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TITLE

Heated humidification improves clinical outcomes compared to a heat-and-moisture exchanger in children with tracheostomies

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CONFLICTS OF INTERESTS

Dr McNamara

- advisory board member for Glaxo Smith Kline NZ

- received travel and conference accommodation from Boehringer Ingelheim

Professor Asher

- has no relevant conflicts of interest

Professor Rubin

- Research grants from the NIH, CF Foundation, Denny Hamlin Foundation, Glaxo SmithKline, Teleflex Medical, Reckitt Benckiser, and Fisher & Paykel to study airway mucus clearance and therapies

- Patents held on aerosol surfactant and aerosol Dapsone for the therapy of inflammatory airways disease

- Research grant and International Registry to study plastic bronchitis

- Consultant to Philips Respironics, Pharmaxis, Boehringer Ingelheim Bayer, and GSK

Mr Alistair Stewart

- has no relevant conflicts of interest

Dr Byrnes

-received grants from Health Research Council of NZ

-Conference organiser for national respiratory conference that is sponsored by Boerhinger Ingelheim

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ABSTRACT

Background: The upper airway humidifies and warms inspired gases before they reach the trachea, a process bypassed by the insertion of a tracheostomy, necessitating humidification of inspired gases. The optimal method of humidification is not known.

Methods: We conducted a short term 20-hour and a long term 10-week randomised cross-over studies comparing a heated humidifier (HH) to a heat-and-moisture exchanger (HME) in children with established tracheostomies. Participants were assessed for clinical events, clinical examination findings, airway cytokine levels and airway secretion viscoelasticity.

Results: Fifteen and 14 children were recruited to the short and long term studies respectively. Children wearing the HH had decreased respiratory examination score ($p < 0.001$) and improved oxygenation ($p=0.012$) but no change in clinical events over the short-term. There was a decrease in acute clinical events ($p=0.008$) in the long term study. No differences were found in airway secretion viscoelasticity results or cytokine levels in either study, but these sample numbers were limited.

Conclusion: Over 20 hours use of HH compared to HME improved work of breathing. Over a longer 10 week treatment period HH resulted in decreased adverse clinical events.

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KEY WORDS

Child, Tracheostomy, Humidity, Mucociliary Clearance, Rheology, Inflammation, Randomized Controlled Trial

ABBREVIATIONS

HH – heated humidifier

HME – heat and moisture exchanger

ELISA - Enzyme-linked immunosorbent assay

ETT – endotracheal tube

IL - interleukin

LRTI – lower respiratory tract infection

mmHg – millimetres of mercury pressure

RR – respiratory rate

SpO_2 – oxygen saturation

TNFα – Tumor necrosis factor alpha

INTRODUCTION

The upper airway plays an important role in the physical defence of the lung by filtering, humidifying and warming inspired gases before they reach the trachea, preventing dehydration of airway secretions. The nose and oropharynx perform most of this conditioning. [1, 2] Insertion of a tracheostomy bypasses the upper airway resulting in relatively cool and dry ambient room air entering the trachea directly. This may have adverse effects, causing cooling and drying of the mucosa with slowing of mucociliary clearance and airway inflammation. [3]The American Thoracic Society guidelines for care of a child with a chronic tracheostomy state that the “target for inspired gas temperature should be 32˚ to 34˚ C and the target for inspired humidity should be 36 to 40 mg H_2O/L”. [3] Aerosol nebulisers, heated humidifiers (HHs) and

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heat and moisture exchangers (HMEs) are all used to condition inspired gases for children spontaneously breathing through tracheostomy tubes.

In our institution the standard is to provide a HH during sleep and a HME for time awake for children with long-standing tracheostomies. This practice developed after successful HH treatment was instituted for two children with tracheostomies and thick secretions resulting in decreased admissions for pneumonia. [4] Our hypothesis was that appropriate humidification of the airway would have positive effects in terms of secretions and clinical outcomes. For that purpose we conducted two studies over two periods of time, a short-term study and a long-term study. The aims of the first study were to compare the effectiveness of a HH compared to HME when used over a 20-hour treatment period as determined by emergency tracheostomy changes, the need for overnight suctioning, work of breathing, airway inflammation and secretion viscoelasticity. The aims of the second study were to compare the effectiveness of a HH compared to HME when used over a longer 10-week treatment period, as determined by the occurrence of major clinical events (hospital admission, lower respiratory tract infections, treatment failure), work of breathing and airway inflammation.

