Maternal Transdermal Nitroglycerin Use and Early Childhood Development

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Abstract

Objective: Our randomized, double-blind, placebo-controlled trial of transdermal nitroglycerin (GTN) for preterm labour demonstrated a significant reduction in neonatal morbidity and mortality. The objective of this study was to evaluate developmental performance in the children born to women who participated in the GTN trial after one year and two years of follow-up.

Methods: The Ages and Stages Questionnaires (ASQ) were used for the assessments, and five domains of child development (communication, gross motor skills, fine motor skills, problem-solving, and personal social skills) were evaluated. Supplementary analyses were performed after stratifying study subjects by gestational age at birth (< 28, 28 to 32, 33 to 36, ≥ 37 weeks) or by defining study subjects as normal or abnormal using standard cut-offs.

Results: A total of 153 infants born to women who participated in the GTN trial were included in the initial follow-up. Among them, 111 (72.5%) children (55 in the GTN arm and 56 in the placebo arm) at 12 months of age and 83 (54.2%) children (42 in the GTN arm and 41 in the placebo arm) at 24 months of age completed the full ASQ. There were no differences in ASQ total score and five subscores between the GTN arm and the placebo arm at the one-year and two-year follow-up evaluations, in overall study subjects, or after stratifying study subjects by gestational age. A trend towards reduced abnormalities in the GTN arm at the two-year follow-up was observed, although there was no statistical significance.

Conclusion: Maternal GTN use for preterm labour had no impact on children's long-term development, but larger studies are needed to confirm the preliminary findings of this study.

Key Words: Developmental assessment, transdermal nitroglycerin, Ages and Stages Questionnaires, follow-up

Competing Interests: None declared.

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Résumé

Objectif : Notre essai comparatif contre placebo randomisé à double insu portant sur l'administration de nitroglycérine transdermique (GTN) pendant le travail préterme a démontré qu'une telle pratique entraînait une baisse significative de la morbidité et de la mortalité néonatales. Cette étude avait pour objectif d'évaluer le rendement développemental des enfants issus des participantes à l'essai GTN à la suite d'un an et de deux ans de suivi.

Méthodes : Les *Ages and Stages Questionnaires* (ASQ) ont été utilisés aux fins de l'évaluation et cinq domaines de développement infantile (communication, motricité globale, motricité fine, résolution de problème et aptitudes sociales personnelles) ont été évalués. Des analyses supplémentaires ont été menées à la suite de la stratification des sujets d'étude par âge gestationnel à la naissance (< 28, de 28 à 32, de 33 à 36, ≥ 37 semaines) ou en définissant les sujets d'étude comme étant normaux ou anormaux au moyen de seuils standard.

Résultats : Au total, 153 nouveau-nés issus des participantes à l'essai GTN ont été inclus dans le suivi initial. Parmi eux, 111 (72,5 %) enfants (55 dans la branche GTN et 56 dans la branche placebo) à 12 mois et 83 (54,2 %) enfants (42 dans la branche GTN et 41 dans la branche placebo) à 24 mois ont rempli l'ensemble des ASQ. Aucune différence en matière de score total et de cinq sous-scores ASQ n'a été constatée entre la branche GTN et la branche placebo dans le cadre des évaluations à un an et à deux ans de suivi, et ce, chez l'ensemble des sujets d'étude ou à la suite de leur stratification par âge gestationnel. Une tendance vers une baisse du nombre d'anomalies au sein de la branche GTN à deux ans de suivi a été constatée; toutefois, cette baisse n'était pas significative sur le plan statistique.

Conclusion : L'administration maternelle de GTN pendant le travail préterme n'a exercé aucun effet sur le développement de l'enfant à long terme; cependant, la tenue d'études de plus grande envergure s'avère requise pour confirmer les résultats préliminaires de cette étude.

