Emma E. Williams, Shannon Gunawardana, Nicholas K. Donaldson, Theodore Dassios and Anne Greenough*

Postnatal diuretics, weight gain and home oxygen requirement in extremely preterm infants

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Abstract

Objectives: Diuretics are often given to infants with evolving/established bronchopulmonary dysplasia (BPD) with the hope of improving their pulmonary outcomes. We aimed to determine if diuretic use in preterm infants was associated with improved pulmonary outcomes, but poorer weight gain.

Methods: An observational study over a 5 year period was undertaken of all infants born at less than 29 weeks of gestation and alive at discharge in all neonatal units in England who received consecutive diuretic use for at least 7 days. Postnatal weight gain and home supplementary oxygen requirement were the outcomes. A literature review of randomised controlled trials (RCTs) and crossover studies was undertaken to determine if diuretic usage was associated with changes in lung mechanics and oxygenation, duration of supplementary oxygen and requirement for home supplementary oxygen.

Results: In the observational study, 9,457 infants survived to discharge, 44.6% received diuretics for at least 7 days. Diuretic use was associated with an increased probability of supplementary home oxygen of 0.14 and an increase in weight gain of 2.5 g/week. In the review, seven of the 10 studies reported improvements only in short term lung mechanics. There was conflicting evidence regarding whether diuretics resulted in short term improvements in oxygenation.

Conclusions: Diuretic use was not associated with a reduction in requirement for supplemental oxygen on discharge. The literature review highlighted a lack of RCTs assessing meaningful long-term clinical outcomes. Randomised trials are needed to determine the long-term risk benefit ratio of chronic diuretic use.

Keywords: bronchopulmonary dysplasia; diuretic; oxygen; preterm; weight.

Introduction

Bronchopulmonary dysplasia (BPD) is associated with long-term adverse pulmonary outcomes such as supplementary oxygen requirement at home, rehospitalisation and reduced pulmonary function in childhood [1, 2]. To reduce such morbidity, preterm infants are often given medications, such as diuretics, in the hope of improving their respiratory status [3]. There appears, however, to have been little consideration to dosage regimes, weaning strategies and adverse effects. Indeed, a large multicentre cohort study in the United States of America reported marked variation in loop diuretic use between hospitals, but with no observed differences in mortality rates [4], suggesting a need for evidence-based guidelines.

Retrospective analyses have demonstrated that, in infants with developing or established chronic lung disease, diuretic administration was associated with lower ventilatory pressures and less supplemental oxygen, but at the expense of reduced postnatal weight gain and electrolyte imbalance [5]. Furthermore, some studies have suggested that chronic diuretic treatment is associated

***Corresponding author: Professor Anne Greenough**, Department of Women and Children's Health, School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London, SE5 9RS, UK; Neonatal Intensive Care Centre, King's College Hospital NHS Foundation Trust, 4th Floor Golden Jubilee Wing, Denmark Hill, London, SE5 9RS, UK; Asthma UK Centre for Allergic Mechanisms in Asthma, King's College London, SE1 9RT, London, UK; and National Institute for Health Research (NIHR), Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London, SE1 9RT, London, UK, Phone: +44 0203 299 3037, E-mail: anne.greenough@kcl.ac.uk

Emma E. Williams, Department of Women and Children's Health, School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK. https://orcid.org/0000-0001-6480-468X

Shannon Gunawardana, Neonatal Intensive Care Centre, King's College Hospital NHS Foundation Trust, London, UK

Nicholas K. Donaldson, Diabetes Foot Clinic, King's College Hospital NHS Foundation Trust, London, UK

Theodore Dassios, Department of Women and Children's Health, School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK; and Neonatal Intensive Care Centre, King's College Hospital NHS Foundation Trust, London, UK

with increased use of sodium and potassium supplementation among infants with severe BPD [6]. Sodium deficiency has indeed been linked to postnatal growth failure, but with adequate supplementation enhanced postnatal weight gain can occur [7]. We have analysed data from a whole population and undertaken a review of the literature to determine if diuretic administration influenced clinically relevant pulmonary and growth outcomes.

