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Contents

Habitual Snoring is Probably Pathological in Children

Habitual snoring is a common symptom of obstructive sleep apnea syndrome (OSAS) and OSAS is a common problem in children in Asia and a position statement was produced by Asian Paediatric Pulmonology Society.[1] The current issue saw Prof. Huang YS *et al*. giving an updated views on management of childhood sleep-disordered breathing (SDB) and this will surely help improve the long-term outcomes of children with SDB, which includes habitual snoring. Chan MC *et al*. published an original study looking at the occurrence of symptoms of neurobehavioral disorder, i.e., attention deficit, impulsiveness, and hyperactivity, in children with so-called "primary snoring". It further strengthens the view that habitual snoring is not free of pathology given the constraints of the current definition of OSAS in children.

Acute bronchiolitis is the most common cause of acute respiratory distress in infants, and hypertonic saline nebulization was commonly used. Recently, a lot of advance has been made in the nebulizer technology. In a prospective randomized trial, Lai SH *et al*. compared the small volume nebulizer (SVN) and the vibrating mesh nebulizer (VMN) and found the latter to be more acceptable by parents. This might be important clinically as one often finds young children frightened by the noise of the SVN and pushed the mask away leading to decreased effectiveness of SVN. VMN might well be the answer.

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Review Article

A Review of Treatment Options in Paediatric Sleep-disordered Breathing

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Abstract

The clinical presentation of paediatric obstructive sleep apnoea (OSA) is different from that reported in adults. Children with paediatric OSA have more disturbed nocturnal sleep than excessive daytime sleepiness and present with more behavioural problems such as hyperactivity. They have sleep-related issues such as nocturnal enuresis and sleep-terrors and psychiatric problems such as depression and insomnia. Adenotonsillectomy has been the recommended treatment for paediatric OSA, but this practice as the initial treatment for all children has been questioned. The orthodontic approaches have been studied in children. Preliminary studies have suggested that rapid maxillary expansion and mandibular advancement with functional appliances may be effective even in children. Mandibular advancement devices, however, are not recommended for pre-pubertal children. These devices have been used in children in the late-teens, but long-term follow-up data are still lacking. Another non-invasive treatment is myofunctional therapy that has not been widely investigated. In syndromic children and where hypoventilation during sleep is present, positive airway pressure ventilation can be given. Nasal allergies are common in children. Increased nasal resistance impacts on breathing during sleep. Therefore, the treatment of nasal allergies with anti-inflammatory agents is an integral part of the management of paediatric OSA. Another important aspect of paediatric OSA is the presence of a short lingual frenulum and less frequently, a short nasal frenulum. They have been shown to cause abnormal growth of oral-facial region leading to OSA. Gastroesophageal reflux is both a cause and consequence of OSA and should be treated if present. The recent advance in the understanding of the pathogenesis of paediatric OSA lends hope that early recognition and management of factors that lead to the development of OSA may reduce the frequency of this disease and its sequelae. However, these factors are mostly unknown or ignored by specialists and general paediatricians during the early childhood orofacial development.

Keywords: Adenotonsillectomy, lingual frenulum, myofunctional therapy, paediatric obstructive sleep apnoea

Introduction

Paediatric obstructive sleep apnoea (OSA) was initially described in 1976.[1] In 1981, Guilleminault *et al*. published a review of fifty paediatric patients[2] which demonstrated that the clinical features of paediatric OSA were different from adults. The authors emphasised that these children had more disturbed nocturnal sleep than excessive daytime sleepiness, presented with more behavioural problems, especially school-related problems with attention deficit and hyperactivity (attention deficit hyperactivity syndrome) resulting in poor school performance. They can also present with nocturnal enuresis, sleep-terrors, sleep-walking and confusional arousals which are classified as non-rapid eye movement parasomnias. Hypersomnias, depression, insomnia and psychiatric problems are also noted. In Asia, Huang *et al*. reported that the common symptoms of paediatric OSA were similar with poor attention span, loud snoring, difficulty awakening and mouth breathing being the most commonly observed.[3]

The underlying causes of paediatric OSA are complex. Adenotonsillar hypertrophy, obesity, anatomical and neuromuscular factors are involved. In 1978, adenotonsillectomy (T&A) was suggested as a treatment of OSA. This was based on the concept that the presence of soft-tissue such as enlarged adenoids and tonsils could cause narrowing of the

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upper-airway, increased the risk of collapse of hypopharyngeal tissue during inspiration. This is still often considered as the treatment of choice in children. Following T&A, some patients still have features of OSA and others have reported an increased weight gain. There is currently no consensus as to the best mode of treatment for paediatric OSA probably because the best treatment should be tailored to the cause(s) of the OSA in each individual child.

Treatment Options for Paediatric Obstructive Sleep Apnoea Syndrome

There are no universally accepted guidelines for treatment of paediatric obstructive sleep apnoea syndrome. Treatment options for paediatric sleep-disordered breathing (SDB) include:

1. T&A: The most common treatment for paediatric OSA
2. Treatment of nasal allergies and radiofrequency treatment of enlarged turbinates
3. Continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP); positive airway pressure (PAP) ventilation can be used in all age groups
4. Weight reduction in overweight/obese children
5. Medications: Nasal decongestants, nasal steroids, and leukotriene inhibitors (montelukast) may be a therapeutic option for children with mild or residual OSA
6. Palatal expanders and oral appliances, while mandibular advancement devices (MADs) can be considered for adolescents
7. Other surgical procedures, for example, epiglottoplasty, mandibular distraction osteogenesis and maxillomandibular advancement and tracheotomy, which may be indicated in selected cases despite the fact that some of the surgical procedures performed in adults such as uvulopalatopharyngoplasty have been strongly recommended to avoid in children by the American Academy of Sleep Medicine.

The decision for the type of treatment is based on a combination of the available knowledge about potential cardiovascular, metabolic and neurocognitive sequelae and the clinical judgement of individual health-care professionals.

Adenotonsillectomy

For years, T&A has been the recommended treatment for paediatric OSA. In recent years, this practice has been put into question. First, many studies showed that T&A in paediatric OSA patients had variable results in achieving an apnoea-hypopnoea index (AHI) of 1 or less, with such results been observed in about 50% of cases and as low as 32% in obese children.[4-8] Furthermore, a long-term polysomnography (PSG) follow-up study[9] performed in children with OSA aged 6–12-year-old who had undergone T&A with sleep PSG performed 6 months, 12 months, 24 months and 36 months after T&A. It showed progressive worsening of AHI with time in 68% of the cohort.

The Childhood Adenotonsillectomy Trial study looked at children with low but abnormal AHI who delayed having a T&A. A repeat PSG after the initial investigation without T&A showed a change from the baseline study, but clinical symptoms may still be present.

Another study showed that T&A alone did not lead to the elimination of mouth breathing during sleep.[10] This might be due to the fact that children who were mouth-breathers for a certain length of time had a 'dis-use' of their nose when breathing during sleep and removal of the adenoids and tonsils did not restore them to normal nasal breathing during sleep.[10]

Paediatric OSA may be related to other factors limiting the size of the upper airway during sleep such as abnormalities of oral-facial structures. These abnormalities need to be corrected to restore normal airway flow.

