2013). The aim of our study was to contrast cost and effectiveness of fenoterol therapy in pregnant women at risk of preterm labor during two consecutive years: 2012 - when fenoterol had been widely used (group A), and 2013 when its extensive use had been withdrawn (group B).*

Material and methods: *Retrospective cohort study of 129 pregnant women: 76 treated with intravenous fenoterol, followed by continuous oral administration (November 2012; group A), and 53 treated with intravenous fenoterol only for 48-72 hours (November 2013; group B).*

Results: *Perinatal out.c.omes (based on the Apgar score and neonatal weight) were comparable in both groups. Continuous oral application of fenoterol resulted in earlier gestational age at delivery and lower cost of hospitalization among women from group A as compared to group B. Regardless, the difference was not statistically significant (37 hbd vs. 35 hbd, p=0.626; 4334,700PLN vs. 5232,470PLN, p= 0.533).*

Conclusions: *A 3-day intravenous application of fenoterol is as effective as oral continuous therapy and is characterized by reduced risk of negative side effects.*

Key words: **fenoterol** / **preterm delivery** / **tocolysis** /

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Streszczenie

Cel pracy: *Beta-agoniści odgrywają istotną rolę w terapii tokolitycznej. Z uwagi na ostatnie zmiany w polskim systemie opieki medycznej, przeprowadziliśmy retrospektywne badanie kohortowe oceniające skuteczność ciągłego doustnego leczenia fenoterolem (w 2012 roku) oraz tylko trzy dniowego podawania dożylnego w 2013 roku. Celem pracy było porównanie efektywności i kosztów leczenia fenoterolem ciężarnych z ryzykiem wystąpienia porodu przedwczesnego.*

Materiał i metody: *Retrospektywne badanie kohortowe 129 ciężarnych. Grupa A: 76 ciężarnych (listopad 2012), leczona dożylnym wlewem oraz kontynuacja doustnej formy fenoterolu oraz grupa B: 53 ciężarne (listopad 2013), leczona dożylnie przez 48-72 godziny.*

Wyniki: *Punktacja w skali Apgar i masa urodzeniowa noworodków nie różniły się statystycznie istotnie. W grupie A pacjentki rodziły w wyższych tygodniach ciąży, a koszty hospitalizacji były niższe; Jednak w porównaniu z grupą B, nie ma istotnej różnicy statystycznej (37 t.c. vs 35 t.c., p= 0,626; 4334,700 zł vs 5232,470 zł, p= 0,533).*

Wnioski: *Podsumowując, trzydniowa, dożylna terapia tokolityczna fenotrolem jest tak skuteczna, jak terapia ciągła, a cechuje się zmniejszonym ryzykiem wystąpienia negatywnych skutków ubocznych.*

Słowa kluczowe: **poród przedwczesny** / **tokoliza** / **fenoterol** /

Introduction

Premature delivery (PTD) and its consequences constitute the key issue in contemporary obstetrics, affecting 7% of all pregnancies in Poland annually. Predominantly, uterine contractions and cervical changes are the reasons of PTD, with or without premature rupture of membranes. Four main pathogenic factors can be described: activation of the hypothalamic- pituitary-adrenal axis (maternal or fetal), inflammation (due to chorioamnionitis or systemic), decidual hemorrhage (placenta previa, placental abruption), and pathological dilation of the uterus [1]. In some way, PTD also appears to be heritable [2]. Furthermore, it is a well-known fact that proper development of a fetus and a child is directly proportional to gestational age [3]. Thus, prematurity is associated with perinatal mortality and morbidity [4], as well as other chronic dysfunctions: apnea of prematurity, hypoxic-ischemic encephalopathy (HIE), retinopathy of prematurity (ROP), developmental disability, transient hyperammonemia of a newborn, cerebral palsy and intraventricular hemorrhage, respiratory distress syndrome (RDS or IRDS), chronic lung disease (previously called bronchopulmonary dysplasia or BPD), neonatal hypoglycemia, necrotizing enterocolitis (NEC), anemia of prematurity, thrombocytopenia, and hyperbilirubinemia (jaundice) that can lead to kernicterus, infection, including sepsis, pneumonia, and urinary tract infection [5, 6, 7]. In addition, literature reports show that PTD is associated with various social problems in future life, e.g. lower educational level and difficulties in establishing a family [8]. Due to the severity of all PTD-related neonatal complications, adequate preventive measures and therapy are required.