Materials and methods

Population based study

Study design and subjects: An observational, whole population study, spanning 5 years over all Neonatal Intensive Care Units in England. A predefined set of data was acquired from the National Neonatal Research Database (NNRD), Imperial College London, UK.

Ethical approval: The study was approved by the National Research Ethics Committee (10/H0803/151).

The population comprised all infants live born before 28 completed weeks of gestational age and admitted between 1st January 2014 and 31st December 2018. Postnatal diuretic use was defined as the administration of diuretics (frusemide, spironolactone, potassium canreonate or chlorthiazide) for at least seven consecutive days. The standardised weight z-scores at birth and discharge were calculated using the UK-World Health Organization (WHO) preterm reference chart and the Microsoft Excel add-in LMS Growth (version 2.77; www.healthforchildren.co.uk)*.

The following variables, extracted from the database, were assessed in the analysis: maternal age (years), antenatal steroids (yes/no), gestational age at birth (weeks), birth weight (kg), head circumference at birth (cm), Apgar score at 5 min of age, sex (male/female), surfactant administration (yes/no), duration of invasive ventilation (days), respiratory support at 36 weeks of PMA (yes/no), death before 36 weeks PMA (yes/no), BPD development defined as any need for respiratory support at 36 weeks PMA (yes/no), postnatal corticosteroids (dexamethasone or hydrocortisone for more than five consecutive days – yes/no), surgery for necrotising enterocolitis (NEC) (yes/no), ligation of patent ductus arteriosus (PDA) (yes/no), intraventricular haemorrhage (IVH) grade 3–4 (yes/no), periventricular leukomalacia (PVL) (yes/no), duration of parenteral nutrition (PN) (days), breastfeeding at discharge (yes/no), death before discharge from neonatal care (yes/no), PMA at discharge (weeks) and weight at discharge (kg).

Main outcomes: Discharged home on supplementary oxygen and weekly weight gained between birth and discharge. The need for supplemental home oxygen was coded as a binary indicator (yes/no). The weekly weight gain was calculated by dividing the weight change from birth to discharge by the number of weeks spanned. This was subsequently converted into standard units.

Statistical analysis

Multivariate Distance Matching (MDM) with a Mahalanobis kernel was used to correct for treatment selection bias [8], based on three matching covariates: gestational age, birth weight and gender, which were deemed to have influenced treatment assignment. A logistic regression was used to check whether the matching covariates did in fact influence treatment assignment, and descriptive statistics and visualizations were used to validate, or otherwise, whether the two matched groups were balanced in terms of the matching covariates. Following this, as in any propensity score matching procedure, the MDM algorithm was carried out in two steps: the matching step and the estimation of effects step. First, in the matching step, the procedure sought to match every neonate in the treated group with *one or more* neonates in the untreated group in terms of the three matching covariates. Second, in the estimation step, for each treated neonate, the procedure created the *counterfactual*: a hypothetical untreated neonate with an outcome estimated as the average of the outcome values observed in the untreated neonates that were matches. It also calculated the difference in outcome between the treated and its counterfactual. The mean of these differences, for all the treated neonates that were matched, is known as the *average treatment effect for the treated* (ATT), which was the treatment difference reported in this study.

Review of the effect of diuretics on BPD

The review was conducted using a pre-determined protocol. A comprehensive literature search was conducted of the following databases: Embase, MEDLINE, Web of science core collection, Elsevier, Cochrane and CINAHL. The following search terms were used: (diuretic*) AND (bronchopulmonary dysplasia OR BPD) and were combined using Boolean operators. Search terms were limited to abstract, title and keyword. Searches were performed without limitation on publication year or language.

