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Feasibility of Aerosol drug delivery to sleeping infants

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Key words: Aerosol, face-mask, sleep, deposition, compliance

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Conflict of Interest: Israel Amirav and Michael Newhouse have patents rights for devices for delivering aerosols to infants including those in the current study. The other authors have no conflicts of interest relevant to this article to disclose.

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Contributors' Statement

Israel Amirav: Dr. Amirav conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript, reviewed and approved the final manuscript as submitted.

Michael T. Newhouse: Dr. Newhouse was involved in the study design, reviewed and approved the final manuscript as submitted.

Anthony S. Luder: Dr. Luder reviewed and approved the final manuscript as submitted.

Asaf Halamish: Mr. Halamish was involved in the study design, designed the data collection instruments, and coordinated and supervised data collection. He reviewed and approved the final manuscript as submitted.

Hamza Omar: Mr. Omar carried out the nuclear medicine studies and initial analyses, reviewed and approved the final manuscript as submitted.

Miguel Gorenberg: Dr. Gorenberg was involved in the study design, designed the nuclear data collection, reviewed and approved the final manuscript as submitted.

List of abbreviations

MDI- metered dose inhaler

VHC- valved aerosol holding chamber

DTPA-Diethylene Triamine Pentacaetic Acid

SM- SootherMask

IC- InspiraChamber

Abstract

Rationale: Delivery of inhaled medications to infants is usually very demanding and is often associated with crying and mask rejection. It has been suggested that aerosol administration during sleep may be an attractive alternative. Previous studies in sleeping children were disappointing as most of the children awoke and rejected the treatment.

The SootherMask™ (SM) is a new, gentle and innovative approach for delivering inhaled medication to infants and toddlers. The present pilot study describes the feasibility of administering inhaled medications during sleep using the SM.

Methods and Results: Thirteen sleeping infants who regularly used pacifiers and were <12 months old were studied. Right lung aerosol deposition was measured scintigraphically using technetium99mDTPA-labeled normal saline aerosol delivered via a Respimat® (Boehringer Ingelheim, Germany) aerosol generator and SM + InspiraChamber® (IC; InspiRx Inc., New Jersey). All infants who fulfilled the inclusion criteria successfully received the SM treatment during sleep without difficulty. Mean lung deposition (±SD) averaged 1.6±0.5% in the right lung**.**

Conclusions: This study demonstrated that the combination of Respimat, InspiraChamber® and SootherMask™ was able to administer aerosol therapy to all the sleeping infants who were regular pacifier users. Provision of aerosols during sleep is advantageous since all of the sleeping children accepted the mask and ensuing aerosol therapy under these conditions, in contrast to previous studies that resulted in frequent mask rejection using currently available devices.

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Strengths

- Delivery of inhaled medications to infants is often associated with crying and mask rejection. Treatment during sleep may be an attractive alternative yet previous studies failed to confirm this suggestion as most of the infants woke up during treatment.
- The present study describes a new way how to overcome these problems during sleep
- Treatment during sleep by means of a special mask which includes the infants' own pacifier, was accepted by all infants with no awakening and improved lung deposition.

Limitations

- Only infants who regularly use pacifiers were enrolled thus the results may not be generally applicable.
- As the study involved scintigrapy, no control healthy infants were included.

Introduction

Delivery of inhaled medications to awake infants and toddlers is often very demanding and is frequently associated with considerable crying and rejection of the mask. It was suggested that administration of inhaled medicine during sleep may be an attractive alternative. An *in-vitro* study suggested that since sleep is associated with more regular breathing patterns and lung delivery is greater during sleep this may translate into improved in vivo results.[1]

A real life study using pMDI with a VHC in young children a few years ago,[2] provided disappointing results; 69% of the children awoke during aerosol administration, there was poor compliance and neglible benefit. No similar study followed this failure and a recent Canadian report discourages parents from this practice.[3]

The SootherMask® (SM) is a new approach for delivering inhaled medication to infants. The SM utilizes the infant's own pacifier (or the teat of an infant formula bottle), whose nipple is inserted through a slot in the anterior wall of the mask. The infant, sucking on the mask, keeps the mask sealed to its facial contours, by means of sub-atmospheric pressure, with little additional applied force and can nasally inhale the medication generated by means of a nebulizer or from a metered dose inhaler (MDI)+valved aerosol holding chamber (VHC) attached to the SM. By virtue of its design the SM can initially be applied to the face without the VHC or nebulizer attached. The infant can retain the SM for prolonged periods of time and subsequent gentle mating of the VHC with MDI attached or nebulizer rarely upsets the infant. Pilot observations suggested a high degree of acceptance of the SM in sleeping infants who appear to regard it as being no

different from their pacifier alone. Caregivers are advised to acclimatize the infant to the SM by routinely providing the pacifier in the SM instead of using the pacifier alone.

The present study describes the feasibility of administering inhaled medications during sleep using the SM. Infants, shortly after falling asleep, were given 99m Tc in normal saline as placebo aerosolized medication using the SM attached to a VHC and both right lung and total lung deposition were evaluated scintigraphically.

Methods

This was part of larger study that explored the relationship between use of pacifiers and reduction in sudden infant death syndrome mortality (NCT01120938). The infants received the Respimat- generated radiolabeled aerosol through a SootherMask attached to a valved holding chamber (InspiraChamber®[IC]) (InspiRx Inc, NJ USA) and their lung deposition was measured.

Inclusion criteria: Wheezy infants (Age 0-12 months) on intermittent or regular inhaled therapy at home, and who were regular users of pacifiers (at least two hours/day of pacifier use per parents' report).

Exclusion criteria: Patients whose parents reported histories or symptoms of airway abnormalities (eg, previous airway surgery, tracheotomy, obstructive sleep apnoea, snoring, anatomical anomalies of mouth palate nose, pharynx and trachea) as well as those with chronic cardiopulmonary disease such as bronchopulmonary dysplasia, congenital heart disease, immune deficiency, or cystic fibrosis.

Procedures:

99mTc labelled aerosol generated by an MDI (Respimat®, Boehringer Ingelheim, Ingelheim, Germany) was administered to the infants via the IC+SM. The Respimat is powered by compressed air produced by means of a spring-driven piston within a small cylinder and generates a slowly moving aerosol bolus into the IC. The medication solution reservoir is a multidose plastic cartridge. We found the Respimat system ideal for this study because it is possible to readily radio-label the medication solution in the cartridge. For each trial, the MDI cartridge was filled with 3.0 mL of 99m Tc-labelled normal saline. Addition of 99m Tc has no physical effect on aerosol characteristics.[4]

After priming the Respimat by discharging the inhaler 5 times to a hooded exhaust system, the emitted dose in terms of radioactive counts was measured by placing bacterial filters over the outlet mouthpiece of the inhaler and firing 5 puffs directly into the filter. The filters were immediately placed in a well counter (Capintec Ramsey New Jersey, USA) and were tested each morning (X4) for reproducibility. Infants arrived at the Nuclear Medicine department in the morning and were fed. The care giver inserted the infant's pacifier into the SM, the SM was then offered and accepted and they were put down to sleep sucking on the pacifier nipple in the SM. Treatment commenced within 10 minutes after the infant fell asleep. The average time from arrival to sleep in this strange environment ranged between half to one and a half hours. The Respimat was attached to the back of the IC, and the ‘mouthpiece’ of the IC was gently ‘docked’ to the orifice of the SM applied snugly to the infant’s face by suction on the pacifier nipple. Two successive ‘puffs‘from the Respimat were then fired into the IC and the mask-VHC-inhaler combination was kept on the infant's face, by

the care giver, for one minute. This ensured complete evacuation of the aerosol from the VHC.[5] The SM+VHC were then removed.

Scintigraphic scans of 60 seconds duration were obtained immediately after each treatment and gamma camera counts (corrected for decay and tissue attenuation) of both the anterior and the posterior chest were measured as previously reported [6] and the following regions of interest (ROIs) were evaluated: 1. Upper airway, 2. Stomach and 3. Lungs. Aerosol deposition in each of the areas defined above was expressed as a percentage of the total amount of radioactivity previously emitted (2 puffs) from the Respimat.

Patients received the treatment in a special room within the nuclear medicine department, used only for this purpose. No person other than the patient's parent and physician was allowed in the room. Radioactivity protection monitoring was carried out regularly and following each study, to ensure that no excess radioactivity was present in the room following treatments. To avoid contamination of the infant's chest and the environment during treatment, thus interfering with lung gamma camera counting, the infant's chest and the VHC were enclosed in a special disposable large volume nylon wrap.

The radiation dose of 99m Tc aerosol used in this study was calculated according to the Medical Internal Radiation Dose Committee.[7] The dose of 99m Tc to be given to each patient determined before the inhalation procedure was found to be 15μci/kg.[8] As inhalation exposure is 0.05 RAD/mci, (9) or 0.00075 RAD/Kg, the maximum exposure for a 20 kg child was 0.015 RAD. It was equivalent to the radiation received during cosmic-ray exposure of 3 weeks or a 12 hour flight

and is much lower than the dose used in diagnostic imaging procedures. 99m Tc is a pure gamma emitter and has a 6 hour physical half-life.[7]

The deposition method suggested here has been in use clinically world-wide for several decades and has been used in a number of previous paediatric studies.[6,10] It has regularly received ethical approval in the past and ethics approval was obtained for this study from the local research committee and the Ministry of Health in Israel. Parents signed an informed consent.

Results

Thirteen infants were enrolled. Ten infants completed the study. Reasons for non-completion were: One infant did not fall asleep during the observation period; One infant awoke after completing aerosol administration and due to excessive movement, image acquisition could not be undertaken, although aerosol administration had apparently been achieved; The third infant was subsequently found to be sick with a respiratory illness. She showed abnormally high deposition in only one lung and was therefore excluded. All the infants accepted the treatment without rejection and no leaks were observed reflecting a good mask to face seal.

A typical scintigram is shown in Figure 1. The individual deposition results of the 10 patients are shown in Table 1.

Right Lung deposition in all 10 infants ranged between 0.83 to 2.37 % of delivered dose with a mean value of 1.61 $\pm$ 0.56 %. The mean deposition in both lungs (which includes oesophageal and carinal deposition) was 4.17 %. The amount of drug deposited in the upper airway averaged 16 .7% and in the

stomach 1.4%. There was no correlation between deposition and age of the infants.

Discussion

The present study demonstrates that aerosol administration in infants during sleep is a successful way to achieve potentially 'therapeutic' lung deposition when treatment is accomplished by means of a VHC attached to a calming and relatively non-intrusive mask such as the SM. All of the infants readily accepted the treatment with little difficulty and did not awaken, cry or demonstrate fear of the mask or the subsequent aerosol therapy.

Previous studies have stressed the difficulty of delivering inhaled medications to infants. There are, potentially, both anatomic and physiological reasons for this. The epiglottis in infants is situated high in the upper respiratory tract (URT) very close to the base of the infant's tongue,[11] The infant pharynx and supraglottic tissue areas characteristically are less rigid compared to adults and thus more susceptible to collapse and obstruction of the URT, particularly during inspiration. Additionally, the airways of infants are narrower and are prone to collapse, while tidal volume and flow velocity are relatively low. Currently available conventional face masks are essentially miniaturized adult masks, with a relatively large dead space, are poorly contoured, if at all, and require a considerable external force of more than 1 kg,[12] to apply them snugly to the infant's face, thus often upsetting the child.[13] The behavioural aspect of aerosol therapy in infants is most important for achieving adequate delivery of aerosols to their lungs and they frequently refuse the application of a face mask

by attempting to push it away as well as vigorously squirming and crying. Crying has been shown to greatly reduce lung deposition of inhaled medication to a negligible fraction of what is considered a therapeutic dose.[6,10,14,15]

It was previously suggested, by several investigators, that sleep may provide a non-threatening opportunity for aerosol administration to infants. Furthermore, compared to the awake state, sleep is associated with slower and more regular breathing, and a lower inspiratory flow velocity,[16-18] factors that have been shown to improve aerosol delivery to the lungs. Administration of inhaled drugs to infants during sleep may thus be a good alternative, particularly for uncooperative young children. Murakami [14] demonstrated, in seven sleepy infants, that scintigraphic deposition of nebulized aerosol appeared significantly better than when they were wide awake. The mean deposition during sleep appeared as good as that in co-operative older (3-14 years) awake children. However sleep was induced by means of sedation, and it was thus not a "real life" study.

In an aerosol 'therapy' study, Janssens et al [1] recorded the breathing patterns of awake and sleeping babies (age 11 $\pm$ 5.1 months), then applied the results by means of a breathing simulator. They captured the delivered aerosol (generated by MDI and delivered into a VHC) on filters located at the tracheal port of an infant airway model, the Sophia Anatomical Infant Nose-Throat (SAINT) model. They showed that treatment during 'sleep' greatly improved VHC aerosol delivery and almost doubled the dose compared to the 'awake' state; 11.3 $\pm$ 3.9 compared to 6.5 $\pm$ 3.2 μg of a 200 μg total delivered dose (5.5% vs 3.2%).

These promising 'in vitro' results were somewhat contradicted during attempts to translate them to real life conditions. Noble et al [19] showed that although mask VHC aerosol administration during sleep was successful in most of the infants and toddlers that he studied, a subgroup of 17% of the patients awakened during the procedure. In a more recent study that assessed the effects of sleep on aerosol delivery by VHC, it was found that 70% of infants awoke during application of the mask and 75% of those became distressed and uncooperative. Not surprisingly, the delivered dose in this study was only about half of that in awake, cooperative infants.[2] Based on these disappointing studies, a recent Canadian guideline discourages parents from delivering aerosols to their infants during sleep.[3]

The SM is a new face mask concept that integrates the infant's own pacifier in the treatment process. The mask has evidence-based facial contours and an extremely small dead space (18.2 ml) resulting from 3D computerized face analysis technology developed with the assistance of the Computer Science department at Technion University.[20] Infants suck on their pacifier and the rim of the mask is gently sealed to their face, mainly by suction on the pacifier. We postulate that the very gentle touch of the contoured mask rim is thus not considered as intrusive and frightening as currently available masks that require application of considerable force in order to achieve a good seal and also fail to provide the calming effect of the infant's familiar pacifier. We have previously shown adequate lung deposition when nebulized drug was administered to awake infants through the SM.[21] Nebulization may require up to 15 min or more of treatment which may, with current masks, be too long for the infant to tolerate. Treatment by VHC+MDI is much quicker and the overall duration of the therapy

(taking into account preparation and cleaning) is considerably shorter (<5 min *vs*. >20 min). It has been recently shown that no more than 2-3 breaths are necessary following each puff to empty the VHC in young children [5] and thus actual aerosol administration time, after application of the SM, can be as short as 10-15 seconds per puff. The current study is the first to employ the SM in combination with a MDI+VHC.

