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ORIGINAL ARTICLE

Effect of prophylactic CPAP in very low birth weight infants in South America

JR Zubizarreta[1,2,10], SA Lorch[3,4,5,6,10], G Marshall[7,8], I D'Apremont[9] and JL Tapia[9] for the South American Neocosur Network

OBJECTIVE: The objective of this study was to examine the effect of prophylactic continuous positive airway pressure (CPAP) on infants born in 25 South American neonatal intensive care units affiliated with the Neocosur Neonatal Network using novel multivariate matching methods.

STUDY DESIGN: A prospective cohort was constructed of infants with a birth weight 500 to 1500 g born between 2005 and 2011 who clinically were eligible for prophylactic CPAP. Patients who received prophylactic CPAP were matched to those who did not on 23 clinical and sociodemographic variables ($N = 1268$). Outcomes were analyzed using the McNemar's test.

RESULTS: Infants not receiving prophylactic CPAP had higher mortality rates (odds ratio (OR) = 1.69, 95% confidence interval (CI) 1.17, 2.46), need for any mechanical ventilation (OR = 1.68, 95% CI 1.33, 2.14) and death or bronchopulmonary dysplasia (BPD) (OR = 1.47, 95% CI 1.09, 1.98). The benefit of prophylactic CPAP varied by birth weight and gender.

CONCLUSIONS: The implementation of this process was associated with a significant improvement in survival and survival free of BPD.

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INTRODUCTION

With an increasing number of infants delivering prematurely throughout the world, there is growing attention toward optimizing the disease-free survival of these patients, particularly surrounding short- and long-term pulmonary outcomes. Since 2008, there have been several randomized trials in both the developed and developing world to investigate the impact of using prophylactic continuous positive airway pressure (CPAP) during or immediately following the initial resuscitation of the very low birth weight (VLBW) infant.[1] These trials suggest that prophylactic CPAP reduces the need for surfactant and mechanical ventilation compared with either prophylactic intubation with surfactant or oxyhood alone. However, rates of mortality and bronchopulmonary dysplasia were not conclusively lower in infants treated with CPAP because of either insufficient sample size or the size of the clinical effect. With this published evidence, more policies support the use of CPAP in the initial resuscitation of VLBW infants.[2,3]

What is less understood is how the outcomes of VLBW infants are modified when implementing prophylactic CPAP into standard clinical practice. Although there is some evidence showing improvement in infection rates with the implementation of infection control programs in China[4] and Nicaragua,[5] there is little information on the outcomes of implementing such a change in respiratory management in populations outside of Europe and the United States,[6] where there are different patient populations that survive to delivery, different medical systems, and fewer resources to obtain and use CPAP effectively.[7,8] There is limited evidence to assess the impact of CPAP for infants of different birth weights, which may be important to optimize outcomes in hospitals where CPAP is a rare, limited resource for use in the delivery room. Finally, the association between CPAP and the outcomes may be influenced by selection bias: children receiving CPAP may have a lower illness severity than infants intubated in the delivery room, which may influence the observed outcomes.

Thus, the goal of this project was to evaluate the effect of prophylactic CPAP on rates of mortality and bronchopulmonary dysplasia in 25 hospitals participating in the Neocosur network between 2005 and 2011. Neocosur is a voluntary nonprofit network of neonatal intensive care units (NICUs) in Argentina, Brasil, Chile, Paraguay, Peru and Uruguay, whose main goal is to continuously improve neonatal health in the region (www.neocosur.org). Use of CPAP has gradually increased in the Network, with use of CPAP at any time of the hospital stay increasing from 27% in 2001 to 60.9% in 2012. Prophylactic CPAP was rarely used before 2005; however, after at least two workshops were held to teach the correct use of prophylactic CPAP, this rate has increased to 15.5% in 2012 (non-published data, Neocosur Network). To handle the potential problem of selection bias in the infants receiving prophylactic CPAP, we exclude infants whose clinical status may have resulted in the immediate use of mechanical ventilation, use recent optimal multivariate matching methods to control for selection bias based on observed covariates and conduct sensitivity analyses of the results to bias from unobserved covariates.