Orthodontic Treatment

Preliminary studies[11-14] suggested that orthodontic treatments, such as rapid maxillary expansion (RME) or mandibular advancement with functional appliances, may be effective in handling paediatric snoring and OSA. The introduction of RME or bi-maxillary expansion[15,16] has shown that some children may not need T&A. These preliminary results suggested that the correction of mild abnormalities of cranio-facial structures reduced snoring and OSA in children and young adolescents and may be sufficient to avoid T&A and bring back nasal breathing during sleep.[15,16]

RME is aimed at increasing the width of the palate by its action on the cartilaginous intermaxillary suture, an active facial growth centre active till 13–16 years of age. Bi-maxillary expansion combines the treatment on the intermaxillary suture with the expansion of the mandibular teeth as the alveolo-dental growth centre is also active till the same age. Mandibular expansion has less impact than RME.[17-19]

Studies combining the use of T&A and RME have shown that combination approach often provides better results than the single approach: There is a continuous interaction between nasal breathing and facial growth. Enlarged adenoids and tonsils impair nasal breathing which impacts on oral-facial growth which further narrows the upper airway.

Myofunctional Therapy

The non-restoration of nasal breathing during sleep leads to the recurrence of SDB. This was shown by both retrospective and prospective studies involving T&A alone and T&A with orthodontic therapies.

The use of myofunctional therapy (MFT) alone when dealing with paediatric SDB has not been widely investigated. Results of studies done on children with orthodontic problems have shown that isolated extensive and well-controlled MFT can lead to return to normal orofacial anatomy.[20,21] In adults, there is reported improvement of OSA and snoring, but the

long-term effect on SDB is unknown. Treatments with T&A or orthodontics without concomitant MFT has been shown to lead to persistence or recurrence of paediatric SDB.

MFT and proper tongue positioning in the oral cavity have been described since 1918 as leading to improvement in mandibular growth, nasal breathing and facial appearance. MFT is comprised of isotonic and isometric exercises that target oral (lip, tongue) and oropharyngeal structures (soft palate, lateral pharyngeal wall). Breathing, particularly nasal breathing, swallowing, mastication and suction are some of the daily functions that help the oral cavity gain growth during early childhood and participates in the normal development of the oral-facial structures. Normal development of oral-facial structures is important for air exchange, particularly during sleep. During childhood sleep, the tongue will be positioned against the palate and help widen the palate (the adult palatal width is between 40 and 50 mm). The continuous interaction of the tongue with active inter-maxillary synchondrosis and the alveolo-dental growth region are factors in the normal development of oral-facial structures.[20-23] MFT[20-23] aims to obtain appropriate head posture and positioning of the tongue on the palate against the upper teeth, appropriate swallowing and mastication using both sides and posterior chewing, appropriate breathing through the nose while keeping the mouth closed, and appropriate speech and articulation. MFT requires active parental involvement to obtain good results. Specialised educators exist in many countries, but educational programs vary widely in depth. A meta-analysis[20-23] showed that MFT in association with other therapeutic approaches may lead to complete remission of OSA in about 60% of children with whom it is used. The major problem is compliance with daily exercises and continuous parental involvement with the training exercises of the child. This treatment approach is called 'active MFT'.[20-23]

A 'passive MFT'[24] was reported recently. It calls upon the use of mandibular devices that will lead to sensory stimulation of the tongue leading to increased tongue muscle activity, but more work is needed. It showed that 6 months of passive MFT using an oral appliance with a tongue bead during sleep led to a reduction in the AHI in 63.6% of children.[24]

Dental Devices in Paediatric Obstructive Sleep Apnoea

MADs are not usually recommended in paediatric OSA and in particular pre-pubertal individuals. It has been tried in teenagers, but there is no long-term outcome information. Functional jaw appliances such as the Herbst appliance and Frankel functional appliances have been tried in children in the hope of increasing mandibular growth, but studies have shown that no growth beyond age-related growth could be seen with such appliances. In Taiwan, we have placed some children on the Herbst appliance between 12 and 17 years of age. The results were similar to that described in adult studies with dental devices. There was an improvement in the AHI when the teenager was wearing the device, but the OSA recurred once the appliance was removed. All these children underwent maxilla-mandibular-advancement surgery at 18 years of age. A similar experience was obtained with 6 children wearing the Biobloc™ devices. There was no long-term benefit demonstrated in children put on mandibular advancement devices. The only prospective study of devices in paediatric OSA compared with a controlled group which showed a benefit is the study post-usage of the device used to perform in passive MFT, and this study involves a small number of children.[24]

Positive Airway Pressure Ventilation

PAP ventilation can be considered in children with hypoventilation during sleep or in syndromic children or when other treatments have failed. It can be applied to children of all ages.[25]

Continuous-positive airway-pressure (CPAP) is usually considered in children with isolated upper airway problems. However, children with other problems besides upper airway obstruction such as obesity, syndromic children, connective tissues disorders (e.g., Marfan's, Ehlers–Danlos syndrome) or neuromuscular disorders (e.g., myotonic dystrophy, Duchenne muscular dystrophy), BiPAP is commonly required.

Compliance to treatment is a problem and parents have to be supported by the medical team during the training. Behavioural therapy during the daytime may be needed before children accept wearing the mask during sleep. Regular follow-up is needed as facial growth is continuous and dynamic during childhood. Re-calibration of pressures will be needed over time.

The major problem associated with PAP therapy in children is its effect on mid-facial growth due to the pressure of the masks on the developing facial bones.[26] Such changes occur as early as 12 months of starting therapy and are more obvious after 2 years of usage. The younger the child, the greater and more rapid is the impact. However, it can occur at any age.[27,28] The use of chin-strap increases this negative effect. To reduce this effect, masks have been developed that apply pressure over the forehead instead of the midface structures. Regular orthodontic evaluation and daytime MFT have also been recommended to counteract this problem.

Treatment of Nasal Obstruction

Increased nasal resistance impacts on breathing during sleep. Nasal allergies are common in children and will lead to enlargement of the inferior and middle nasal turbinates leading to mouth breathing.[29] Allergies are associated with an increase in inflammatory mediators that play a role in enlarging the soft tissues located in the upper airway. The nasal passages should always be evaluated when OSA is suspected as the presence of enlarged nasal turbinates, a deviated nasal septum and enlarged adenoids and tonsils can contribute to upper airway obstruction.

The treatments for reducing nasal turbinate include the use of topical corticosteroid nasal spray especially in the presence of nasal allergies. These can be applied either intermittently or continuously for 3 months. In the case of intermittent use, the nasal sprays are applied for 4–6 weeks with a rest for 4 weeks before reapplying for a further 4–6 weeks. Leukotriene receptor antagonists such as montelukast can be given to reduce nasal congestion and for its anti-inflammatory properties. The treatment of nasal allergies also includes immunotherapy against a specific allergen identified on skin prick tests if indicated. Radiofrequency ablation therapy of the turbinates can be applied in children with severe nasal obstruction.

The management of a deviated nasal septum is not as clear. In the presence of complete obstruction of the nasal passage, surgery may be required. However, recurrences can occur if performed in a young child. If the deviated nasal septum is associated with a high and narrow palatal vault, orthodontic treatment with RME should be the first line treatment as widening the palatal vault will allow more space for spontaneous expansion of the nasal septum.