Lung aerosol deposition in infants treated with MDI+VHC has been studied infrequently. Tal et al [10] studied 15 infants and young children with airway obstruction who were given inhaled medications via Aerochamber and mask. Seven of these were infants under the age of 12 months and their average lung deposition was 0.77%, approximately half of the present study ($p<0.01$).

Respiratory symptoms such as cough and breathlessness in infancy are common during sleep.[22] The present study supports, not only the use of chronic anti-inflammatory treatments (inhaled cortico-steroids) during sleep, but also suggests that the use of acute treatments such as inhaled bronchodilators at the time of an episode of nocturnal breathlessness and coughing may be rapidly effective, possibly without awaking the child. Parents can be assured that using this technique the infants will most likely accept and receive the necessary treatment. Thus, the use of the SM is more likely than in the past to allow aerosol therapy to be administered to infants during sleep without awaking them.

Furthermore, given the very high success rate with the SM approach, paediatricians may now more confidently prescribe MDI+VHC+SM to achieve more rapid and acceptable aerosol therapeutics, instead of providing more expensive compressor+nebulizer systems and solution vials that involve about 20

minutes of administration time from start to finish and the need to clean the nebulizer after treatment is finished. Use of nebulizers require that a mask be applied to the face for a much longer period of time which is more likely to arouse the infant, further adding to the its distress, or the need to resort to the 'blow-by' technique that provides a relatively small and unpredictable dose of aerosol medication to the child.

A limitation of the present study stems from the fact that treatment was given within 10 minutes of the commencement of sleep. Although we do not have assessment of sleep stages, this may be a stage during which the child is less likely to awaken if stimulated by such things as the application of a mask. We see no reason, however, to suspect that the likelihood of awakening the child will be greater at even a later stage of deep sleep, although this requires further 'real-life' evaluation with sleep stage assessment. Another limitation may be our enrolment only of infants who regularly use pacifiers and a study in non-pacifier users is warranted. However, the virtually complete success rate in these 'suckling' infants is exceptional and supports the use of sleep as a unique opportunity to deliver aerosol to infants, particularly to pacifier users by means of the SM.

References

1. Janssens HM, van der Wiel EC, Verbraak AF et al. Aerosol therapy and the fighting toddler: is administration during sleep an alternative? *J Aerosol Med*. 2003;16(4):395-400.

2. Esposito-Festen J, Ijsselstijn H, Hop W et al. Aerosol therapy by pressured metered-dose inhaler-spacer in sleeping young children: to do or not to do? *Chest*. 2006;130(2):487-92.

3. Smith C, Goldman RD. Nebulizers versus pressurized metered-dose inhalers in preschool children with wheezing. *Can Fam Physician*. 2012;58(5):528-30.

4. Newman SP. Scintigraphic assessment of therapeutic aerosols. *Crit Rev Ther Drug Carrier Syst* 1993;10:65-109.

5. Schultz A, Le Souëf TJ, Venter A et al. Aerosol inhalation from spacers and valved holding chambers requires few tidal breaths for children. *Pediatrics*. 2010;126(6):e1493-8.

6. Amirav I, Balanov I, Gorenberg M, et al. Nebulizer Hood Compared to Mask in Wheezy Infants: Aerosol Therapy Without Tears! , *Arch Dis Child* 2003;88:719-723.

7. Atkins HL, Weber DA, Susskind H et al. MIRD dose estimate report no. 16: radiation absorbed dose from technetium-99m-diethylenetriaminepentaacetic acid aerosol. *J Nucl Med* 1992;33:1717-1719.

8. Eggli DF. Pediatric radiopharmaceutical dosages. In Clinical Practice of Nuclear Medicine. Edited by Taylor A and Datz FL. Churchill Livingstone 1991,p450.

9. Becquemin MH, Swift DL, Bouchikhi A et al. Particle deposition and resistance in the noses of adults and children, *Eur. Respir. J* 1991;4: 694–702.

10. Tal A, Golan H, Grauer N, et al. Deposition pattern of radiolabeled salbutamol inhaled from a metered-dose inhaler by means of a spacer with mask in young children with airway obstruction. *J Pediatr* 1996;128:479-484.

11. Sasaki CT, Levine PA, Laitman JT et al. Postnatal descent of the epiglottis in man. A preliminary report. *Arch Otolaryngol*. 1977;103(3):169-71.

12. Shah SA, Berlinski AB, Rubin BK. Force-dependent static dead space of face masks used with holding chambers. *Respir Care* 2006;51:140-4.

13. Amirav I, Newhouse MT, Review of optimal characteristics of face-masks for valved-holding chambers (VHCs) *Pediatr Pulmonol*. 2008;43(3):268-74.

14. Murakami G, Igarashi T, Adachi Y et al. Measurement of bronchial hyperreactivity in infants and preschool children using a new method. *Ann Allergy* 1990;64:383-7.

15. Iles R, Lister P, Edmunds AT. Crying significantly reduces absorption of aerosolised drug in infants. *Arch Dis Child* 1999;81:163-165.

16. Morley, C.J., Thornton AJ, Fowler MA et al. Respiratory rate and severity of illness in babies under 6 months old. *Arch Dis Child* 1990;65:834-7.

17. Marks, M.K., M. South and J.B. Carlin. Reference ranges for respiratory rate measured by thermistry (12-84 months). *Arch Dis Child* 1993;69:569-72.

18. Rusconi, F., M. Castagneto, L. Gagliardi et al. Reference values for respiratory rate in the first 3 years of life. *Pediatrics* 1994;94:350-5.

19. Noble V, Ruggins NR, Everard ML et al. Inhaled budesonide for chronic wheezing under 18 months of age. *Arch Dis Child* 1992;67:285-288.

20. Newhouse M, Luder A, Chalamish A, et al. Evidence Based Design Of Face Masks For Children Using Computerized 3d Face Analysis. *Am J Respir Crit Care Med* 2012;185:A5628

21. Amirav I, Luder A, Chleechel A et al. Lung aerosol deposition in suckling infants. *Arch Dis Child* 2012; 97(6):497-501.

22. Clarisse B, Demattei C, Nikasinovic L et al. Bronchial obstructive phenotypes in the first year of life among Paris birth cohort infants. *Pediatr Allergy Immunol* 2009;20:126–33.

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Table 1

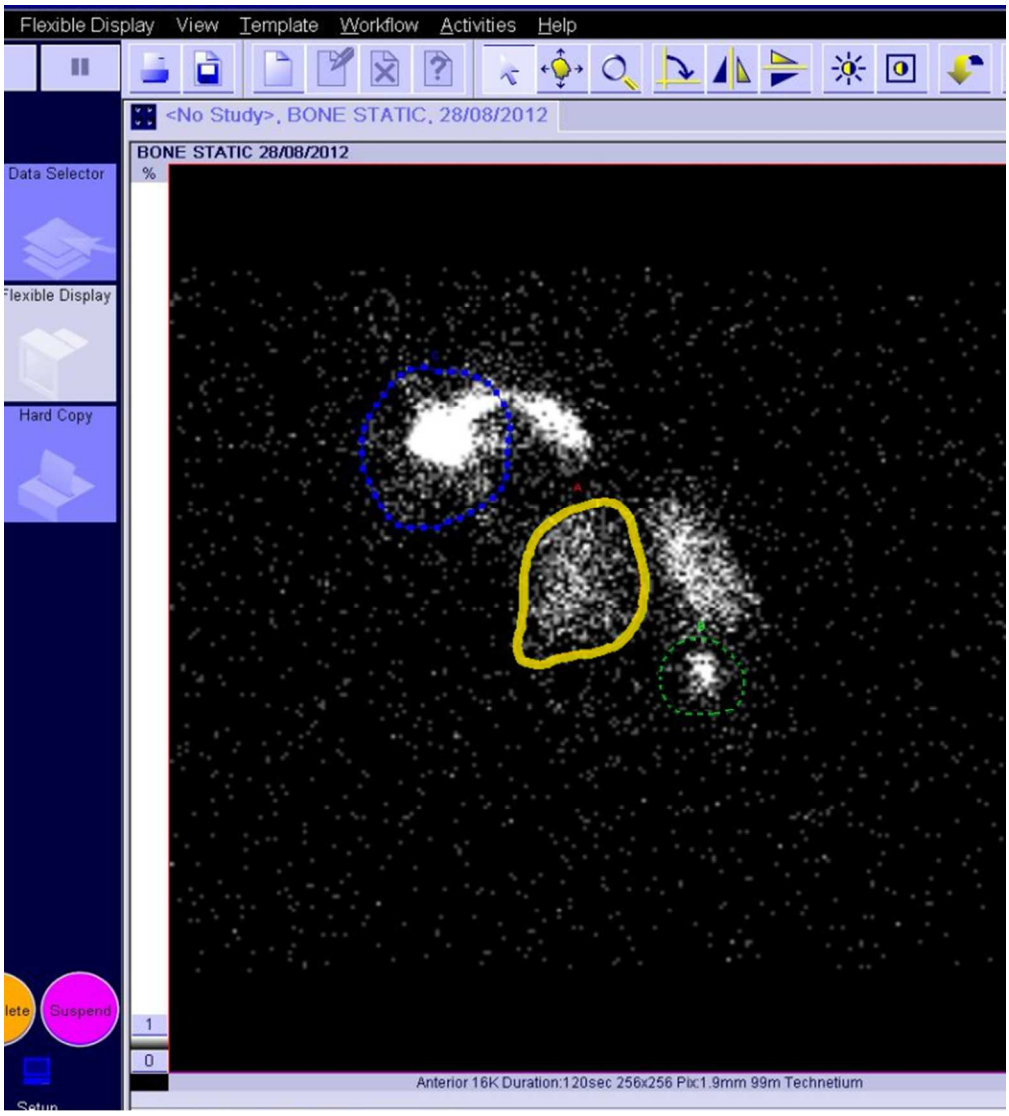
Individual Deposition values (% of emitted dose)

Pt. #	Rt. lung	Both Lungs	Stomach	Upper airway
1	**0.99**	4.16	0.09	7.80
2	**1.44**	2.97	0.72	16.90
3	**0.83**	2.38	3.29	25.84
4	**1.94**	5.26	2.11	15.59
5	**1.47**	4.51	1.26	9.76
6	**2.37**	6.33	0.80	32.81
7	**2.29**	4.88	1.58	16.50
8	**1.40**	4.02	1.13	8.37
9	**1.19**	2.41	2.52	15.01
10	**2.23**	4.75	0.72	18.95
Mean	**1.61**	**4.17**	**1.42**	**16.75**
SD	0.56	1.27	0.97	7.81

Figures Legend

Figure 1:

A typical scintigram, the green dashed circle denotes the stomach, the blue dotes denote upper airways, and solid yellow- right lung.



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Aerosol delivery to infants *without tears*- Back to Sleep!

Israel Amirav[1]MD, Michael T. Newhouse[4] MD., MSc, FRCP(C), Anthony Luder[1]MD, Asaf Halamish[2], Hamza Omar[3], Miguel Gorenberg[3]MD

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Abstract

Rationale: Delivery of inhaled medications to infants is usually very demanding and is often associated with crying and mask rejection. It has been suggested that aerosol administration during sleep may be an attractive alternative. Previous studies in sleeping children were disappointing as most of the children awoke and rejected the treatment.

The SootherMask™ (SM) is a new, gentle and innovative approach for delivering inhaled medication to infants and toddlers. The present pilot study describes the feasibility of administering inhaled medications during sleep using the SM. The two major outcomes of this study were the acceptability of the treatment and the lung deposition (% of emitted dose)

Methods and Results: Thirteen sleeping infants who regularly used pacifiers and were <12 months old were studied. Right lung aerosol deposition was measured scintigraphically using technetium99mDTPA-labeled normal saline aerosol delivered via a Respimat® Soft Mist Inhaler (SMI) (Boehringer Ingelheim, Germany) and SM + InspiraChamber® (IC; InspiRx Inc., New Jersey). All infants who fulfilled the inclusion criteria successfully received the SM treatment during sleep without difficulty. Mean lung deposition (±SD) averaged 1.6±0.5% in the right lung**.**

Conclusions: This study demonstrated that the combination of Respimat, InspiraChamber® and SootherMask™ was able to administer aerosol therapy to all the sleeping infants who were regular pacifier users with good lung deposition. Provision of aerosols during sleep is advantageous since all of the sleeping children accepted the mask and ensuing aerosol therapy under these conditions, in contrast to previous studies that resulted in frequent mask rejection using currently available devices.

Strengths

- Delivery of inhaled medications to infants is often associated with crying and mask rejection. Treatment during sleep may be an attractive alternative yet previous studies failed to confirm this approach as most of the infants awoke during treatment.
- The present study describes a novel approach to overcoming these problems during sleep.
- Treatment during sleep by means of a unique mask which includes the infants' own pacifier, was accepted by all infants with no awakening and improved lung deposition.

Limitations

- Only infants who regularly used pacifiers were enrolled, thus these results may not be generally applicable.
- As the study involved scintigrapy, no control healthy infants could be included.

Introduction

Delivery of inhaled medications to awake infants and toddlers is often very demanding and is frequently associated with considerable crying and rejection of the mask. It was suggested that aerosol therapy during sleep may be an attractive alternative. An *in-vitro* study suggested that since sleep is associated with more regular breathing patterns, and lung targeting of aerosol is greater during sleep, this may translate into improved in vivo results.[1]

A previous real life study using a pressurized metered dose inhaler (pMDI) with a valved aerosol holding chamber (VHC) in young children,[2] provided disappointing results; 69% of the children awoke during aerosol administration, there was poor compliance and neglible benefit. No similar study followed this failure and a recent Canadian report discourages parents from this practice.[3]

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sleeping infants who appear to regard it as being no different from their pacifier alone.

The present study describes the feasibility of administering inhaled medications during sleep using the SM. Infants, shortly after falling asleep, were given 99m Tc in normal saline as placebo aerosolized medication using the SM attached to a VHC and both right lung and total lung deposition were evaluated scintigraphically. Both acceptability of the treatment and fractional lung deposition served as the primary outcomes.

Methods

This was part of larger study that explored the relationship between use of pacifiers and reduction in sudden infant death syndrome mortality (NCT01120938). The infants received the Respimat- generated radiolabeled aerosol through a SootherMask attached to a valved holding chamber (InspiraChamber®[IC]) (InspiRx Inc, NJ USA) and their lung aerosol deposition was measured scintigraphically.

Inclusion criteria: Infants (Age 0-12 months) who were prescribed intermittent or regular inhaled therapy by a paediatric pulmonologist because of recurrent (>3x within the past 2 months) episodes of wheezing that responded to bronchodilator treatments, and who were regular users of pacifiers (at least two hours/day of pacifier use per parents' report). Patients had to be asymptomatic for at least 2 weeks prior to the study. Demographic details are shown in Table 1.

Exclusion criteria: Patients whose parents reported a history or symptoms of airway abnormalities (eg, previous airway surgery, tracheotomy, obstructive sleep apnoea, snoring, anatomical anomalies of mouth palate nose, pharynx and

trachea) as well as those with chronic cardiopulmonary disease such as bronchopulmonary dysplasia, congenital heart disease, immune deficiency, or cystic fibrosis.