[1]Division of Decision, Risk and Operations, Columbia University, New York, NY, USA; [2]Department of Statistics, Columbia University, New York, NY, USA; [3]Center for Outcomes Research, The Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Division of Neonatology, Department of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, PA, USA; [5]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, PA, USA; [6]Senior Fellow, Leonard Davis Institute for Health Economics, University of Pennsylvania, Philadelphia, PA, USA; [7]Department of Statistics, Pontificia Universidad Catolica de Chile, Santiago, Chile; [8]Department of Public Health, Pontificia Universidad Catolica de Chile, Santiago, Chile and [9]Division de Pediatria, Departamento de Neonatologia, Escuela de Medicina, Pontificia Universidad Catolica de Chile, Santiago, Chile. Correspondence: Dr SA Lorch, Pediatrics, Center for Outcomes Research, Children's Hospital of Philadelphia, 3535 Market Street, Suite 1029, Philadelphia, PA 19104, USA.
E-mail: lorch@email.chop.edu
[10]Co-first author.
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MATERIALS AND METHODS

Study site and patients

The study population was all the infants with birth weights between 500 and 1500 g, born in one of the 25 NICUs in Neocosur between 2005 and 2011. This network provides a continuous database that prospectively gathers information from all inborn VLBW infants (birth weight from 500 to 1500 g) from the participating centers using predefined diagnostic criteria and online data entry. Information includes sociodemographic information, maternal and pregnancy data, and detailed clinical information about the treatment received by VLBW infants in each NICU. The network data entry is reviewed by two trained nurses who contact centers in case of missing or inconsistent data. In addition, at least once a year, the database is checked by a statistician and a physician belonging to the Database Unit to assess the validity of the data. The Ethics Committee of Pontificia Universidad Catolica de Chile approved this study. From all eligible patients included in the Neocosur data set, we excluded all the infants that died in the delivery room, had missing values for the treatment variable or one of the outcomes below, or whose clinical status would make them ineligible for prophylactic CPAP. Those infants would either be intubated as part of their initial resuscitation in the delivery room or have a 5- min APGAR score less than or equal to 7.

Covariates and matching methodology

Among others, the Neocosur data included prospective information on potential confounders of the treatment such as gestational age, birth weight, delivery type, number of fetuses, 1- min APGAR score and use of prenatal corticosteroids. It also included mother's age, hypertension, diabetes, educational level and pregnancy controls. In total, we had 23 covariates for which we needed to adjust in the analysis (see Tables 1, 2 and 3 for a list of these covariates). To adjust for these covariates, we used optimal multivariate matching,[1,9,10] specifically matching based on mixed integer programming that can adjust for observed covariates in a transparent manner.[11-15] This type of matching allows the investigator to enforce precise forms of covariate balance in the matched samples by design.[16-19]

We enforced three different forms of balance depending on the prognostic importance of the covariates. To account for potential differences in practice styles, we matched pairs exactly for NICU and also for gender.[2,4,9,20-22] For other important nominal covariates, including gestational age, delivery type, prenatal corticosteroids, year of birth and mother's education, we matched with fine balance.[4,21] Fine balance results in perfect balance of the marginal distributions of nominal covariates across the matched groups, but unlike exact matching, it does not require pairs to be matched within the same category of the nominal covariate. For the rest of the covariates, such as birth weight and 1-min APGAR score, we matched with mean balance.

