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**LONG-TERM OUTCOME OF PRETERM INFANTS
TREATED WITH NASAL
CONTINUOUS POSITIVE AIRWAY PRESSURE**

THESE

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RESUME

DEVENIR A LONG-TERME DES ENFANTS PREMATURES TRAITÉS PAR VENTILATION EN PRESSION POSITIVE CONTINUE

La ventilation en pression positive continue (Continuous Positive Airway Pressure, CPAP), utilisée pour la première fois chez les prématurés en 1971, est une technique actuellement très largement utilisée dans les unités néonatales. L'utilisation de la CPAP présente de nombreux avantages à court terme: diminution de la fraction maximale inspirée d'oxygène, de la durée de l'oxygénothérapie, du taux d'intubation et donc du recours à une ventilation mécanique, réduction de l'utilisation des amines, des curares et de la morphine, possible prévention de l'apparition d'une bronchodysplasie pulmonaire, et possibles réductions du nombre d'infections postnatales et des entérocolites nécrosantes. Mais peu d'études existent concernant les effets à long terme de la CPAP sur le neurodéveloppement et la croissance, qui constituent l'objectif de la présente étude.

L'utilisation systématique de la CPAP comme alternative à la ventilation mécanique a été introduite à Lausanne en 1998. La population cible de cette étude est constituée des prématurés nés à moins de 32 semaines de gestation ou pesant moins de 1500 g à la naissance; ils ont été systématiquement suivis jusqu'en âge préscolaire dans le cadre de l'étude de cohorte «Unité de Développement, CHUV». L'originalité de ce travail réside dans le fait d'évaluer le neurodéveloppement et la croissance à long terme d'enfants prématurés traités préférentiellement avec la CPAP, en comparaison avec un groupe historique contrôle traité par d'autres modes ventilatoires, en tenant compte de nombreux autres paramètres néonataux.

Du point de vue du neurodéveloppement, l'usage de la CPAP montre une tendance à diminuer l'incidence d'hémorragie intraventriculaire et le risque d'avoir un mauvais neurodéveloppement à 6 mois. Ces résultats positifs sur le neurodéveloppement s'estompent à l'âge de 18 mois, où persiste néanmoins une valeur plus élevée du quotient de développement, et disparaissent complètement en âge préscolaire.

Du point de vue de la croissance, l'utilisation de la CPAP ne montre aucun effet sur le poids, mais par contre un effet positif sur la taille à 6 et 18 mois et sur le périmètre crânien à 6 mois, 18 mois et en âge préscolaire.

Malgré le caractère non randomisé de cette étude, les résultats positifs obtenus ici permettent sans conteste de s'assurer d'une utilisation de la CPAP sans effet négatif sur le neurodéveloppement et la croissance, et fournissent donc un argument supplémentaire pour l'utilisation systématique de la CPAP chez les prématurés.

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Long-term outcome of preterm infants treated with nasal continuous positive airway pressure

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Abstract This study's aim was to assess neurodevelopmental and growth outcome until the age of 4 years of premature infants placed on early nCPAP, in the setting of the neonatal intensive care unit (NICU) and follow-up program of the Division of Neonatology of the Department of Pediatrics of the University Hospital, Lausanne, Switzerland. All consecutive inborn infants weighing <1500 g or <32 weeks of gestational age admitted to the NICU during two periods of 12 months—7.1996–6.1997 and 7.1998–6.1999—were compared before and after the systematic application of early nCPAP. Of 172 infants admitted to the NICU, 150 (87%) survived. 126 (84%) were tested at 6 months' corrected age, 121 (81%) at 18 months' corrected age, and 117 (78%) at the age of 4 years. Detailed perinatal data were collected. Follow-up included neurological examination, developmental testing and measurement of growth parameters. Statistical analyses were performed. Early application of nCPAP and avoidance of mechanical ventilation showed no adverse effects on neurodevelopment and growth. A significantly higher developmental quotient was found in the nCPAP group at 18 months' corrected age. Several trends were also noted in the nCPAP group with a decrease of intraventricular hemorrhage and in "abnormal neurodevelopment" at 6 months corrected age, a bigger

head circumference at all different tested ages and a greater height at 6 and 18 months corrected ages. In conclusion, our study of developmental outcome documents the absence of any harmful effect of early application of nCPAP to treat respiratory failure in very low birthweight infants.