Studies were eligible if they included newborn infants, and diuretics were used to prevent or treat BPD as a primary or secondary outcome. The populations of interest were infants with BPD, as defined by a supplementary oxygen requirement for at least 28 days with severity classified at 36 weeks postmenstrual age according to respiratory support [9], or premature infants with low birth weight who were at high risk of developing BPD. Articles that evaluated preclinical effects, dosing strategy comparisons or prevalence of treatment modalities were excluded.

Originally, only randomised controlled trials (RCTs) were considered for inclusion, however, due to the paucity of articles of this design, only three RCTs were found, randomised crossover studies were also included. Retrospective cohort studies, point prevalence studies and case studies were excluded from this review. Non-clinical studies or manuscripts consisting of expert opinion alone were not eligible for inclusion in the review. Furthermore, non-English language articles and conference abstracts were not considered for inclusion.

The search was conducted by the primary reviewer and yielded initially 599 articles. Following removal of duplicated articles (n=273), papers were screened first by title, and then by abstract and full text, if necessary. All papers were screened by two reviewers working independently to decide eligibility and assign a study design. Any disagreement between reviewers as to the type of study, was resolved by a third reviewer. This selection process resulted in a total of 10 studies (Table 1).

Table 1: Studies included in the review.

Author	Comparison Type of study	Inclusion criteria	Gestational age, weeks	Birthweight, grams	Number of infants recruited	Primary outcome	Results
Kao et al. [13]	Furosemide Randomised crossover study	BPD – Radiographic evidence of stage III–IV BPD. Requires ≥ 30% supplemental O_2 and mechanical ventilation at 30 days of life Control – infants without heart or lung disease	C=38 BPD = 30	C=2,730 BPD = 1,370	C=16 BPD = 10	TGV, Raw, SGaw, Cdyn	Diuretic treatment had improvements at 1 h in Raw ($p<0.05$), SGaw ($p<0.005$) and Cdyn ($p<0.025$); after 1 h levels returned to baseline. No significant change in TGV.
Kao et al. [14]	Spironolactone + chlorothiazide Randomised crossover study	BPD – Radiographic evidence of stage III–IV BPD. Requires ≥ 30% supplemental O_2 at 30 days of life. Required ventilation in first 5 days. Born <34 weeks GA. Control – infants without heart or lung disease	C=38 BPD = 29	C=2,700 BPD=1,200	C=16 BPD = 10	TGV, Raw, SGaw, Cdyn	Diuretics treatment had improvements in Raw ($p<0.001$), SGaw ($p<0.001$) and Cdyn ($p<0.001$). No significant change in TGV.
Logvinoff et al. [44]	Furosemide Crossover study (non-randomised)	Radiographic evidence of stage IV BPD. Requires supplemental O_2 for at least 3 months. Required ventilation.	32	1,310 (890–2,300)	10	Cdyn, TPR, WoB, TV, SO_2	Furosemide increased Cdyn ($p<0.01$) and improved lung function. No change in TPR, WoB, TV or SO_2.
Engelhardt et al. [10]	Furosemide Randomised crossover study	Radiographic evidence of BPD. Continuous O_2 requirement since birth. Postnatal age ≥ 28 days. Arterial pCO2 >45 torr	27–32	–	16	PO_2grad, PCO_2, Cdyn, TPR, urine output	One-hour post treatment there were improvements in Cdyn and PCO_2 ($p<0.04$), but no change to TPR. After 1 week, there were improvements in TPR, Cdyn, PO_2grad ($p<0.04$) and urine output ($p<0.02$).
Kao et al. [15]	Theophylline vs. Theophylline + chlorothiazide + spironolactone vs. Chlorothiazide + spironolactone + placebo Randomised crossover study	Radiographic evidence of stage III–IV BPD. Requires supplemental O_2. Did not require ventilation at study time.	29	1,150	19	Cdyn, Raw, VmaxFRC, tc	Combined placebo and diuretic improved Cdyn ($p<0.05$), Raw ($p<0.001$), VmaxFRC ($p<0.02$) and time constant ($p<0.05$). Combined theophylline and diuretic improved Cdyn ($p<0.001$), Raw ($p<0.02$), VmaxFRC ($p<0.02$) and time constant ($p<0.01$).

