Tocolysis with the β-2-sympathomimetic hexoprenaline increases occurrence of infantile haemangioma in preterm infants

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ABSTRACT

Background Infantile haemangioma (IH) is the most commonly observed tumour in children. Off-label pharmacological treatment of IH with the beta-blocker propranolol induces regression of IH. Based on the fact that IH are more frequently observed in premature babies than in mature babies and the evidence that beta-blocker therapy leads to regression of IH, the authors generated the hypothesis that the use of β-2-sympathomimetics during pregnancy for inhibiting premature labour might increase occurrence of IH in preterm infants.

Methods For group comparison t test, Mann–Whitney U test and Fisher's exact test were used. Logistic regression was carried out by the forward stepwise method with Wald statistics.

Results Data of 328 preterm infants (<32 gestational weeks) or with a birth weight of less than 1500 g (<36 gestational weeks) born between January 2006 and December 2008 were analysed. A total of 15 were excluded due do death within the 1st month of life, 38 because of lost to follow-up and six due to incomplete data. Complete data of 269 preterm infants were retrospectively analysed. During the follow-up period of median 1.6 years, 50 infants developed one or more IH within their first 6 months of life. IH occurred in 40/181 patients with intrauterine exposure to the β-2-sympathomimetic hexoprenaline and in 10/88 without exposure (OR=4.3; 95% CI 1.4 to 13.8). Furthermore, the influence of antenatal exposure to glucocorticosteroids for induction of lung development was analysed. Prenatally exposed subjects showed reduced occurrence of IH (OR=0.2; 95% CI 0.05 to 0.8).

Conclusion Intrauterine exposure to the β-2-sympathomimetic hexoprenaline might increase the occurrence of IH in preterm infants.

What is already known on this topic

- Treatment with propranolol leads to regression of IH. It is also known that agonist and antagonist of β-adrenergic receptors act antithetic via same intracellular pathways.
- Glucocorticosteroids were used for IH treatment for years. Recently it has been shown in IH murine model that treatment of haemangioma-derived stem cells in vitro before implantation with glucocorticosteroids inhibited vasculogenesis in vivo.

What this study adds

- We could show for the first time that intrauterine exposure to the β-2-sympathomimetic hexoprenaline might increase the occurrence of IH in preterm infants.
- Intrauterine exposure to glucocorticosteroids might reduce the occurrence of IH in preterm infants.

INTRODUCTION

Infantile haemangioma (IH) is the most common tumour in children. Pathogenesis of IH is still not completely understood.[1] Although the majority of IH is benign, a significant subset causes permanent visual loss, disfigurement, pain from ulceration and a small subset is even life threatening.[2]

The incidence of IH inversely correlates with the degree of immaturity, for every 500 g decrease in birth weight, the risk of IH increases by 40%.[3] IH are observed in 4%–5% of term born and in 12.7% of preterm born infants with a higher incidence in those with lower birth weight (15.6% of those with a birth weight <1500 g; 22.9% of those with a birth weight <1000 g).[4 5]

IH are unique tumours, which are absent at birth and arise in infancy with a characteristic history of growth early in infancy followed by spontaneous involution.[2] There are several hypotheses on the development of IH.[2 6–8]

For decades, glucocorticoids have been the mainstay of therapy of life-threatening IH although their mechanism of action is poorly understood.

In 1992, it was first shown that interferon α 2a (IFNα 2a) has prominent antiangiogenic properties in life-threatening IH by decreasing endothelial cell proliferation by downregulation of basic fibroblast growth factor (bFGF), however, due to neurotoxicity, the therapeutic use of IFNα is limited.[2 9]

Vincristine – another traditional therapeutic option – interferes with mitotic spindle microtubules and induces apoptosis in tumour cells in vitro and has also been shown to be effective in treatment of life-threatening IH.[10]

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Recently, it was incidentally found that the beta-blocker propranolol induces regression of IH, this detection led to revolution of treatment of life-threatening and disfiguring IH. Several investigators reported impressive regression potential of propranolol when administered for treatment of IH,[11–13] but little is known on the mechanism of action of propranolol in IH.

STUDY RATIONALE

Treatment with propranolol – a well-known beta-blocker – leads to regression of IH. However, it is known that agonist and antagonist of β-adrenergic receptors act antithetic via same intracellular pathways, therefore the question rose, if exposure to β-2-sympathomimetics like the tocolytic agent hexoprenaline increases the occurrence of IH. As IH occur more frequently in preterm neonates and tocolytic agents are used more often in that age group, investigation was done in preterm neonates born before 32 weeks of gestation and in preterm neonates born before 36 weeks of gestation with a birth weight of less than 1500 g.