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INTRODUCTION

From May 2001 to July 2006, a randomized, double-blind, placebo-controlled trial of transdermal nitroglycerin for preterm labour was conducted by the Queen's Perinatal Research Unit and Ottawa Health Research Institute. In this trial, 153 women who were in clinical preterm labour at between 24 and 32 weeks' gestation were randomly allocated to have either a GTN or a placebo patch applied.[1] The trial demonstrated that there was a significant reduction in neonatal morbidity and mortality by using GTN for preterm labour.[1]

In recent years, economical and effective methods to evaluate child development have been developed.[2–6] Among them, the Ages and Stages Questionnaire is frequently used because of its low cost, flexibility across a range of ages and cultures, and wide applicability in both preterm and term infants.[2,6] It can be used as a first-level screening tool to identify infants and children who may require further in-depth assessment, and can also be a screening tool to monitor children who are at risk for developmental disabilities or delays.[2]

The purpose of this study was to use the ASQ to evaluate developmental performance in the children born to women who participated in the GTN trial at one year and two years of age.

METHODS

The GTN trial was a multicentre, randomized controlled trial comparing placebo patches with GTN patches for the treatment of preterm labour.[1] The trial was conducted in 14 centres, and 158 women meeting all criteria were enrolled. All 153 children born to women recruited for the GTN trial were eligible for follow-up with the ASQ. At 12 months and 24 months of age, they were invited to be assessed with the respective ASQ tests.

In this study, we used the second edition of the ASQ, which is a parent-completed, child-monitoring system, published in 1999 by Brookes Publishing Company.[2] The ASQ is a screening tool designed to assess children's developmental performance between the ages of four months and 60 months, with age adjusted for gestation at birth. The age-specific questionnaires each consist of 30 developmental items to assess five domains of child development: communication, gross motor, fine motor, problem solving, and personal-social. For each item, there is a choice of three responses: "Yes," "Sometimes," and "Not Yet" to represent the children's ability to perform a task, with scores of 10, 5, and 0 assigned to each answer, respectively. Domain scores are obtained by the sum of the item scores and then compared with established screening cut-off points. Children who scored below the cut-off point for any domain were considered screen positive, and they were offered further diagnostic testing. In addition to the 30 items, each questionnaire also had seven or eight open-ended questions, depending on the age of assessment, regarding parents' concerns about their child's general health. The ASQ requires 10 to 15 minutes to complete and two to three minutes to score. The psychometric properties of the ASQ such as validity and reliability have been studied extensively, and questionnaires are currently available in English, French, Spanish, Norwegian, Danish, and Korean.[7–10] It has moderate to high sensitivity (0.70 to 0.90) and specificity (0.76 to 0.91) and excellent reliability (test–retest reliability 0.95; interrater reliability 0.95), with the 12- and 24-month intervals having the highest sensitivity and specificity in the first 24 months of life.[11]

All women enrolled in the GTN trial were contacted by the local centre research nurse. When children were 12 months and 24 months of age, the research nurse mailed the questionnaires and counselled parents in its use. Before returning the questionnaires, the parents were interviewed by telephone to ensure that the answers they provided were correct and complete.

Baseline characteristics between those who participated in the ASQ follow-up and those who did not participate in the follow-up study were first compared. Supplementary analyses after stratifying study subjects by gestational age (< 28, 28 to 32, 33 to 36, and ≥ 37 weeks) and by normal versus abnormal scores were performed. One year cut-off points (15.8, 18.0, 28.4, 25.2, and 20.1 in communication, gross motor, fine motor, problem solving, and personal-social) and two year cut-off points (36.5, 36.0, 36.4, 32.9, and 35.6 in communication, gross motor, fine motor, problem solving, and personal-social) were used to identify the abnormal scores.[2]

Data were examined by the parametric method using the t test for continuous data, while the Wilcoxon rank-sum test was used for nonparametric data. Chi-square tests were used for categorical data. Statistical analysis was performed using SAS version 9.1 (SAS Institute Inc, Cary NC). $P < 0.05$ was set as the level of significance.

The multicentre Canadian trial was approved by the research ethics board at each centre. The protocol, as used for the pilot study, was reviewed by Health Canada.