Table 1: (continued)

Author	Comparison Type of study	Inclusion criteria	Gestational age, weeks	Birthweight, grams	Number of infants recruited	Primary outcome	Results
Albersheim et al. [17]	Spironolactone + hydrochlorothiazide RCT	Radiographic evidence of BPD. Requires ≥ 30% supplemental O_2 and ventilation at 1 month. Full enteral feeding.	T=26 C=26	T=838 C=876	T=19 C=15	Survival rate, total hospital days, ventilator days, post treatment chest X-ray, FiO_2, PIP, MAP	Alive at discharge 84% (T) vs. 47% (C) (p=0.025). Improvement in post treatment chest X-ray (p=0.09) and FiO_2 at 8 weeks (p=0.05). No significant difference between total hospital days, ventilator days, PIP or MAP.
Engelhardt et al. [16]	Spironolactone + hydrochlorothiazide RCT	Radiographic evidence of CLD. Requires supplemental O_2 and ventilation at birth. Postnatal age >28 days.	T=28 C=27	T=995 C=920	T=12 C=9	Cdyn, TPR, SO_2, urine output	Treatment significant increased urine output (p<0.05). No significant change to Cdyn (p=0.53), TPR (p=0.28) or SO_2.
Rush et al. [11]	Alternate-day furosemide therapy Randomised crossover study	Radiographic evidence of stage III–IV BPD. Requires supplemental O_2 or ventilation at birth. Ongoing O_2 requirement. Postnatal age >28 days. Enteral feeds >75%	28	962	11	Cdyn, TPR, electrolytes in serum and urine	Furosemide treatment improved Cdyn and TPR (p=0.032). No significant change to urine output, electrolyte abnormalities or urinary calcium excretion.
Kao et al. [18]	Spironolactone + chlorothiazide RCT	Radiographic evidence of stage III–IV BPD. Requires 30–50% supplemental O_2 and ventilation >1 month. Stable post extubation with >1.5 kg weight.	T =28 C=28	T=960 C=1,030	T =22 C=21	Cdyn, Raw, TGV, VmaxFRC, total days of supplemental O_2	During treatment period improvements in Cdyn (p<0.001) and Raw (p<0.05). At 4 weeks diuretic group needed less supplemental O_2 (p<0.01). No difference in lung function after stopping diuretics or total days of supplemental O_2.
Kugelman et al. [12]	Single dose furosemide Randomised crossover study	Radiographic evidence of BPD. Requires ≥ 30% supplemental O_2 and ventilation at 21 days of life. Born <32 weeks GA. BW 500–2,500 g	29	1,100 (620–2,000)	9	Cdyn, dynamic resistance, TV	No significant changes to Cdyn dynamic resistance or TV.

BPD, bronchopulmonary dysplasia; T, treatment; C, control; O_2, oxygen; TGV, thoracic gas volume; Cdyn, dynamic lung compliance; Raw, airway resistance; SGaw, specific airway conductance; TPR, total pulmonary resistance; WoB, work of breathing; TV, tidal volume; SO_2, oxyhaemoglobin saturations; VmaxFRC, maximum expiratory flow at functional residual capacity; tc, time constant; FiO_2, fractional inspired oxygen; PIP, peak inspiratory pressure; MAP, mean airway pressure; PO_2grad, change in alveolar skin surface PO_2 gradient; PCO_2, change in transcutaneous CO_2.

