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ORIGINAL ARTICLE

Diuretics for very low birth weight infants in the first 28 days: a survey of the US neonatologists

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Objective: The objective of this study was to describe factors influencing diuretic use by neonatologists caring for very low birth weight neonates.

Study Design: We surveyed 400 US neonatologists. Respondents made therapeutic decisions in clinical scenarios involving very low birth weight infants at 7, 14 and 28 days of age.

Result: Response rate was 39%. Diuretic therapy was chosen in 31% of scenario decisions, with *pro re nata* dosing selected early and regular dosing more common at later ages. Diuretic use was strongly associated with method of respiratory support, and was chosen less often by those also choosing fluid restriction and those concerned about patent ductus arteriosus risk. After adjusting for these factors, excessive weight gain, expected improvement in work of breathing and expected decrease in ventilator days were also associated with diuretic use.

Conclusion: The extent of and expectations for diuretic therapy by neonatologists caring for very low birth weight neonates may exceed evidence for efficacy.
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Introduction

Few data are available to evaluate the utility of diuretic therapy in very low birth weight (VLBW, <1500 g birth weight) infants with lung disease. Randomized controlled trials assessing the benefits and risks of diuretics in preterm infants with surfactant deficiency, or early or established chronic lung disease, tend to focus on short-term physiological parameters rather than on important long-term outcomes.[1–4] The only evidence of long-term benefit of diuretic therapy in VLBW infants is in ventilator-dependent infants more than 1 month of age, who showed decreased mortality when treated with hydrochlorothiazide and spironolactone compared with placebo.[5] However, this small 1980s cohort preceded many now-standard therapies and important evolution in the disease itself.[6] Evidence is particularly lacking to guide the use of diuretics in the first weeks of life when VLBW infants might have acute surfactant deficiency, patent ductus arteriosus (PDA) or evolving early chronic lung disease. Most studies addressing diuretic use in this population were performed before the routine use of antenatal steroids, surfactant replacement therapy, fluid restriction or current ventilator technologies. Nevertheless, diuretics are used commonly in US neonatal intensive care units (NICUs).[7,8]

To better understand the extent of and expectations for diuretic use in VLBW neonates in US NICUs, we conducted a national web-based survey of neonatologists. The aims of this study were to describe patterns of diuretic use among neonatologists caring for VLBW infants in the first 4 weeks of life, a population for which there is no evidence for long-term benefit, and to identify factors that influence neonatologists' decision to use diuretic therapy in this population.

Methods

In autumn of 2006, we invited 400 neonatologists to participate in a 20-question internet-based survey. Invitations were sent via E-mail to two groups: (1) academic neonatologists, including medical directors of NICUs with accredited neonatal–perinatal fellowship programs ($n=97$), as well as all staff neonatologists at 10 tertiary centers in Connecticut, Massachusetts and Rhode Island ($n=63$); and to (2) medical directors of NICUs staffed by neonatologists in a large private practice (Pediatrix Medical Group, $n=240$). The invitation included an Internet link to the survey. A cover letter preceding the survey explained the purpose of the study. Reminders of the survey termination date were sent weekly for 6 weeks. This survey was exempted by the institutional review board at the University of Connecticut Health Center. Consent to participate in the study was implied at the time the survey was completed.

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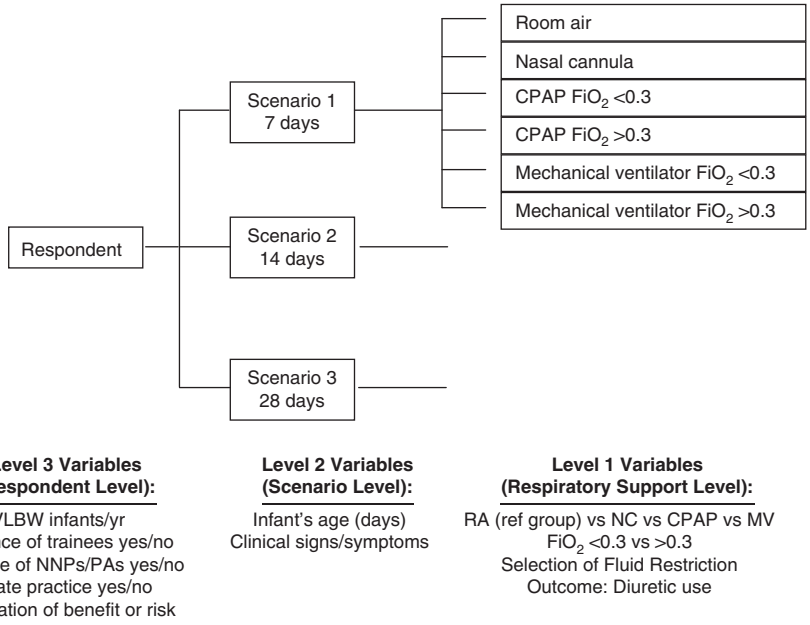