Procedures:

99mTc labelled aerosol generated by the Respimat SMI was administered to the infants via the IC+SM. The Respimat is powered by compressed air produced by means of a spring-driven piston within a small cylinder and generates a slowly moving aerosol bolus into the IC. The medication solution reservoir is a multidose plastic cartridge. We found the Respimat SMI preferable to pressurized metered dose inhalers (pMDI) because it is possible to readily radio-label the medication solution in the cartridge. As both pMDI and SMI, would, in infants, be used with a VHC, the Respimat served as an ideal clinical surrogate. For each trial, the SMI cartridge was filled with 3.0 mL of 99m Tc-labelled normal saline. Addition of 99m Tc has no physical effect on aerosol characteristics.[5]

After priming the Respimat by discharging the inhaler 5 times to a hooded exhaust system the emitted dose in terms of radioactive counts was measured by placing bacterial filters over the mouthpiece of the SMI and firing 5 puffs directly into the filter. The filters were immediately placed in a well counter (Capintec Ramsey New Jersey, USA) and were evaluated each morning (x4) for reproducibility.

Infants arrived at the Nuclear Medicine department in the morning and were fed. The care-giver inserted the infants' pacifier into the SM which was then offered and accepted. They were put down to sleep sucking on the pacifier nipple in the

SM. Treatment commenced within 10 minutes after the infant fell asleep. The average time from arrival to sleep in this strange environment ranged between half and one and a half hour. The Respimat was inserted into the back of the IC, and the 'mouthpiece' of the IC was gently 'docked' into the orifice of the SM sealed to the infant's face by its suction on the pacifier nipple. Two successive 'puffs'from the Respimat, each followed by one minute of tidal breathing, were then fired into the IC and the mask-VHC-inhaler combination was kept on the infant's face, by the care giver, for one minute (see Figure 1 and Video1). This ensured complete evacuation of the aerosol from the VHC.[6] The SM+VHC were then removed.

The infant was placed supine under a double (anterior and posterior) plate scanner (Symbia, Siemens GMBH, Munich, Germany) which enabled image acquisition without moving the infant or the cameras. Scintigraphic scans of 60 seconds duration were obtained and gamma camera counts (corrected for decay and tissue attenuation) of both the anterior and the posterior chest were measured as previously reported [7]. Similarly counts were measured for the VHC and mask to account for all the emitted dose. The tissue attenuation factor was determined based on our own experience with similar age infants (8). In brief, a hollow acrylic disc, filled with a solution of a known amount of 99mTc (37–74 MBq) served as the flood source. The square root of the ratio of transmission scan counts obtained without the infant (No) to the geometric mean of the counts with the infant (Nt) provided the attenuation correction factor ($\sqrt{}$ No/Nt) .

The following regions of interest (ROIs) were evaluated: 1. Upper airway, 2. Stomach and 3. Lungs. Aerosol deposition in each of these regions was

expressed as the percent of the total radioactivity previously emitted (2 puffs) from the Respimat.

Treatments were administered in a special room within the nuclear medicine department, used only for this purpose. Only the patient's parent and physician were allowed in the room. Radioactivity protection monitoring was carried out regularly and following each study, to ensure that no excess radioactivity was present in the room following the treatments. To avoid contamination of the infant's chest and the environment during treatment, which would interfere with lung scintigraphy , the infant's chest and the VHC were enclosed in a special disposable large volume nylon wrap which was removed immediately prior to imaging.

The radiation dose of 99m Tc aerosol used in this study was calculated according to the Medical Internal Radiation Dose Committee [9]. The dose of 99m Tc to be given to each patient determined before the inhalation procedure was found to be 15μci/kg [10]. As inhalation exposure is 0.05 RAD/mci, or 0.00075 RAD/Kg, the maximum exposure for a 20 kg child was 0.015 RAD. This is equivalent to the radiation received during normal cosmic-ray exposure of 3 weeks or a 12 hour flight and is much lower than the dose used in diagnostic imaging procedures. 99m Tc is a pure gamma emitter and has a 6 hour physical half-life.[9]

The deposition method suggested here has been in use clinically world-wide for several decades and has been used in a number of previous paediatric studies [7,11]. It has regularly received ethics committee approval in the past and approval was obtained for this study from the local hospital research committee

(#0007-09-ZIV) and the Ministry of Health in Israel (#920090101). Parents provided written informed consent.

Results

Thirteen infants were enrolled. Ten infants completed the study. Reasons for non-completion were: One infant did not fall asleep during the observation period; One infant awoke after completing aerosol administration and due to excessive movement, image acquisition could not be undertaken, although aerosol administration had apparently been achieved; The third infant was subsequently found to be sick with a respiratory illness. She showed abnormally high deposition in only one lung and was therefore excluded. All the infants accepted the treatment without mask rejection and no leaks were observed reflecting a good mask to face seal. All infants were asleep flat and supine during their scintigraphic image acquisition.

A typical scintigram is shown in Figure 2. Lung deposition results for the 10 patients are shown in Table 1.

Right Lung deposition in all 10 infants ranged between 0.83 and 2.37 % of the total delivered dose with a mean of 1.61 $\pm$ 0.56 %. The mean deposition in both lungs (which includes oesophageal and carinal deposition) was 4.17 %. The amount of drug deposited in the upper airway averaged 16 .7% and in the stomach 1.4%. There was no correlation between deposition and age of the infants.

Discussion

The present study demonstrates that aerosol administration to infants while asleep is a successful way to achieve potentially 'therapeutic' lung deposition when treatment is accomplished by means of a VHC attached to a calming and relatively non-intrusive mask such as the SM. All of the infants readily accepted the treatment with little difficulty and did not awaken, cry or demonstrate fear of the mask or the subsequent aerosol therapy.

Previous studies have stressed the difficulty of delivering inhaled medications to infants and it has been suggested that sleep may provide a non-threatening opportunity for aerosol administration to them. Furthermore, compared to the awake state, sleep is associated with slower and more regular breathing, and a lower inspiratory flow velocity [1], factors that have been shown to improve aerosol delivery to the lungs. Administration of inhaled medication to infants and toddlers during sleep may thus be a good alternative, particularly if they are uncooperative while awake. Murakami [12] demonstrated, in seven sedated sleepy infants, that scintigraphic deposition of nebulized aerosol appeared significantly better than when they were wide awake. The mean deposition during sleep appeared as good as that in co-operative older (3-14 years) awake children.

In an aerosol 'therapy' study, Janssens et al [1] recorded the breathing patterns of awake and sleeping babies (age 11 $\pm$ 5.1 months), then applied the results by means of a breathing simulator. They captured the delivered aerosol (generated by MDI and delivered into a VHC) on filters located at the tracheal port of an infant airway model, the Sophia Anatomical Infant Nose-Throat (SAINT) model.

They showed that treatment during 'sleep' greatly improved VHC aerosol delivery and almost doubled the lung dose compared to the 'awake' state; 11.3 ± 3.9 compared to 6.5 ± 3.2 μg of a 200 μg total delivered dose (5.5% vs 3.2%).

These promising 'in vitro' results were somewhat contradicted during attempts to translate them to real life conditions. Noble et al [13] showed that although mask VHC aerosol administration during sleep was successful in most of the infants and toddlers that he studied, a subgroup of 17% of the patients awakened during the procedure. In a more recent study that assessed the effects of sleep on aerosol delivery by VHC, it was found that 70% of infants awoke during application of the mask and 75% of those became distressed and uncooperative. Not surprisingly, the delivered dose in this study was only about half of that in awake, cooperative infants.[2] Based on these disappointing studies, a recent Canadian guideline discourages parents from attempting to deliver aerosols to their infants during sleep.[3]

The SM is a new face mask concept that integrates the infant's *own* pacifier into the treatment process. The mask has evidence-based facial contours and an extremely small dead space (18.2 ml) resulting from 3D computerized face analysis technology developed with the assistance of the Computer Science department at Technion University [4]. When infants suck on the mask-integrated pacifier, the rim of the mask becomes gently sealed to their face, mainly by suction on the pacifier and with minimal, if any, additional applied force.

We postulate that the very gentle touch of the contoured mask rim is thus not considered as intrusive and frightening as currently available masks that require

application of considerable force in order to achieve a good seal [14] and also fail to provide the calming effect of the infant's familiar pacifier. We have previously shown adequate lung deposition when nebulized drug was administered to awake infants through the SM [15]. Nebulization may require up to 15 min or more which may, with current masks, be too long for the infant to tolerate. Treatment by VHC+MDI is much faster and less expensive per dose than nebulisation and the overall duration of therapy (taking into account preparation and cleaning) is considerably shorter (<5 min *vs*. >20 min).

It has been recently shown that no more than 2-3 breaths are necessary following each puff to empty the VHC in young children [6] and thus actual aerosol administration time, after application of the SM, can be as short as 10-15 seconds per puff. The current study is the first to employ the SM in combination with a VHC.

Respiratory symptoms such as cough and breathlessness in infancy are common during sleep.[16] The present study supports, not only the use of chronic anti-inflammatory treatments (e.g. inhaled cortico-steroids) during sleep, but also suggests that the use of acute treatments such as inhaled bronchodilators at the time of an episode of nocturnal breathlessness and coughing may be rapidly effective, possibly without awaking the child. Parents can be assured that using this technique the infants will most likely accept and receive the necessary treatment. Thus, the use of the SM is more likely than in the past to allow aerosol therapy to be administered to infants during sleep without awaking them.

Furthermore, given the high success rate with the SM approach, paediatricians may now more confidently prescribe VHC+SM to achieve more rapid and

acceptable aerosol therapeutics, instead of providing more expensive compressor+nebulizer systems and solution vials that involve about 20 minutes of administration time and the need to clean the nebulizer after the treatment is complete. Use of nebulizers requires that a mask be applied to the face for a much longer period of time which is more likely to arouse the infant, further adding to the its distress, or the need to resort to the 'blow-by' technique that provides a relatively small and unpredictable dose of aerosol medication to the child.

The lack of control subjects using currently available masks is acknowledged as a limitation of the present study and a control group was originally incorporated. However, we felt that it would be unethical and unjustified to expose a control group of infants, particularly since several historical scintigraphic studies are available. Another limitation may be our enrolment only of infants who regularly use pacifiers and a future study in non-pacifier users is certainly warranted.

This pilot study with the SM is, we think, clinically important as it demonstrates a unique, innovative and apparently effective approach to providing infants and toddlers with aerosol therapy during sleep. It has the potential for encouraging pediatricians to use this technique in future clinical studies.

Funding source: None

Financial Disclosure: Dr. Newhouse is the consulting Chief Medical Officer of InspiRx Inc, developer of the SootherMask®. All other authors have indicated they have no financial relationships relevant to this article to disclose.

Conflict of Interest: Israel Amirav and Michael Newhouse have patents rights for devices for delivering aerosols to infants including those in the current study. The other authors have no conflicts of interest relevant to this article to disclose.

Clinical Trial registry: NCT01120938

Data Sharing: There is no additional data avai

Contributors' Statement

Israel Amirav: Dr. Amirav conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript, reviewed and approved the final manuscript as submitted.

Michael T. Newhouse: Dr. Newhouse was involved in the study design, reviewed and approved the final manuscript as submitted.

Anthony S. Luder: Dr. Luder reviewed and approved the final manuscript as submitted.

Asaf Halamish: Mr. Halamish was involved in the study design, designed the data collection instruments, and coordinated and supervised data collection. He reviewed and approved the final manuscript as submitted.

Hamza Omar: Mr. Omar carried out the nuclear medicine studies and initial analyses, reviewed and approved the final manuscript as submitted.

Miguel Gorenberg: Dr. Gorenberg was involved in the study design, designed the nuclear data collection, reviewed and approved the final manuscript as submitted.

List of abbreviations

MDI- metered dose inhaler

VHC- valved aerosol holding chamber

DTPA-Diethylene Triamine Pentacaetic Acid

SM- SootherMask

IC- InspiraChamber

References

1. Janssens HM, van der Wiel EC, Verbraak AF et al. Aerosol therapy and the fighting toddler: is administration during sleep an alternative? *J Aerosol Med*. 2003;16(4):395-400.

2. Esposito-Festen J, Ijsselstijn H, Hop W et al. Aerosol therapy by pressured metered-dose inhaler-spacer in sleeping young children: to do or not to do? *Chest*. 2006;130(2):487-92.

3. Smith C, Goldman RD. Nebulizers versus pressurized metered-dose inhalers in preschool children with wheezing. *Can Fam Physician*. 2012;58(5):528-30.

4. Amirav I, Luder AS, Halamish A, Raviv D, Kimmel R, Waisman D, Newhouse MT Design of Aerosol Face Masks for Children Using Computerized 3D Face Analysis. J Aerosol Med Pulm Drug Deliv. 2013 Sep 28.

5. Newman SP. Scintigraphic assessment of therapeutic aerosols. *Crit Rev Ther Drug Carrier Syst* 1993;10:65-109.

6. Schultz A, Le Souëf TJ, Venter A et al. Aerosol inhalation from spacers and valved holding chambers requires few tidal breaths for children. *Pediatrics*. 2010;126(6):e1493-8.

7. Amirav I, Balanov I, Gorenberg M, et al. Nebulizer Hood Compared to Mask in Wheezy Infants: Aerosol Therapy Without Tears! , *Arch Dis Child* 2003;88:719-723.

8. Amirav I, Balanov I, Gorenberg M, Luder AS, Newhouse MT, Groshar D. Beta Agonist Aerosol Distribution in RSV Bronchiolitis in Infants. J Nucl Med, 2002; 43: 487-491

9. Atkins HL, Weber DA, Susskind H et al. MIRD dose estimate report no. 16: radiation absorbed dose from technetium-99m-diethylenetriaminepentaacetic acid aerosol. *J Nucl Med* 1992;33:1717-1719.

10. Eggli DF. Pediatric radiopharmaceutical dosages. In Clinical Practice of Nuclear Medicine. Edited by Taylor A and Datz FL. Churchill Livingstone 1991,p450.

11. Tal A, Golan H, Grauer N, et al. Deposition pattern of radiolabeled salbutamol inhaled from a metered-dose inhaler by means of a spacer with mask in young children with airway obstruction. *J Pediatr* 1996;128:479-484.

12. Murakami G, Igarashi T, Adachi Y et al. Measurement of bronchial hyperreactivity in infants and preschool children using a new method. *Ann Allergy* 1990;64:383-7.

13. Noble V, Ruggins NR, Everard ML et al. Inhaled budesonide for chronic wheezing under 18 months of age. *Arch Dis Child* 1992;67:285-288.

14. Shah SA, Berlinski AB, Rubin BK. Force-dependent static dead space of face masks used with holding chambers. *Respir Care* 2006;51:140-4.