Results

Of the 9,457 neonates that survived to discharge, the proportion assigned to diuretics was 44.6%: 95% CI (43.6%, 46%). The logistic regression modelling treatment assignment on a random sample of 1,173 neonates, confirmed that male sex, lower gestational age and lower birthweight significantly increased the chance of receiving diuretics. The odds of receiving diuretics were 43% more for boys (OR = 1.43; 95% CI [1.12, 1.82]; p=0.004); 20% less for each additional week in gestational age (OR = 0.80; 95% CI [0.70, 0.91]; p=0.001) and 28% less for each additional standard unit in birthweight (OR = 0.72; 95% CI [0.61, 0.85]; p<0.001).

At the estimation of effects step, the full matched models were adjusted for: antenatal steroids, Apgar score greater than seven, PDA-ligation, surgery for NEC, PN for 23 days or more, postnatal steroids, respiratory support at 36 weeks PMA, receiving breastmilk at discharge and length of stay.

In the full model for the weekly weight gain, the ATT was 0.07 standard units (ATT = 0.07; 95% CI [0.02, 0.12]; p=0.01), indicating that, in relation to those not receiving diuretics, those on diuretics gained weight faster by 2.5 g per week. The probability of being discharged home on supplementary oxygen was 0.14 greater for those on diuretics (ATT = 0.14; 95% CI [0.11, 0.17]; p<0.001). Treatment interactions were explored and found significant for mechanical ventilation, postnatal corticosteroids and breastfeeding.

Review of the effect of diuretics on BPD

The included studies assessed the effects of postnatal diuretics given to treat BPD. Improvements to lung compliance were reported at 1 h and 1 week following frusemide therapy [10]. Furthermore, alternate-day frusemide treatment was found to have a positive effect on lung compliance (p<0.03) in preterm infants (median gestational age 28 weeks) studied at 9 weeks postnatally, with the authors reporting no electrolyte abnormalities within the cohort [11]. A single dose of inhaled frusemide given to ventilator dependent infants with severe BPD had no significant effect on pulmonary mechanics at 1 and 2 h post administration [12]. One study, however, reported the positive effects on lung mechanics to be acute and short-lived, with the improvements to airway resistance (p<0.05) and lung compliance (p<0.03) returning to baseline 1 h post administration [13]. Conflicting results with spironolactone and chlorthiazide were reported with improvements in lung compliance (p<0.001), airway resistance (p<0.001) [14] and greater maximum expiratory flow at functional residual capacity (p<0.02) [15] in two studies, yet no changes to lung compliance (p=0.05) or oxygen saturations in another study despite a significant diuresis [16]. In one study, there was a reduction in the oxygen requirement in relation to spironolactone and chlorthiazide use, with lower fraction of inspired oxygen (FiO_2) at 4 weeks (p<0.01), but by the eighth week of treatment this was non-significant (p=0.05) [17]. Furthermore, the oxygen requirement was less at 4 weeks of diuretic therapy in another study, yet after stopping treatment there was no reduction in the duration of oxygen therapy [18]. The latter study was the only one to report the effects of diuretics on pulmonary mechanics of oxygen dependent infants with BPD beyond the course of treatment; no differences at 1 year of age were reported between the placebo and intervention groups with regards to lung compliance, airway resistance or rate of rehospitalization within the first year after birth.

Discussion

We have demonstrated that diuretic use did not reduce the need for supplemental oxygen on discharge home from the neonatal intensive care unit and was associated with greater weight gain from birth to discharge in those extremely preterm infants. The review of the literature yielded conflicting results with most studies assessing acute effects on pulmonary mechanics and only one RCT reporting longer term outcomes.