Outcomes

Our outcomes included: death outside the delivery room; any use of mechanical ventilation; supplemental oxygen at discharge; supplemental oxygen at 36 weeks, administered by any method (nasal cannula, CPAP, mechanical ventilation); death outside the delivery room or oxygen at 36 weeks; any administration of surfactant; late-onset sepsis diagnosed by a positive blood culture; and intraventricular hemorrhage, made by cranial ultrasound or autopsy and classified according to Papile *et al*. and Bursten *et al*.[23,24]

Statistical analysis

The matches were found using the R package mipmatch.[13,25] Covariate balance after matching was assessed using Fisher's exact test for categorical covariates[26] and Wilcoxon's rank-sum test for continuous covariates.[27] Binary outcomes were analyzed using the McNemar's test.[27] The sensitivity of results to bias of unmeasured confounders was assessed using Rosenbaum bounds.[28-30] This method quantifies the amount of unmeasured bias that would need to be present to explain away the conclusions of the study. All statistical calculations analyses were conducted using R version 3.0.0.[25]

Table 1. Distribution of gender and NICUs in the full and study samples before matching and after matching

Covariate	*Before matching* (n = *4968*)				*After matching* (n = *1268*)			
	CPAP (n = *887*)		*Other* (n = *4081*)		*CPAP* (n = *634*)		*Other* (n = *634*)	
	Prop.	*Freq.*	*Prop.*	*Freq.*	*Prop.*	*Freq.*	*Prop.*	*Freq.*
Gender								
Male	0.51	451	0.49	1988	0.51	321	0.51	321
Female	0.49	436	0.51	2090	0.49	313	0.49	313
NICU								
A	0.00	3	0.06	229	0.00	0	0.00	0
B	0.25	220	0.05	216	0.25	157	0.25	157
C	0.00	2	0.05	222	0.00	0	0.00	0
D	0.02	15	0.07	280	0.02	15	0.02	15
E	0.07	62	0.07	276	0.08	48	0.08	48
F	0.06	53	0.07	280	0.06	38	0.06	38
G	0.01	7	0.04	151	0.00	0	0.00	0
H	0.30	262	0.09	356	0.34	213	0.34	213
I	0.14	123	0.05	213	0.14	86	0.14	86
J	0.01	10	0.03	109	0.00	1	0.00	1
K	0.02	20	0.09	353	0.02	14	0.02	14
L	0.05	48	0.03	125	0.06	39	0.06	39
M	0.02	19	0.03	114	0.01	5	0.01	5
N	0.00	0	0.01	21	0.00	0	0.00	0
O	0.02	18	0.03	122	0.02	12	0.02	12
P	0.01	9	0.09	386	0.01	6	0.01	6
Q	0.00	0	0.02	91	0.00	0	0.00	0
R	0.01	9	0.02	78	0.00	0	0.00	0
S	0.00	2	0.05	201	0.00	0	0.00	0
T	0.00	3	0.05	210	0.00	0	0.00	0
U	0.00	2	0.01	25	0.00	0	0.00	0
V	0.00	0	0.00	6	0.00	0	0.00	0
W	0.00	0	0.00	1	0.00	0	0.00	0
X	0.00	0	0.00	16	0.00	0	0.00	0
Y	0.00	0	0.00	0	0.00	0	0.00	0

Abbreviations: CPAP, continuous positive airway pressure; NICU, neonatal intensive care unit. Proportions and frequencies are displayed. We matched pairs exactly for gender and NICU (i.e., within a given NICU, we matched a female to a female and a male to a male), and as a result, both genders and every NICU are equally represented in the treated and control groups after matching.

RESULTS

Covariate balance

Before matching, the sample was composed of 887 infants that received CPAP and a pool of 4081 controls that received other forms of treatment. From this sample, the matching algorithm found 634 pairs that satisfied the desired covariate balance. Tables 1, 2 and 3 display the covariate balance before and after matching. Before matching, the distribution of important covariates differed between the treatment and control population. These differences reached statistical significance for factors such as NICU, gestational age, receipt of antenatal corticosteroids, maternal age, maternal diabetes or hypertension, and multiple gestation pregnancy. After matching, the means of the covariates in Table 3 have differences that are not significant with standardized differences smaller than 0.05. Standardized differences less than 0.2 (ideally less than 0.1) are considered adequate.[31,32] Furthermore, the entire marginal distributions of the means, variances and higher moments of the covariates in Table 2 are perfectly balanced. Finally, the whole joint distribution of the covariates in Table 1 is perfectly balanced via exact matching. These patterns of covariate balance show that the case and control infants are very similar after matching.