METHODS

The study was approved by the regional ethics committee and registered with the Australasian Clinical Trials Registry (short-term study ACTRN12605000263695, long-term study ACTRN12605000673640).

Participants

After obtaining parental consent, children with a tracheostomy who were hospital inpatients or resident in a rehabilitation facility and who had safely undergone at least

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one tracheostomy tube change (for the short term study) and were older than six months of age with a tracheostomy tube in place for at least three months (for the long term study) were recruited. Exclusion criteria included subjects with cystic fibrosis, primary ciliary dyskinesia, primary immune deficiency, or under palliative care. For the long term study, children were also excluded if the planned tracheostomy time, as determined by their primary otolaryngologist, was less than the study period of 20 weeks. Recruitment took place from November 2004 to August 2006.

Study Design

Randomisation to one of two groups was performed using a computer generator table.

Short-term Study: Each treatment period was preceded by a night of HH treatment and then a four hour wash-out period with no treatment. Group A then underwent twenty hours of treatment with the HH followed by a recovery night (standard treatment with HH) and then twenty hours of treatment with the HME. Group B underwent treatment in the reverse order. Assessments were performed at the start of treatment (end of wash-out), after two hours of treatment and after 20 hours of treatment. Treatment allocation was unable to be concealed from families or the investigator for this study; but was concealed from persons performing laboratory analysis.

Long-term Study: Group A underwent 10 weeks of treatment with the HH at night, HME during day followed by 10 weeks of treatment with the HME over the 24 hour period. Group B underwent treatment in the reverse order. The first two weeks of each period was considered a "wash-in" period and clinical events were not counted unless the child was unable to tolerate treatment. Assessments were performed at recruitment and at the end of each treatment period. Treatment was concealed to

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those conducting clinical examination and laboratory measurements but for practical reasons was not concealed from the primary investigator or the families of participants.

Study Interventions:

The HH used in this study was a Fisher & Paykel Healthcare MR850 humidifier (Fisher & Paykel Healthcare, Auckland, New Zealand) set to deliver air conditioned to 37°C and 100% relative humidity. The humidified system was made up of HC211 CPAP flow source to generate the air flow, the MR850 HH with the HC300 or MR290 humidifier chamber, a heated breathing circuit (HC505 Fisher & Paykel Healthcare) and a paediatric tracheostomy mask (Hudson RCI, Arlington Heights, Illinois, USA) to the patient's tracheostomy. The mask is loosely applied over the tracheostomy so that no CPAP pressure is applied to the patient's airway. Airflow was adjusted to remove CO_2 from the dead space of the circuit, and not to provide clinical benefit on work of breathing, according to the formula: Flow in L/min = Respiratory Rate x Weight in kg x 3 + 5.

The HME was the Thermovent-T Heat and Moisture Exchanger (Sims Portex, Myers, Florida, USA) in which filter paper absorbs exhaled warmth and moisture and delivers it to the next inhaled breath. This is the HME device commonly used in our hospital and throughout New Zealand for children with tracheostomies. This device delivers humidification of 25 mg H_2O/L and 34°C at a tidal volume of 1000mL according to the manufacturer's specifications; however performance is likely to be higher in children who have lower expiratory flows. Participants received oxygen as prescribed by their treating physician, titrated prior to the study using continuous overnight oximetry recordings.

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Outcome measures:

For the short-term study we monitored the occurrence of overnight clinical events; emergency tracheostomy tube changes, tracheostomy tube blockages, the need for suctioning or the need for additional saline instillation to loosen secretions and assist suctioning. Tracheostomy tube blockage was defined as obstruction of the tracheostomy tube with secretions which did not clear with suctioning, and required an emergency tube change. All airway cares were undertaken according to our usual clinical guidelines and were recorded.