15. Amirav I, Luder A, Chleechel A et al. Lung aerosol deposition in suckling infants. *Arch Dis Child* 2012; 97(6):497-501.

16. Clarisse B, Dematteï C, Nikasinovic L et al. Bronchial obstructive phenotypes in the first year of life among Paris birth cohort infants. *Pediatr Allergy Immunol* 2009;20:126–33.

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Table 1

Individual Deposition values (% of emitted dose)

Pt. #	Age (m)	Gender	Rt. lung	Both Lungs	Stomach	Upper airway
1	6.4	M	**0.99**	4.16	0.09	7.8
2	3.9	F	**1.44**	2.97	0.72	16.9
3	6.4	M	**0.83**	2.38	3.29	25.84
4	7.1	F	**1.94**	5.26	2.11	15.59
5	5.4	F	**1.47**	4.51	1.26	9.76
6	11.7	M	**2.37**	6.33	0.8	32.81
7	5.0	F	**2.29**	4.88	1.58	16.5
8	10.8	F	**1.4**	4.02	1.13	8.37
9	5.4	M	**1.19**	2.41	2.52	15.01
10	5.4	M	**2.23**	4.75	0.72	18.95
Mean	9.28		**1.61**	4.17	1.42	16.75
SD	0.68		0.56	1.27	0.97	7.81

Figures and Video Legend

Figure 1:

Photograph illustrating the method of aerosol administration to a sleeping infant showing the Respimat inhaler, InspiraChamber and SootherMask™

Figure 2:

A typical scintigram, the green dashed circle denotes the stomach, the blue dotes denote upper airways, and solid yellow- right lung.

Video:

Video illustrating the method of aerosol administration to a sleeping infant showing the Respimat inhaler, InspiraChamber and SootherMask™

Aerosol delivery to infants *without tears*- Back to Sleep!

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2. Technosaf, Karkur, Israel
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4. Firestone Institute for Respiratory Health, St. Joseph's Hospital, McMaster University, Hamilton, Ontario, Canada.

Short title: Aerosol delivery during sleep

Key words: Aerosol, face-mask, sleep, deposition, compliance

Funding source: None

Financial Disclosure: Dr. Newhouse is the consulting Chief Medical Officer of InspiRx Inc, developer of the SootherMask®. All other authors have indicated they have no financial relationships relevant to this article to disclose.

Conflict of Interest: Israel Amirav and Michael Newhouse have patents rights for devices for delivering aerosols to infants including those in the current study. The other authors have no conflicts of interest relevant to this article to disclose.

Clinical Trial registry: NCT01120938

Total word count: 2693

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Contributors' Statement

Israel Amirav: Dr. Amirav conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript, reviewed and approved the final manuscript as submitted.

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Hamza Omar: Mr. Omar carried out the nuclear medicine studies and initial analyses, reviewed and approved the final manuscript as submitted.

Miguel Gorenberg: Dr. Gorenberg was involved in the study design, designed the nuclear data collection, reviewed and approved the final manuscript as submitted.

List of abbreviations

MDI- metered dose inhaler

VHC- valved aerosol holding chamber

DTPA-Diethylene Triamine Pentacaetic Acid

SM- SootherMask

IC- InspiraChamber

Abstract

Rationale: Delivery of inhaled medications to infants is usually very demanding and is often associated with crying and mask rejection. It has been suggested that aerosol administration during sleep may be an attractive alternative. Previous studies in sleeping children were disappointing as most of the children awoke and rejected the treatment.

The SootherMask™ (SM) is a new, gentle and innovative approach for delivering inhaled medication to infants and toddlers. The present pilot study describes the feasibility of administering inhaled medications during sleep using the SM. The two major outcomes of this study were the acceptability of the treatment and the lung deposition (% of emitted dose)

Methods and Results: Thirteen sleeping infants who regularly used pacifiers and were <12 months old were studied. Right lung aerosol deposition was measured scintigraphically using technetium99mDTPA-labeled normal saline aerosol delivered via a Respimat® Soft Mist Inhaler (SMI) (Boehringer Ingelheim, Germany) ~~aerosol generator~~ and SM + InspiraChamber® (IC; InspiRx Inc., New Jersey). All infants who fulfilled the inclusion criteria successfully received the SM treatment during sleep without difficulty. Mean lung deposition (±SD) averaged 1.6±0.5% in the right lung**.**

Conclusions: This study demonstrated that the combination of Respimat, InspiraChamber® and SootherMask™ was able to administer aerosol therapy to all the sleeping infants who were regular pacifier users with good lung deposition. Provision of aerosols during sleep is advantageous since all of the sleeping children accepted the mask and ensuing aerosol therapy under these conditions, in contrast to previous studies that resulted in frequent mask rejection using currently available devices.

Word count: **229**

Strengths

- Delivery of inhaled medications to infants is often associated with crying and mask rejection. Treatment during sleep may be an attractive alternative yet previous studies failed to confirm this ~~suggestion~~ approach as most of the infants awoke ~~up~~ during treatment.
- The present study describes a novel approach to ~~overcome~~ overcoming these problems during sleep.
- Treatment during sleep by means of a ~~special~~ unique mask which includes the infants' own pacifier, was accepted by all infants with no awakening and improved lung deposition.

Limitations

- Only infants who regularly used pacifiers were enrolled, thus these results may not be generally applicable.
- As the study involved scintigrapy, no control healthy infants ~~were~~ could be included.

Introduction

Delivery of inhaled medications to awake infants and toddlers is often very demanding and is frequently associated with considerable crying and rejection of the mask. It was suggested that ~~administration of inhaled medicine~~aerosol therapy during sleep may be an attractive alternative. An *in-vitro* study suggested that since sleep is associated with more regular breathing patterns, and lung ~~delivery~~ targeting of aerosol is greater during sleep, this may translate into improved in vivo results.[1]

A previous real life study using a pressurized metered dose inhaler (pMDI) with a valved aerosol holding chamber (VHC) in young children ~~a few years ago~~,[2] provided disappointing results; 69% of the children awoke during aerosol administration, there was poor compliance and neglible benefit. No similar study followed this failure and a recent Canadian report discourages parents from this practice.[3]

The SootherMask® (SM) is a ~~new~~ novel approach for delivering inhaled medication to infants (4). The SM utilizes the infant's own pacifier (or the teat of an infant formula bottle), whose nipple is inserted through a slot in the anterior wall of the mask. The infant, sucking on the mask, keeps the mask sealed to its facial contours, by means of sub-atmospheric pressure, with little additional applied force and can nasally inhale the medication generated by ~~means of~~ a nebulizer or from a metered dose inhaler (MDI)+ ~~valved aerosol holding chamber (~~VHC~~)~~ attached to the SM. By virtue of its design the SM can initially be applied to the face without the VHC or nebulizer attached. The infant can retain the SM for prolonged periods of time and subsequent gentle mating of the

VHC with MDI ~~attached~~ or nebulizer rarely upsets the infant. Pilot observations suggested a high degree of acceptance of the SM in sleeping infants who appear to regard it as being no different from their pacifier alone. ~~Caregivers are advised to acclimatize the infant to the SM by routinely providing the pacifier in the SM instead of using the pacifier alone.~~

The present study describes the feasibility of administering inhaled medications during sleep using the SM. Infants, shortly after falling asleep, were given 99m Tc in normal saline as placebo aerosolized medication using the SM attached to a VHC and both right lung and total lung deposition were evaluated scintigraphically. Both acceptability of the treatment and fractional lung deposition served as the primary outcomes.

Methods

This was part of larger study that explored the relationship between use of pacifiers and reduction in sudden infant death syndrome mortality (NCT01120938). The infants received the Respimat- generated radiolabeled aerosol through a SootherMask attached to a valved holding chamber (InspiraChamber®[IC]) (InspiRx Inc, NJ USA) and their lung aerosol deposition was measured scintigraphically. ~~d.~~

Inclusion criteria: ~~Wheezy I~~infants (Age 0-12 months) ~~on~~ who were ~~intermittent~~prescribed intermittent or regular inhaled therapy ~~at home~~by a paediatric pulmonologist because of recurrent (>3x within the past 2 months) episodes of wheezing that responded to bronchodilator treatments, and who were regular users of pacifiers (at least two hours/day of pacifier use per parents'

report). Patients had to be asymptomatic for at least 2 weeks prior to the study. Demographic details are shown in Table 1.

Exclusion criteria: Patients whose parents reported a ~~histories~~ history or symptoms of airway abnormalities (eg, previous airway surgery, tracheotomy, obstructive sleep apnoea, snoring, anatomical anomalies of mouth palate nose, pharynx and trachea) as well as those with chronic cardiopulmonary disease such as bronchopulmonary dysplasia, congenital heart disease, immune deficiency, or cystic fibrosis.

Procedures:

99mTc labelled aerosol generated by ~~an MDI~~the Respimat SMI ~~(Respimat®, Boehringer Ingelheim, Ingelheim, Germany)~~ was administered to the infants via the IC+SM. The Respimat is powered by compressed air produced by means of a spring-driven piston within a small cylinder and generates a slowly moving aerosol bolus into the IC. The medication solution reservoir is a multidose plastic cartridge. We found the Respimat SMI preferable to pressurized metered dose inhalers (pMDI) ~~system ideal for this study~~ because it is ~~-~~possible to readily radio-label the medication solution in the cartridge. As both pMDI and SMI, would, in infants, be used with a VHC, the Respimat served as an ideal clinical surrogate. For each trial, the SMI cartridge was filled with 3.0 mL of 99m Tc-labelled normal saline. Addition of 99m Tc has no physical effect on aerosol characteristics.[~~4~~5]

After priming the Respimat by discharging the inhaler 5 times to a hooded exhaust system the emitted dose~~,~~ in terms of radioactive counts~~,~~ was measured by placing bacterial filters over the ~~outlet~~ mouthpiece of the ~~inhaler~~ SMI and firing 5

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puffs directly into the filter. The filters were immediately placed in a well counter (Capintec Ramsey New Jersey, USA) and were ~~tested~~ evaluated each morning (~~X4~~x4) for reproducibility.

Infants arrived at the Nuclear Medicine department in the morning and were fed. The ~~care~~ care-giver inserted the infant~~'~~s' pacifier into the SM~~, the SM~~ which was then offered and accepted. ~~and they~~ They were put down to sleep sucking on the pacifier nipple in the SM. Treatment commenced within 10 minutes after the infant fell asleep. The average time from arrival to sleep in this strange environment ranged between half ~~to~~ and one and a half hours. The Respimat was ~~attached~~ inserted into the back of the IC, and the 'mouthpiece' of the IC was gently 'docked' into the orifice of the SM ~~applied snugly~~sealed to the infant's face by its suction on the pacifier nipple. Two successive 'puffs'from the Respimat, each followed by one minute of tidal breathing, were then fired into the IC and the mask-VHC-inhaler combination was kept on the infant's face, by the care giver, for one minute (see Figure 1 and Video1). This ensured complete evacuation of the aerosol from the VHC.[~~5~~6] The SM+VHC were then removed.

The infant was placed supine under a double (anterior and posterior) plate scanner (Symbia, Siemens GMBH, Munich, Germany) which enabled image acquisition without moving the infant or the cameras. Scintigraphic scans of 60 seconds duration were obtained ~~immediately after each treatment~~ and gamma camera counts (corrected for decay and tissue attenuation) of both the anterior and the posterior chest were measured as previously reported [~~6~~7]. Similarly counts were measured for the VHC and mask to account for all the emitted dose. The tissue attenuation factor was determined based on our own experience with similar age infants (8). In brief, a hollow acrylic disc, filled with a solution of a

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known amount of 99mTc (37–74 MBq) served as the flood source. The square root of the ratio of transmission scan counts obtained without the infant (No) to the geometric mean of the counts with the infant (Nt) provided the attenuation correction factor (√ No/Nt) .

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The radiation dose of 99m Tc aerosol used in this study was calculated according to the Medical Internal Radiation Dose Committee [~~7~~9]. The dose of 99m Tc to be given to each patient determined before the inhalation procedure was found to be 15μci/kg [~~8~~10]. As inhalation exposure is 0.05 RAD/mci, ~~(9)~~ or 0.00075 RAD/Kg, the maximum exposure for a 20 kg child was 0.015 RAD. ~~It~~ This ~~was~~ is equivalent to the radiation received during normal cosmic-ray exposure of 3

weeks or a 12 hour flight and is much lower than the dose used in diagnostic imaging procedures. 99m Tc is a pure gamma emitter and has a 6 hour physical half-life.[~~7~~9]

The deposition method suggested here has been in use clinically world-wide for several decades and has been used in a number of previous paediatric studies [~~6~~7,~~10~~11]. It has regularly received ~~ethical~~ ethics committee approval in the past and ~~ethics~~ approval was obtained for this study from the local hospital research committee (#0007-09-ZIV) and the Ministry of Health in Israel (#920090101). Parents ~~signed an~~provided written informed consent.

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Results

Thirteen infants were enrolled. Ten infants completed the study. Reasons for non-completion were: One infant did not fall asleep during the observation period; One infant awoke after completing aerosol administration and due to excessive movement, image acquisition could not be undertaken, although aerosol administration had apparently been achieved; The third infant was subsequently found to be sick with a respiratory illness. She showed abnormally high deposition in only one lung and was therefore excluded. All the infants accepted the treatment without mask rejection and no leaks were observed reflecting a good mask to face seal. All infants were asleep flat and supine during their scintigraphic image acquisition.

A typical scintigram is shown in Figure ~~1~~2. ~~The individual d~~Lung deposition results ~~of~~ for the 10 patients are shown in Table 1.

Right Lung deposition in all 10 infants ranged between 0.83 ~~to~~ and 2.37 % of the total delivered dose with a mean ~~value~~ of 1.61 ± 0.56 %. The mean deposition in both lungs (which includes oesophageal and carinal deposition) was 4.17 %. The amount of drug deposited in the upper airway averaged 16 .7% and in the stomach 1.4%. There was no correlation between deposition and age of the infants.

Discussion

The present study demonstrates that aerosol administration ~~in~~ to infants ~~during~~ while asleep ~~sleep~~ is a successful way to achieve potentially 'therapeutic' lung deposition when treatment is accomplished by means of a VHC attached to a calming and relatively non-intrusive mask such as the SM. All of the infants readily accepted the treatment with little difficulty and did not awaken, cry or demonstrate fear of the mask or the subsequent aerosol therapy.