Figure 1 Three-level hierarchical structure of data. RA, room air; NC, nasal cannula; CPAP, continuous positive airway pressure; MV, mechanical ventilation; NNP, neonatal nurse practitioner; PA, physician assistant.

Respondents answered questions regarding their NICU staffing, VLBW population and presence of fellows or residents in their unit. Because this analysis addressed diuretic management in the first 28 days of life, respondents were excluded if they provided only convalescent care to VLBW infants.

Respondents were then presented with clinical scenarios for VLBW infants at 7, 14 and 28 days of age. The scenarios described the infant's clinical appearance, partial pressure of carbon dioxide on capillary blood gas and chest radiograph findings. For each scenario, respondents were asked to make six therapeutic decisions for infants on different modes of respiratory support. Respondents were able to select among several therapeutic options, including no active therapy, restricting fluids and initiating *pro re nata* (prn) or routine diuretics. Further questions addressed the impact on their prescribing decisions of specific clinical signs and symptoms and potential side effects.

Statistical methods

We performed descriptive, univariate and multivariate analyses with SPSS 16.0 (SPSS, Chicago IL, USA) and HLM 6.0 (SSI Scientific Software, Lincolnwood, IL, USA). Univariate analyses used Student's *t*-test or Mann–Whitney *U*-test for independent continuous variables and χ^2 for independent categorical variables. Univariate comparisons of factors correlated because of multiple responses were performed with three-level hierarchical logistic regression adjusted only for the variable of interest. The primary outcome was selection of diuretic by the neonatologist. For some analyses, selection of prn and regularly dosed diuretic use were combined into a single outcome. A *P*-value less than 0.05 was considered statistically significant.

Patient and respondent characteristics associated with selection of diuretic therapy were identified with three-level multivariate hierarchical logistic regression to adjust for multiple responses from each respondent and clustering of responses within the scenarios.[9] The hierarchical structure of the analyzed data is shown in Figure 1. Respondent characteristics tested at the top-most level of hierarchical modeling included number of VLBW admissions/year, practice in a setting with a training program or with neonatal nurse practitioners or physician assistants, private vs non-private practice, and respondent expectations of therapeutic effects and complications of diuretic use. Scenario characteristics tested included infant's chronological age, and survey responses regarding clinical signs and symptoms influencing decisions regarding use of diuretic. Finally, because respondents made several decisions regarding diuretic use within each scenario depending on ventilator support or fraction of inspired oxygen, respiratory support variables were tested at the lowest level of the data hierarchy.

Results

A total of 155 out of 400 surveys were returned (39%), including 84 of 160 (52%) from academic centers and 74 of 240 (31%) from neonatologists in private practice. Four respondents provided only convalescent care and were excluded from further analysis, resulting in a cohort of 151 respondents who made a total of 2718

decisions regarding diuretic use. A majority (85%) of included respondents reported working with advanced practice registered nurses or physician assistants, whereas approximately half worked with residents (58%) or fellows (47%).

Approximately, 32% ($n = 48$) of respondents stated that under no circumstances would they use diuretic therapy at 7 days; 13% ($n = 20$) at 14 days and 8% ($n = 12$) at 28 days. Respondents who would consider diuretic therapy in the first 28 days of life reported increased work of breathing (63%), need for mechanical ventilation (62%), need for supplemental oxygen (62%) and presence of excessive weight gain (58%), rales (53%) or hazy chest radiograph (55%) as the clinical signs and symptoms influencing their selection of diuretic therapy. Hypercarbia (31%), edema (33%) or oliguria (38%) were cited less commonly.

Approximately, 76% of respondents expected a transient improvement in pulmonary mechanics as a benefit of diuretic therapy. Other benefits expected with selection of diuretic therapy were decreased oxygen requirement (72%), transient improvement in work of breathing (69%), sustained improvement in pulmonary mechanics (67%), decreased ventilator days (66%) and decreased length of stay (59%). Although many cited bone demineralization (83%), electrolyte imbalance (86%) and nephrocalcinosis (81%) as potential side effects of diuretic therapy, fewer indicated increased risk of PDA (33%), hearing loss (30%) or renal failure (35%) as potential side effects influencing their decisions.