Keywords Continuous positive airway pressure · Neurodevelopment · Growth · Newborn · Very low birthweight infants

Abbreviations

nCPAP	nasal continuous positive airway pressure
VLBW	very low birth weight
DQ	developmental quotient
GII	general intellectual index
NBRS	neurobiological risk score
IVH	intraventricular hemorrhage
PVL	periventricular leukomalacia
ROP	retinopathy of prematurity
AER	auditory evoked responses
DQ	developmental quotient
GII	general intellectual index

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Introduction

Early nasal continuous positive airway pressure (nCPAP) use for premature infants with respiratory distress of various origins has recently been widely introduced in neonatal intensive care. It has been shown to lower the intubation rate and shorten O₂ therapy without altering neonatal mortality and morbidity [1, 7, 14, 21, 28]. A decreased incidence of bronchopulmonary dysplasia has

diagnosis of clinical chorioamnionitis included a pathological placenta or at least two of the following conditions (or only one if associated with an antibiotic treatment): maternal temperature $>38^{\circ}\text{C}$ on two occasions, maternal CRP >20 mg/L, maternal leukocytosis ($>20 \times 10^9/\text{L}$ white blood cells), or positive bacterial culture of amniotic fluid obtained by amniocentesis. Duration of the different types of respiratory support (nCPAP, mechanical ventilation, oxyhood, and high-frequency oscillatory ventilation) was precisely collected. Intubation rate and incidence of pneumothorax were noted. Chronic lung disease was considered if infants had either supplemental O_2 requirements ≥ 28 days, or beyond 36 weeks [3, 35]. Therapies including sedation and pressor support were compared between the groups.

Short-term outcome included results of ultrasonographic examination of the brain [10, 29], retinopathy of prematurity (ROP) screening [6] and auditory evoked responses (AER) [30]. Infants were evaluated at follow-up with a medical history, a physical examination, a standard neurological examination and developmental testing. Development was tested routinely by using at 6 and 18 months of corrected age the Griffiths' Developmental Scales with calculation of a "developmental quotient" (DQ) [15], and mean and standard-deviations were those defined in the revised version of the Griffiths scales [20]. At the age of 4 years the McCarthy developmental scales with calculation of a "general intellectual index" (GII) [27] was used. Certified testers who performed the neurological and developmental examinations were not implicated in the analyses of this study. Major impairments included conditions that almost inevitably had a major effect on the child's life such as cerebral palsy, severe visual impairment, neurosensory hearing loss, mental retardation, epilepsy and severe psychological disorder, as defined by Fawer et al. [13]. Neuropsychological anomalies involved less severe organic conditions including neuromotor signs, minor visual impairment, minor hearing loss, language disorder and behavior disorder, as defined by Fawer et al. [13]. Patients were classified as "normal" if their developmental testing scores were less than one standard-deviation below average, as "mild retardation" if scores were between one and two standard-deviations below average, and as "severe retardation" if scores were more than two standard-deviations below average [15, 20, 27]. Patients were classified as having an "abnormal neurodevelopment" if they had at least one minor neurological abnormality or if their developmental testing scores were more than one standard-deviation below average. Weight, height and head circumference measured at the different testing ages were expressed in percentiles derived by relating the measures to the infants' corrected age, according to the Swiss national growth curves [22].

Differences in neonatal data and neurodevelopmental outcome between the groups were assessed in an univariate approach by the nonparametric Wilcoxon rank-sum (Mann-Whitney) test for continuous values or Fisher's exact test for categorical data.

For research questions (related to the effects of nCPAP) the p value was set at 0.001 applying a Bonferroni correction for the 50 tests that were performed.