Matched analysis

Table 4 shows that infants that did not receive CPAP have a higher odds of death outside the delivery room than those that

Table 2. Distribution of gestational age, delivery type, prenatal corticosteroids, year of birth and mother's education in the full and study samples before and after matching

	Before matching (n = *4968*)					*After matching* (n = *1268*)				
Covariate	*CPAP* (n = *887*)		*Other* (n = *4081*)		P-*value*	*CPAP* (n = *634*)		*Other* (n = *634*)		P-*value*
Gestational age	*Prop.*	*Freq.*	*Prop.*	*Freq.*		*Prop.*	*Freq.*	*Prop.*	*Freq.*	
21	0.00	0	0.00	2	1.000	0.00	0	0.00	0	1.000
22	0.00	0	0.00	1	1.000	0.00	0	0.00	0	1.000
23	0.00	1	0.01	29	0.031	0.00	1	0.00	1	1.000
24	0.01	7	0.02	96	0.002	0.01	7	0.01	7	1.000
25	0.03	25	0.04	157	0.167	0.03	22	0.03	22	1.000
26	0.04	39	0.06	251	0.048	0.05	33	0.05	33	1.000
27	0.09	82	0.08	329	0.253	0.10	62	0.10	62	1.000
28	0.14	127	0.12	496	0.083	0.16	100	0.16	100	1.000
29	0.18	158	0.13	513	< 0.001	0.17	106	0.17	106	1.000
30	0.22	197	0.15	623	< 0.001	0.18	116	0.18	116	1.000
31	0.14	126	0.11	434	0.003	0.13	85	0.13	85	1.000
32	0.07	65	0.11	439	0.002	0.08	50	0.08	50	1.000
33	0.04	33	0.08	314	< 0.001	0.05	30	0.05	30	1.000
34	0.03	23	0.06	235	< 0.001	0.03	19	0.03	19	1.000
35	0.00	2	0.02	101	< 0.001	0.00	2	0.00	2	1.000
36	0.00	2	0.01	48	0.008	0.00	1	0.00	1	1.000
37	0.00	0	0.00	7	0.616	0.00	0	0.00	0	1.000
38	0.00	0	0.00	3	1.000	0.00	0	0.00	0	1.000
39	0.00	0	0.00	1	1.000	0.00	0	0.00	0	1.000
40	0.00	0	0.00	1	1.000	0.00	0	0.00	0	1.000
Delivery type										
Vaginal	0.27	237	0.23	950	0.033	0.20	125	0.20	125	1.000
C-section without labor	0.54	477	0.54	2190	0.970	0.52	332	0.52	332	1.000
C-section with labor	0.19	172	0.23	940	0.018	0.28	177	0.28	177	1.000
Prenatal corticosteroids										
Full dosage (2 or more)	0.92	812	0.80	3279	< 0.001	0.89	567	0.89	567	1.000
Incomplete dosage (1)	0.08	75	0.19	775	< 0.001	0.11	67	0.11	67	1.000
No doses (0)	0.00	0	0.01	27	0.009	0.00	0	0.00	0	1.000
Year of birth										1.000
2005	0.11	94	0.15	616	< 0.001	0.10	65	0.10	65	1.000
2006	0.13	117	0.15	624	0.119	0.15	97	0.15	97	1.000
2007	0.19	166	0.16	671	0.103	0.17	107	0.17	107	1.000
2008	0.20	173	0.17	685	0.056	0.18	116	0.18	116	1.000
2009	0.18	158	0.16	671	0.321	0.20	125	0.20	125	1.000
2010	0.18	162	0.17	689	0.326	0.19	119	0.19	119	1.000
2011	0.02	16	0.03	118	0.085	0.01	5	0.01	5	1.000
Mother's education										
Illiterate	0.00	3	0.01	24	0.458	0.00	3	0.00	3	1.000
Primary School	0.37	329	0.28	1144	< 0.001	0.40	253	0.40	253	1.000
Secondary School	0.48	424	0.43	1742	0.006	0.45	288	0.45	288	1.000
Higher Education	0.10	93	0.16	662	< 0.001	0.11	67	0.11	67	1.000
Education NA	0.04	38	0.12	509	< 0.001	0.04	23	0.04	23	1.000