As far as treatment is concerned, a number of tocolytic agents, including beta-adrenergic agonists, calcium channel blockers, magnesium sulphate, prostaglandin synthetase inhibitors, and oxytocin receptor antagonists, are currently available [4]. Nevertheless, extensive research suggests that continuous tocolytic medication is not as effective as was previously claimed [9, 10]. In Poland, the approval for chronic oral use in outpatient and inpatient settings of the most commonly used beta-mimetic, fenoterol, has already been withdrawn [11, 12].

Furthermore, since October 30, 2013 fenoterol has only been recommended for short inpatient tocolytic therapy in order to administer steroids which improve lung and respiratory system development [11, 13]. The drug is alleged to have significant side effects for both, the mother and the newborn [5]. Taking into account the changes in PTD treatment, our study focused on comparing cost and effectiveness of fenoterol therapy in pregnant women at risk of preterm labor in our hospital for two consecutive years: 2012 – when fenoterol was widely used, and 2013 – when restrictions were introduced.

Material and methods

A retrospective cohort study was conducted on all pregnant patients with threatened premature delivery since November 2012. Next, we compared their results with those of patients treated in our hospital since November 2013. The inclusion criteria were identical for both groups and from the same season of the year to eliminate confusing factors. None of our internal hospital treatment standards changed during the analyzed period, except for cessation of continuous oral treatment with fenoterol. The inclusion criteria were: 24 to 34 weeks of gestation, singleton live fetus. The exclusion criteria were: preterm placental ablation or other life-threatening conditions in the fetus on admission to the hospital.

The first group (group A) consisted of 76 pregnant women (mean age: 31) hospitalized in 2012.The patients were continuously treated with both, p.o. and i.v. fenoterol due to the risk of preterm birth. The second group (group B) included 53 women (mean age: 32) treated with a 3-day- tocolytic therapy (intravenous fenoterol) in 2013. All data were analyzed using Mann-Whitney test, Chi- square test, and Spearman Correlation test. Mean number of pregnancies was 2 in both groups. The diagnosis of preterm delivery was based on uterine contractions as well as cervical insufficiency.

Fenoterol (0.5mg/10ml i.v.) was administered by constant intravenous infusion with the flow of 8 ml/h. Fenoterol (5mg p.o.) was recommended in various doses: from 4x5 mg/day to 8x5 mg/day to achieve resolution of uterine contractions confirmed by cardiotocography (CTG).

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Table I. Comparison of group A and group B.

Parameter	Group A	Group B	p-value
Parity	2	2	0.467
Mean week of delivery	37	35	0.626
Mode of delivery	nd- 45% cc- 50% vac- 5%	nd-43% cc- 49% vac- 8%	0.941
Neonatal weight	2553g	2494g	0.702
Delivery at term	51%	42%	0.358
Apgar 1 min.	9	10	0.301
Apgar 5 min.	9	8	0.421
Apgar 10 min.	8	7.5	0.710
HGB after delivery	6.7 mg/dl	6.6 mg/dl	0.377
CRP after delivery	31.67	29.95	0.681
Celeston administration	55%	68%	0.206
Antibiotics	3 antibiotics- 7% 2 antibiotics- 18% 1 antibiotics- 28% 0 antibiotics- 47%	3 antibiotics- 2% 2 antibiotics- 11% 1 antibiotics- 27% 0 antibiotics- 60%	0.370
Average cost of hospitalization	4334.700PLN	5232.470PLN	0.533

nd-natural delivery, cc- caesarean section, vac- vacuum

Results

Cesarean section rate was higher than natural delivery in both groups. However, women from group A gave birth mostly at term, while subjects from group B delivered prematurely in the majority of cases. Regardless, neither group A nor B differed markedly in terms of statistics. Mean week of delivery was 37 and 35 in groups A and B, respectively. Hence, no statistically significant differences were observed (p=0.626).