Univariate analyses

Overall, respondents selected fluid restriction in 26% (699/2718) of therapeutic decisions and some form of diuretic therapy in 31% (833/2718, including prn diuretic therapy (20%), regularly dosed diuretics (11%)). Selection of diuretic therapy showed little variation overall with chronological age, however, there was a decrease in selection of prn diuretic and increase in regularly dosed diuretic with increasing infant age (Figure 2). Selection of fluid restriction, prn diuretic, regularly dosed diuretic and overall diuretic all became progressively more common with escalating respiratory support (Figure 3). Diuretic therapy was chosen less frequently by those also choosing fluid restriction (139/699 of therapeutic decisions, 19.9%) compared with those not choosing fluid restriction (694/2019, 34.4%, $P<0.001$, univariate three-level hierarchical regression).

Selection of diuretic use did not differ by private vs non-private practice (26.8 vs 34% of therapeutic decisions, respectively, not significant). There was no significant difference in selection of diuretic use by neonatologists that reported the presence of trainees vs those that did not.

Multivariate analyses

Patient and respondent characteristics independently associated with selection of diuretic therapy were identified with three-level multivariate hierarchical logistic regression analyses. Table 1 shows factors associated with selection of prn diuretic, whereas factors associated with selection of regularly dosed diuretic are shown in Table 2. Mode of respiratory support was strongly associated with selection of both prn and regularly dosed diuretic therapy. Compared with room air, odds of selecting diuretic were increased for nasal cannula, continuous positive airway pressure and mechanical ventilation. After adjusting for respiratory support mode, selection of diuretic was more likely with fraction of inspired oxygen >0.3 versus <0.3.

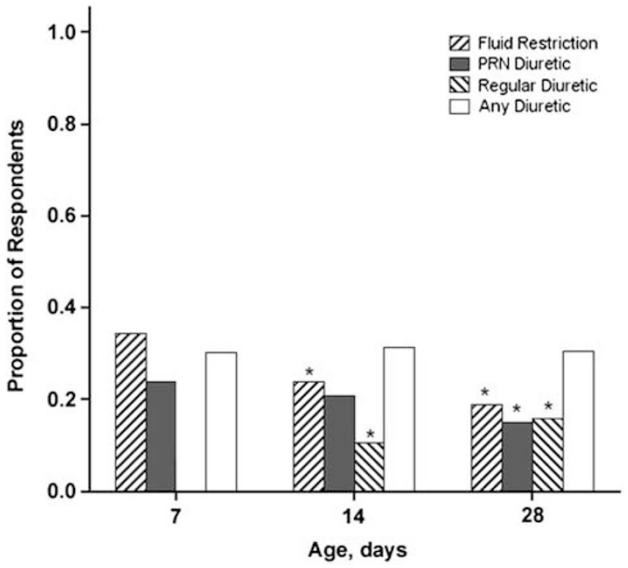

Figure 2 Fluid restriction and diuretic use by chronological age. *$P<0.05$ compared with same intervention at previous age category, univariate three-level hierarchical regression.

After adjusting for other factors, selection of prn diuretic was less likely with increasing age compared with 7 days, and was less likely for respondents who practiced in a setting with neonatal nurse practitioners or physician assistants. Selection of prn diuretic was also less likely for respondents who reported concern for PDA as a possible side effect of diuretic therapy, and for those who chose fluid restriction as a therapeutic option. Presence of excessive weight gain as an infant characteristic and respondent expectation of transient improvement in work of breathing as a therapeutic benefit were associated with increased adjusted odds of selecting prn diuretic therapy. After adjusting for these factors, respondent expectation of decreased ventilator days as a therapeutic benefit was also associated with increased adjusted odds of selecting prn diuretic therapy.

In multivariate analysis, selection of regularly dosed diuretic was more likely at 28 days compared with earlier scenarios, and for respondents expecting a transient improvement in work of breathing. Selection of regular diuretic was significantly less likely for respondents choosing fluid restriction as a therapeutic option, and for those in private practice.