In order to control the plausible effects of the neonatal variables that were statistically different between the two groups on outcome, and to determine the exact influence of nCPAP, all comparisons at the different ages were adjusted for these variables. Baseline comparisons of the two treatment groups was set at $p < 0.01$ to determine the neonatal variables for which an adjustment was warranted in later comparisons. The level of 0.01 was chosen to be sure to include all variables that might be different between the two groups and then have a plausible impact.

Furthermore, in order to control the effects of gestational age and intrauterine growth retardation, considered important determinants of outcome, we performed a complementary analysis. Using children in the two groups who were tested at the different ages, a matched pair analysis was performed using gestational age (± 2 days) and small for gestational age status as matching criteria, choosing (arbitrarily) the first born match when several were available.

All calculations and tests were performed using the statistical software package Stata, Release 8.2 (Stata Corp., College Station, TX).

Results

The main neonatal characteristics of our population are described in Table 1. The two groups were comparable regarding most perinatal and neonatal data, except gestational age, clinical infection, thrombocytopenia, hypomagnesaemia, chorioamnionitis and hypothermia. Of note, there was no statistical difference in birth weight, sex distribution, socio-economic status, or total hospital stay. There was also no statistical difference in neurobiological risk score. The survival rate in infants weighing <1500 g or born at <32 weeks gestational age was 88% ($n=82$) in the control group and 86% ($n=68$) in the nCPAP group. The mortality rates of the control group and the nCPAP group were 12% (11/93) and 14% (11/79), respectively, and were not statistically different. This is in general accordance with what has been previously described in the literature [26], describing a mean mortality rate in VLBW of 8% with a range between 3 and 14%. Among the twenty-two deceased patients (13%), 7 died during the first day (extreme prematurity, one in the control group and six in the nCPAP

Table 2 includes the short-term outcome measurements (intraventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity, and auditory evoked responses) and compares the findings of both groups including either the entire group or the findings restricted to survivors included in the long-term follow-up. There was no statistical difference between the two groups on the incidence of intraventricular hemorrhage and periventricular leukomalacia. Numbers of retinopathy of prematurity stages 3 or above and abnormal auditory evoked response were similar between the two groups.

Tables 3, 4 and 5 present the results of the neurodevelopmental examination at 6 months, 18 months, and at 4 years of age, respectively. The only significant difference

was a higher mean developmental quotient restricted to the 18 month examination in the patient group with preferential use of nCPAP ($p=0.0002$). The two modes of ventilatory approach had no statistical influence on the other neurodevelopmental data.

Figure 1 presents the evolution of growth parameters at the different ages. The only significant difference was a taller height equally restricted to the 18-month examination in the nCPAP group ($p=0.001$). The other comparisons did not show any statistical difference.

Perinatal variables that were statistically different between the two groups were gestational age, clinical infection, thrombocytopenia, hypomagnesaemia, chorioamnionitis and hypothermia, as detailed in Table 1. Because