Abbreviations: CPAP, continuous positive airway pressure; NA, not available. Proportions and frequencies are displayed. We matched pairs with fine balance for these covariates, meaning that after matching each category of every covariate is equally represented in the two groups, but without necessarily constraining two infants from the same covariate category to be matched.

received CPAP (odds ratio = 1.69, 95% confidence interval 1.17, 2.46). This reduction in mortality translated into a 5.3% absolute reduction in mortality (10.0% mortality in prophylactic CPAP group versus 15.3% in the no prophylactic CPAP group). Use of mechanical ventilation and surfactant was significantly higher among infants that did not receive CPAP: odds ratio = 1.68 (95% confidence interval 1.33, 2.14) and odds ratio = 1.75 (95% confidence interval 1.37, 2.24), respectively. After a Bonferroni correction for multiple testing, we obtained a significance threshold of 0.006 and all significant results remained significant at the 5% level.

Figure 1 shows the estimated probability of death versus birth weight by gender for the infants that received CPAP versus those that did not. We observe that the probability of death decreases with birth weight and that, for all birth weights, this probability is higher for infants that did not receive CPAP (dashed curve) than for those that received CPAP (solid curve). Treatment appears to affect female infants differently than male infants: for female infants, the greatest reduction in mortality is for birth weights between 750 and 1100 g, whereas for male infants, the improvement in mortality increases with birth weights smaller than 1000 g. These differences are not statistically

Table 3. Distribution of covariates in the study cohort before and after matching

Covariate	*Before matching* (n = *4968*)			*After matching* (n = *1268*)		
	Mean CPAP (n = *887*)	*Mean other* (n = *4081*)	P-*value*	*Mean CPAP* (n = *634*)	*Mean other* (n = *634*)	P-*value*
Pregnancy control	0.92	0.91	0.359	0.93	0.93	0.913
Pregnancy control NA	0.00	0.00	1.000	0.00	0.00	1.000
Age mother	27.00	28.16	< 0.001	26.55	26.25	0.489
Age mother NA	0.00	0.00	0.365	0.00	0.00	1.000
Diabetes mother	0.05	0.03	0.007	0.03	0.03	0.505
Diabetes mother NA	0.00	0.00	0.558	0.00	0.00	1.000
Hypertension mother	0.35	0.31	0.028	0.31	0.30	0.808
Hypertension mother NA	0.00	0.00	0.155	0.00	0.00	1.000
More than one fetus	0.18	0.23	< 0.001	0.18	0.18	0.883
More than one fetus NA	0.01	0.01	0.219	0.01	0.01	1.000
Birth weight	1175.03	1156.16	0.321	1161.14	1149.33	0.445
Birth weight NA	0.00	0.00	1.000	0.00	0.00	1.000
APGAR 1: 0–3	0.00	0.00	1.000	0.00	0.00	1.000
APGAR 1: 4–6	0.02	0.03	0.002	0.01	0.02	0.500
APGAR 1: 7–10	0.17	0.21	0.002	0.18	0.19	0.561
APGAR 1: NA	0.82	0.75	< 0.001	0.81	0.79	0.398

Abbreviations: CPAP, continuous positive airway pressure; NA, not available. Before applying the matching algorithm, several important covariates had statistically significant differences between the CPAP and non-CPAP groups. After matching, these covariates were statistically similar.