For the long-term study, major adverse clinical events included episodes of acute lower respiratory tract infection (LRTI), acute hospital admission for any cause, acute hospital admission for a respiratory cause, tracheostomy tube occlusion, emergency tracheostomy tube changes, and withdrawal from the study or "treatment failure". LRTI was defined as an increase in respiratory effort and airway secretions associated with new changes on chest xray or on auscultation and where either oral or intravenous antibiotics were prescribed. Treatment failure, or inability to tolerate one treatment, occurred when airway secretions were persistently thick, requiring hourly suction for a period of ≥ 3 days, or the parent/caregiver and/or the primary medical team or investigator believed it was unsafe to continue. Parents of participants were asked to contact the primary investigator if any of these events occurred and were also contacted by phone on a fortnightly basis during the study to collect clinical event data.

A respiratory clinical score developed for children with asthma and bronchiolitis was used for both studies. [5] This is a four-point (0-3) scoring system of increasing severity for: i) respiratory rate (RR) measured over one minute compared to normal for age, ii) retractions, iii) wheeze, iv) dyspnoea (judged according to feeding, activity and level

of consciousness), and v) crackles on auscultation of the chest. [5] Oxygen saturation (SpO_2) was measured by a pulse oximeter (Masimo Radical Oximeter, Masimo, Irvine, California) during a two-minute period of quiet breathing. For the short-term study, overnight oximetry saturations and pulse rate were continuously recorded for a 12-hour period and the mean data analysed (Profox Escondido, California) excluding periods of artefact. SpO_2 was not analysed for children on oxygen as the fraction of inspired oxygen could not be precisely replicated between the two treatments.

For both studies, suction of airway secretions from the tracheostomy was standardised. The HME was removed and the external lumen of the tracheostomy tube wiped clean with sterile gauze. A size 8g French suction catheter with thumb trap (Triflo suction catheter with control port, Allegiance Healthcare Corporation) was inserted to a predetermined depth of one cm beyond the terminal end of the tube. Suction of 100 mmHg was applied and the suction catheter slowly withdrawn with gentle swirling until at the tracheostomy stoma opening and then repeated once. The sample of airway secretions acquired in the thumb trap was visually inspected and a visual secretion assessment score on a three-point scale applied for difficulty of catheter insertion, the colour of the secretions, the volume of the secretions and the thickness of the secretions after one mL of normal saline had been aspirated through the catheter. [6, 7]

Inflammatory cytokines were measured for both studies. Secretions obtained by suctioning were transferred to a pre-weighed 0.5 mL Nunc tube with o-ring and stored at -80°C. Samples were thawed on ice for analysis and resuspended in sterile phosphate-buffered solution (PBS) at a final concentration of 100 mg sputum/mL PBS. The samples were then ultracentrifuged at 90,000xg for 1.5 hours at 4°C (Beckman L70 Ultracentrifuge using a type 50.4 Ti ultracentrifuge rotor). Supernatants were aliquoted in sterile 1.5mL Eppendorf tubes (at least four aliquots).

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Samples were then stored at -80°C until required for ELISA analysis. Inflammatory cytokines were analysed using ELISA and according to manufacturers' instructions; Interleukin-8 (IL-8) was analysed using PeproTech human IL-8 ELISA kit, IL-1beta (IL-1β) using a Biosciences OptEIA™ IL-1β ELISA kit, and tumour necrosis factor-alpha (TNFα) using a PeproTech human TNFα ELISA development kit.

For the short-term study the viscoelastic properties of airway secretions were measured using a cone and plate rheometer with specially instrumented shallow cone (AR1000; TA Instruments; New Castle, DE). We did not attempt to extract and separately analyse the mucus component from the airway secretions. Elastic modulus (storage modulus, G') and viscous modulus (loss modulus, G'') were determined by measuring stress strain curves of thawed 20 μL samples at driving frequencies of from 0.01 to 10000 rad/s. The G' and the G" of the specimen were determined from these curves over the linear portion between 1 and 100 rad/sec using nondestructive creep transformation. [8] Due to difficulties obtaining adequate volume samples, with cytokine measurement taking priority, only 10 samples on treatment were available for rheology measurement with 2 and 20 hour results pooled for analysis.