Previous studies have stressed the difficulty of delivering inhaled medications to infants~~. There are, potentially, both anatomic and physiological reasons for this. The epiglottis in infants is situated high in the upper respiratory tract (URT) very close to the base of the infant's tongue,[11] The infant pharynx and supraglottic tissue areas characteristically are less rigid compared to adults and thus more susceptible to collapse and obstruction of the URT, particularly during inspiration. Additionally, the airways of infants are narrower and are prone to collapse, while tidal volume and flow velocity are relatively low. Currently available conventional face masks are essentially miniaturized adult masks, with a relatively large dead space, are poorly contoured, if at all, and require a~~

~~considerable external force of more than 1 kg,[12] to apply them snugly to the infant's face, thus often upsetting the child.[13] The behavioural aspect of aerosol therapy in infants is most important for achieving adequate delivery of aerosols to their lungs and they frequently refuse the application of a face mask by attempting to push it away as well as vigorously squirming and crying. Crying has been shown to greatly reduce lung deposition of inhaled medication to a negligible fraction of what is considered a therapeutic dose.[6,10,14,15]~~

~~It was previously~~and it has been suggested~~, by several investigators,~~ that sleep may provide a non-threatening opportunity for aerosol administration to ~~infants~~them. Furthermore, compared to the awake state, sleep is associated with slower and more regular breathing, and a lower inspiratory flow velocity ~~,~~[~~16-18~~1], factors that have been shown to improve aerosol delivery to the lungs. Administration of inhaled ~~drugs~~ medication to infants and toddlers during sleep may thus be a good alternative, particularly ~~for~~ if they are uncooperative while awake. ~~young children.~~ Murakami [~~14~~12] demonstrated, in seven sedated sleepy infants, that scintigraphic deposition of nebulized aerosol appeared significantly better than when they were wide awake. The mean deposition during sleep appeared as good as that in co-operative older (3-14 years) awake children. ~~However sleep was induced by means of sedation, and it was thus not a "real life" study.~~

In an aerosol 'therapy' study, Janssens et al [1] recorded the breathing patterns of awake and sleeping babies (age 11 $\pm$ 5.1 months), then applied the results by means of a breathing simulator. They captured the delivered aerosol (generated by MDI and delivered into a VHC) on filters located at the tracheal port of an infant airway model, the Sophia Anatomical Infant Nose-Throat (SAINT) model.

They showed that treatment during 'sleep' greatly improved VHC aerosol delivery and almost doubled the lung dose compared to the 'awake' state; 11.3 ± 3.9 compared to 6.5 ± 3.2 μg of a 200 μg total delivered dose (5.5% vs 3.2%).

These promising 'in vitro' results were somewhat contradicted during attempts to translate them to real life conditions. Noble et al [~~19~~13] showed that although mask VHC aerosol administration during sleep was successful in most of the infants and toddlers that he studied, a subgroup of 17% of the patients awakened during the procedure. In a more recent study that assessed the effects of sleep on aerosol delivery by VHC, it was found that 70% of infants awoke during application of the mask and 75% of those became distressed and uncooperative. Not surprisingly, the delivered dose in this study was only about half of that in awake, cooperative infants.[2] Based on these disappointing studies, a recent Canadian guideline discourages parents from attempting to deliver~~ing~~ aerosols to their infants during sleep.[3]

The SM is a new face mask concept that integrates the infant's *own* pacifier into the treatment process. The mask has evidence-based facial contours and an extremely small dead space (18.2 ml) resulting from 3D computerized face analysis technology developed with the assistance of the Computer Science department at Technion University ~~.~~[~~20~~4]. When ~~Infants~~ infants suck on the~~ir~~ mask-integrated pacifier, ~~and~~ the rim of the mask ~~is~~ becomes gently sealed to their face, mainly by suction on the pacifier and with minimal, if any, additional applied force.

We postulate that the very gentle touch of the contoured mask rim is thus not considered as intrusive and frightening as currently available masks that require

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application of considerable force in order to achieve a good seal [14] and also fail to provide the calming effect of the infant's familiar pacifier. We have previously shown adequate lung deposition when nebulized drug was administered to awake infants through the SM [~~21~~15]. Nebulization may require up to 15 min or more ~~of treatment~~ which may, with current masks, be too long for the infant to tolerate. Treatment by VHC+MDI is much ~~quicker~~ faster and less expensive per dose than nebulisation and the overall duration of ~~the~~ therapy (taking into account preparation and cleaning) is considerably shorter (<5 min *vs*. >20 min).

It has been recently shown that no more than 2-3 breaths are necessary following each puff to empty the VHC in young children [~~5~~6] and thus actual aerosol administration time, after application of the SM, can be as short as 10-15 seconds per puff. The current study is the first to employ the SM in combination with a ~~MDI+~~VHC.

~~Lung aerosol deposition in infants treated with MDI+VHC has been studied infrequently. Tal et al [10] studied 15 infants and young children with airway obstruction who were given inhaled medications via Aerochamber and mask. Seven of these were infants under the age of 12 months and their average lung deposition was 0.77%, approximately half of the present study (p<0.01).~~

Respiratory symptoms such as cough and breathlessness in infancy are common during sleep.[~~22~~16] The present study supports, not only the use of chronic anti-inflammatory treatments (e.g. inhaled cortico-steroids) during sleep, but also suggests that the use of acute treatments such as inhaled bronchodilators at the time of an episode of nocturnal breathlessness and coughing may be rapidly

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effective, possibly without awaking the child. Parents can be assured that using this technique the infants will most likely accept and receive the necessary treatment. Thus, the use of the SM is more likely than in the past to allow aerosol therapy to be administered to infants during sleep without awaking them.

Furthermore, given the ~~very~~ high success rate with the SM approach, paediatricians may now more confidently prescribe ~~MDI+~~VHC+SM to achieve more rapid and acceptable aerosol therapeutics, instead of providing more expensive compressor+nebulizer systems and solution vials that involve about 20 minutes of administration time ~~from start to finish~~ and the need to clean the nebulizer after the treatment is ~~finished~~complete. Use of nebulizers requires that a mask be applied to the face for a much longer period of time which is more likely to arouse the infant, further adding to the its distress, or the need to resort to the 'blow-by' technique that provides a relatively small and unpredictable dose of aerosol medication to the child.

The lack of control subjects using currently available masks is acknowledged as a limitation of the present study and a control group was originally incorporated. However, we felt that it would be unethical and unjustified to expose a control group of infants, particularly since several historical scintigraphic studies are available.

~~A limitation of the present study stems from the fact that treatment was given within 10 minutes of the commencement of sleep. Although we do not have assessment of sleep stages, this may be a stage during which the child is less likely to awaken if stimulated by such things as the application of a mask. We see no reason, however, to suspect that the likelihood of awakening the child will be~~

~~greater at even a later stage of deep sleep, although this requires further 'real-life' evaluation with sleep stage assessment~~. Another limitation may be our enrolment only of infants who regularly use pacifiers and a future study in non-pacifier users is certainly warranted.

This pilot study with the SM is, we think, clinically important as it demonstrates a unique, innovative and apparently effective approach to providing infants and toddlers with aerosol therapy during sleep. It has the potential for encouraging pediatricians to use this technique in future clinical studies.~~However, the virtually complete success rate in these 'suckling' infants is exceptional and supports the use of sleep as a unique opportunity to deliver aerosol to infants, particularly to pacifier users by means of the SM.~~

References

1. Janssens HM, van der Wiel EC, Verbraak AF et al. Aerosol therapy and the fighting toddler: is administration during sleep an alternative? *J Aerosol Med*. 2003;16(4):395-400.

2. Esposito-Festen J, Ijsselstijn H, Hop W et al. Aerosol therapy by pressured metered-dose inhaler-spacer in sleeping young children: to do or not to do? *Chest*. 2006;130(2):487-92.

3. Smith C, Goldman RD. Nebulizers versus pressurized metered-dose inhalers in preschool children with wheezing. *Can Fam Physician*. 2012;58(5):528-30.

4. Amirav I, Luder AS, Halamish A, Raviv D, Kimmel R, Waisman D, Newhouse MT Design of Aerosol Face Masks for Children Using Computerized 3D Face Analysis. J Aerosol Med Pulm Drug Deliv. 2013 Sep 28.

45. Newman SP. Scintigraphic assessment of therapeutic aerosols. *Crit Rev Ther Drug Carrier Syst* 1993;10:65-109.

56. Schultz A, Le Souëf TJ, Venter A et al. Aerosol inhalation from spacers and valved holding chambers requires few tidal breaths for children. *Pediatrics*. 2010;126(6):e1493-8.

67. Amirav I, Balanov I, Gorenberg M, et al. Nebulizer Hood Compared to Mask in Wheezy Infants: Aerosol Therapy Without Tears! , *Arch Dis Child* 2003;88:719-723.

8. Amirav I, Balanov I, Gorenberg M, Luder AS, Newhouse MT, Groshar D. Beta Agonist Aerosol Distribution in RSV Bronchiolitis in Infants. J Nucl Med, 2002; 43: 487-491

79. Atkins HL, Weber DA, Susskind H et al. MIRD dose estimate report no. 16: radiation absorbed dose from technetium-99m-diethylenetriaminepentaacetic acid aerosol. *J Nucl Med* 1992;33:1717-1719.

810. Eggli DF. Pediatric radiopharmaceutical dosages. In Clinical Practice of Nuclear Medicine. Edited by Taylor A and Datz FL. Churchill Livingstone 1991,p450.

9. Becquemin MH, Swift DL, Bouchikhi A et al. Particle deposition and resistance in the noses of adults and children, *Eur. Respir. J* 1991;4: 694-702.

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~~10~~11. Tal A, Golan H, Grauer N, et al. Deposition pattern of radiolabeled salbutamol inhaled from a metered-dose inhaler by means of a spacer with mask in young children with airway obstruction. *J Pediatr* 1996;128:479-484.

12. Murakami G, Igarashi T, Adachi Y et al. Measurement of bronchial hyperreactivity in infants and preschool children using a new method. *Ann Allergy* 1990;64:383-7.

13. Noble V, Ruggins NR, Everard ML et al. Inhaled budesonide for chronic wheezing under 18 months of age. *Arch Dis Child* 1992;67:285-288.

~~11. Sasaki CT, Levine PA, Laitman JT et al. Postnatal descent of the epiglottis in man. A preliminary report. *Arch Otolaryngol.* 1977;103(3):169-71.~~

~~12~~14. Shah SA, Berlinski AB, Rubin BK. Force-dependent static dead space of face masks used with holding chambers. *Respir Care* 2006;51:140-4.

15. Amirav I, Luder A, Chleechel A et al. Lung aerosol deposition in suckling infants. *Arch Dis Child* 2012; 97(6):497-501.

16. Clarisse B, Demattei C, Nikasinovic L et al. Bronchial obstructive phenotypes in the first year of life among Paris birth cohort infants. *Pediatr Allergy Immunol* 2009;20:126–33.

~~13. Amirav I, Newhouse MT, Review of optimal characteristics of face-masks for valved-holding chambers (VHCs) *Pediatr Pulmonol.* 2008;43(3):268-74.~~

~~14. Murakami G, Igarashi T, Adachi Y et al. Measurement of bronchial hyperreactivity in infants and preschool children using a new method. *Ann Allergy* 1990;64:383-7.~~

~~15. Iles R, Lister P, Edmunds AT. Crying significantly reduces absorption of aerosolised drug in infants. *Arch Dis Child* 1999;81:163-165.~~

~~16. Morley, C.J., Thornton AJ, Fowler MA et al. Respiratory rate and severity of illness in babies under 6 months old. *Arch Dis Child* 1990;65:834-7.~~

~~17. Marks, M.K., M. South and J.B. Carlin. Reference ranges for respiratory rate measured by thermistry (12-84 months). *Arch Dis Child* 1993;69:569-72.~~

~~18. Rusconi, F., M. Castagneto, L. Gagliardi et al. Reference values for respiratory rate in the first 3 years of life. *Pediatrics* 1994;94:350-5.~~

~~19. Noble V, Ruggins NR, Everard ML et al. Inhaled budesonide for chronic wheezing under 18 months of age. *Arch Dis Child* 1992;67:285-288.~~

20. Newhouse M, Luder A, Chalamish A, et al. Evidence Based Design Of Face Masks For Children Using Computerized 3d Face Analysis. *Am J Respir Crit Care Med* 2012;185:A56287

21. Amirav I, Luder A, Chleechel A et al. Lung aerosol deposition in suckling infants. *Arch Dis Child* 2012; 97(6):497-501.

22. Clarisse B, Demattei C, Nikasinovic L et al. Bronchial obstructive phenotypes in the first year of life among Paris birth cohort infants. *Pediatr Allergy Immunol* 2009;20:126-33.

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Table 1

Individual Deposition values (% of emitted dose)

Pt. #	Rt. lung	Both Lungs	Stomach	Upper airway
1	0.99	4.16	0.09	7.80
2	1.44	2.97	0.72	16.90
3	0.83	2.38	3.29	25.84
4	1.94	5.26	2.11	15.59
5	1.47	4.51	1.26	9.76
6	2.37	6.33	0.80	32.81
7	2.29	4.88	1.58	16.50
8	1.40	4.02	1.13	8.37
9	1.19	2.41	2.52	15.01
10	2.23	4.75	0.72	18.95
Mean	1.61	4.17	1.42	16.75
SD	0.56	1.27	0.97	7.81

Pt. #	Age (m)	Gender	Rt. lung	Both Lungs	Stomach	Upper airway
1	6.4	M	0.99	4.16	0.09	7.8
2	3.9	F	1.44	2.97	0.72	16.9
3	6.4	M	0.83	2.38	3.29	25.84
4	7.1	F	1.94	5.26	2.11	15.59

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5	5.4	F	**1.47**	4.51	1.26	9.76	
6	11.7	M	**2.37**	6.33	0.8	32.81	
7	5.0	F	**2.29**	4.88	1.58	16.5	
8	10.8	F	**1.4**	4.02	1.13	8.37	
9	5.4	M	**1.19**	2.41	2.52	15.01	
10	5.4	M	**2.23**	4.75	0.72	18.95	
Mean	9.28		**1.61**	4.17	1.42	16.75	
SD	0.68		0.56	1.27	0.97	7.81	