Role of the Frenula

A short lingual frenulum and less frequently, the nasal frenulum are known to cause abnormal growth of the oral-facial region leading to OSA.[30,31] The presence of short frenula should be recognised at birth and surgical release should be done. It is controversial as to how early this clipping should be done. The current evidence suggest that surgical release should be performed within the 1st month of life for the best results. No long-term studies on its effect on tongue motility and oral-facial development is available. One important factor is the practice of 'stretching' the frenulum three to 4 weeks before and after the surgery, and this is done using daily MFT. Such a recommendation is crucial in treating a short frenulum.[32-35]

Role of Gastroesophageal Reflux

Gastroesophageal reflux (GER) is both a cause and consequence of OSA and should be treated if present. It has also been associated with a short lingual frenulum. The abnormal inspiratory effort seen with obstructed breathing during sleep is associated not only with an increase in pleural pressure but also with an increase in abdominal pressure, leading to the development of GER. The presence of GER results in the presence of acid in the upper-airway that leads to inflammation and impairment of upper airway reflexes during sleep. This worsens any SDB even in the absence of aspiration. The aggressive treatment of GER must be initiated if present.

Conclusion

The progress has been made in our understanding of paediatric OSA, and we can now identify factors leading to its development or worsening.[22] However, a lot of general paediatricians are still unaware of these advances and of the treatment options available, particularly those addressing the risk-factors leading to increased risk of collapse of the upper-airway during sleep. The frequency of paediatric OSA can be significantly decreased if the basic functions such as nasal breathing, sucking, swallowing, masticating, and phonation were to be regularly investigated evaluated for appropriate development of upper-airway[23] and for early correction of abnormal development if present. Greater awareness by the paediatricians will lead to earlier diagnosis and treatment options for the parents.

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Conflicts of interest

There are no conflicts of interest.

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Prevalence and Risk Factors for Symptoms of Attention Deficit and Hyperactivity in Primary Snoring Children

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Abstract

Aim: Primary snoring was reported to affect 7.2% of school children in Hong Kong, and emerging evidence suggested that neurobehavioural symptoms were more frequently found among this group of children. The current study investigated the prevalence of symptoms of attention deficit hyperactivity disorder (ADHD) i.e., attention deficit, hyperactivity and impulsivity (ADHI), in Chinese children with primary snoring. **Materials and Methods:** Polysomnography results and relevant clinical notes for all Chinese children aged 4–18-year performed from January 2009 to December 2010 in our sleep laboratory were retrospectively reviewed. Data of the Chinese version of modified Epworth Sleepiness Scale and C-domain of Paediatric Sleep Questionnaire were analysed. **Results:** In primary snorers, the presence of excessive daytime sleepiness (EDS) and higher apnoea–hypopnea index (AHI) were risk factors for symptoms of AD with adjusted odds ratio of 3.2 (95% confidence interval [CI] = 1.2–8.1) and 4.7 (95% CI = 1.1–20.7), respectively. Primary snorer with AD symptoms had higher AHI, 0.32 ± 0.31 compared those without symptoms, 0.21 ± 0.29, $P = 0.038$. EDS was an independent risk factor for ADHI with odds ratio of 4.7 (95% CI = 1.1–20.0). **Conclusion:** Early screening for symptoms of ADHD should be performed in children with primary snoring.

Keywords: Attention deficit hyperactivity disorder, excessive somnolence disorders, polysomnography, sleep-disordered breathing

Introduction

The prevalence of habitual snoring ranged from 3% to 35% in children aged under 13 years and 8%–12% in children aged 2–8 years.[1] In Hong Kong, it was reported that the prevalence of habitual snoring was 7.2%–10.9% in children aged 5–14 years.[2,3] Snoring is often the presenting symptom of sleep disordered breathing, a spectrum that ranges from primary snoring (PS) to obstructive sleep apnoea syndrome (OSAS).[4] PS, defined as children who snore but do not demonstrate apnoea on polysomnography (PSG) i.e., apnoea–hypopnea index (AHI) ≤1/h, was found to occur in 6.1% of primary school children.[5] PS is considered as a benign condition and treatment is usually not considered necessary. However, there is increasing evidence that neurocognitive and behavioural symptoms such as hyperactivity, attention deficit (AD), poor school performance, excessive daytime sleepiness (EDS) and executive function difficulties were more frequently found in children with PS compared to those who never snored.[6,7] In the present study, a retrospective analysis was undertaken to estimate the prevalence of symptoms of AD hyperactivity disorder (ADHD) i.e., AD, hyperactivity and impulsivity (ADHI) in a cohort of Chinese children aged 4- to 18-year of age referred to the sleep laboratory for suspected OSAS.

Materials and Methods

PSG and relevant clinical notes of eligible Chinese children aged 4–18-year were reviewed. The PSG was conducted from January 2009 to December 2010. It was approved by the Clinical Research Ethics Committee, Kowloon West Cluster, Hospital Authority, Hong Kong.

Data of the Chinese version of modified Epworth Sleepiness Scale (mESS)[8] and the C-domain of Paediatric Sleep

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Questionnaire (PSQ)[9] were also reviewed. mESS is a validated tool to assess daytime sleepiness in Chinese children. It includes 8 questions with a 4-point rating scale for each of the questions (0 = never; 1 = slight chance; 2 = moderate chance and 3 = high chance). A score of more than 8 points is considered to be significant. PSQ is a questionnaire developed by Chervin *et al*.[10] in 1999 to evaluate children aged 2–18 years for sleep-related breathing disorder and symptoms. There are 3 domains: (a) Breathing symptoms; (b) EDS symptoms and (c) inattention/hyperactive behaviour. In domain C, items for inattention and hyperactivity are taken from DSM-V category A symptoms for attention-deficit hyperactivity disorder.[11] The answer to each question is either 'Yes' or 'No' or 'Don't know'.

In the current study, the validated Chinese version of PSQ was used[9] and the C-domain, which contained 18 ADHI-related questions, was the focus. Questions C1–C9 were about symptoms of AD. The presence of more than 6 symptoms was suggestive of AD. Questions C10-18 were related to symptoms of HI. The presence of more than 6 symptoms was suggestive of problems with HI. The PSQ questionnaire only enquired for the presence of symptoms suggestive of ADHI, without the details required in DSM-V criteria for the diagnosis of ADHD.

Polysomnography

PSG studies were performed overnight in a single room in all individuals with the Siesta Profusion-3 system (Compumedics, Victoria, Australia). No sedative was used. Continuous video recording using an infrared video camera was performed after obtaining written consent from the parents. The following parameters were recorded during the study; four electroencephalographic channels (C3-A2, C4-A1, O1-A2 and O2-A1), right and left electrooculogram tracings, submental electromyogram, tibial electromyogram, electrocardiogram, snoring sound, nasal airflow, oral airflow, chest and abdominal wall motion, body position, oxygen saturation and end-tidal carbon dioxide monitor (Novametrix 7100 CO2SMO Capnograph/Pulse Oximeter, USA). All data were stored for off-line analysis. Sleep architecture was scored manually according to the prevailing American Academy of Sleep Medicine Paediatric scoring criteria. Obstructive apnoea was defined as the cessation of airflow despite breathing effort for more than two respiratory cycles. Obstructive hypopnea was defined as the decrease of airflow by >50% but <80% of baseline associated with a desaturation of ≥3% or arousal despite breathing effort. The obstructive AHI was the summation of the number of obstructive apnoea and obstructive hypopnea and mixed apnoea per hour of sleep. In the current study, we used AHI >1.0/h to define OSA.[12]

Exclusion criteria

Children with the following conditions were excluded: Syndromal disorders such as Down's syndrome, neuromuscular disorders, craniofacial anomalies, previous tonsillectomy or adenoidectomy or have ever received or was on long-term psychostimulants during the time of PSG (e.g., methylphenidate, atomoxetine, modafinil, adrafinil, armodafinil, amphetamine), alpha 2-agonist (e.g., clonidine) or antidepressants.