Statistical analyses

Paired comparisons allowing for period effects and fixed subject effects were conducted using generalised linear models and within-subject contrasts using SAS 9.1 software (SAS Institute Inc., Cary, NC, USA) as recommended for analysis of cross-over studies. [9] For the 20-hour study a model was used that incorporated both the 2 and 20 hour time periods, so only a single p value is presented. For non-normally distributed data log or square root transformations were performed.

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The outcomes for the short-term and the long-term studies were the occurrence of clinical events as presented here. As recorded in the trial registry, when planning the study we had included radioaerosol mucociliary clearance (MCC) scans as a primary outcome. However we were unable to obtain repeatable results in children initially completing the study due to variable radioaerosol deposition with inconsistent breathing patterns between scans and movement artefact between images. We therefore abandoned this as an outcome. For the long-term study, a power calculation assuming a 50% reduction in major clinical events over an 8-week period from 90% of the study population to 45%, showed a sample size of 13 participants would be required to give a power of 80% at a significance level of 0.05.For the short-term study a sample size calculation was based on assuming a difference for mucus viscoelastic modulus between the means of 0.3 and a standard deviation of the difference of 0.5 indicated a sample size of 15 gave a power of 80% and significance of 5%.

RESULTS

For the short-term study 15 children were enrolled, eight male, mean age 4 years 6 months (range 1 month to 17 years) and mean duration of tracheostomy 1 years 3 months (range 5 months to 16 years 9 months). Craniofacial abnormalities, including Pierre Robin sequence, (n=4) and neurologic causes (n=4) were the most common indications for tracheostomy. Two thirds of the children had co-morbidities with neurological conditions being the most common. All children completed the study with no protocol violations.

No episodes of tracheostomy occlusion occurred during either treatment period. There was one unscheduled tracheostomy tube change for oxygen desaturation that occurred during treatment with HH. Five of the children were on oxygen for all or part of the study and were not assessed for SpO_2. No significant differences were found

between HH and HME for the overnight suctioning frequency (6.8 ± 5.0 vs. 7.7 ± 5.0, p = 0.33), or number requiring normal saline instillation (1.40 ± 2.16 vs. 1.07 ± 1.39, p = 0.42). There was also no difference in mean overnight SpO_2 (97.4% ± 1.3 vs. 97.7% ± 1.3, p= 0.46) or mean pulse rate (115.7 ± 26.9/min vs. 112.3 ± 31.8/min, p = 0.45).

The RR was lower (p = 0.038) on HH compared to HME after 2 hours (38.5 ± 18.8/min vs. 44.1 ± 17.4/min) and after 20 hours (40.5 ± 16.7/min vs. 42.5 ± 18.6/min) (Table 1). SpO_2 in children breathing room air was similar on HH compared to HME (p=0.06). The total respiratory examination score was lower during treatment with HH compared to HME (p < 0.001) after 2 hours (2.4 ± 2.2 vs. 3.6 ± 2.4) and after 20 hours (2.5 ± 2.0 vs 3.7 ± 2.6). There were also significant differences in the components of the total score severity of retractions (p = 0.011) and severity of wheeze (p = 0.02).

For the long-term study a total of thirty-six children were identified during the study period (Figure 1). Four were considered ineligible due to dependence on home ventilation and four to an inability to gain informed consent. Two families were not approached due to parental distress. Of the remaining 26 families approached, 12 declined consent. Fourteen children were therefore enrolled, eight male, mean age 2 years 10 months (range 5 months to 15 years 3 months), and mean duration of tracheostomy 2 years 4 months years (range 2 months to 15 years). Craniofacial syndromes, including Pierre-Robin sequence, were the most common indication for tracheostomy and nine of the children had co-morbidities. None were reportedly exposed to environmental tobacco smoke. Two children withdrew during the first period while on treatment with HME. One family declined the randomisation order and had treatment order reassigned to HH then HME and one child underwent the two treatment periods separated by 12 months but were included in the analysis.