Table 4. Odds ratios after matching for infants not receiving CPAP in the delivery room, compared to infants who received CPAP

Outcome	*OR*	*95% CI*	P-*value*
Death	1.69	(1.17, 2.46)	0.005
Mechanical ventilation	1.68	(1.33, 2.14)	0.000
Oxygen at discharge	1.55	(0.95, 2.57)	0.081
Oxygen at 36 weeks	1.05	(0.76, 1.47)	0.808
Death or oxygen at 36 weeks	1.47	(1.09, 1.98)	0.001
Surfactant	1.75	(1.37, 2.24)	0.000
Late-onset sepsis	0.80	(0.58, 1.10)	0.184
Necrotizing enterocolitis	0.79	(0.56, 1.10)	0.165
Intracranial hemorrhage	1.32	(0.86, 2.03)	0.218

Abbreviations: CI, confidence interval; OR, odds ratio. After a Bonferroni correction for multiple testing, all significant results at the 5% level remain significant. We observe that infants that did not receive CPAP have significantly worse outcomes for death, mechanical ventilation, death or oxygen at 36 weeks and surfactant.

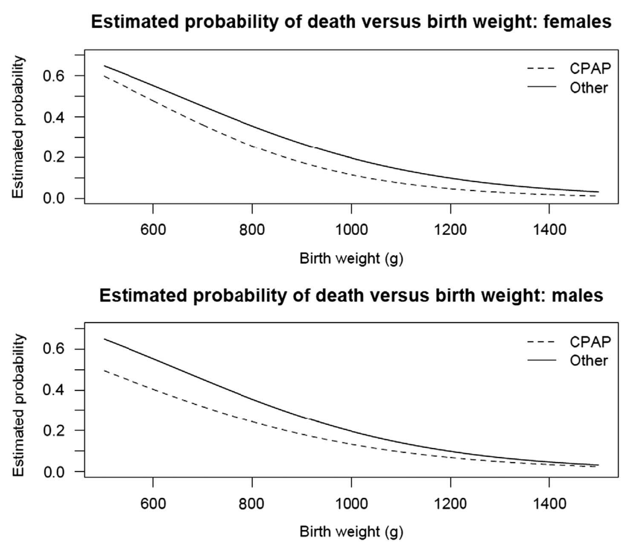

Figure 1. Estimated probability of death with (dashed line) and without (solid line) administration of prophylactic CPAP, for female (top panel) and male infants (bottom panel).

significant when tested with an interaction term in a logistic regression model.

Sensitivity of results to unmeasured bias

The previous results are insensitive to moderate biases due to unmeasured confounders but not to biases of large size. For mortality, we would have to have an unobserved covariate that increased the odds of not receiving prophylactic CPAP and the odds of death by a factor of 1.95 times to explain away the significance of this result, but a smaller unmeasured bias would not.[33] For mechanical ventilation and surfactant, the results are more robust: the unmeasured confounder would have to increase the odds of not receiving prophylactic CPAP and increase the likelihood of receiving either mechanical ventilation or surfactant by a factor of 2.38 times to explain away the estimated effects. There are few, if any, unobserved factors that meet these criteria. For details, see the Supplementary Appendix.

We additionally reran the models excluding the APGAR score requirement. The association between CPAP administration, mortality and mechanical ventilation was stronger, suggesting that without this exclusion criterion, the illness severity of infants in the control group was much greater than their matched counterparts.