Statistical analysis

Univariate logistic regression models for AD and HI were developed to explore the relative contributions of the various risk factors. The potential risk factors used for both models were gender, age, EDS, sleep duration, body mass index (BMI) z score, presence of habitual snoring, arousal index and AHI.[13] Any potential risk factors with $P < 0.2$ in the univariate logistic regression model were entered into the multivariate logistic regression. The significant level for all statistical analysis was $P < 0.05$. All analyses were conducted using IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp. in Armonk, NY, USA).

Results

During the study, a total of 104 eligible primary snorers were identified. There were 59 boys (57%). The mean (standard deviation [SD]) age was 11.5 (3.4) years. The mean (SD) BMI-z was 0.85 (1.1). The mean (SD) AHI was 0.3 (0.3)/h. The mean (SD) arousal index was 7.91 (6.8)/h. The mean (SD) sleep duration was 8.4 (1.4) h [Table 1].

There was a male predominance (M:F 57% vs. 43%) among our PS individuals. Twenty-seven (26%) of the individuals had EDS (mESS score >8). Twenty-three (22%) and seven (8%) of the subjects had significant symptoms of AD

Table 1: Demographics, sleep and respiratory data of primary snorers without attention deficit, hyperactivity and impulsivity versus with attention deficit symptoms versus with hyperactivity or impulsivity symptoms versus attention deficit + hyperactivity or impulsivity

	Whole group (*n*=104)	Asymptomatic (*n*=64)	AD (*n*=23)	HI (*n*=7)	AD + HI (*n*=10)
Male gender, *n* (%)	59 (57)	30 (47)	18 (78)	6 (86)	5 (50)
Age (years)	11.54 (3.42)	11.72 (3.66)	12.19 (2.92)	9.26 (2.30)	10.46 (2.60)
BMI Z score	0.85 (1.11)	0.85 (1.12)	0.81 (1.16)	0.9 (0.99)	0.99 (0.70)
EDS (mESS >8), *n* (%)	27 (26.0)	14 (21.9)	8 (34.8)	0	5 (50)
Habitual snoring, *n* (%)	58 (55.8)	31 (48.4)	14 (60.9)	6 (85.7)	7 (70.0)
AHI	0.26 (0.30)	0.21 (0.29)	0.32 (0.31)	0.33 (0.29)	0.36 (0.33)
Arousal index	7.93 (6.77)	7.22 (6.66)	9.14 (6.35)	10.34 (9.37)	8.03 (5.27)
Sleep duration (h)	8.44 (1.39)	8.43 (1.54)	8.30 (1.16)	8.93 (0.72)	8.46 (1.14)

Values are expressed as mean (SD). AD: Attention deficit, HI: Hyperactivity or impulsivity, EDS: Excessive daytime sleepiness, mESS: Modified Epworth Sleepiness Scale, AHI: Apnoea–hypopnea index, SD: Standard deviation, BMI: Body mass index

and HI respectively with male predominance i.e., 3.6:1 and 6:1 respectively. Ten (10%) of the individuals had combined symptoms of AD and HI.

In the current group of primary snorers, those with EDS and higher AHI were more likely to have symptoms of AD. The adjusted odds ratios (95% confidence interval [CI]) of having AD symptoms in those with EDS and higher AHI were 3.2 (1.2–8.1) and 4.7 (1.1–20.7), respectively. The AHI of primary snorers with AD symptoms was significantly higher than those without AD symptoms, 0.32 ± 0.31 vs. 0.21 ± 0.29, $P = 0.038$. Results from multivariate logistic regression showed that EDS and AHI were significant risk factors for AD [Table 2]. There was no significant risk factor identified for HI [Table 3]. EDS was a significant risk factor identified for symptoms of ADHI with odds ratio of 4.7 (95% CI = 1.1-20.0), $P = 0.036$ [Table 4].

Table 2: Risk factors for attention deficit by multivariate logistic regression analysis

Parameters	Adjusted OR (95% CI)	Regression coefficient	*P*
Male gender	2.46 (0.97-6.22)	0.90	0.057
EDS (mESS >8)	3.16 (1.24-8.05)	1.15	0.016*
AHI	4.74 (1.09-20.70)	1.56	0.038*

*$P<0.05$, two-tailed test. All covariates of $P<0.2$ in the univariate analysis were incorporated in the multivariable analysis.
EDS: Excessive daytime sleepiness, mESS: Modified Epworth Sleepiness Scale, AHI: Apnoea–hypopnea index, OR: Odds ratio, CI: Confidence interval

Table 3: Risk factors for hyperactivity and impulsivity by multivariate logistic regression analysis

Parameters	Adjusted OR (95% CI)	Regression coefficient	*P*
Age (years)	0.87 (0.74-1.03)	−0.14	0.101
Habitual snoring	2.80 (0.81-9.60)	1.03	0.102
AHI	3.14 (0.56-17.59)	1.14	0.193

All covariates of $P<0.2$ in the univariate analysis were incorporated in the multivariable analysis.
AHI: Apnoea–hypopnea index, OR: Odds ratio, CI: Confidence interval

Table 4: Risk factor for attention deficit, hyperactivity and impulsivity by univariate logistic regression analysis

Parameters	OR (95% CI)	Regression coefficient	*P*
Male gender	0.70 (0.17-2.90)	−0.36	0.620
Age (years)	0.92 (0.72-1.17)	−0.08	0.494
BMI Z score	1.32 (0.67-2.59)	0.28	0.422
EDS (mESS >8)	4.71 (1.11-20.00)	1.55	0.036*
Habitual snoring	1.62 (0.34-7.67)	0.48	0.544
AHI	5.41 (0.51-58.01)	1.70	0.163
Arousal index	0.99 (0.89-1.10)	−0.01	0.836
Sleep duration (h)	0.96 (0.55-1.70)	−0.04	0.862

*$P<0.05$, two-tailed test. ADHI: Attention deficit, hyperactivity and impulsivity, EDS: Excessive daytime sleepiness, mESS: Modified Epworth Sleepiness Scale, AHI: Apnoea-hypopnea index, OR: Odds ratio, CI: Confidence interval

Discussion

The worldwide prevalence of ADHD was 5.29%.[14] In China, Taiwan and the United States, the prevalence were 5.9%,[15,16] 9.9%[17] and 9.5%[18] respectively. The prevalence of ADHD was higher in boys, with male to female ratio between 3:1[17,19] and 9:1[11] worldwide and in the United States, male to female ratio in AD, HI and ADHI were 1.3:1, 1.8:1 and 2.8:1 respectively.[20] In Hong Kong, the prevalence of ADHD in Chinese schoolboys was estimated to be 8.9% according to the DSM III-R criteria.[21]

Our findings corroborated previous studies that neurobehavioural symptoms were more frequently found in children with PS compared to those who never snored.[5,22] In a 4-year prospective cohort study, Chervin *et al*. also found that habitual snoring or loud snoring were strong risk factors for future emergence or exacerbation of hyperactive behaviour.[23] However, no risk factors were identified for symptoms of HI in the current study. This could be related to the small sample size. The mechanism for the link between PS and neurobehavioural symptoms remains unclear. The postulated mechanisms were sleep fragmentation and sleep disruption in children.[5] Sleep fragmentation resulting in EDS was suggested to be contributory to neurobehavioural impairment.[22]

In the current study, within the normal AHI range, a higher AHI index was associated with higher risk of having AD symptoms, supporting the suggestion that children with AHI within the normal range may also be clinically abnormal as suggested by Guilleminault and Lee.[24]

The current study showed that 9.6% of children with PS had symptoms of ADHI. EDS was an additional risk factor for ADHI symptoms in primary snorer. Even in primary snorer, those with higher AHI were more likely to have AD symptoms.