Factors not significantly associated with selection of either prn or regular diuretic in multivariate analysis were presence of edema,

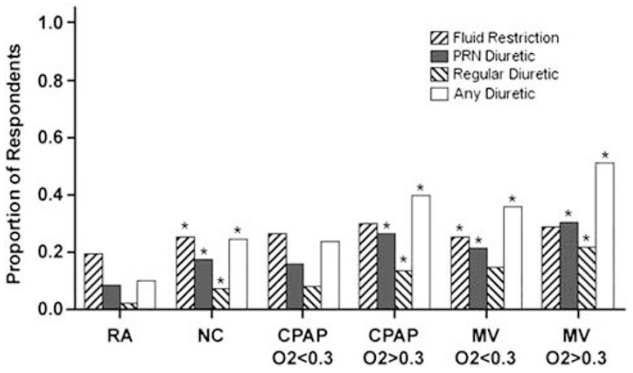

Figure 3 Fluid restriction and diuretic use, by respiratory support. *$P<0.05$ compared with same intervention at previous respiratory support category, univariate three-level hierarchical regression. RA, room air; NC, nasal cannula; CPAP O2<0.3: continuous positive airway pressure with FiO_2 <0.3; CPAP O_2>0.3: continuous positive airway pressure with FiO_2 >0.3; MV O_2<0.3: mechanical ventilation with FiO_2 < 0.3; MV O_2>0.3: mechanical ventilation with FiO_2 >0.3.

haziness on chest radiograph, rales or oliguria; expectation of sustained improvement in pulmonary function, decrease in oxygen or length of stay; concern for electrolyte disarray, hearing loss, nephrocalcinosis or acute renal failure; or practice in a setting with a training program.

Discussion

Historically, care of preterm infants has been plagued by a series of well-intended therapeutic misadventures, resulting in a gradual and still ongoing transition from anecdotal physician experience to prospective randomized controlled trials as the basis for widespread adoption of new therapies and technologies. Although interventions such as surfactant were subjected to rigorous trials before Food and Drug Administration approval and implementation, other common NICU interventions such as anti-reflux medications, pulse oximetry or therapy with loop or distal diuretics were not studied extensively in a prospective fashion before adoption as 'standard therapy.' Nevertheless, diuretics are used commonly in the US NICUs.[7,8] Their frequent use in the absence of clearly defined benefit has caused some to label diuretic therapy among the most abused of all the adjunctive therapies in neonatal intensive care.[10]

The results of this survey suggest that diuretic therapy for VLBW infants in the first 28 days of life is a common choice among US neonatologists despite limited evidence of efficacy from randomized trials. No randomized controlled study of premature infants in the first 28 days of life has demonstrated a beneficial effect of loop or distal diuretic therapy on clinically important outcomes such as mortality, duration of mechanical ventilation or oxygen supplementation, length of hospitalization or incidence of subsequent chronic lung disease. Nevertheless, respondents chose either prn or ongoing diuretic therapy in 31% of therapeutic decisions overall and 43% when the infant was on mechanical ventilator. Decisions to begin diuretic therapy were associated with both postnatal age and respiratory support requirement. Even a modest increase in respiratory support, that is, nasal cannula, resulted in significantly enhanced willingness to prescribe diuretics compared with room air. Respondents who selected fluid restriction as a therapeutic option were less likely to simultaneously select diuretic therapy.

A majority of respondents expected sustained improvement in pulmonary mechanics, decreased days on mechanical ventilator and decreased length of hospital stay as benefits of diuretic therapy. An expectation of decreased ventilator days remained significantly associated with selection of prn diuretic use even after adjusting for other important influences on therapeutic decisions. The current literature lacks a foundation for such expectations. There is little or no evidence to support a benefit of diuretic administration in non-intubated patients.[2] Enteral furosemide produces minimal effect in preterm infants $\leqslant 3$ weeks of age with chronic lung disease.[11] Chronic furosemide therapy improves pulmonary compliance, oxygen requirement and minute ventilation in preterm infants $\geqslant 3$

Table 1 Three-level multivariable hierarchical logistic model of factors associated with selection of prn diuretic therapy

	OR	*95% CI*	P-*value*
Presence of excessive weight gain	1.16	1.1, 1.23	<0.001
Expect transient improvement in work of breathing	1.10	1.04, 1.17	0.002
Expect decreased ventilator days	1.06	1, 1.12	0.04
Concern for PDA	0.93	0.88, 0.98	0.006
Choice of fluid restriction	0.85	0.8, 0.91	<0.001
Practice in a setting with NNPs or PAs	0.92	0.86, 0.99	0.018
14 days compared with 7 days	0.94	0.9, 0.98	0.004
28 days compared with 7 days	0.88	0.83, 0.93	<0.001
Nasal cannula compared with room air	1.11	1.07, 1.14	<0.001
CPAP compared with room air	1.10	1.05, 1.14	<0.001
Ventilator compared with room air	1.15	1.1, 1.19	<0.001
FiO_2 >0.3 compared with <0.3	1.11	1.08, 1.14	<0.001

Abbreviations: CI, confidence interval; CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; NNP, neonatal nurse practitioner; OR, odds ratio; PA, physician assistant; PDA, patent ductus arteriosus; prn, *pro re nata*.