DISCUSSION

These data support the ability of the NICUs in the Neocosur network of South American hospitals to implement a change in their respiratory management of infants in the immediate post-delivery period. Previous work from South American NICUs focused on variations in practice or outcomes,[33,34,35] with less information on methods to improve outcomes of VLBW infants. After using novel multivariate matching techniques that better adjust for observed confounders, eligible VLBW infants who receive prophylactic CPAP in the delivery room exhibit 5.3% absolute decrease in overall mortality compared to those that did not receive the treatment. These results support the use of prophylactic CPAP as an initial treatment strategy for infants born in NICUs across Latin America.

Several recent randomized trials found lower rates of mechanical ventilation and surfactant administration in VLBW infants who received CPAP initially.[1,9-12] This result is similar to our findings. Only one study found an improvement in survival: the SUPPORT study found a 27% reduction in mortality for the 24 to 25 week subgroup of patients treated with CPAP, even though the overall study only found a reduction in mortality and bronchopulmonary dysplasia or mortality that did not reach statistical significance.[36] Similar trends in mortality and bronchopulmonary dysplasia were found in other randomized studies. Our study found a 5.3% overall reduction in mortality for infants treated with CPAP without any increase in other adverse outcomes (with the exception of two outcomes, but these were not statistically significant), even though the control population included patients who did not receive prophylactic CPAP and never required additional respiratory support, as well as infants who later required CPAP or mechanical ventilation.[16-19] The matching algorithm provided improved comparisons of the infants who received prophylactic CPAP; control infants were similar, and thus had a similar presentation, to these infants, which improves the assessment of how prophylactic CPAP affected outcomes in these infants. Improved methods of distinguishing which infants in the delivery room may require mechanical ventilation at a later time would likely increase the improvement in mortality of infants receiving prophylactic CPAP in the delivery room.

One potential reason for this difference is the implementation of a change in respiratory practice. The implementation of evidence-based practice can be challenging. There are multiple studies of the difficulty in choosing interventions to implement, overcoming the multiple barriers that exist within and between different health-care organizations, and showing a change in outcomes associated with the implementation.[37-41] As a result, there continues to be practice variation in all aspects of pediatric care throughout the world.[34,41] With the successful implementation of one treatment, though, there may be improvements in other respiratory processes of care that may improve outcomes.

These data also suggest that the effect of CPAP varies by birth weight and gender. There may be several explanations for this finding. The effect of CPAP may be limited in infants with a birth weight under 750 g, as there are fewer numbers of infants who are spontaneously breathing at birth or whose pulmonary development is sufficient to tolerate CPAP. For infants over 1250 g, the risk of mortality is low enough that the study may not be powered to detect the added benefit of CPAP. Gender differences may reflect different overall risk of mortality between sexes or differences in the overall severity of RDS in male infants. The lack of any adverse outcomes in these patient groups, though, supports recommendations that attempt to place spontaneously breathing infants on CPAP first.[2,3]

To control for selection bias due to observed covariates, we used recent optimal multivariate matching methods. In observational studies, matching is an attractive method for covariate adjustment because it controls for observed covariates in a very transparent manner, while attempting to replicate the structure of a controlled experiment. As shown in Tables 1, 2 and 3, we adjusted very precisely for the observed covariates obtaining a matched design that greatly simplifies the conditions of observation of the effects of the treatment on the outcomes.[42] Matching is also attractive because its analysis does not rely on strong functional or distributional assumptions (such as linearity and normality), and because it allows to conduct sensitivity analyses of results to unmeasured biases in a straightforward way. As said above, our results appeared to be insensitive to biases of small to moderate size.