Conclusion

Therefore, children with PS should be screened for symptoms of ADHI to be followed by objective measures on neurocognitive and behavioural function assessment so as to better quantify the impact of PS on the brain. Further studies to investigate the underlying mechanism between PS and the development of neurobehavioural disorders are warranted.

Limitations

In our study, children who were screened to have significant ADHI symptoms did not have further evaluation according to the DSM-V criteria to confirm the diagnosis. Other limitations included the absence of information about respiratory event-related arousal and flow limitation which were part of sleep disordered breathing that may account for the neuro-behaviour disorders as well as the absence of information about other risk factors such as prematurity,[25] prenatal exposure to tobacco, alcohol and illicit drugs[26,27] and low paternal education.[27]

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Conflicts of interest
There are no conflicts of interest.

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Original Article

Utilization of Vibrating Mesh Nebulizer in the Treatment of Infants with Acute Bronchiolitis: A Randomized, Controlled Trial

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Abstract

Background: Bronchiolitis is a disease that is predominantly caused by the infection of peripheral airway due to respiratory syncytial virus (RSV). The occurrence is highly prevalent among childhood stage with seasonal outbreak peak during fall and spring. Treatment of bronchiolitis invariably involves lengthy hospitalization, which places significant socio-economic burden on family caregivers and healthcare system. Aerosolizing hypertonic saline using small-volume jet nebulizer (SVN) remains as one of the effective therapies to alleviate symptoms in infants with acute bronchiolitis. However, such approach not only restraints treatment to hospitalization and can irritate patients with loud noise. It is unclear whether an alternative aerosol therapy that offers similar efficacy yet enhances portability, convenience and quiet operation is available. **Materials and Methods:** Herein we showed that a vibrating mesh nebulizer (VMN) offered quiet delivery and undisturbed nebulization yet harnessed similar improvement in clinical symptoms in contrast with SVN when treating hospitalized infants with acute bronchiolitis. **Results:** A total of 64 hospitalized infants (<12 months of age) with acute bronchiolitis were enrolled. Subjects were randomly assigned to SVN (n=32) and VMN (*n*=32) groups and had received the same aerosol treatment protocol during hospitalization. Besides respiratory rate, the initial overall severity score; hospital stay duration; and intravascular-line day for both groups (SVN vs VMN) were similar. The data were 4.30±1.44 vs 4.92±1.3; 3.97±1.88 vs 3.94±1.66 days; 2.31±1.47 vs 2.16±1.46 days correspondingly. However, a higher satisfaction score (4.8/5) was shown in a corresponding questionnaire indicating user preference in VMN due to enhanced portability, ease of clean and operation, and less-noise. These advantages could potentially facilitate bronchiolitis treatment and follow-up maintenance at home. **Conclusion:** In sum, the treatment outcome for infants with acute bronchiolitis was equivalent between SVN and VMN. Easy portability and simple operation features of VMN may present a much favored therapeutic option for home care users.

Keywords: Bronchiolitis, infants, small-volume jet nebulizer, vibrating mesh nebulizer

Introduction

Bronchiolitis, a seasonal viral-induced lower airway infection, usually outbreaks in autumn and spring. The most common pathogen is respiratory syncytial virus, followed by human rhinovirus, parainfluenza virus, and human metapneumovirus, coronavirus, and adenovirus.[1] It is highly prevalent among young children that typically result in substantial healthcare burden and hospital admission worldwide. Pathology of the disease comprises of diffuse inflammation and edema of bronchioles, mucus hypersecretion, necrosis, and sloughing of epithelial cells.[2] The resulting clinical manifestation of bronchiolitis usually encompasses sputum over-production, crackles, wheezing, dyspnea, and even respiratory failure.

Except for some supportive care, there are only a few effective therapies for infants with acute bronchiolitis.[3] Nebulizing hypertonic saline has been considered as a potential therapy. Several meta-analyses had supported that it could shorten hospital length of stay in hospitalized infants and improve the clinical severity score in both inpatients and outpatients.[4,5] Concurrently, the American Academy of Pediatrics has recently recommended hypertonic saline nebulization treatment delivery to inpatient children with acute bronchiolitis.[3]

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In traditional inhalation drug delivery, small-volume jet nebulizer (SVN) has been regarded as an inexpensive therapeutic approach to deliver aerosolized medications. Although SVN seems to be favored among young children who are incompliant with the usage of metered-dose inhaler, the resultant loud decibel generated; large residual volume postadministration, and inconsistent drug concentration throughout delivery significantly impedes the widespread acceptance among young children population. Hence, a more affable nebulization methodology is in great need. With the advent of vibrating mesh nebulizer (VMN), it has shown surpassing advantages over conventional SVN, including (1) stable and high aerosol output efficiency; (2) delivery of high-quality fine-particle aerosol; (3) low-residual nebulizer-solution volume; (4) ability to deliver ultra-small volume; and (5) provide undisturbed and quiet administration.[6,7] Given clear benefits, the possibility of delivering medication through VMN to patients with bronchiolitis remained uncertain.

Although VMN can successfully deliver bronchodilators, inhaled corticosteroids, and antibiotics,[8] the administration of hypertonic saline aerosols to infants with acute bronchiolitis has not heretofore been demonstrated. In the study, we investigated the therapeutic effects of VMN and SVN in nebulizing hypertonic saline to treat infants with acute bronchiolitis. The primary outcome examined the length of hospital stay. User experience analysis of VMN was the secondary outcome.

Materials and Methods

Patients

The current study was performed at Chang Gung Memorial Hospital from March 2015 to March 2016. Children that were 12 months or younger; diagnosed with acute bronchiolitis and hospitalized were eligible for the study. The diagnosis of bronchiolitis was defined as a history of viral upper respiratory tract infection plus wheezing and/or crackles on chest auscultation with respiratory distress. This study was approved by the Chang Gung Ethics Committee [Figure 1]. The written informed consents were obtained from parents or legal guardians of the infants. Records and clinical information of all patients were anonymized and deidentified before analysis. Children born prematurely (gestational age <36 weeks), those with major birth defects or congenital structural anomalies of the upper airway or neuromuscular disorders, those who were hemodynamically unstable, and those with a history of severe lower airway infection with intensive care unit admission were excluded from the study.