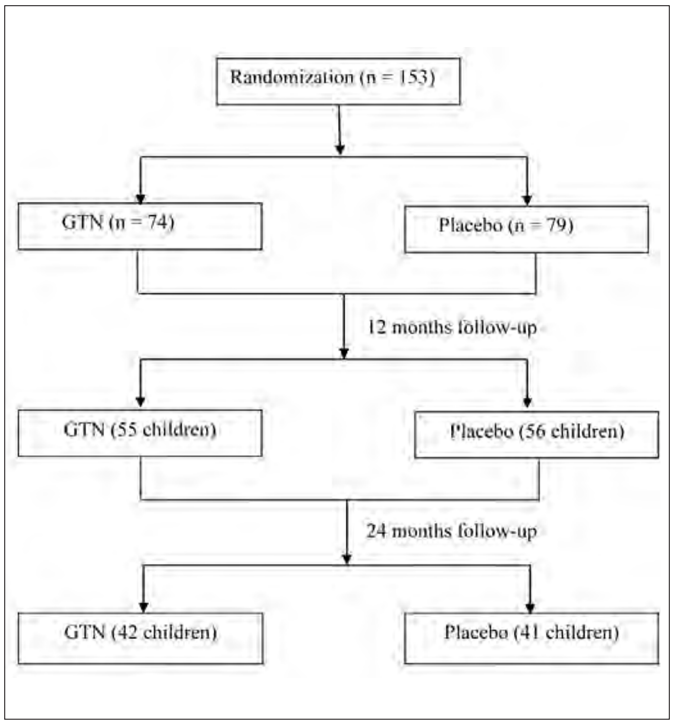
ABBREVIATIONS

ASQ	Ages and Stages Questionnaire
GTN	glyceryl trinitrate (nitroglycerin)

Table 1. Baseline characteristics of those who participated in the follow-up study of the children and those who did not

	One year			Two year		
	Loss of follow-up (n = 42)	Follow-up (n = 111)	*P*	Loss of follow-up (n = 70)	Follow-up (n = 83)	*P*
0.96						
Race, %			0.83			0.96
Black	9.52	5.50		7.04	6.10	
White	85.71	89.91		88.73	89.02	
Asian	2.38	1.83		1.41	2.44	
Other	2.38	2.75		2.82	2.44	
Educational level, %			0.19			0.54
Grade school	4.76	8.26		7.04	7.32	
High school	40.48	25.69		33.80	25.61	
Post-secondary	54.76	66.06		59.15	67.07	
Marital status, %			0.99			0.91
Married/common law	80.95	80.73		80.28	82.93	
Separated/divorced	2.38	2.75		2.82	2.44	
Single	16.67	16.51		16.90	14.63	
Street drug use, %			0.72			0.23
Yes	2.38	3.54		1.37	4.76	
No	97.62	96.46		98.63	95.24	
Preterm birth, %			0.09			0.15
Yes	61.90	46.43		56.16	44.58	
No	38.10	53.57		43.84	55.42	

Recruitment of participants



RESULTS

A total of 153 infants born to women who participated in the GTN trial in preterm labour were contacted for the follow-up study. Among them, 111 (72.5%) children (55 in the GTN arm and 56 in the placebo arm) at 12 months of age and 83 (54.2%) children (42 in the GTN arm and 41 in the placebo arm) at 24 months of age completed the ASQ assessment (Figure).

There were no differences in baseline characteristics between those who participated in the follow-up study of the children and those who did not (Table 1).

Total ASQ scores and domain scores between the two arms are presented in Table 2. There were no significant differences in total score and domain scores between the two arms, at either the one-year or two-year follow-up.

The results after stratifying by four gestational age groups (< 28, 28 to 32, 33 to 36, and ≥ 37 weeks) at delivery are shown in Tables 3 and 4. Again, there were no significant differences in ASQ total score and domain scores between the two arms at one and two years.