Table 2 Short-term outcome

	Control group all patients, <i>n</i> =93	nCPAP group all patients, <i>n</i> =79	<i>p</i> * (adjusted <i>p</i>)	Control group survivors	nCPAP group survivors	<i>p</i> * (adjusted <i>p</i>)	Matched pair analysis <i>p</i> *
Intraventricular hemorrhage (IVH)							
Number of examined infants	<i>n</i> =88	<i>n</i> =78		<i>n</i> =78	<i>n</i> =68		
Grades † [<i>n</i> (%)]			0.4 (0.03)			0.2 (0.09)	0.1
Grade 0	64 (72.7)	60 (76.9)		61 (78.2)	56 (82.4)		
Grade 1	7 (8.0)	9 (11.5)		6 (7.7)	9 (13.2)		
Grade 2	9 (10.2)	3 (3.9)		9 (11.5)	2 (2.9)		
Grade 3	2 (2.3)	3 (3.9)		1 (1.3)	1 (1.5)		
Grade 4	6 (6.8)	3 (3.9)		1 (1.3)	0 (0.0)		
Periventricular leukomalacia (PVL)							
Number of examined infants	<i>n</i> =88	<i>n</i> =78		<i>n</i> =78	<i>n</i> =68		
Grades ‡ [<i>n</i> (%)]			0.8 (0.8)			0.8 (0.7)	0.7
Grade 0	76 (86.4)	68 (87.2)		67 (85.9)	60 (88.2)		
Grade 1	8 (9.1)	9 (11.5)		7 (9.0)	7 (10.3)		
Grade 2	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		
Grade 3	3 (3.4)	1 (1.3)		3 (3.9)	1 (1.5)		
Grade 4	1 (1.1)	0 (0.0)		1 (1.3)	0 (0.0)		
Retinopathy of prematurity (ROP)							
Number of examined infants	<i>n</i> =67	<i>n</i> =61		<i>n</i> =67	<i>n</i> =60		
Stages § [<i>n</i> (%)]			1.0			1.0	
Stage 3 or above	2 (3.0)	1 (1.6)		2 (3.0)	1 (1.7)		
Auditory evoked responses (AER)							
Number of examined infants	<i>n</i> =43	<i>n</i> =41		<i>n</i> =43	<i>n</i> =40		
Classification [<i>n</i> (%)]			0.02 (0.8)			0.02 (0.9)	0.03
0 = normal	29 (67.4)	30 (73.2)		29 (67.4)	30 (75.0)		
1 = first recording abnormal (second recording normal)	6 (14.0)	11 (26.8)		6 (14.0)	10 (25.0)		
2 = second recording abnormal (first recording normal)	3 (7.0)	0 (0.0)		3 (7.0)	0 (0.0)		
3 = first and second recordings abnormal	5 (11.6)	0 (0.0)		5 (11.6)	0 (0.0)		

* For research questions relating to the effects of nCPAP, *p* (and adjusted *p*) < 0.001 was used to determine significant effects. Adjusted *p* represented the *p* values of analyses performed again after adjusting for the variables that were statistically different between the two groups

† Classification of PVL, according to de Vries et al. [10]

§ Classification of ROP, according to the International Committee for the Classification of the late Stages of Retinopathy of Prematurity [6]

|| Classification of AER, according to Pasman et al. [30]

Table 5 Neurodevelopmental outcome at age of 4 years

	Control group, <i>n</i> =57†	nCPAP group, <i>n</i> =60 †	<i>p</i> * (adjusted <i>p</i>)	Matched pair analysis, <i>p</i> *
Age at testing, months [mean±SD]	48.9±5.4	47.2±3.3	0.04	
Neurodevelopmental outcome				
General intellectual index (GII) †				
General intellectual index (GII) [mean±SD]	101.6±17.1	99.7±17.7	0.2 (0.6)	0.8
Ranges			0.4 (1.0)	1.0
1 = normal=>84 [<i>n</i> (%)]	46 (80.7)	47 (78.3)		
2 = mild retardation=68–84 [<i>n</i> (%)]	8 (14.0)	12 (20.0)		
3 = severe retardation=<68 [<i>n</i> (%)]	3 (5.3)	1 (1.7)		
Neurological status			0.08 (0.7)	0.6
0 = normal [<i>n</i> (%)]	23 (40.4)	26 (43.3)		
1 = 1 neuropsychological anomaly [<i>n</i> (%)]	21 (36.8)	24 (40.0)		
2 = >1 neuropsychological anomalies [<i>n</i> (%)]	8 (14.0)	7 (11.7)		
3 = 1 major impairment [<i>n</i> (%)]	0 (0.0)	3 (5.0)		
4 = 1 major impairment + ≥1 neuropsychological anomalies [<i>n</i> (%)]	5 (8.8)	0 (0.0)		
5 = >1 major impairments [<i>n</i> (%)]	0 (0.0)	0 (0.0)		
6 = ≥1 major impairments + ≥1 neuropsychological anomalies [<i>n</i> (%)]	0 (0.0)	0 (0.0)		
"Abnormal neurodevelopment" ‡	34 (59.7)	36 (60.0)	1.0 (0.9)	0.5