Study design

After enrollment, all infants admitted to the hospital were treated according to the same clinical pathway, i.e., nebulized hypertonic saline, to ensure consistent care and minimize data variation. Nebulizers (SVN or VMN) were randomly assigned by simple randomization table as the device for delivering hypertonic-saline aerosol. The flow chat of enrollment was

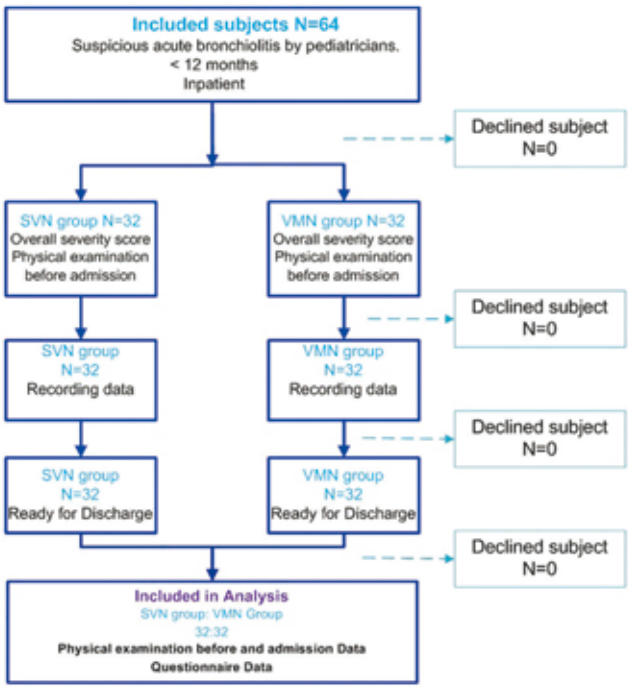


Figure 1: Flow chart of enrollment.

shown in Figure 1. SVN and VMN used in this study were from Gale Med Nebulizer Kits (GaleMed Corporation, Taipei, Taiwan) and PocketAir™ Portable Nebulizer (MicroBase Technology, Taoyuan, Taiwan), respectively. The delivery of hypertonic-saline aerosol prescription was designed as 4 ml of 3% saline solution (three times a day) using nebulizer.

After admission, respiratory rate, heart rates, respiratory effort, and oxygen saturation (while breathing room air) were observed and recorded daily till discharge. Daily infant conditions such as respiratory rate, oxygen saturation, and respiratory effort (classified as mild, moderate, or severe in accord to daily severity score) were presented in Table 1. The total hospitalized duration and supplemental intravenous fluid were also documented after discharge. In addition, a questionnaire regarding the usage of VMN device was completed for VMN enrollment group. A total of five items pertaining quality of device (i.e., weight, aerosol flow, noise in operation, ease of cleaning, and performance) were main assessments within questionnaire. The total score ranged from 0 to 5 and the full mark was 5.

Particle characterization

Particle characteristics generated by SVN and VMN were measured with Spraytec (Malvern Instruments, UK). In brief, 4 ml of 3% hypertonic saline solution was added to medication cup of SVN or VMN. SVN was driven by compressed air from a gas cylinder at 8 L/min. On nebulization, particle characteristics were measured by Spraytec for 75 s. After that, several parameters, including volume diameters (Dv10, Dv50, and Dv90), relative span factor (RSF), and percentage of droplet volume under 5 μm was used to compare

the difference between SVN and VMN. Dv10, Dv50, and Dv90 represented 10%, 50%, or 90%, respectively, of droplet volume in diameter smaller or equal to the stated value. RSF was calculated by (Dv90-Dv10)/Dv50 and which represented the uniformity of the droplet volume distribution. The results of triplicate run for four samples of either SVN or VMN were collected and compared. $P < 0.05$ was considered to be statistically significant.

Statistical analysis

Results were expressed as mean ± standard error values. Statistical comparisons between groups were performed using Mann–Whitney test for continuous variables, and Fisher exact test for categorical variables. $P < 0.05$ was considered statistically significant. Comparisons of hospitalization days, intravenous fluid administration days, and oxygen supplement between groups were performed by Student's *t*-test. All analyses were performed using IBM SPSS software v. 20 (Armonk, NY, USA).

Table 1: Overall Severity Score and normal range of respiratory rate depending on different age

Overall severity score	a + b + c <2 Mild	a + b + c 2-3 Moderate	a + b + c >3 Severe
a. Respiratory-effort scores			
Score			
0		Not present	
1		Mild-to-moderate	
2		Severe	
Weighted scores			
1		Intercostal recession	
1		Subcostal recession	
1		Substernal recession	
1.5		Tracheal tug	
1.5		Nasal flaring	
Respiratory-effort scores			
0		0-4.9 Mild	
1		5.0-8.9 Moderate	
2		9.0-12.0 Severe	
b. Oxygen saturation breathing ambient air			
0		95%-100% Moderate	
0		90%-94% Moderate	
1		<90% Severe	
c. Respiratory rate compared with that age of healthy			
0		<2 SD	
1		2-3 SD	
2		>3 SD	

Normal range of respiratory rate		
Age (months)	Mean±SD	
	Awake	Sleep
0-2	48±9.1	39.8±8.7
2-6	44.1±9.9	33.4±7.0
6-12	39.1±8.5	29.6±7.0

SD: Standard deviation

Results

A total of 64 infants (32 patients in each of SVN or VMN group) were enrolled in this study [Figure 1]. The demographic and baseline clinical severity of both groups were shown in Table 2. Despite an overall male predominance in both groups (SVN group 62.5%; VMN group 65.6%), the demographic data were similar across SVN and VMN groups [Table 2]. Except for the higher score of respiratory rate in VMN group, the remaining baseline clinical characteristics were statistically equivalent between patients that were enrolled into SVN or VMN group [Table 2].

We first tested whether VMN could engender an overlapping clinical outcome concerning severity score, oxygen saturation, and respiratory rate throughout hospitalization when compared with SVN. Figure 2 showed that the values across three different parameters were consistently maintained from day 1 till discharge and that no significant inter-device deviation was observed.

We then investigated whether VMN was able to establish matching primary clinical outcome when compared with SVN. Patients treated with the same clinical pathway yielded comparable length of hospital stay irrespective of device groups (SVN vs. VMN, 3.97 ± 1.88 vs. 3.94 ± 1.66 days; [Table 3]). Moreover, other confounding factors potentially interfering with the length of hospital stay were also considered. For instance, paramedical complications, such as but not limited to, administrative and social/behavioral factors, have been shown to disturb hospitalized duration thus, we explored the days of intravenous-fluid supplement. Table 3 showed that SVN versus VMN was 2.31 ± 1.47 versus 2.16 ± 1.46 days correspondingly and that no difference was found.

While, different devices had generated parallel clinical outcomes, our study further examined if VMN had preferential improvements on various physiological parameters. According to Table 4, patients treated with VMN revealed more significant improvements in overall severity score, respiratory effort, and respiratory rate, in respect to SVN. Other physiological remained unchanged.

After treatment period, questionnaires exploring user experience feedbacks were included in the current study. A total of 62 questionnaires (SVN, $n = 32$; VMN, $n = 30$) were received from guardians of enrollers in both groups. The mean scores of SVN and VMN group were 3.3 and 4.8 (out of 5), respectively. Our data showed that guardians were particularly

satisfied with the portability, ease of cleaning and usage, and the quiet operation features provided by VMN. There were, however, 5 guardians who had suggested that the aerosol flow rate generated from VMN could be minimized for infant application. Nonetheless, difficulty in clearance ($n = 18$), noisy operation ($n = 13$), strong aerosol flow ($n = 10$), and poor performance ($n = 10$) were among the common complaints for SVN.