Neonatal condition was compared (weight and Apgar score at 1, 5 and 10 minutes). There were no statistically significant differences between the two groups (Table I).

Comparison of maternal laboratory blood results revealed that the hemoglobin decrease and CRP (C-reactive protein) increase postpartum were similar in both groups, with no statistically significant differences (Table I).

The need for antibiotics in both groups was also compared. Again, there was no statistically significant differences between the two groups. As most of the patients did not need antibiotics, it seems safe to conclude that in those cases inflammation was not the main cause of preterm delivery. Application of other drugs (commonly used in case of risk for preterm delivery) is presented in Table II. Kalii hydroaspartas 250mg, Magnesii hydroaspartas 250mg (p.o) and diazepam 5 mg (p.o. or i.v.) were the most frequently administered drugs (Table III).

Interestingly, no side effects of fenoterol therapy were observed in our patients.

Finally, the cost of both treatments was calculated, including hospitalization time before the delivery, as well as the medical care afterwards. Among other things, the cost of oral and intravenous (2012), as well as only intravenous (2013) fenoterol therapy was included. There were no statistically significant differences between mean costs in both groups (Table I).

Table II. Application of additional drugs in case of risk of preterm delivery.

Additional medications	Group A	Group B
Progesterone 50mg (p.v. or s.l.)	10%	15%
Kalii hydroaspartas 250mg, Magnesiihydroaspartas 250mg (p.o)	39%	38%
Drotaverini hydrochloridum 80mg (p.o)	10%	7%
Diazepam 5mg (p.o or i.v.)	40%	31%
Magnesium sulphate 200mg/ml (i.v.)	2%	9%

Further analyses revealed no correlation between the time of delivery and CRP and leukocyte levels before delivery. On the other hand, a positive correlation between the time of delivery and hemoglobin (Hgb), erythrocyte, and hematocrit levels before delivery was found for group A (Hgb: Rs= - 0.502, p< 0.0001). However, no such correlation was detected in group B.

Discussion

Uterine contractions constitute the most frequent cause of preterm delivery. The commonly used drugs, tocolytics, are numerous but still ineffective, as they do not treat the reason of preterm uterine activity. Tocolytics can be divided into two groups,

with the first acting through intracellular messengers (beta-adrenergic-receptor agonists, nitric oxide donors, magnesium sulphate and calcium channel blocker), and the second through inhibition of myometrial stimulants (oxytocin antagonists or prostaglandin synthesis inhibitors). Direct mechanisms are described in Table III [14].

Commonly known side effects of continuous fenoterol therapy include tachycardia, muscle tremor, hyperglycemia, hyperkalemia and, the most serious, lung edema [15]. As far as the harmful impact on the heart is concerned. Meinen pointed out that fenoterol does not cause myocardial necrosis, either in the woman or the fetus. Moreover, Willstein et al. did not observe a decreased activity of the heart-muscle-specific isoenzym creatinkinase MB (cardiac damage marker) even in a long-term high-dose tocolytic therapy [17]. On the other hand, Monod and De Grandi, described an association between beta-mimetics and cardiac muscle necrosis resulting in cardiopathy [18]. Nonetheless, neither experiments on animals nor fetal and neonatal out.c.omes confirmed the cardiotic damage related to their immature sympathetic innervation [19]. Despite the evidence of unaffected condition of the newborn, infant and early childhood development, the obtained data indicate a connection between fenoterol therapy during pregnancy and autism in children [20, 21]. In light of these reports, short-term administration seems to be a reasonable solution, if proved effective. In comparison, no additional side effects of oral administration of fenoterol in 2012 were observed in our study.