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Figures Legend

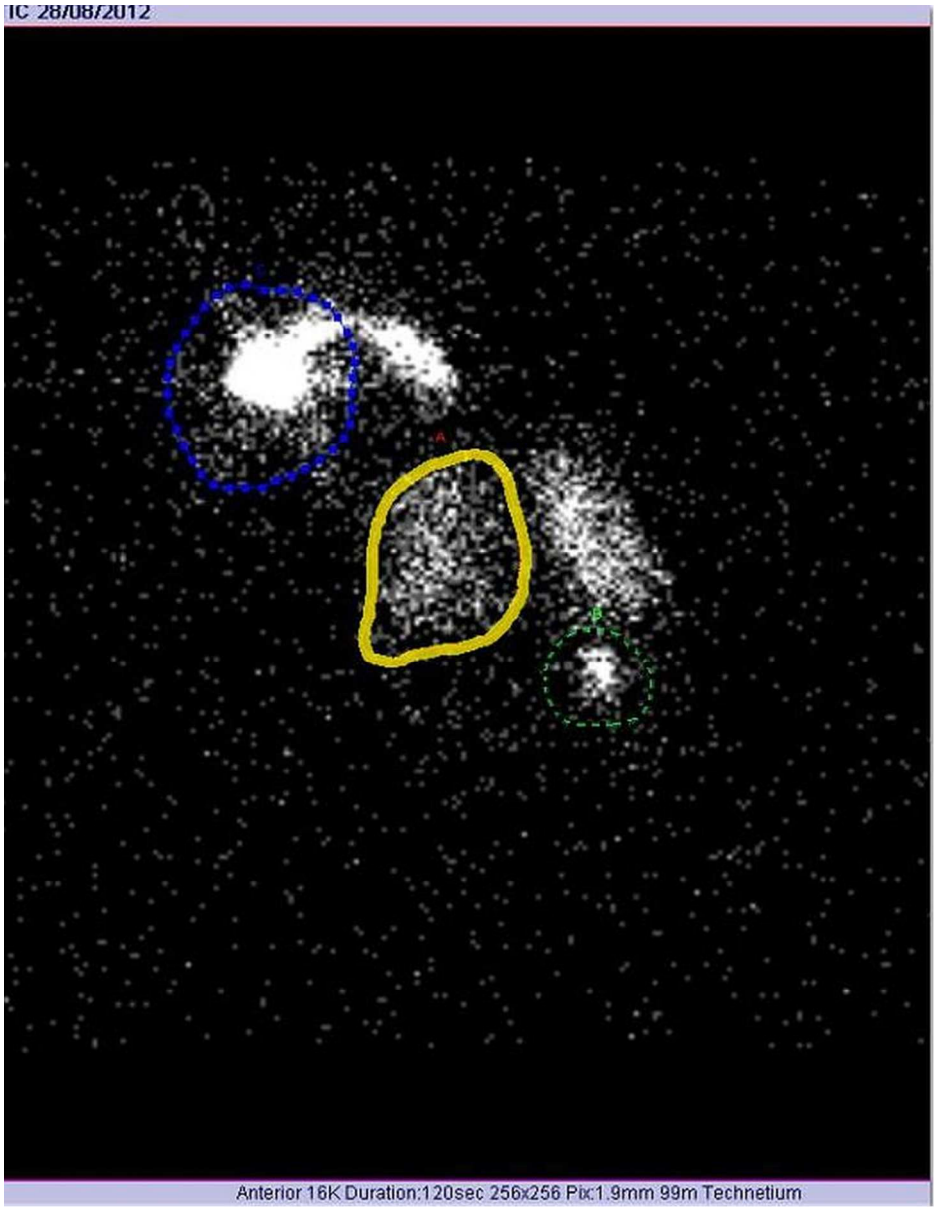
Figure 1:

Photograph illustrating the method of aerosol administration to a sleeping infant showing the Respimat inhaler, InspiraChamber and SootherMask™

Figure ~~1~~2:

A typical scintigram, the green dashed circle denotes the stomach, the blue dotes denote upper airways, and solid yellow- right lung.

112x90mm (300 x 300 DPI)



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Feasibility of Aerosol drug delivery to sleeping infants

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Feasibility of Aerosol Drug Delivery to Sleeping Infants

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Short title: Aerosol delivery during sleep

Key words: Aerosol, face-mask, sleep, deposition, compliance

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Abstract

Objectives: Delivery of inhaled medications to infants is usually very demanding and is often associated with crying and mask rejection. It has been suggested that aerosol administration during sleep may be an attractive alternative. Previous studies in sleeping children were disappointing as most of the children awoke and rejected the treatment.

The SootherMask™ (SM) is a new, gentle and innovative approach for delivering inhaled medication to infants and toddlers. The present pilot study describes the feasibility of administering inhaled medications during sleep using the SM.

Design: Prospective observational study

Setting: Out patients

Participants: Thirteen sleeping infants with recurrent wheezing who regularly used pacifiers and were <12 months old.

Intervention: Participants inhaled technetium99mDTPA-labeled normal saline aerosol delivered via a Respimat® Soft Mist Inhaler (SMI) (Boehringer Ingelheim, Germany) and SM + InspiraChamber® (IC; InspiRx Inc., New Jersey).

Outcomes: The two major outcomes were the acceptability of the treatment and the lung deposition (% of emitted dose)

Results: All infants who fulfilled the inclusion criteria successfully received the SM treatment during sleep without difficulty. Mean lung deposition (±SD) averaged 1.6±0.5% in the right lung**.**

Conclusions: This study demonstrated that the combination of Respimat, InspiraChamber® and SootherMask™ was able to administer aerosol therapy to all the sleeping infants who were regular pacifier users with good lung deposition. Provision of aerosols during sleep is advantageous since all of the sleeping children accepted the mask and ensuing aerosol therapy under these

conditions, in contrast to previous studies that resulted in frequent mask rejection using currently available devices.

Word count: **253**

Strengths

- Delivery of inhaled medications to infants is often associated with crying and mask rejection. Treatment during sleep may be an attractive alternative yet previous studies failed to confirm this approach as most of the infants awoke during treatment.
- The present study describes a novel approach to overcoming these problems during sleep.
- Treatment during sleep by means of a unique mask which includes the infants' own pacifier, was accepted by all infants with no awakening and improved lung deposition.

Limitations

- Only infants who regularly used pacifiers were enrolled, thus these results may not be generally applicable.
- As the study involved scintigraphy, no control infants using conventional masks could be included.

Introduction

Delivery of inhaled medications to awake infants and toddlers is often very demanding and is frequently associated with considerable crying and rejection of the mask. It was suggested that aerosol therapy during sleep may be an attractive alternative. An *in-vitro* study suggested that since sleep is associated with more regular breathing patterns, and lung targeting of aerosol is greater during sleep, this may translate into improved in vivo results.[1]

A previous real life study using a pressurized metered dose inhaler (pMDI) with a valved aerosol holding chamber (VHC) in young children,[2] provided disappointing results; 69% of the children awoke during aerosol administration, there was poor compliance and neglible benefit. No similar study followed this failure and a recent Canadian report discourages parents from this practice.[3]

The SootherMask® (SM) is a novel approach for delivering inhaled medication to infants (4). The SM utilizes the infant's own pacifier (or the teat of an infant formula bottle), whose nipple is inserted through a slot in the anterior wall of the mask. The infant, sucking on the mask, keeps the mask sealed to its facial contours, by means of sub-atmospheric pressure, with little additional applied force and can nasally inhale the medication generated by a nebulizer or from a metered dose inhaler (MDI)+ VHC attached to the SM. By virtue of its design the SM can initially be applied to the face without the VHC or nebulizer attached. The infant can retain the SM for prolonged periods of time and subsequent gentle mating of the VHC with MDI or nebulizer rarely upsets the infant. Pilot observations suggested a high degree of acceptance of the SM in

sleeping infants who appear to regard it as being no different from their pacifier alone.

The present study describes the feasibility of administering inhaled medications during sleep using the SM. Infants, shortly after falling asleep, were given 99m Tc in normal saline as placebo aerosolized medication using the SM attached to a VHC and both right lung and total lung deposition were evaluated scintigraphically. Both acceptability of the treatment and fractional lung deposition served as the primary outcomes.

Methods

This was part of larger study that explored the relationship between use of pacifiers and reduction in sudden infant death syndrome mortality (NCT01120938). The infants received the Respimat- generated radiolabeled aerosol through a SootherMask attached to a valved holding chamber (InspiraChamber®[IC]) (InspiRx Inc, NJ USA) and their lung aerosol deposition was measured scintigraphically.

Inclusion criteria: Infants (Age 0-12 months) who were prescribed intermittent or regular inhaled therapy by a paediatric pulmonologist because of recurrent (>3x within the past 2 months) episodes of wheezing that responded to bronchodilator treatments, and who were regular users of pacifiers (at least two hours/day of pacifier use per parents' report). Patients had to be asymptomatic for at least 2 weeks prior to the study. Demographic details are shown in Table 1.

Exclusion criteria: Patients whose parents reported a history or symptoms of airway abnormalities (eg, previous airway surgery, tracheotomy, obstructive sleep apnoea, snoring, anatomical anomalies of mouth palate nose, pharynx and

trachea) as well as those with chronic cardiopulmonary disease such as bronchopulmonary dysplasia, congenital heart disease, immune deficiency, or cystic fibrosis.

Procedures:

99mTc labelled aerosol generated by the Respimat SMI was administered to the infants via the IC+SM. The Respimat is powered by compressed air produced by means of a spring-driven piston within a small cylinder and generates a slowly moving aerosol bolus into the IC. The medication solution reservoir is a multidose plastic cartridge. We found the Respimat SMI preferable to pressurized metered dose inhalers (pMDI) because it is possible to readily radio-label the medication solution in the cartridge. As both pMDI and SMI, would, in infants, be used with a VHC, the Respimat served as an ideal clinical surrogate. For each trial, the SMI cartridge was filled with 3.0 mL of 99m Tc-labelled normal saline. Addition of 99m Tc has no physical effect on aerosol characteristics.[5]

After priming the Respimat by discharging the inhaler 5 times to a hooded exhaust system the emitted dose in terms of radioactive counts was measured by placing bacterial filters over the mouthpiece of the SMI and firing 5 puffs directly into the filter. The filters were immediately placed in a well counter (Capintec, Ramsey New Jersey, USA) and were evaluated each morning (x4) for reproducibility.

Infants arrived at the Nuclear Medicine department in the morning and were fed. The care-giver inserted the infants' pacifier into the SM which was then offered and accepted. They were put down to sleep sucking on the pacifier nipple in the

SM. Treatment commenced within 10 minutes after the infant fell asleep. The average time from arrival to sleep in this strange environment ranged between half and one and a half hour. The Respimat was inserted into the back of the IC, and the 'mouthpiece' of the IC was gently 'docked' into the orifice of the SM sealed to the infant's face by its suction on the pacifier nipple. Two successive 'puffs' from the Respimat, each followed by one minute of tidal breathing, were then fired into the IC and the mask-VHC-inhaler combination was kept on the infant's face, by the care giver, for one minute (see Figure 1 and Video1). This ensured complete evacuation of the aerosol from the VHC.[6] The SM+VHC were then removed.

The infant was placed supine under a double (anterior and posterior) plate scanner (Symbia, Siemens GMBH, Munich, Germany) which enabled image acquisition without moving the infant or the cameras. Scintigraphic scans of 60 seconds duration were obtained and gamma camera counts (corrected for decay and tissue attenuation) of both the anterior and the posterior chest were measured as previously reported [7]. Similarly counts were measured for the VHC and mask to account for all the emitted dose. The tissue attenuation factor was determined based on our own experience with similar age infants (8). In brief, a hollow acrylic disc, filled with a solution of a known amount of 99mTc (37–74 MBq) served as the flood source. The square root of the ratio of transmission scan counts obtained without the infant (No) to the geometric mean of the counts with the infant (Nt) provided the attenuation correction factor ($\sqrt{No/Nt}$) .

The following regions of interest (ROIs) were evaluated: 1. Upper airway, 2. Stomach and 3. Lungs. Aerosol deposition in each of these regions was

expressed as the percent of the total radioactivity previously emitted (2 puffs) from the Respimat.

Treatments were administered in a special room within the nuclear medicine department, used only for this purpose. Only the patient's parent and physician were allowed in the room. Radioactivity protection monitoring was carried out regularly and following each study, to ensure that no excess radioactivity was present in the room following the treatments. To avoid contamination of the infant's chest and the environment during treatment, which would interfere with lung scintigraphy, the infant's chest and the VHC were enclosed in a special disposable large volume nylon wrap which was removed immediately prior to imaging.

The radiation dose of 99m Tc aerosol used in this study was calculated according to the Medical Internal Radiation Dose Committee [9]. The dose of 99m Tc to be given to each patient determined before the inhalation procedure was found to be 15μci/kg [10]. As inhalation exposure is 0.05 RAD/mci, or 0.00075 RAD/Kg, the maximum exposure for a 20 kg child was 0.015 RAD. This is equivalent to the radiation received during normal cosmic-ray exposure of 3 weeks or a 12 hour flight and is much lower than the dose used in diagnostic imaging procedures. 99m Tc is a pure gamma emitter and has a 6 hour physical half-life.[9]

The deposition method suggested here has been in use clinically world-wide for several decades and has been used in a number of previous paediatric studies [7,11]. It has regularly received ethics committee approval in the past and approval was obtained for this study from the local hospital research ethics

committee (#0007-09-ZIV) and the Ministry of Health in Israel (#920090101). Parents provided written informed consent.

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Thirteen infants were enrolled. Ten infants completed the study. Reasons for non-completion were: One infant did not fall asleep during the observation period; One infant awoke after completing aerosol administration and due to excessive movement, image acquisition could not be undertaken, although aerosol administration had apparently been achieved; The third infant was subsequently found to be sick with a respiratory illness. She showed abnormally high deposition in only one lung and was therefore excluded. All the infants accepted the treatment without mask rejection and no leaks were observed reflecting a good mask to face seal. All infants were asleep flat and supine during their scintigraphic image acquisition.

A typical scintigram is shown in Figure 2. Lung deposition results for the 10 patients are shown in Table 1.

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Discussion

The present study demonstrates that aerosol administration to infants while asleep is a successful way to achieve potentially 'therapeutic' lung deposition when treatment is accomplished by means of a VHC attached to a calming and relatively non-intrusive mask such as the SM. All of the infants readily accepted the treatment with little difficulty and did not awaken, cry or demonstrate fear of the mask or the subsequent aerosol therapy.

Previous studies have stressed the difficulty of delivering inhaled medications to infants and it has been suggested that sleep may provide a non-threatening opportunity for aerosol administration to them. Furthermore, compared to the awake state, sleep is associated with slower and more regular breathing, and a lower inspiratory flow velocity [1], factors that have been shown to improve aerosol delivery to the lungs. Administration of inhaled medication to infants and toddlers during sleep may thus be a good alternative, particularly if they are uncooperative while awake. Murakami [12] demonstrated, in seven sedated sleepy infants, that scintigraphic deposition of nebulized aerosol appeared significantly better than when they were wide awake. The mean deposition during sleep appeared as good as that in co-operative older (3-14 years) awake children.

In an aerosol 'therapy' study, Janssens et al [1] recorded the breathing patterns of awake and sleeping babies (age 11 $\pm$ 5.1 months), then applied the results by means of a breathing simulator. They captured the delivered aerosol (generated by MDI and delivered into a VHC) on filters located at the tracheal port of an infant airway model, the Sophia Anatomical Infant Nose-Throat (SAINT) model.

They showed that treatment during 'sleep' greatly improved VHC aerosol delivery and almost doubled the lung dose compared to the 'awake' state; 11.3 ± 3.9 compared to 6.5 ± 3.2 μg of a 200 μg total delivered dose (5.5% vs 3.2%).