The aim of this study was to investigate whether administration of the tocolytic agent hexoprenaline during pregnancy increases the occurrence of IH in preterm-born infants.

METHODS

We recruited preterm infants born before 32 weeks of gestation or with a birth weight of less than 1500 g born before 36 weeks of gestation between January 2006 and December 2008 for this retrospective study. The following parameters were collected from hospital charts:

Maternal data: date of birth, applied tocolysis, tocolytic agent used (hexoprenaline or atosiban), begin and end of tocolysis (date and gestational week), cumulative dose of tocolytic agents, dose and time-point of glucocorticosteroids given for induction of fetal lung maturation in nearing preterm birth.

Children's data: date of birth, gender, mode of delivery, Apgar score (1 and 5 min), multiple gestation, gestational age, birth weight, birth length, head circumference, length of stay in neonatal intensive care unit (NICU) and total length of hospital stay.

The diagnosis of IH was confirmed by physical examination and clinical behaviour of the lesion. All patients were examined completely including a full skin examination at least once a week totally undressed during their stay in the neonatal intensive care unit, and on the neonatal ward by neonatologists. Further physical examinations were done and sufficiently documented in the charts on day of discharge, and at the routine follow-up visits which were performed for neuromotor development every 3 months by neonatologists until the age of 2 years and facultative controls thereafter.

The research protocol was approved by the local ethics committee, which waived informed consent due to the retrospective design of the study.

STATISTICAL ANALYSIS

Comparisons of groups

All data sets of metric variables were checked for normal distribution (test of normality: Kolmogorov-Smirnov with Lilliefors significance correction, type I error = 5%). For group comparisons of metric variables with normally distributed data sets, the t test for independent samples was used. Metric variables without normally distributed data sets and ordinal variables were analysed with the Mann–Whitney U test. Data of dichotomous variables were compared by the Fisher's Exact test. All tests are two tailed with a CI of 95% ($p<.05$). No adjustment for the type I error was made; therefore only the analysis of the primary endpoint is confirmatory, the p values of all other analyses are only descriptive.

Logistic regression

The analyses were carried out by the forward stepwise method with Wald statistics; OR and 95% CI were calculated. Missing values were not replaced (dosage of hexoprenaline was not reported in 1 case, age of the mother in 1 case, Apgar-Score in 2 cases).

The department of Applied Systems Research and Statistics, University of Linz, Austria performed the statistical analysis of data. For all calculations, PASW Statistics 18 (SPSS, IBM Company Headquarters, 233 S Wacker Drive, Chicago, Illinois, USA) was used.

RESULTS

Three hundred and twenty-eight preterm-born babies admitted to our tertiary care centre were assessed for eligibility during the study period and matched inclusion criteria. Two hundred and ninety-one were born in our centre, 37 were born outside and transferred for different reasons, in the majority of cases for surgical reasons (figure 1).

Fifteen patients died within the first month of life and were therefore excluded from analysis, six were excluded due to incomplete data and 38 were excluded because of lost to follow-up as follow-up controls were done at the referring hospitals. Data of the remaining study cohort of 269 subjects was statistically analysed.

Fifty of 269 infants developed one or more infantile haemangioma (IH group) within their first 6 months of life. All patients characteristics are given in table 1.

Comparison of groups (IH group vs non IH group)

Demographic data of patients and their mothers did not differ between the groups (table 1). The comparison between the groups revealed that IH occur significantly more frequently in female infants ($p=0.004$) and in patients exposed to hexoprenaline at any time of gestation ($p=0.044$). Neither the cumulative amount of administered hexoprenaline, nor the gestational week, when administered during pregnancy, significantly differed between the groups (table 1).

Logistic regression

In forward stepwise logistic regression again female sex (OR 2.6; $p=0.012$) and exposure to hexoprenaline (OR 4.3; $p=0.013$) turned out to be independent variables that positively influence the occurrence of IH. The logistic regression also showed a trend for the positive influence of the cumulative hexoprenaline dose on the occurrence of IH ($p=0.06$). In our clinic, hexoprenaline and atosiban were exclusively used for tocolysis. Atosiban had no influence on the occurrence of IH in our cohort ($p=0.91$).

Glucocorticosteroids, when given before birth for induction of fetal lung maturation turned out to be an independent variable negatively influencing the later development of IH (OR 0.2; $p=0.027$) (table 2).