Finally, to understand critical differences in functional performance between two devices, we compared aerosol generation capacity. Figure 3 indicated that aerosol diameter in ranges of Dv50 ($P = 0.35$) and Dv90 ($P = 0.14$) delivered by both devices was relatively similar. The percentage of hypertonic saline aerosol <5 μm generated by SVN and VMN were 52.56 ± 5.4 and 48.7 ± 1.91 ($P = 0.25$), respectively. No significantly difference was found. However, it was evident that the span of aerosol diameters (RSF) was narrower for VMN (1.46 ± 0.1) than SVN (2.07 ± 0.12). Therefore, VMN data had demonstrated a tighter and more concentrated (higher volume frequency) aerosol range that was characteristic of better aerosol quality [Figure 3].

Table 2: Baseline clinical characteristics

	SVN group	VMN group	*P*
Age (month)	5.69±3.03	6.66±2.85	0.944
Male:female	20:12	21:11	0.798
BH (cm)	67.39±10.7	68.11±6.93	0.460
BW (kg)	9.42±9.64	8.13±1.67	0.751
Baseline overall severity score	4.30±1.44	4.92±1.31	0.652
Respiratory-effort scores	4.27±1.46	4.83±1.37	0.866
SpO_2 scores	0.03±0.18	0.06±0.25	0.243
Respiratory rate (score)	0	0.03±0.18	0.043

SVN: Small-volume jet nebulizer, VMN: Vibrating mesh nebulizer, BH: Body height, BW: Body weight

Table 3: Primary outcome

	SVN group	VMN group	*P*
Hospital stay day	3.97±1.88	3.94±1.66	0.944
Overall severity score (at discharge)	2.55±1.16	2.59±1.07	0.654
IV days	2.31±1.47	2.16±1.46	0.671

SVN: Small-volume jet nebulizer, VMN: Vibrating mesh nebulizer, IV: Intravenous

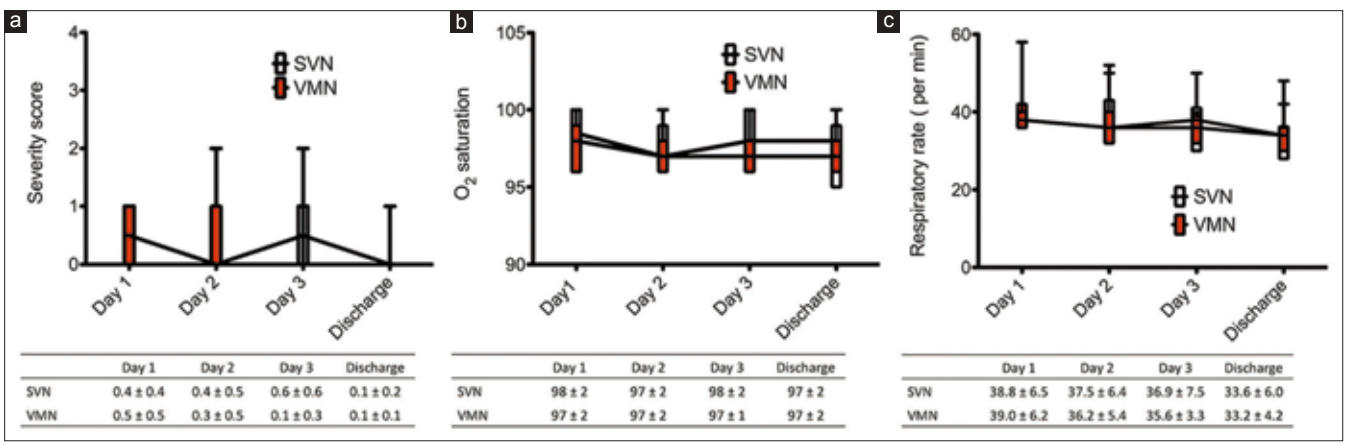
Discussion

Recent studies have demonstrated the usage of SVN in delivering aerosolized saline to treat patients with acute bronchiolitis. However, due to limitations associated with traditional SVN, the possibility of administering aerosol through VMN to achieve equivalent therapeutic goal has yet to be established. Herein, we showed for the first time that VMN could successfully nebulize hypertonic saline medication in treating hospitalized young children (infants) with acute bronchiolitis.

Table 4: Recording physiological parameters during hospitalization

	SVN group			VMN group		
	Admission	Discharge	Difference#	Admission	Discharge	Difference#
Overall severity score	4.30±1.44	2.55±1.16	−1.75±1.55	4.92±1.31	2.59±1.07	−2.33±1.35*
Respiratory-effort scores	4.27±1.46	2.52±1.13	−1.72±1.54	4.83±1.37	2.56±1.08	−2.27±1.29*
SpO_2 scores	0.03±0.18	0.03±0.18	0.0±0.04	0.06±0.25	0.03±0.18	−0.03±0.31
Respiratory rate (score)	0	0	0	0.03±0.18	0	−0.03±0.18*
SpO_2 value (%)	98.13±1.86	97.41±1.9	−0.72±2.12	97.34±2.04	97.41±3.68	+0.44±2.14
Heart rate (/min)	143.8±21.1	131.9±18.5	−12.0±19.0	140.7±14.7	130.2±15.9	−10.5±17.6

*$P<0.05$, #Comparing VMN group with SVN group. SVN: Small-volume jet nebulizer, VMN: Vibrating mesh nebulizer

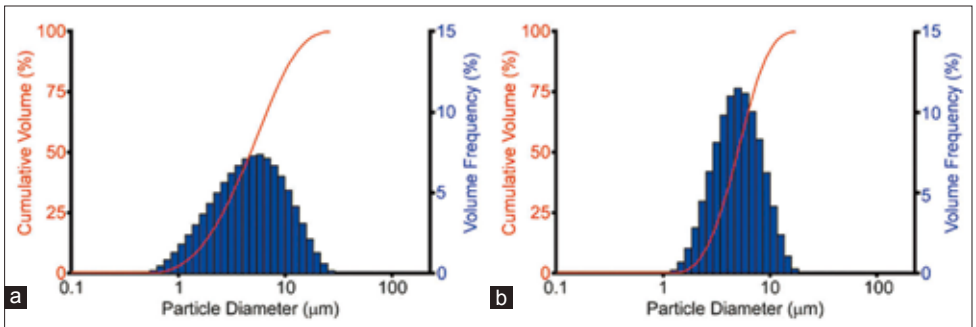


	Day 1	Day 2	Day 3	Discharge
SVN	0.4 ± 0.4	0.4 ± 0.5	0.6 ± 0.6	0.1 ± 0.2
VMN	0.5 ± 0.5	0.3 ± 0.5	0.1 ± 0.3	0.1 ± 0.1

	Day 1	Day 2	Day 3	Discharge
SVN	98 ± 2	97 ± 2	98 ± 2	97 ± 2
VMN	97 ± 2	97 ± 2	97 ± 1	97 ± 2

	Day 1	Day 2	Day 3	Discharge
SVN	38.8 ± 6.5	37.5 ± 6.4	36.9 ± 7.5	33.6 ± 6.0
VMN	39.0 ± 6.2	36.2 ± 5.4	35.6 ± 3.3	33.2 ± 4.2

Figure 2: Clinical trend, (a) Respiratory-effort scores (b) oxygen saturation (c) respiratory rate, after admission.