These promising 'in vitro' results were somewhat contradicted during attempts to translate them to real life conditions. Noble et al [13] showed that although mask VHC aerosol administration during sleep was successful in most of the infants and toddlers that he studied, a subgroup of 17% of the patients awakened during the procedure. In a more recent study that assessed the effects of sleep on aerosol delivery by VHC, it was found that 70% of infants awoke during application of the mask and 75% of those became distressed and uncooperative. Not surprisingly, the delivered dose in this study was only about half of that in awake, cooperative infants.[2] Based on these disappointing studies, a recent Canadian guideline discourages parents from attempting to deliver aerosols to their infants during sleep.[3]

The SM is a new face mask concept that integrates the infant's *own* pacifier into the treatment process. The mask has evidence-based facial contours and an extremely small dead space (18.2 ml) resulting from 3D computerized face analysis technology developed with the assistance of the Computer Science department at Technion University [4]. When infants suck on the mask-integrated pacifier, the rim of the mask becomes gently sealed to their face, mainly by suction on the pacifier and with minimal, if any, additional applied force.

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application of considerable force in order to achieve a good seal [14] and also fail to provide the calming effect of the infant's familiar pacifier. We have previously shown adequate lung deposition when nebulized drug was administered to awake infants through the SM [15]. Nebulization may require up to 15 min or more which may, with current masks, be too long for the infant to tolerate. Treatment by VHC+MDI is much faster and less expensive per dose than nebulisation and the overall duration of therapy (taking into account preparation and cleaning) is considerably shorter (<5 min *vs*. >20 min).

It has been recently shown that no more than 2-3 breaths are necessary following each puff to empty the VHC in young children [6] and thus actual aerosol administration time, after application of the SM, can be as short as 10-15 seconds per puff. The current study is the first to employ the SM in combination with a VHC. Lung deposition in the present study was comparable to previous reports in infants (7,8,11,12,15) and is likely to exert comparable clinical efficacy.

Respiratory symptoms such as cough and breathlessness in infancy are common during sleep.[16] The present study supports, not only the use of chronic anti-inflammatory treatments (e.g. inhaled cortico-steroids) during sleep, but also suggests that the use of acute treatments such as inhaled bronchodilators at the time of an episode of nocturnal breathlessness and coughing may be rapidly effective, possibly without awaking the child. Parents can be assured that using this technique the infants will most likely accept and receive the necessary treatment. Thus, the use of the SM is more likely than in the past to allow aerosol therapy to be administered to infants during sleep without awaking them.

Furthermore, given the high success rate with the SM approach, paediatricians may now more confidently prescribe VHC+SM to achieve more rapid and acceptable aerosol therapeutics, instead of providing more expensive compressor+nebulizer systems and solution vials that involve about 20 minutes of administration time and the need to clean the nebulizer after the treatment is complete. Use of nebulizers requires that a mask be applied to the face for a much longer period of time which is more likely to arouse the infant, further adding to the its distress, or the need to resort to the 'blow-by' technique that provides a relatively small and unpredictable dose of aerosol medication to the child.

The lack of control subjects using currently available *conventional* masks is acknowledged as a limitation of the present study and a control group was originally incorporated. However, we felt that it would be unethical and unjustified to expose an additional control group of infants to scintigraphy, particularly since several historical scintigraphic studies are available. Another limitation may be our enrolment only of infants who regularly use pacifiers and a future study in non-pacifier users is certainly warranted. Similarly, the possibility that sleep may be disturbed when infants are sick need to be also considered in the future.

This pilot study with the SM is clinically important as it demonstrates a unique, innovative and apparently effective approach to providing infants and toddlers with aerosol therapy during sleep. It has the potential for encouraging pediatricians to use this technique in future clinical studies including more patients.

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Financial Disclosure: Dr. Newhouse is the consulting Chief Medical Officer of InspiRx Inc, developer of the SootherMask®. All other authors have indicated they have no financial relationships relevant to this article to disclose.

Contributors' Statement

Israel Amirav: Dr. Amirav conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript, reviewed and approved the final manuscript as submitted.

Michael T. Newhouse: Dr. Newhouse was involved in the study design, reviewed and approved the final manuscript as submitted.

Anthony S. Luder: Dr. Luder reviewed and approved the final manuscript as submitted.

Asaf Halamish: Mr. Halamish was involved in the study design, designed the data collection instruments, and coordinated and supervised data collection. He reviewed and approved the final manuscript as submitted.

Hamza Omar: Mr. Omar carried out the nuclear medicine studies and initial analyses, reviewed and approved the final manuscript as submitted.

Miguel Gorenberg: Dr. Gorenberg was involved in the study design, designed the nuclear data collection, reviewed and approved the final manuscript as submitted.

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Data Sharing Statement: No additional data

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VHC- valved aerosol holding chamber

DTPA-Diethylene Triamine Pentacaetic Acid

SM- SootherMask

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References

1. Janssens HM, van der Wiel EC, Verbraak AF et al. Aerosol therapy and the fighting toddler: is administration during sleep an alternative? *J Aerosol Med*. 2003;16(4):395-400.

2. Esposito-Festen J, Ijsselstijn H, Hop W et al. Aerosol therapy by pressured metered-dose inhaler-spacer in sleeping young children: to do or not to do? *Chest*. 2006;130(2):487-92.

3. Smith C, Goldman RD. Nebulizers versus pressurized metered-dose inhalers in preschool children with wheezing. *Can Fam Physician*. 2012;58(5):528-30.

4. Amirav I, Luder AS, Halamish A, et al. Design of Aerosol Face Masks for Children Using Computerized 3D Face Analysis. J Aerosol Med Pulm Drug Deliv. 2013 Sep 28.

5. Newman SP. Scintigraphic assessment of therapeutic aerosols. *Crit Rev Ther Drug Carrier Syst* 1993;10:65-109.

6. Schultz A, Le Souëf TJ, Venter A et al. Aerosol inhalation from spacers and valved holding chambers requires few tidal breaths for children. *Pediatrics*. 2010;126(6):e1493-8.

7. Amirav I, Balanov I, Gorenberg M, et al. Nebulizer Hood Compared to Mask in Wheezy Infants: Aerosol Therapy Without Tears! , *Arch Dis Child* 2003;88:719-723.

8. Amirav I, Balanov I, Gorenberg M, et al. Beta Agonist Aerosol Distribution in RSV Bronchiolitis in Infants. J Nucl Med, 2002; 43: 487-491

9. Atkins HL, Weber DA, Susskind H et al. MIRD dose estimate report no. 16: radiation absorbed dose from technetium-99m-diethylenetriaminepentaacetic acid aerosol. *J Nucl Med* 1992;33:1717-1719.

10. Eggli DF. Pediatric radiopharmaceutical dosages. In Clinical Practice of Nuclear Medicine. Edited by Taylor A and Datz FL. Churchill Livingstone 1991,p450.

11. Tal A, Golan H, Grauer N, et al. Deposition pattern of radiolabeled salbutamol inhaled from a metered-dose inhaler by means of a spacer with mask in young children with airway obstruction. *J Pediatr* 1996;128:479-484.

12. Murakami G, Igarashi T, Adachi Y et al. Measurement of bronchial hyperreactivity in infants and preschool children using a new method. *Ann Allergy* 1990;64:383-7.

13. Noble V, Ruggins NR, Everard ML et al. Inhaled budesonide for chronic wheezing under 18 months of age. *Arch Dis Child* 1992;67:285-288.

14. Shah SA, Berlinski AB, Rubin BK. Force-dependent static dead space of face masks used with holding chambers. *Respir Care* 2006;51:140-4.

15. Amirav I, Luder A, Chleechel A et al. Lung aerosol deposition in suckling infants. *Arch Dis Child* 2012; 97(6):497-501.

16. Clarisse B, Dematteï C, Nikasinovic L et al. Bronchial obstructive phenotypes in the first year of life among Paris birth cohort infants. *Pediatr Allergy Immunol* 2009;20:126–33.

Table 1

Individual Deposition values (% of emitted dose)

Pt. #	Age (m)	Gender	Rt. lung	Both Lungs	Stomach	Upper airway
1	6.4	M	**0.99**	4.16	0.09	7.8
2	3.9	F	**1.44**	2.97	0.72	16.9
3	6.4	M	**0.83**	2.38	3.29	25.84
4	7.1	F	**1.94**	5.26	2.11	15.59
5	5.4	F	**1.47**	4.51	1.26	9.76
6	11.7	M	**2.37**	6.33	0.8	32.81
7	5.0	F	**2.29**	4.88	1.58	16.5
8	10.8	F	**1.4**	4.02	1.13	8.37
9	5.4	M	**1.19**	2.41	2.52	15.01
10	5.4	M	**2.23**	4.75	0.72	18.95
Mean	9.28		**1.61**	4.17	1.42	16.75
SD	0.68		0.56	1.27	0.97	7.81

Figures and Video Legend

Figure 1:

Photograph illustrating the method of aerosol administration to a sleeping infant showing the Respimat inhaler, InspiraChamber and SootherMask™

Figure 2:

A typical scintigram, the green dashed circle denotes the stomach, the blue dotes denote upper airways, and solid yellow- right lung.

Video:

Video illustrating the method of aerosol administration to a sleeping infant showing the Respimat inhaler, InspiraChamber and SootherMask™

Feasibility of Aerosol Drug Delivery to Sleeping Infants ~~Aerosol delivery to infants *without tears* Back to Sleep!~~

Israel Amirav[1,5]MD, Michael T. Newhouse[4] MD., MSc, FRCP(C), Anthony Luder[1]MD, Asaf Halamish[2], Hamza Omar[3], Miguel Gorenberg[3]MD

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Short title: Aerosol delivery during sleep

Key words: Aerosol, face-mask, sleep, deposition, compliance

Funding source: None

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MDI- metered dose inhaler

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SM- SootherMask

IC- InspiraChamber

Abstract

~~Rationale~~**Objectives:** Delivery of inhaled medications to infants is usually very demanding and is often associated with crying and mask rejection. It has been suggested that aerosol administration during sleep may be an attractive alternative. Previous studies in sleeping children were disappointing as most of the children awoke and rejected the treatment.

The SootherMask™ (SM) is a new, gentle and innovative approach for delivering inhaled medication to infants and toddlers. The present pilot study describes the feasibility of administering inhaled medications during sleep using the SM. ~~The two major outcomes of this study were the acceptability of the treatment and the lung deposition (% of emitted dose)~~

~~**Methods and Results**~~**Design:** Prospective observational study

Setting: Out patients

Participants: Thirteen sleeping infants with recurrent wheezing who regularly used pacifiers and were <12 months old ~~were studied~~.

Intervention: Participants inhaled technetium99mDTPA-labeled normal saline aerosol delivered via a Respimat® Soft Mist Inhaler (SMI) (Boehringer Ingelheim, Germany) and SM + InspiraChamber® (IC; InspiRx Inc., New Jersey).

Outcomes: The two major outcomes were the acceptability of the treatment and the lung deposition (% of emitted dose)

~~Right lung aerosol deposition was measured scintigraphically using technetium99mDTPA-labeled normal saline aerosol delivered via a Respimat® Soft Mist Inhaler (SMI) (Boehringer Ingelheim, Germany) and SM + InspiraChamber® (IC; InspiRx Inc., New Jersey).~~

Results: All infants who fulfilled the inclusion criteria successfully received the SM treatment during sleep without difficulty. Mean lung deposition (±SD) averaged 1.6±0.5% in the right lung.

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Conclusions: This study demonstrated that the combination of Respimat, InspiraChamber® and SootherMask™ was able to administer aerosol therapy to all the sleeping infants who were regular pacifier users with good lung deposition. Provision of aerosols during sleep is advantageous since all of the sleeping children accepted the mask and ensuing aerosol therapy under these conditions, in contrast to previous studies that resulted in frequent mask rejection using currently available devices.

Word count: ~~250~~253

Strengths

- Delivery of inhaled medications to infants is often associated with crying and mask rejection. Treatment during sleep may be an attractive alternative yet previous studies failed to confirm this approach as most of the infants awoke during treatment.
- The present study describes a novel approach to overcoming these problems during sleep.
- Treatment during sleep by means of a unique mask which includes the infants' own pacifier, was accepted by all infants with no awakening and improved lung deposition.

Limitations

- Only infants who regularly used pacifiers were enrolled, thus these results may not be generally applicable.
- As the study involved scintigraphy, no control ~~healthy~~ infants using conventional masks could be included.

Introduction

Delivery of inhaled medications to awake infants and toddlers is often very demanding and is frequently associated with considerable crying and rejection of the mask. It was suggested that aerosol therapy during sleep may be an attractive alternative. An *in-vitro* study suggested that since sleep is associated with more regular breathing patterns, and lung targeting of aerosol is greater during sleep, this may translate into improved in vivo results.[1]

A previous real life study using a pressurized metered dose inhaler (pMDI) with a valved aerosol holding chamber (VHC) in young children,[2] provided disappointing results; 69% of the children awoke during aerosol administration, there was poor compliance and neglible benefit. No similar study followed this failure and a recent Canadian report discourages parents from this practice.[3]

The SootherMask® (SM) is a novel approach for delivering inhaled medication to infants (4). The SM utilizes the infant's own pacifier (or the teat of an infant formula bottle), whose nipple is inserted through a slot in the anterior wall of the mask. The infant, sucking on the mask, keeps the mask sealed to its facial contours, by means of sub-atmospheric pressure, with little additional applied force and can nasally inhale the medication generated by a nebulizer or from a metered dose inhaler (MDI)+ VHC attached to the SM. By virtue of its design the SM can initially be applied to the face without the VHC or nebulizer attached. The infant can retain the SM for prolonged periods of time and subsequent gentle mating of the VHC with MDI or nebulizer rarely upsets the infant. Pilot observations suggested a high degree of acceptance of the SM in

sleeping infants who appear to regard it as being no different from their pacifier alone.

The present study describes the feasibility of administering inhaled medications during sleep using the SM. Infants, shortly after falling asleep, were given 99m Tc in normal saline as placebo aerosolized medication using the SM attached to a VHC and both right lung and total lung deposition were evaluated scintigraphically. Both acceptability of the treatment and fractional lung deposition served as the primary outcomes.

Methods

This was part of larger study that explored the relationship between use of pacifiers and reduction in sudden infant death syndrome mortality (NCT01120938). The infants received the Respimat- generated radiolabeled aerosol through a SootherMask attached to a valved holding chamber (InspiraChamber®[IC]) (InspiRx Inc, NJ USA) and their lung aerosol deposition was measured scintigraphically.

Inclusion criteria: Infants (Age 0-12 months) who were prescribed intermittent or regular inhaled therapy by a paediatric pulmonologist because of recurrent (>3x within the past 2 months) episodes of wheezing that responded to bronchodilator treatments, and who were regular users of pacifiers (at least two hours/day of pacifier use per parents' report). Patients had to be asymptomatic for at least 2 weeks prior to the study. Demographic details are shown in Table 1.

Exclusion criteria: Patients whose parents reported a history or symptoms of airway abnormalities (eg, previous airway surgery, tracheotomy, obstructive sleep apnoea, snoring, anatomical anomalies of mouth palate nose, pharynx and

trachea) as well as those with chronic cardiopulmonary disease such as bronchopulmonary dysplasia, congenital heart disease, immune deficiency, or cystic fibrosis.