Table 2. Scores of ASQ between the GTN and placebo arms

	One-year follow-up		Two-year follow-up	
	GTN (n = 55) Mean score (±SD)	Placebo (n = 56) Mean score (±SD)	GTN (n = 42) Mean score (±SD)	Placebo (n = 41) Mean score (±SD)
Communication	45.00 (14.24)	42.86 (12.71)	54.41 (11.22)	51.46 (15.38)
Gross motor	42.55 (18.66)	46.16 (16.46)	53.10 (11.89)	49.88 (17.01)
Fine motor	49.73 (12.11)	47.98 (12.49)	52.86 (7.25)	48.17 (13.21)
Problem solving	47.55 (12.21)	44.74 (13.18)	50.48 (10.41)	47.07 (14.49)
Personal-social	46.20 (13.17)	46.49 (13.85)	50.83 (10.76)	47.81 (14.67)
Total score	230.91 (47.51)	227.59 (51.30)	261.67 (39.96)	245.12 (68.03)

No statistical differences were found between the two arms in one-year or two-year follow-up.

Table 3. Total score and domain score of ASQ between the GTN and placebo arms by gestational age category in one-year follow-up (mean score [±SD])

	n	Communication	Gross motor	Fine motor	Problem solving	Personal-social	Total score
< 28 weeks							
GTN	4	30.00 (21.21)	53.75 (9.46)	51.25 (11.82)	48.75 (8.54)	41.67 (17.56)	225.00 (52.92)
Placebo	9	41.11 (16.35)	32.78 (21.23)	42.22 (11.49)	40.56 (12.86)	43.33 (14.36)	200.00 (57.99)
P		0.32	0.09	0.22	0.27	0.87	0.53
28 to 32 weeks							
GTN	13	41.92 (14.37)	37.31 (21.37)	50.77 (7.03)	46.92 (11.99)	46.92 (11.28)	223.85 (48.52)
Placebo	6	44.17 (11.58)	48.33 (14.38)	48.33 (12.52)	47.50 (12.94)	43.33 (12.91)	231.67 (50.66)
P		0.74	0.27	0.59	0.93	0.55	0.75
33 to 36 weeks							
GTN	9	37.78 (15.02)	34.44 (21.42)	41.11 (16.35)	35.56 (15.09)	45.00 (15.81)	193.89 (49.29)
Placebo	10	39.00 (16.79)	35.50 (21.53)	41.82 (16.62)	43.18 (16.32)	41.36 (21.69)	196.00 (72.72)
P		0.87	0.92	0.93	0.30	0.68	0.94
≥ 37 weeks							
GTN	29	50.69 (10.15)	45.86 (16.48)	51.72 (11.89)	51.38 (9.53	46.72 (13.32)	246.38 (41.64)
Placebo	31	44.36 (12.57)	53.07 (7.82)	51.77 (9.96)	45.97 (12.41)	49.84 (9.62)	245.00 (32.19)
P		0.05	0.18	0.99	0.06	0.30	0.89

Abnormal scores below the established standard cut-off points in five domains are shown in Table 5. At the two-year follow-up, the frequencies of abnormal domain scores in the placebo arm appeared to be higher than those in the GTN arm, although the differences were not statistically significant.

DISCUSSION

Our follow-up study of infants born to mothers enrolled in the GTN trial did not find significant differences in the developmental performance between the GTN and placebo arms. This finding suggests that GTN use had no impact on child developmental performance. Most studies of tocolytic agents have only examined maternal and neonatal morbidity, mortality, and side effects; very few studies have examined the long-term impact on child developmental performance.[12,13] No differences in development or neurodevelopmental outcomes were reported after use of either ritodrine or placebo[12] or after use of either GTN patches or standard β2 agonist.[13]

As our trial suggested, the use of transdermal GTN may reduce neonatal morbidity and mortality by both a prolongation of pregnancy itself and a potential nontocolytic effect of GTN such as a direct effect on uterine or placental