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	Dv10 (μm)	Dv50 (μm)	Dv90 (μm)	RSF	<5 μm (%)
SVN	1.60 ± 0.14	4.80 ± 0.53	11.55 ± 1.44	2.07 ± 0.12	52.56 ± 5.4
VMN	2.67 ± 0.11	5.09 ± 0.13	10.13 ± 0.64	1.46 ± 0.10	48.70 ± 1.91
p-value	$2.6 \times 10^{-5*}$	3.5×10^{-1}	1.4×10^{-1}	$3.5 \times 10^{-4*}$	2.5×10^{-1}

n=4, RSF: Relative Span Factor, * Statistical significance $p < 0.01$

Figure 3: Particle characteristics of SVN and VMN. (a) Drop size distribution of SVN. (b) Drop size distribution of VMN. (c) Particle characteristics comparison of SVN and VMN. SVN: Small-volume jet nebulizer, VMN: Vibrating mesh nebulizer.

Aerosol generated from hypertonic saline is known to minimize airway edema, reduce mucus plugging, improve mucociliary clearance, and rehydrate epithelial surface in infants with acute bronchiolitis.[9] A large meta-analysis has confirmed that patients inhaling hypertonic saline aerosol showed significantly reduced hospitalization period (–0.45 days) than those receiving isotonic saline nebulization.[4] As of now, the predominant choice of delivery has been confined to jet nebulizers (SVN) for cost-effective reasons. Nonetheless, such device inevitably suffers from slow delivery rate; external compressor requirement during operation; noisy nebulization; uneven drug concentration; drug temperature variation; significant residual volume; and inability to be reprocessed. Consequently, the aforementioned shortcomings severely hinder SVN application in young children population. To circumvent the dilemma, vibrating mesh technology has been shown to achieve parallel, if not even better, therapeutic efficacy; thus, making the substitution with VMN highly likely. Our trial therefore had evaluated the differences in clinical outcome presented by infants with acute bronchiolitis after inhaling hypertonic saline delivered by either SVN or VMN.

We first tested if different nebulization methodologies (SVN and VMN) would affect hospital stay duration. Table 3 showed no significant differences in length of hospital stay. Our average hospital stay data (3.96 ± 1.78 days) was supported by a meta-analysis report documenting that the length of hospital stay was approximately 2.2–5.8 days for hypertonic saline group. Moreover, results from Table 3 further illustrated that device-dependent effect on overall severity score and intravenous infusion period was insignificant due to overlapping data range. Interestingly, despite the nondifferential effects on clinical outcome between both treatment groups, VMN treatment seemed to have produced more significant improvements in overall severity score, respiratory effort, and respiratory score [Table 4]. The outcomes suggested that both devices have equivalent performance as shown by analogous clinical outcome. We surmised that the high degree of resemblance in clinical outcome could be attributed to an intersecting range of aerodynamic diameters of saline aerosol. Data from Figure 3c has verified that size range of hypertonic saline aerosol (Dv50, Dv90 and <5 μm [%]) generated by both devices had coincided. In support of our analysis, reports have also documented that other commercially available VMN could deliver similar inhaled mass and median aerodynamic diameter as jet nebulizer.[10] Figure 3a and b also reported that VMN displayed a narrower aerosol size range (RSF) with better quality and more concentrated output which could potentially explain the enhanced improvement in clinical severity among patients with bronchiolitis [Table 4]. Finally, the elevated satisfactory score for VMN group signified that device friendliness and convenience were the critical parameters contributing to user preference.

Our clinical trial outcome was corroborated by prior studies detailing the advantages of VMN such as, but not limited to, small size, portability, convenience, and silent operation. These properties were strongly advocated when applied to treatment for children population.[10,11] While VMN has been authenticated to deliver a wide range of medications including bronchodilators, corticosteroids, or antibiotics aerosols for elder children with asthma or cystic fibrosis;[8,12,13] nonetheless, our study was the first to demonstrate successful VMN employment to young children population by offering comparable, if not even better, therapeutic improvements on clinical severity, when compared with SVN. Together with apparent operational advantages that were preferentially favored among parents/guardians of patients, VMN could be well suited for aerosol therapy in young children suffering from acute bronchiolitis.

There were some potential limitations in our current study. First, the patient number could be enumerated to enhance the validity of clinical findings. Although the sample size ($n = 32$) of each group was relatively small, the statistical power was able to achieve 0.7 in the *post hoc* analysis. To definitely clarify therapeutic efficiency, our clinical trial could be strengthened by quantifying *in vivo* deposition of delivered aerosol in patients using scintillator. The proposition was supported by previous experiments claiming that VMN could achieve higher lung deposition.[11] Moreover, since VMN group had displayed a higher baseline of a respiratory severity score, the analysis of clinical severity improvement could be biased. Such problem could be eliminated by expanding enrollment and perform further investigation. Finally, apparent user preference shown by questionnaire might be biased due to the esthetically designed novel VMN, possibly tempering with objectivity. However, significant residue, uneven delivery, and noise were the major drawbacks of SVN.

Conclusion

Our study exhibited that VMN offered equivalent treatment efficacy and clinical effects in acute young children with bronchiolitis receiving hypertonic saline nebulization when contrasting with SVN. Majority of parents/guardians praised the operational experience provided by VMN. Therefore, VMN may serve as an alternative yet advanced option when delivering aerosolized medication, targeting a wider population spectrum, for various respiratory disorders in different environments.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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The Asian Paediatric Pulmonology Society (APPS) Position Statement on Childhood Obstructive Sleep Apnea Syndrome

In the article titled "The Asian Paediatric Pulmonology Society (APPS) Position Statement on Childhood Obstructive Sleep Apnea Syndrome", published in pages 26-38, issue 2, vol. 1 of Pediatric Respirology and Critical Care Medicine,[1] the name of one of the authors and affiliation is missing. The name of the author is "Shakil Ahmed" and the author's affiliation is "Associate Professor of Pediatrics, Shaheed Suhrawardy Medical College, Dhaka, Bangladesh".

Reference

1. Ng DK, Huang YS, Teoh OH, Preutthipan A, Xu ZF, Sugiyama T, *et al*. The Asian Paediatric Pulmonology Society (APPS) position statement on childhood obstructive sleep apnea syndrome. Pediatr Respirol Crit Care Med 2017;1:26-38.

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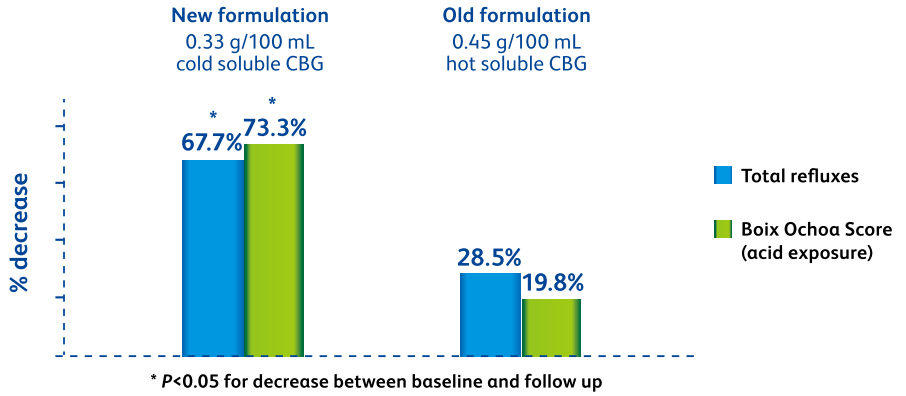

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Reference: Georgieva M, Manios Y, Rasheva N, Pancheva R, Dimitrova E, Schaafsma A. Effects of carob-bean gum thickened formulas on infants' reflux and tolerance indices, *World J Clin Pediatr*, 2016 February 8; 5(1): 118-127.

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