Diuretics have been shown to be commonly prescribed to infants who are discharged on supplemental oxygen [19], yet with a lack of consensus on subsequent weaning regimes [20]. Growth failure after weaning off oxygen has been described in infants with BPD [21, 22], with one study highlighting the reduced weight gain in those infants who had more frequent desaturations whilst weaning from home oxygen [23]. The administration of diuretics to infants with BPD has previously been shown to reduce the amount of supplemental oxygen support, yet with no reduction in the duration of supplemental oxygen required on the neonatal unit [18]. In a retrospective cohort study of preterm infants with BPD, there was no significant difference in the duration of home oxygen requirement in those receiving diuretics, who had a longer length of neonatal stay [24]. Thus, our finding of no significant difference in home supplementary oxygen use between those who did

and did not receive diuretics is consistent with the literature.

Diuretics act to improve lung compliance and oxygenation by removal of lung fluid [25] with the amount of pulmonary fluid present correlating with BPD severity [26]. One study used lung ultrasound to assess the positive respiratory effects of diuretics by measurement of extravascular lung water in a cohort of preterm infants born before 32 weeks of gestation [27]. Infants receiving diuretics who were successfully weaned from respiratory support had a lower lung ultrasound score 48 h post treatment than the group not able to be weaned (lung ultrasound score 6 vs. 14; p=0.03). The improvement in short term pulmonary mechanics by reduction of extracellular fluid and re-absorption of pulmonary fluid [28] could reduce the work of breathing in infants with BPD, indeed one study showed a reduction in the work of breathing following diuretic therapy [29]. The greater postnatal weight in the infants receiving postnatal diuretics in the current study thus was an unexpected finding and may reflect that infants with BPD are often intolerant of fluid loads and some are in incipient right heart failure.

The immaturity of the kidneys and slower renal and metabolic elimination could account for the greater side effect profile of diuretics in premature infants as compared to adults [30]. Adverse effects reported are nephrocalcinosis, sensorineural hearing loss and hypertension. The reported associations between diuretic exposure and sensorineural hearing loss, nephrocalcinosis and hypertension within the preterm population are, however, not strong enough to be able to draw significantly meaningful conclusions as there is a lack of randomised control trials assessing such long-term outcomes [31–35]. Indeed, a recent position statement from the Thoracic Society of Australia and New Zealand gave no recommendation on the suitability of long-term diuretic treatment to preterm infants with BPD. The development of side effects is related to electrolyte imbalance – specifically hypophosphatemia and hyponatremia [36]. To alleviate such systemic side effects various modes of administration have been investigated, yet with inconsistent results. Nebulised frusemide administration has been shown to result in less urinary electrolyte loss compared to other routes of administration [37], however, intravenous infusion vs. bolus injection was found to have no impact on urinary electrolyte losses [38].

Thiazide use has been shown to improve pulmonary mechanics, however, only a limited number of randomised control trials have been performed yielding little evidence to support routine use [39]. Infants exposed to longer courses of frusemide postnatally had reduced rates of BPD and or death in one study [40], however, the cumulative duration of treatment has been associated with greater probability of developing severe metabolic bone disease and nephrocalcinosis [41, 42]. Furthermore, the European Respiratory Society (ERS) guideline on the long-term management of infants and children with BPD found low evidence to support routine diuretic use when assessing the longer term outcomes [43].

Our observational study has strengths and some limitations. We do not report results from a RCT, however, we included all extremely preterm infants surviving to discharge over a 5 year period from the whole population in England. The database did not have longitudinal data further than point of discharge from the neonatal unit, so we were unable to comment on the effect of diuretics on the duration of home oxygen, but do report that diuretics had no significant effect on the requirement for home supplementary oxygen.

In conclusion, postnatal diuretic use was associated with greater postnatal weight gain, but with no reduction in the need for supplemental oxygen on discharge home from the neonatal intensive care unit. Our literature search highlighted a paucity of RCTs and we suggest there is a need for such trials which importantly determine long-term benefits and risks of chronic diuretic treatment.

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Informed consent: Not applicable.

Ethical approval: A predefined set of data was acquired from the National Neonatal Research Database (NNRD), Imperial College London, UK, approved by the National Research Ethics Committee (10/H0803/151).

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