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Fewer subjects had an adverse clinical event during the HH period compared to the HME period (5 vs. 11, p = 0.008) (Figure 2). The events included LRTIs (4 vs. 8), acute respiratory admissions (2 vs. 5) and tracheostomy tube occlusions/emergency changes (2 vs. 5). There were also fewer treatment failures and/or study withdrawal during the HH period (0 vs. 3). However, no differences were found comparing RR, oxygenation or work of breathing as measured by the clinical examination score. Children receiving HH during sleep used fewer HMEs per day (3.3 ± 1.9 vs 4.0 ± 1.7, p = 0.02).

Adherence data for the HH period was downloaded for nine participants and showed the machine was switched on for 94.8% of days (standard deviation 9.2%) and for a mean of 11.8 hours per day on days used (standard deviation 2.8 hours). More parents reported satisfaction with the HH as compared to the HME (11 vs. 9 satisfied, 0 vs. 2 not satisfied, p=0.018) with no statistical difference in final preference (8 vs. 2, p=0.07). No differences were detected between treatments in terms of visual secretion assessment in either study (Table 1).

No significant treatment effects were found for any of the inflammatory cytokines measured. In the short-term study calculated p values were 0.73, 0.59 and 0.49 for IL-8, IL1β and TNFα, respectively. Values for the long-term study were 0.21, 0.54 and 0.66. There were no significant differences found for rheology measurements between treatments in the short-term study (p = 0.69 for the viscous modulus at 1 and 100 rad/s, p = 0.55 and 0.84 for the elastic modulus). Only ten samples were available of adequate quality for this analysis.

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Discussion

Children using HH over 20 hours of treatment had lower (better) respiratory examination scores but no differences in adverse clinical events compared to using an HME. Over ten-week treatment periods, fewer children with long-term tracheostomies had an adverse clinical event when treated with HH as compared to HME, with no treatment failure while on treatment with HH but two participants withdrawing from the study while on HME. The effects of inadequate humidification are known to increase with duration,[10] which may explain the differences in clinical events between the 20-hour and 10-week studies.

It has been reported that in adults mechanically ventilated in ICU, there were fewer ETT occlusions with the use of a HH compared to HME [11-15] despite participants with "thick" airway secretions being excluded from all trials. [16] In tracheostomised adult patients there has been one published long-term study of humidification, comparing HME to no treatment describing a decrease in the occurrence of pneumonia. [17] A more recent study in laryngectomised adult patients found improved cough and adherence to HME compared to HH in the immediate post-operative period. [18] The humidifier in that study did not use heated tubing which may have resulted in condensate, potentially affecting outcomes. In the long-term study we also documented significantly fewer LRTIs, acute respiratory admissions, tracheostomy tube occlusions/emergency changes and treatment failures during the HH period. This is important clinically and significant to parents and child alike, not only because of potential adverse effects of the single events, but also improving parental confidence, rather than feeling the need to constantly monitor the child. The decreased use of almost 1 additional HME per day when on the HH overnight also represents a significant cost saving equivalent to US$360 per month (see Table 2 for total annual costs).

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During the short-term study we found a difference in clinical examination findings while using HH compared to HME, but the investigator was not masked to treatment group. During the long-term study, no difference between treatments was found during blinded clinical examination - this lack of difference may have been due to all participants wearing the HME at the time of assessment.

The increased RR and respiratory examination score found at 20 hours in the HME group may have been a direct mechanical effect with increased dead space and increased airway resistance. The HME had a dead space of 7 mL and resistance of 2 mmH_2O. In ambulatory adults spontaneously breathing through tracheostomies, an HME did not decrease respiratory function, [19] but in adults ventilated for respiratory failure, an HME decreased ventilation with a compensatory increase in work of breathing. [20-25] This dead space increase is relatively greater in an infant or small child than an adult. We recruited children from one month to 16 years of age in our study. The youngest child in this study was 3.41 kg at enrolment and would have had a tidal volume of approximately 10 mL (3-5 mL/kg); the oldest child was 17 years of age with a weight of 56.5 kg and approximate tidal volume of 280 mL. While the increased work of breathing may not be clinically significant, it can increase the energy and caloric requirements for respiration.