Procedures:

99mTc labelled aerosol generated by the Respimat SMI was administered to the infants via the IC+SM. The Respimat is powered by compressed air produced by means of a spring-driven piston within a small cylinder and generates a slowly moving aerosol bolus into the IC. The medication solution reservoir is a multidose plastic cartridge. We found the Respimat SMI preferable to pressurized metered dose inhalers (pMDI) because it is possible to readily radio-label the medication solution in the cartridge. As both pMDI and SMI, would, in infants, be used with a VHC, the Respimat served as an ideal clinical surrogate. For each trial, the SMI cartridge was filled with 3.0 mL of 99m Tc-labelled normal saline. Addition of 99m Tc has no physical effect on aerosol characteristics.[5]

After priming the Respimat by discharging the inhaler 5 times to a hooded exhaust system the emitted dose in terms of radioactive counts was measured by placing bacterial filters over the mouthpiece of the SMI and firing 5 puffs directly into the filter. The filters were immediately placed in a well counter (Capintec, Ramsey New Jersey, USA) and were evaluated each morning (x4) for reproducibility.

Infants arrived at the Nuclear Medicine department in the morning and were fed. The care-giver inserted the infants' pacifier into the SM which was then offered and accepted. They were put down to sleep sucking on the pacifier nipple in the

SM. Treatment commenced within 10 minutes after the infant fell asleep. The average time from arrival to sleep in this strange environment ranged between half and one and a half hour. The Respimat was inserted into the back of the IC, and the 'mouthpiece' of the IC was gently 'docked' into the orifice of the SM sealed to the infant's face by its suction on the pacifier nipple. Two successive 'puffs' from the Respimat, each followed by one minute of tidal breathing, were then fired into the IC and the mask-VHC-inhaler combination was kept on the infant's face, by the care giver, for one minute (see Figure 1 and Video1). This ensured complete evacuation of the aerosol from the VHC.[6] The SM+VHC were then removed.

The infant was placed supine under a double (anterior and posterior) plate scanner (Symbia, Siemens GMBH, Munich, Germany) which enabled image acquisition without moving the infant or the cameras. Scintigraphic scans of 60 seconds duration were obtained and gamma camera counts (corrected for decay and tissue attenuation) of both the anterior and the posterior chest were measured as previously reported [7]. Similarly counts were measured for the VHC and mask to account for all the emitted dose. The tissue attenuation factor was determined based on our own experience with similar age infants (8). In brief, a hollow acrylic disc, filled with a solution of a known amount of 99mTc (37–74 MBq) served as the flood source. The square root of the ratio of transmission scan counts obtained without the infant (No) to the geometric mean of the counts with the infant (Nt) provided the attenuation correction factor ($\sqrt{No/Nt}$) .

The following regions of interest (ROIs) were evaluated: 1. Upper airway, 2. Stomach and 3. Lungs. Aerosol deposition in each of these regions was

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expressed as the percent of the total radioactivity previously emitted (2 puffs) from the Respimat.

Treatments were administered in a special room within the nuclear medicine department, used only for this purpose. Only the patient's parent and physician were allowed in the room. Radioactivity protection monitoring was carried out regularly and following each study, to ensure that no excess radioactivity was present in the room following the treatments. To avoid contamination of the infant's chest and the environment during treatment, which would interfere with lung scintigraphy—, the infant's chest and the VHC were enclosed in a special disposable large volume nylon wrap which was removed immediately prior to imaging.

The radiation dose of 99m Tc aerosol used in this study was calculated according to the Medical Internal Radiation Dose Committee [9]. The dose of 99m Tc to be given to each patient determined before the inhalation procedure was found to be 15μci/kg [10]. As inhalation exposure is 0.05 RAD/mci, or 0.00075 RAD/Kg, the maximum exposure for a 20 kg child was 0.015 RAD. This is equivalent to the radiation received during normal cosmic-ray exposure of 3 weeks or a 12 hour flight and is much lower than the dose used in diagnostic imaging procedures. 99m Tc is a pure gamma emitter and has a 6 hour physical half-life.[9]

The deposition method suggested here has been in use clinically world-wide for several decades and has been used in a number of previous paediatric studies [7,11]. It has regularly received ethics committee approval in the past and approval was obtained for this study from the local hospital research ethics

committee (#0007-09-ZIV) and the Ministry of Health in Israel (#920090101). Parents provided written informed consent.

Results

Thirteen infants were enrolled. Ten infants completed the study. Reasons for non-completion were: One infant did not fall asleep during the observation period; One infant awoke after completing aerosol administration and due to excessive movement, image acquisition could not be undertaken, although aerosol administration had apparently been achieved; The third infant was subsequently found to be sick with a respiratory illness. She showed abnormally high deposition in only one lung and was therefore excluded. All the infants accepted the treatment without mask rejection and no leaks were observed reflecting a good mask to face seal. All infants were asleep flat and supine during their scintigraphic image acquisition.

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Respiratory symptoms such as cough and breathlessness in infancy are common during sleep.[16] The present study supports, not only the use of chronic anti-inflammatory treatments (e.g. inhaled cortico-steroids) during sleep, but also suggests that the use of acute treatments such as inhaled bronchodilators at the time of an episode of nocturnal breathlessness and coughing may be rapidly effective, possibly without awaking the child. Parents can be assured that using this technique the infants will most likely accept and receive the necessary treatment. Thus, the use of the SM is more likely than in the past to allow aerosol therapy to be administered to infants during sleep without awaking them.

Furthermore, given the high success rate with the SM approach, paediatricians may now more confidently prescribe VHC+SM to achieve more rapid and acceptable aerosol therapeutics, instead of providing more expensive compressor+nebulizer systems and solution vials that involve about 20 minutes of administration time and the need to clean the nebulizer after the treatment is complete. Use of nebulizers requires that a mask be applied to the face for a much longer period of time which is more likely to arouse the infant, further adding to the its distress, or the need to resort to the 'blow-by' technique that provides a relatively small and unpredictable dose of aerosol medication to the child.

The lack of control subjects using currently available *conventional* masks is acknowledged as a limitation of the present study and a control group was originally incorporated. However, we felt that it would be unethical and unjustified to expose an additional control group of infants to scintigraphy, particularly since several historical scintigraphic studies are available. Another limitation may be our enrolment only of infants who regularly use pacifiers and a future study in non-pacifier users is certainly warranted. Similarly, the possibility that sleep may be disturbed when infants are sick need to be also considered in the future.

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This pilot study with the SM is~~, we think,~~ clinically important as it demonstrates a unique, innovative and apparently effective approach to providing infants and toddlers with aerosol therapy during sleep. It has the potential for encouraging pediatricians to use this technique in future clinical studies including more patients.

References

1. Janssens HM, van der Wiel EC, Verbraak AF et al. Aerosol therapy and the fighting toddler: is administration during sleep an alternative? *J Aerosol Med*. 2003;16(4):395-400.

2. Esposito-Festen J, Ijsselstijn H, Hop W et al. Aerosol therapy by pressured metered-dose inhaler-spacer in sleeping young children: to do or not to do? *Chest*. 2006;130(2):487-92.

3. Smith C, Goldman RD. Nebulizers versus pressurized metered-dose inhalers in preschool children with wheezing. *Can Fam Physician*. 2012;58(5):528-30.

4. Amirav I, Luder AS, Halamish A, Raviv D, Kimmel R, Waisman D, Newhouse MT. Design of Aerosol Face Masks for Children Using Computerized 3D Face Analysis. J Aerosol Med Pulm Drug Deliv. 2013 Sep 28.

5. Newman SP. Scintigraphic assessment of therapeutic aerosols. *Crit Rev Ther Drug Carrier Syst* 1993;10:65-109.

6. Schultz A, Le Souëf TJ, Venter A et al. Aerosol inhalation from spacers and valved holding chambers requires few tidal breaths for children. *Pediatrics*. 2010;126(6):e1493-8.

7. Amirav I, Balanov I, Gorenberg M, et al. Nebulizer Hood Compared to Mask in Wheezy Infants: Aerosol Therapy Without Tears! , *Arch Dis Child* 2003;88:719-723.

8. Amirav I, Balanov I, Gorenberg M, Luder AS, Newhouse MT, Groshar D. Beta Agonist Aerosol Distribution in RSV Bronchiolitis in Infants. J Nucl Med, 2002; 43: 487-491

9. Atkins HL, Weber DA, Susskind H et al. MIRD dose estimate report no. 16: radiation absorbed dose from technetium-99m-diethylenetriaminepentaacetic acid aerosol. *J Nucl Med* 1992;33:1717-1719.

10. Eggli DF. Pediatric radiopharmaceutical dosages. In Clinical Practice of Nuclear Medicine. Edited by Taylor A and Datz FL. Churchill Livingstone 1991,p450.

11. Tal A, Golan H, Grauer N, et al. Deposition pattern of radiolabeled salbutamol inhaled from a metered-dose inhaler by means of a spacer with mask in young children with airway obstruction. *J Pediatr* 1996;128:479-484.

12. Murakami G, Igarashi T, Adachi Y et al. Measurement of bronchial hyperreactivity in infants and preschool children using a new method. *Ann Allergy* 1990;64:383-7.

13. Noble V, Ruggins NR, Everard ML et al. Inhaled budesonide for chronic wheezing under 18 months of age. *Arch Dis Child* 1992;67:285-288.

14. Shah SA, Berlinski AB, Rubin BK. Force-dependent static dead space of face masks used with holding chambers. *Respir Care* 2006;51:140-4.

15. Amirav I, Luder A, Chleechel A et al. Lung aerosol deposition in suckling infants. *Arch Dis Child* 2012; 97(6):497-501.

16. Clarisse B, Demattei C, Nikasinovic L et al. Bronchial obstructive phenotypes in the first year of life among Paris birth cohort infants. *Pediatr Allergy Immunol* 2009;20:126–33.

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Table 1

Individual Deposition values (% of emitted dose)

Pt. #	Age (m)	Gender	Rt. lung	Both Lungs	Stomach	Upper airway
1	6.4	M	**0.99**	4.16	0.09	7.8
2	3.9	F	**1.44**	2.97	0.72	16.9
3	6.4	M	**0.83**	2.38	3.29	25.84
4	7.1	F	**1.94**	5.26	2.11	15.59
5	5.4	F	**1.47**	4.51	1.26	9.76
6	11.7	M	**2.37**	6.33	0.8	32.81
7	5.0	F	**2.29**	4.88	1.58	16.5
8	10.8	F	**1.4**	4.02	1.13	8.37
9	5.4	M	**1.19**	2.41	2.52	15.01
10	5.4	M	**2.23**	4.75	0.72	18.95
Mean	9.28		**1.61**	4.17	1.42	16.75
SD	0.68		0.56	1.27	0.97	7.81

Figures and Video Legend

Figure 1:

Photograph illustrating the method of aerosol administration to a sleeping infant showing the Respimat inhaler, InspiraChamber and SootherMask™

Figure 2:

A typical scintigram, the green dashed circle denotes the stomach, the blue dotes denote upper airways, and solid yellow- right lung.

Video:

Video illustrating the method of aerosol administration to a sleeping infant showing the Respimat inhaler, InspiraChamber and SootherMask™

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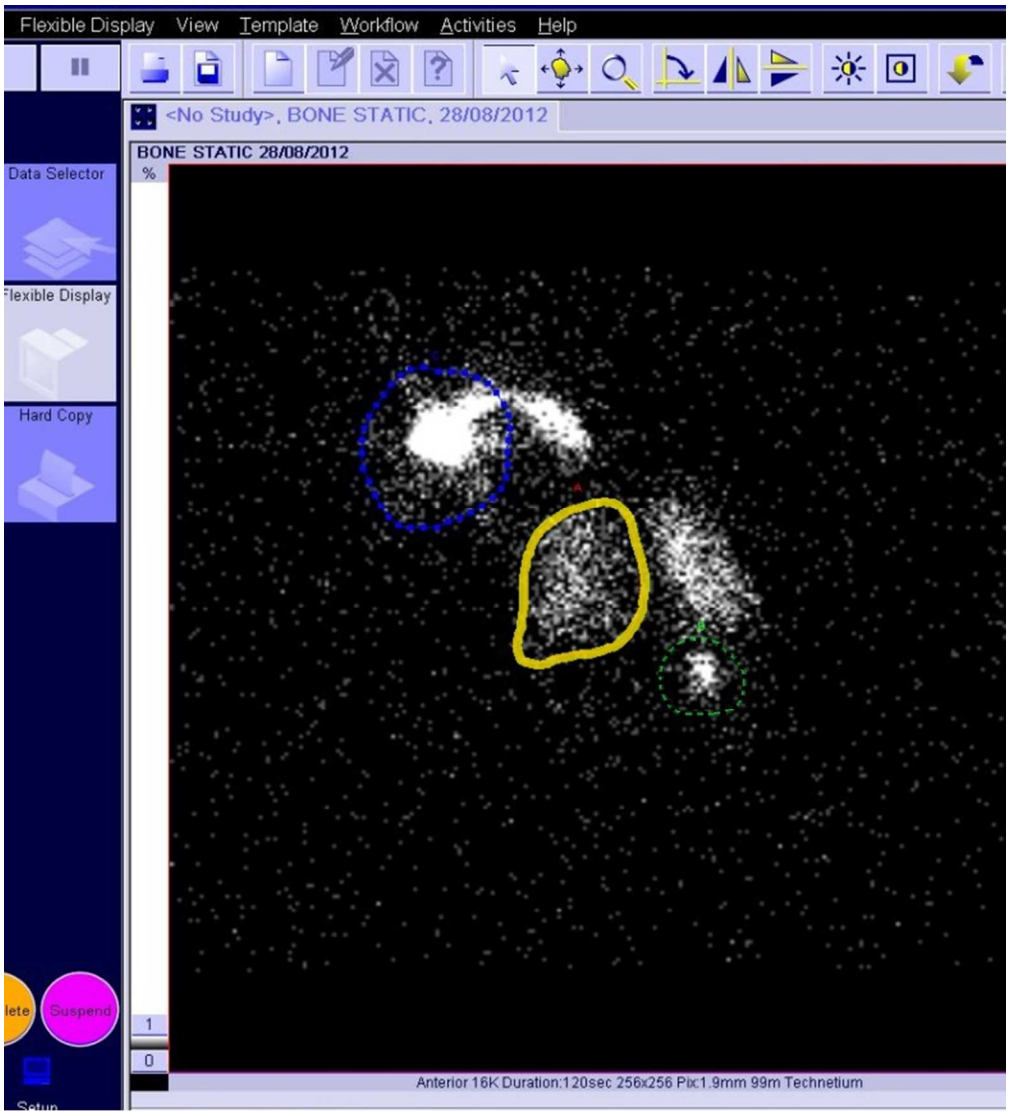

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