* For research questions relating to the effects of nCPAP, *p* (and adjusted *p*)<0.001 was used to determine significant effects. Adjusted *p* represented the *p* values of analyses performed again after adjusting for the variables that were statistically different between the two groups

† General Intellectual Index was calculated using the McCarthy's developmental scales [27]

‡ An "abnormal neurodevelopment" was defined by a general intellectual index more than 1 standard-deviation below average (less than 84) [27] or a pathological neurological status

these significant variables might have a plausible relationship to neurological and growth outcomes, analyses were performed again after adjusting for these variables and the results were similar. Mean developmental quotient at 18 months examination in the patient group with preferential use of nCPAP remained higher (*p*=0.006). Height was taller at 18 months of corrected age, but the difference was not statistically significant (*p*=0.11). Of note, after adjusting for the variables mentioned above, infants with preferential use of nCPAP tended to have a less severe grade of intraventricular hemorrhage (*p*=0.027) with a risk divided by two; however, this finding did not reach statistical significance. In the same way, head circumference tended to be bigger in infants with preferential use of nCPAP at the different tested ages, but this did not reach statistical significance (respectively, *p*=0.039 at 6 months of corrected age, *p*=0.030 at 18 months of corrected age, and *p*=0.12 at the age of 4 years).

Smaller mean gestational age was observed in the nCPAP group (28.8 weeks versus 30.1 weeks for the control group, *p*=0.0007), and intrauterine growth retardation (weight at birth <10th percentile for gestational age) tended to be more frequent in the control group (39% versus 23% in the nCPAP group, *p*=0.033). Considering that these factors are important determinants of outcome we performed an additional paired comparison, as outlined in the methods section. Thirty-eight pairs of children were thus formed and the results reinforced the trends noted in the previous analyses. The value of DQ at 18 months was

significantly higher in the nCPAP group (*p*<0.0001). Height was significantly taller in the nCPAP group at 6 months (*p*<0.0005) and at 18 months (*p*<0.0001). A trend towards a diminution in the incidence of intracranial hemorrhage in the nCPAP group was noted (*p*=0.1, with a risk divided by two, which may be clinically relevant). Head circumference was larger and significantly so at all three postnatal ages in the group with preferential use of nCPAP (*p*<0.001 at 6 months, *p*<0.008 at 18 months and *p*<0.009 at the age of 4 years).

Discussion

The management of respiratory distress in premature newborn infants using preferentially early nasal nCPAP rather than conventional ventilation has gained wider acceptance over the last decade. It has been shown to decrease respiratory morbidity [2, 7–9, 11, 14, 21, 28]. Its influence on other neonatal outcome [7, 11, 12] is debated. Controlled data on long-term neurodevelopmental outcome and somatic growth are not yet available.

The results of our study confirm the favorable influence of nCPAP on early neonatal outcome measurements, and document the safety of this approach in terms of long-term neurodevelopmental outcome and somatic growth. Indeed, follow-up data up to 4 years of age of newborn infants <1500 g and/or <32 weeks gestation treated either with

ductus arteriosus was not different. These combined findings could suggest a favorable influence of nCPAP on cerebral hemodynamics. This could happen via a mechanism including reduced intrathoracic pressure swings and more physiological venous return and cardiac output, the disturbances of which have been implicated as a possible mechanism for intracranial bleeding [7]. In contrast, the incidence of periventricular leukomalacia was unchanged (adjusted $p=0.84$). Of note, the incidence of chorioamnionitis, a known risk factor of periventricular leukomalacia, tended to be more frequent in the nCPAP group, and might then have blurred some positive effects of nCPAP on the incidence of periventricular leukomalacia. However this item was included in the variables that were statistically different between the two groups and the incidence of periventricular leukomalacia was not different between the two groups in the analyses after adjusting for these variables. Moreover, physiopathological mechanisms underlying periventricular leukomalacia seemed to be different from those of intracranial hemorrhage, and might therefore be less subject to the mode of ventilatory support.