We found no difference in the visual assessment of suctioned airway secretions in either study. A study of adults ventilated in ICU showed all subjects had thin secretions while on HH and moderate or thick secretions after several days treatment with HME. [7] The lack of difference in our study may be due to the smaller volume of secretions, the smaller size of the suction catheter used, shear forces of 100 mmHg suction, or smaller volumes of fluid aspirated through the catheter.

While the clinical differences with HH compared with HME may be due to or associated with changes in secretion rheology or inflammation, we could not demonstrate this in our studies. The cytokines were collected at the tracheostomy site and therefore may have been produced hours before in the lower respiratory tract. Cytokine response to an insult may take hours to be produced with interactions between inflammatory triggers, resident inflammatory cells and migration of inflammatory cells to the site of initial injury, similar to the late-response in asthma. [26] Our viscoelasticity results are lower than previous studies which have analysed mucus from airway samples or sputum. Our samples included the entire airway secretion sample, not the mucus component alone, including an amount of periciliary liquid layer and condensate.

We also performed a parallel qualitative study, interviewing the parents of ten children.[27] We found that in managing their child's care, parents of children with tracheostomies balanced the difficulties of using a treatment against the benefits it provided in terms of improvements in the child's health, decreased parental worry, and decreased need for the parent to wake in the night. Most of the interviewed parents elected to continue using the HH, but a few elected to use HME when the difficulties of using the HH outweighed the benefits.

The small sample size is a limitation in both studies, most marked in the number of secretion samples available for analysis. The research planned was based on tracheostomy insertion numbers in preceding years. However, with improved non-invasive ventilation there were fewer patients and those who had tracheostomies were decannulated much more quickly. As well, many of these children were placed in care, making it unsuitable for them to be enrolled in the study.

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Conclusion

In children with tracheostomies, the use of a HH overnight over a period of ten weeks led to reduced acute clinical events, reduced study withdrawal and improved parental satisfaction. Over a short-term 20-hour period children were found to have increased respiratory effort when wearing the HME device as compared to the HH device. We recommend HH use for children with thick secretions, repeated chest infections or recurrent hospital admission for respiratory illness. A multi-centre study would be helpful to investigate the most appropriate method of humidification for children with tracheostomies.

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Figure 1: Diagram for long-term study showing numbers of children eligible, enrolled and withdrawn and final treatment preference as stated by parents.

HH = heated humidifier, HME = heat and moisture exchanger.

Figure 2: Numbers of participants experiencing major clinical events during overnight treatment with HH or HME.

*p < 0.05

HH = heated humidifier, HME = heat and moisture exchanger.

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Table 1: Clinical examination results for short-term study

	Baseline		Two hours		Twenty hours		Overall study period effect p value	Overall study treatment effect p value
	HH (± standard deviation)	HME (± standard deviation)	HH (± standard deviation)	HME (± standard deviation)	HH (± standard deviation)	HME (± standard deviation)		
Mean pulse rate (beats per minute)	134.1 ± 28.1	125.7 ± 28.1	128.2 ± 24.7	125.3 ± 26.8	125.5 ± 25.3	128.0 ± 25.6	0.084	0.97
Mean respiratory rate (breaths per minute)	39.3 ± 20.9	38.1 ± 20.8	38.5 ± 18.8	44.1 ± 17.4	40.5 ± 16.7	42.5 ± 18.6	0.9	0.038*
Mean oxygen saturation (percent)	97.7% ± 2.1	97.3% ± 2.8	98.3% ± 1.7	97.9% ± 1.6	98.4% ± 1.7	97.4% ± 2.4	0.13	0.06
Mean total respiratory examination score†	2.9 ± 2.1	3.4 ± 2.2	2.4 ± 2.2	3.6 ± 2.4	2.5 ± 2.0	3.7 ± 2.6	0.38	< 0.001*
Mean total secretion score† (± standard deviation)	6.9 ± 1.5	6.5 ± 1.0	6.5 ± 1.2	6.5 ± 1.1	6.5 ± 1.4	7.4 ± 1.3	0.31	0.086

*p value < 0.05
HH = heated humidifier, HME = heat and moisture exchanger.