DISCUSSION

In accordance with previously published data[2 15], our study shows that girls face a higher risk than boys to develop an IH when born before 32nd gestational week or <1500 g. The reasons for this female preference are not completely clear so far, but it has previously been shown that haemangiomas are

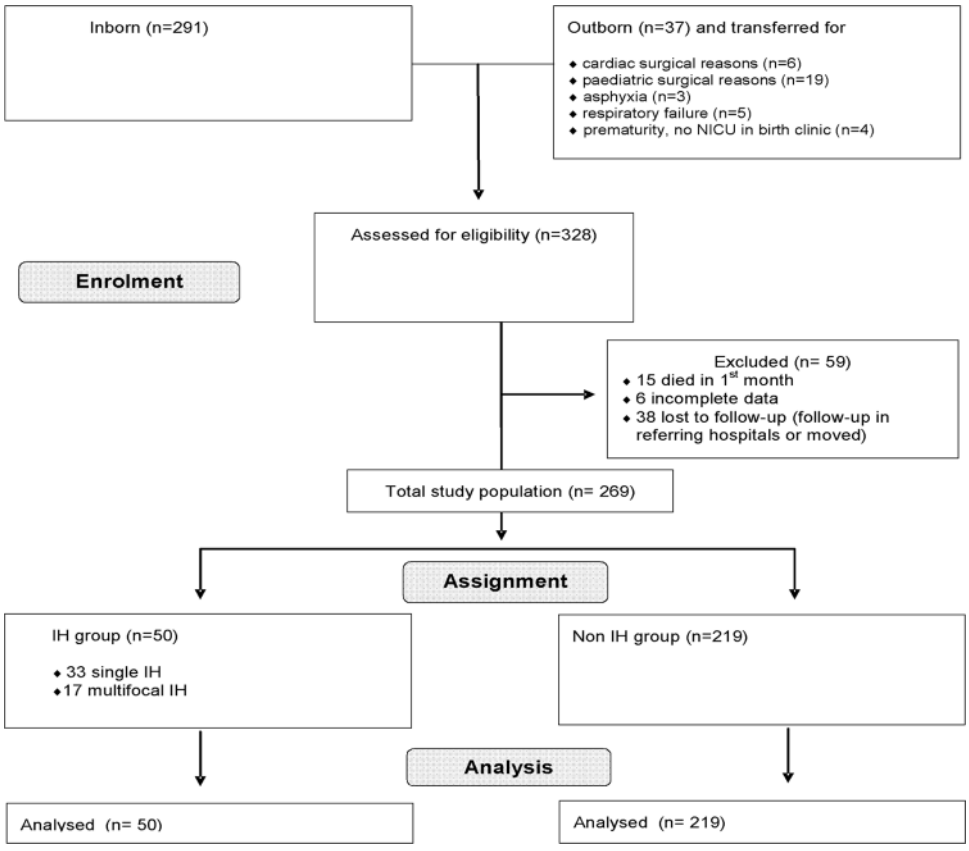

Figure 1 Consort – flow chart.

Table 1 Group analysis, variables of patients with infantile haemangioma (IH group, n=50) compared to patients without infantile haemangioma (non-IH group, n=219). Results are given as mean and SD or number (%). Birth weight and birth length were standardised and expressed as SDS (SD score) using national reference values[14]

Variable	IH group	Non-IH group	p Value
Female gender, number (%)	♀=34/50 (68)	♀=98/219 (45)	0.004
Exposure to hexoprenaline (Primary Endpoint), number (%)	40/50 (80)	141/219 (64)	0.04
Hexoprenaline (gestational week) (SD)	27.0 (2.5)	27.0 (3.1)	0.8
Hexoprenaline (cumulative dose, µg) (SD)	1640 (1515)	1546 (1911)	0.3
Exposure to atosiban, number (%)	8/50 (16)	28/219 (12.8)	0.5
Atosiban (gestational week) (SD)	27.6 (2.0)	26.6 (2.2)	0.3
Prenatal glucocorticosteroids, number (%)	41/46 (89)	193/209 (92)	0.8
Maternal age (years) (SD)	30.5 (5.1)	30.3 (6.0)	0.8
Completed gestational weeks (SD)	28.9 (2.0)	29.0 (2.5)	0.8
Apgar score at 1 min (SD)	6.0 (2.2)	5.8 (2.2)	0.5
Apgar score at 5 min (SD)	7.6 (1.5)	7.6 (1.6)	0.8
Caesarean section, number (%)	33/50 (66)	163/219 (74)	0.2
Twin pregnancy, number (%)	14/50 (28)	57/219 (26)	0.8
Birth weight (g) (SD)	1281 (262)	1252 (411)	0.5
Birth weight (SDS) (SD)	−0.1 (0.7)	−0.3 (1,4)	0.07
Length at birth (cm) (SD)	38.2 (3.0)	38.1 (4.1)	0.8
Length at birth (SDS) (SD)	−0.3 (0.8)	−0.4 (1.0)	0.4
Head circumference at birth (cm) (SD)	26.9 (1.8)	26.8 (2.8)	0.8
Stay in NICU (days) (SD)	25 (18)	32 (55)	0.9
Total hospital stay (days) (SD)	54 (26)	58 (34)	0.9
Follow-up time (years) (SD)	1.6 (1.0)	1.6 (0.9)	0.9