It is important to note that all infants diagnosed with IVH 3-4, PVL 2-4 or ROP 3-4 received mechanical ventilation during the first week of life (duration between one day and more than one week).

With regards to long-term outcome, the use of nCPAP appears to diminish the risk of having an abnormal neurodevelopment at 6 months of age (22% versus 39% in the control group, adjusted $p=0.093$) and to diminish as well the risk of having a DQ (developmental quotient) below one standard deviation at 6 months (2% versus 8% in the control group, adjusted $p=0.12$). This effect on the DQ seems to decrease with advancing age but is still significant at 18 months with values of 110.6 versus 104.8 after adjustment ($p=0.006$), and disappears at the age of 4 years. Some of the neonatal effects of nCPAP on neurodevelopment might be blurred with advancing age (intervening diseases, rehospitalization rate, stimulating environment, resort to special education resources), explaining why there is no more difference at the age of 4 years.

When considering somatic growth, nCPAP use was not associated with any difference in weight whereas height tended to be taller at 6 months ($p=0.04$, adjusted $p=0.084$) and at 18 months as well ($p=0.001$, adjusted $p=0.11$). Head circumference tended to be larger at 6 months, 18 months and at the age of 4 years (respectively, $p=0.086$ /adjusted $p=0.039$ at 6 months corrected age; $p=0.24$ /adjusted $p=0.030$ at 18 months of corrected age; and $p=0.03$ /adjusted $p=0.12$ at age of 4 years). Considering the link between head growth and future cognitive function [16, 17, 33], it seems important that this potential effect on head circumference be further evaluated since it could be an argument in favor of nCPAP use.

In this study, we have collected a large number of neonatal factors known to potentially influence neurodevelopment and growth. We determined for each infant its NBRS [4]; there was no statistical difference in NBRS between the 2 groups, confirming that the infants in both groups were comparably sick and equally at risk. Various perinatal variables were statistically different between the two groups (gestational age, clinical infection, thrombocytopenia, hypomagnesaemia, chorioamnionitis and hypothermia) and analyses were adjusted for these variables.

Considering all neonatal factors that were different between the two groups, and which motivated the adjustment, it is important to refer to gestational age. Gestational age was significantly lower in the nCPAP group (28.8 versus 30.1 weeks gestation in the control group, $p=0.0007$), and could have had a disproportionately stronger negative influence on neurodevelopment [18, 26]. The difference in gestational age between the groups could have therefore canceled some positive effects of nCPAP in comparison to conventional ventilation. The same consideration was given to the association of fetal growth retardation (although not significantly different between the groups, $p=0.36$) [24, 32, 34]. For these reasons we performed additional matched pair analyses (matching individuals according to their gestational age and the presence or absence of fetal growth retardation). The results of these pair analyses have to be considered in view of the reduction in the number of pairs matched (38 pairs) but can be taken to confirm the results of our previous analyses.

This study describes a fairly recent population of consecutively born premature infants who have been managed in a modern neonatal ICU environment during a relatively short period of time (3 years). The design of the study was a retrospective "before-after trial" with a limited sample size, and presented the major limitation of not being a randomized study. It is important to note that neonatal and neurodevelopmental data were collected separately, in a coded and blinded fashion. Certified testers who performed the neurological and developmental examinations were not implicated in the analyses of this study, and were blinded to the type of respiratory support these infants received.

Another limitation is the difference in follow-up ratio between the two study periods, with less drop-outs in the group with preferential use of nCPAP. However, infants who were lost to follow-up did not differ from the studied groups concerning their perinatal and neonatal assessment and their neurobiological risk score. Of the 33 infants lost to follow-up, no information was available for 16 infants who moved away from the test center. Some neurodevelopmental information was obtained with a structured phone interview or a follow-up in another test center for 17 infants (12 in the control group and 5 in the nCPAP group). In the control group, four children were described as

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