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Table 2: HH compared to HME in terms of performance and costs

	Performance*	Dead space*	Resistance*	Cost per item (at time of study)	Annual Cost
Thermovent-T HME	25 mg H_2O/L and 34°C	7 mL	2 mmH_2O	NZ$4	NZ$5840
Fisher and Paykel HH	44mg H_2O/L and 37°C	0	0	NZ$1395	NZ$1753**

*According to manufacturer's specifications

**Calculated costs for HH included costs of purchasing HH and supplying sterile water. Electricity costs not included and borne by caregivers. Costs of HME when awake not included (NZ$4818)

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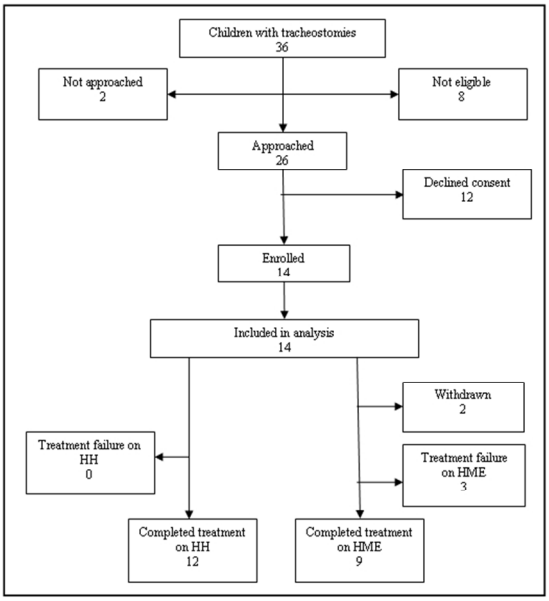

Figure 1: Diagram for long-term study showing numbers of children eligible, enrolled and withdrawn and final treatment preference as stated by parents.

HH = heated humidifier, HME = heat and moisture exchanger.

254x190mm (96 x 96 DPI)

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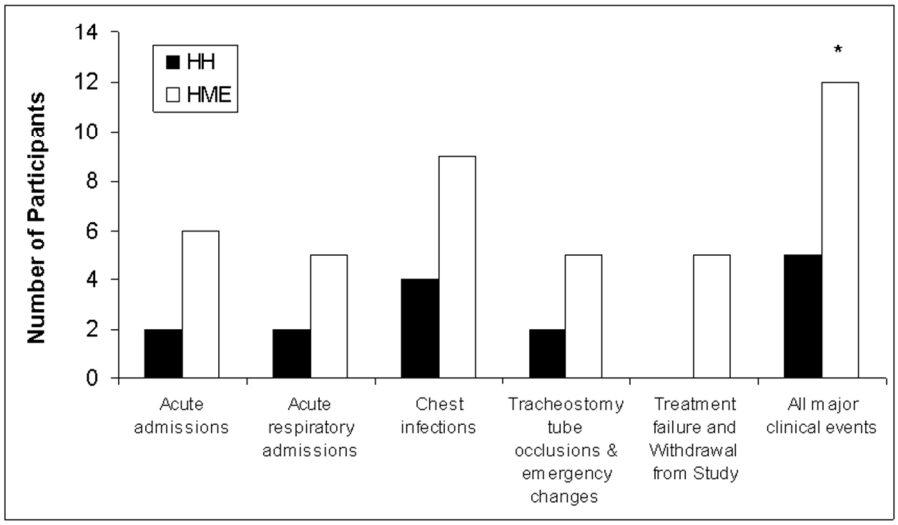

Figure 2: Numbers of participants experiencing major clinical events during overnight treatment with HH or HME.
*p < 0.05
HH = heated humidifier, HME = heat and moisture exchanger.

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