Table 4. Total score and domain score of ASQ between the GTN and placebo arms by gestational age category in two-year follow-up (mean score [±SD])

	n	Communication	Gross motor	Fine motor	Problem solving	Personal-social	Total score
< 28 weeks							
GTN	3	41.67 (31.75)	55.00 (5.00)	55.00 (8.66)	51.67 (14.43)	43.33 (16.07)	246.67 (71.12)
Placebo	5	41.00 (20.43)	45.00 (12.25)	43.00 (13.04)	41.00 (17.10)	46.00 (18.17)	216.00 (75.94)
P		0.97	0.24	0.21	0.40	0.84	0.59
28 to 32 weeks							
GTN	11	52.73 (11.91)	46.36 (14.51)	50.00 (9.49)	46.36 (15.35)	49.55 (11.06)	245.00 (50.89)
Placebo	3	40.00 (26.46)	21.67 (16.64)	40.00 (21.79)	28.33 (20.21)	33.33 (27.54)	163.33 (110.15)
P		0.49	0.22	0.51	0.11	0.42	0.33
33 to 36 weeks							
GTN	7	57.14 (4.88)	49.28 (18.80)	52.14 (6.36)	49.29 (12.05)	51.43 (14.92)	259.29 (47.91)
Placebo	8	50.00 (20.70)	50.63 (20.78)	44.38 (18.79)	46.25 (19.41)	44.38 (19.72)	235.63 (96.93)
P		0.37	0.90	0.30	0.73	0.45	0.57
≥ 37 weeks							
GTN	21	56.19 (6.87)	57.62 (4.90)	54.29 (5.98)	52.86 (4.89)	52.38 (8.46)	273.33 (21.29)
Placebo	25	55.40 (9.23)	54.00 (12.58)	51.40 (9.52)	50.80 (9.54)	51.00 (9.24)	262.60 (42.38)
P		0.75	0.20	0.22	0.33	0.60	0.27

Table 5. Abnormal scores of ASQ between the GTN and placebo arms

	One-year follow-up			Two-year follow-up		
	Abnormal n (%)	Abnormal n (%)		Abnormal n (%)	Abnormal n (%)	
	GTN	Placebo	*P*	GTN	Placebo	*P*
Communication	2 (3.6)	2 (3.6)	0.62	4 (9.5)	4 (9.8)	0.97
Gross motor	6 (10.9)	5 (8.9)	0.73	5 (11.9)	7 (17.1)	0.50
Fine motor	1 (1.8)	2 (3.6)	0.99	1 (2.4)	6 (14.6)	0.17
Problem solving	4 (7.3)	5 (8.9)	0.75	4 (9.5)	6 (14.6)	0.47
Personal-social	4 (7.3)	2 (3.6)	0.66	5 (11.9)	7 (17.1)	0.50

blood flow.[1] We report here no significant impact of GTN use on long-term child developmental performance.

With the current focus on family-centred care, parental involvement in the assessment process and utilization of the parents' unique knowledge of their child's capabilities have become central in the establishment of a child's developmental status.[14] We therefore selected ASQ as our follow-up monitoring tool. Several studies have shown that parents are capable of judging their children's performance well, and that their concerns about their children's developmental delays are well founded.[3–6,15] Hollie et al. reported that ASQ at 12 and 24 months had the highest sensitivity and specificity in detecting children with developmental disabilities or delays.[6,16] The ASQ had been used for developmental monitoring in several large-scale pediatric research studies, including the Magpie Trial,[17] and follow-up monitoring of premature infants and pediatric heart patients.[14,17,18] However, the potential limitation of using ASQ in this study still exists. Although the sensitivities are high, the ASQ is only a screening tool; developmental disabilities or delays are detectable only by definitive clinical assessment and follow-up.

One of the major limitations of this study is the relatively small sample size. Only 111 children at 12 months of age (follow-up rate of 72.5%) and 83 children at 24 months of age (follow-up rate of 54.2%) completed the full ASQ. However, there were no differences in baseline characteristics between those who did and did not complete the ASQ

from the original trial, so the bias introduced by loss of follow-up would be minimal.

CONCLUSION

At two-year follow-up, we found no significant difference in the ASQ domain and total scores between the offspring of women treated for preterm labour with GTN and those who received placebo. Use of GTN as a tocolytic in women with preterm labour resulted in a trend towards reduced abnormalities in the offspring.

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