Even with the matching study design, there are several potential limitations to this work. First, this study only included patients who received care at Neocosur hospitals. The outcomes of these patients may not be representative of patients who live in these countries but do not receive care at these South American hospitals. In addition, these hospitals may have improved outcomes compared with other hospitals from the same South American countries, and thus the results of implementing CPAP in the Neocosur hospitals may not be representative to other hospitals. However, the results that we found in this study are similar to those seen in previous randomized trial data, with the exception that we had the power to find the survival benefit suggested by previous studies. The Neocosur data have clinical data detailing the initial illness severity of the VLBW infants. This information does not include information about why infants failed CPAP or why the attending physician chose to bypass CPAP initially for either early intubation with surfactant administration or for other forms of non-invasive management, such as high flow nasal cannula. Finally, the results that we present are conservative, in that we excluded infants with APGAR scores $\leqslant 7$. Although not a perfect measure, low APGAR scores may suggest some measure of the illness severity of the infant, and the possibility that these infants may not have been clinically stable to safely receive prophylactic CPAP in the delivery room.

In conclusion, these data suggest that the implementation of prophylactic CPAP during the initial resuscitation or immediately after resuscitation of a VLBW infant both reduced the need for mechanical ventilation or surfactant, and was associated with a lower mortality rate. These results also show the ability to implement such a change in management in a setting outside of the United States or Europe to improve patient outcomes. Future work should help determine what additional processes of care further optimize the outcomes of VLBW infants in the developing and developed world.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Brasil: Marynea Vale, MD, Silvia Cavalcante, MD, Patricia Franco, MD, Maria Jose Silva, MD Vanda Maria Ferreira, MD, (Hospital Universidad Federal de Maranhão, Sao Luis).

Chile: Jorge Fabres, MD, Alberto Estay, MD, Alvaro Gonzalez, MD, Jose Luis Tapia, MD, Mariela Quezada, RN, Soledad Urzua, MD, Javier Kattan, MD, (Hospital Clinico Universidad Catolica de Chile, Santiago); Rodrigo Ramirez, MD, Maria Eugenia Hübner, MD, Jaime Burgos, MD, Jorge Catalan, MD (Hospital Clinico Universidad de Chile, Santiago); Lilia Campos, MD, Lilian Cifuentes, MD, Roxana Aguilar, MD, Sergio Treuer, MD, Jimena Giaconi, MD, Aldo Bancalari, MD, Jorge Leon del Pedregal, MD (Hospital Guillermo Grant, Concepcion); Marisol Escobar, MD, Viviana Veas, MD, Daniela

Sandino, MD, Antonio Salvado, MD, Alejandra Nuñez, MD, Jane Standen, MD (Hospital Gustavo Fricke, Viña del Mar); Agustina Gonzalez, MD, Claudia Avila, MD, Ana Luisa Candia, MD, (Hospital San Jose, Santiago); Claudia Toro, MD, Beatriz Milet, MD, Angélica Alegria, MD, Patricia Mena, MD (Hospital Dr. Sotero del Rio, Santiago); Veronica Peña, MD, Rafael Mendizabal, MD, (Hospital San Borja Arriaran, Santiago); Gerardo Flores, MD, Erika Ortiz, RN, Johanne Jahnsen, MD, María Eugenia Aguirre, MD, Rodrigo Donoso, MD, (Hospital de Puerto Montt. Puerto Montt); Ivonne D`Apremont, MD, Mariela Quezada, RN, Solange RojasRN Guillermo Marshall, PhD, Luis Villarroel, PhD Angelica Dominguez, MSC (Unidad Base de Datos, Pontificia Universidad Catolica, Santiago).

Paraguay: Elizabeth Cespedes, MD, Ramon Mir, MD, Elvira Mendieta, MD, Larissa Genes, MD, Jose Lacarruba, MD (Departamento de Hospital de Clinicas de Asuncion).

Peru: Veronica Webb, MD, Fabiola Rivera, MD, Enrique Bambaren, MD, Marilu Rospigliosi, MD, Margarita Llontop, MD, Sicilia Bellomo, MD, Jaime Zegarra, MD (Hospital Cayetano Heredia, Lima); Oscar Chumbes, MD, Anne Castañeda, MD, Walter Cabrera, MD, Raul Llanos, MD, Jorge Mucha, MD, César Garcia, MD, (Hospital Guillermo Almenara, Lima).

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