Table 2 Three-level multivariable hierarchical logistic model of factors associated with selection of regularly dosed diuretic therapy

	OR	*95% CI*	P-*value*
Expect transient improvement in work of breathing	1.12	1.08, 1.17	<0.001
Pediatrix compared with academic centers	0.95	0.91, 0.99	0.02
Choice of fluid restriction	0.95	0.92, 0.98	0.002
28 days compared with 7 or 14 days	1.07	1.02, 1.12	0.007
Nasal cannula compared with room air	1.06	1.04, 1.08	<0.001
CPAP compared with room air	1.06	1.04, 1.09	<0.001
Ventilator compared with room air	1.14	1.11, 1.18	<0.001
FiO_2 >0.3 compared with <0.3	1.07	1.05, 1.09	<0.001

Abbreviations: CI, confidence interval; CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; OR, odds ratio.

weeks of age with bronchopulmonary dysplasia,[12,13] however, no long-term benefit has been documented. Similarly, although chronic chlorthiazide and spironolactone reduced supplemental oxygen requirement in preterm infants with oxygen-dependent bronchopulmonary dysplasia, no reduction in days on supplemental oxygen was observed.[14] Respondents' expectation of transient improvement in pulmonary function as a benefit of diuretic therapy in premature infants with respiratory distress syndrome is supported by the literature,[4] however this is accompanied by increased risk with no evidence of meaningful long-term benefit. Chlorthiazide and spironolactone reduced mortality in a small randomized controlled trial of infants with ventilator-dependent bronchopulmonary dysplasia,[5] however, this 1986–1988 cohort preceded routine antenatal steroid or exogenous surfactant therapy, bronchodilator therapy or current sophisticated ventilator and nutritional interventions. No randomized, controlled study in the modern era of neonatology has demonstrated improvements in mortality, duration of mechanical ventilation, oxygen dependence, length of hospital stay or other clinically significant outcomes to offset the numerous adverse effects that accompany diuretic therapy.

Early or ongoing use of diuretics is associated with many significant adverse effects including ototoxicity, nephrolithiasis, PDA, cholelithiasis (loop diuretics), hypercalcemia, hyperkalemia, (thiazide/potassium-sparing combination), electrolyte disarray, hypovolemia, hypotension, pre-renal failure, bone demineralization, nephrocalcinosis, hyperuricemia, cholestatic jaundice and hyperuricemia (either).[4,10,15] Despite this formidable list, risk of adverse effects appeared to be a lesser consideration in therapeutic decisions by survey respondents. Comparatively few neonatalogists identified risk of PDA, hearing loss, or renal failure as potential complications of diuretic therapy influencing their decisions. In multivariate analysis, PDA was the only adverse effect of diuretic therapy that remained an independent influence on respondent decisions after adjusting for other significant factors including expected benefits.

This study examines reported diuretic use in hypothetical scenarios, and does not measure actual diuretic use during clinical care. Also, as this study focused on premature infants in the first 28 days of life, it does not address the frequency or rationale for use of diuretic therapy in older infants with established chronic lung disease. However, no beneficial effect of diuretic therapy has been reported in established chronic lung disease with respect to duration of oxygen requirement, weaning from mechanical ventilation, duration of hospital stay, incidence of bronchopulmonary dysplasia or long-term outcome.[1,2]

Conclusion

Studies to date have not demonstrated a positive impact of diuretic therapy upon important clinical outcomes. However, despite significant side effects, the results of this study suggest that diuretic therapy appears to be frequently used for treatment of VLBW infants in the first 28 days of life. The extent of use and expected benefits for diuretic therapy in this population may exceed evidence for efficacy. Our results support the need for a reexamination of current practice regarding diuretic use in premature neonates. Randomized trials are needed to assess the effects of early and late diuretic administration on meaningful outcomes including survival, duration of ventilatory support and oxygen administration, length of hospital stay, potential complications and long-term outcome.

Conflict of interest

Dr Staves is employed by the Pediatrix Medical Group. All other authors declare no conflict of interest.

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