IH, infantile haemangioma; NICU, neonatal intensive care unit.

Table 2 Walds's forward stepwise logistical regression

	OR	95% CI	p Value
Female gender	2.6	1.2 to 5.4	0.012
Prenatal exposure to hexoprenaline	4.3	1.4 to 13.8	0.013
Prenatal exposure to glucocorticosteroids	0.2	0.05 to 0.8	0.027

one of the target tissues of oestrogen and oestrogen might play an important role in the development of haemangiomas.[16]

As a second independent variable, hexoprenaline, a β2-sympathomimetic, raised the risk for development of IH in our study. In our study cohort of 269 preterm infants the use of hexoprenaline more than quadrupled the risk for development of IH (OR=4.3). One would suspect that higher cumulative doses of hexoprenaline would increase the risk of IH development. Regarding dose-dependent occurrence of IH in fetuses with exposure to hexoprenaline, a tendency could be seen in logistic regression (p=0.06) but dose did not turn out to be a significant independent variable in our study cohort.

To our knowledge, the influence of prenatal exposure to β-2-sympathomimetics on development of IH has not been investigated so far, but there are studies on the action of the beta-blocker propranolol, a new therapeutic option in treatment of IH first reported in 2008[11–13] via β-adrenergic receptors due to direct blocking of the intracellular signalling pathway.[17 18] Beta-adrenergic agonists lead to vasodilatation via release of NO, stimulate the synthesis of proangiogenic factors (vascular endothelial growth factor (VEGF),[2] bFGF,[2] matrix metallopeptidase 9 (MMP 9))[19] and activate proangiogenic cascades and lead to angiogenesis.[1] Receptor antagonists like propranolol block the signalling pathway and also have other pharmacological effects.[17 18]

It was suspected earlier that the beta adrenergic blockade may provide a clue to the pathogenesis of IH.[20] Our finding, that exposure to hexoprenaline increases occurrence of IH matches the speculation, that vice versa application of β-adrenergic receptor stimulating agents may trigger development of IH.

To our understanding, the betamimetic signal for the development of IH must have happened in utero as betamimetics' exposure in utero more than quadrupled the risk for the occurrence of IH.

Glucocorticosteroids have been used as first line treatment of IH for many years. Recently it has been shown that treatment with dexamethasone led to dose-dependent inhibition of tumour vasculogenesis in the murine IH model.[21] Furthermore, it was shown that pretreatment of haemangioma-derived stem cells in vitro before implantation also inhibited vasculogenesis in vivo.[21] As in our study, intrauterine exposure to glucocorticosteroids turned out to be an independent factor with negative correlation to development of IH, intrauterine exposure to glucocorticosteroids might have a protective effect on development of IH in human fetuses.

LIMITATIONS

One limitation is the retrospective design of the study and therefore not per protocol standardised follow-up visits. As all premature newborns born before 32nd gestational weeks or with a birth weight of <1500 g are enrolled in a standardised follow-up-regime for neuromotor development in our clinic, we are sure that no relevant IH was missed due to regularly, totally undressed performed examinations by neonatologists while in hospital and during regular follow-up visits.

CONCLUSIONS

In our cohort of 269 preterm infants, we found that prenatal exposure to hexoprenaline may account for the increased occurrence rate of IH in preterm babies and prenatal glococorticosteroid treatment may have a protective influence on the occurrence of IH. For confirmation of our hypotheses, prospective studies are needed. As there might be a relationship between hexoprenaline administration to the mother during pregnancy and the occurrence of haemangioma in preterm babies, replacement of β-2-sympathomimetics by other tocolytic agents without this side effect may be considered.

Competing interests None.

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