It is claimed that beta-agonists induce reduction of their receptor m-RNA level (down-regulation) in case of prolonged application [22]. According to Engelhardt S. et al, fenoterol causes selective down-regulation of myometrial beta-adrenergic receptors which is not connected with mRNA changing, alteration of alfa-2-adrenergic receptors, Gs and Gi G-protein alpha-subunit or beta-Adrenergic receptor kinase activity [23]. Taking this into consideration, a long-term administration of beta-agonists seems to increase the side effects rather than the effectiveness.

In conclusion, the goal of our study was to examine the effectiveness and the cost of fenoterol therapy. Our findings demonstrated a lack of significant differences in long- and short-term administration of the drug. Firstly, in the majority of cases, the patients delivered at term and by C-section. There were no differences either in Apgar scores of the newborns or neonatal weight. Maternal hemoglobin decrease and CRP increase after delivery were similar in the examined groups. Kalii hydroaspartas 250mg, Magnesii hydroaspartas 250mg, and Diazepam 5 mg were the most frequently used among the additional drugs. Finally, the cost of the therapies turned out to be comparable.

Table III. The direct mechanism of tocolytic drugs.

Beta-adrenergic receptor agonist (fenoterol)	Increases the level of intracellular c-AMP → inactivation of myosin light chain kinase
Nitric oxide donors	Vasodilator, increase c-GMP in smooth muscle cells→ inactivation of myosin light chain kinase
Magnesium sulphate	Hyperpolarizes plasma membrane, competing with intracellular calcium and inhibits myosin light chain activation
Calcium-channel blockers	Inhibit calcium impact on receptors in cell membrane and sarcoplasmic reticulum
Cyclooxygenase inhibitors	COX-inhibitors decrease prostaglandin production
Oxytocin-receptor antagonist	Competes with oxytocin for binding to receptors in membrane and sarcolemma in myometrium and deciduas

Interestingly, a statistically significantly lower hemoglobin level before delivery correlated with earlier gestational age at delivery in group A. Even though a strong positive correlation was noted, this result was not confirmed in group B. In fact, there are reports showing anemia as the promoting factor for preterm delivery, however not a crucial one [24]. In the first and second trimester, anemia was found to be associated with a higher risk for preterm delivery [25, 26]. It seems further studies are needed to assess the role of anemia in the pathogenesis of preterm delivery.

Although women from group A gave birth at term and the cost of hospitalization was lower, the results revealed that short-term fenoterol therapy is statistically as effective as prolonged administration of the drug. Regardless, shorter treatment proved to be beneficial because it prevents severe side effects, while perinatal results remain similar. However, due to better prognosis of extremely preterm infants connected with increasing gestational age, longer tocolysis in those particular cases might be considered [27].

Beta-adrenergic receptor agonists (fenoterol) and oxytocin-receptor antagonists (atosiban) are currently the two most commonly applied drugs in Poland. Many publications indicate that the effectiveness of both is comparable, while the second is safer. Thus, it seems justifiable for atosiban to be commonly used. Table IV demonstrates the characteristics of the two drugs.

Table IV. Atosiban versus fenoterol – review of the literature [28-31].

	Effectiveness	**Safety**	**Economic aspect**
Wex et al., 2009	Atosiban = beta-mimetics	Atosiban	Atosiban
Hrubý, 2004	–	–	Atosiban <18 h therapy
Nonnenmacher et al., 2009	Atosiban	Atosiban	
European Atosiban Study Group, 2001	Atosiban=terbutaline	Atosiban	

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Conclusions

Perinatal out.c.ome (based on Apgar score and neonatal weight) revealed no differences in the effectiveness of oral continuous fenoterol and short-term intravenous tocolytic treatment.

Oral continuous fenoterol therapy results in higher gestational week at delivery and lower cost of hospitalization. The differences were not statistically significant as compared to group B.

A 3-day fenoterol intravenous therapy is as safe and effective as the continuous treatment.

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