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Feasibility of Aerosol drug delivery to sleeping infants

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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 Pentacetic 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 (\pm SD) averaged $1.6\pm 0.5\%$ 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 scintigraphy, 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 negligible 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

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3 different from their pacifier alone. Caregivers are advised to acclimatize the
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5 infant to the SM by routinely providing the pacifier in the SM instead of using
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7 the pacifier alone.
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10 The present study describes the feasibility of administering inhaled medications
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12 during sleep using the SM. Infants, shortly after falling asleep, were given 99m
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14 Tc in normal saline as placebo aerosolized medication using the SM attached to a
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16 VHC and both right lung and total lung deposition were evaluated
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18 scintigraphically.
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21 22 **Methods**

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24 This was part of larger study that explored the relationship between use of
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26 pacifiers and reduction in sudden infant death syndrome mortality
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28 (NCT01120938). The infants received the Respimat- generated radiolabeled
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30 aerosol through a SootherMask attached to a valved holding chamber
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32 (InspiraChamber®[IC]) (InspiRx Inc, NJ USA) and their lung deposition was
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34 measured.
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38 Inclusion criteria: Wheezy infants (Age 0-12 months) on intermittent or regular
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40 inhaled therapy at home, and who were regular users of pacifiers (at least two
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42 hours/day of pacifier use per parents' report).
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46 Exclusion criteria: Patients whose parents reported histories or symptoms of
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48 airway abnormalities (eg, previous airway surgery, tracheotomy, obstructive
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50 sleep apnoea, snoring, anatomical anomalies of mouth palate nose, pharynx and
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52 trachea) as well as those with chronic cardiopulmonary disease such as
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54 bronchopulmonary dysplasia, congenital heart disease, immune deficiency, or
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56 cystic fibrosis.
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3 Procedures:

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6 ^{99m}Tc labelled aerosol generated by an MDI (Respimat®, Boehringer
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8 Ingelheim, Ingelheim, Germany) was administered to the infants via the IC+SM.
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10 The Respimat is powered by compressed air produced by means of a spring-
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12 driven piston within a small cylinder and generates a slowly moving aerosol
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14 bolus into the IC. The medication solution reservoir is a multidose plastic
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16 cartridge. We found the Respimat system ideal for this study because it is
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18 possible to readily radio-label the medication solution in the cartridge. For each
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20 trial, the MDI cartridge was filled with 3.0 mL of ^{99m}Tc -labelled normal saline.
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23 Addition of ^{99m}Tc has no physical effect on aerosol characteristics.[4]
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27 After priming the Respimat by discharging the inhaler 5 times to a hooded
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29 exhaust system, the emitted dose in terms of radioactive counts was measured by
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31 placing bacterial filters over the outlet mouthpiece of the inhaler and firing 5
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33 puffs directly into the filter. The filters were immediately placed in a well counter
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35 (Capintec Ramsey New Jersey, USA) and were tested each morning (X4) for
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37 reproducibility. Infants arrived at the Nuclear Medicine department in the
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39 morning and were fed. The care giver inserted the infant's pacifier into the SM,
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41 the SM was then offered and accepted and they were put down to sleep sucking
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43 on the pacifier nipple in the SM. Treatment commenced within 10 minutes after
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45 the infant fell asleep. The average time from arrival to sleep in this strange
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47 environment ranged between half to one and a half hours. The Respimat was
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49 attached to the back of the IC, and the 'mouthpiece' of the IC was gently
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51 'docked' to the orifice of the SM applied snugly to the infant's face by suction on
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53 the pacifier nipple. Two successive 'puffs' from the Respimat were then fired into
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55 the IC and the mask-VHC-inhaler combination was kept on the infant's face, by
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3 the care giver, for one minute. This ensured complete evacuation of the aerosol
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5 from the VHC.[5] The SM+VHC were then removed.
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8 Scintigraphic scans of 60 seconds duration were obtained immediately after each
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10 treatment and gamma camera counts (corrected for decay and tissue attenuation)
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12 of both the anterior and the posterior chest were measured as previously reported
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14 [6] and the following regions of interest (ROIs) were evaluated: 1. Upper airway,
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16 2. Stomach and 3. Lungs. Aerosol deposition in each of the areas defined above
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18 was expressed as a percentage of the total amount of radioactivity previously
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20 emitted (2 puffs) from the Respimat.
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24 Patients received the treatment in a special room within the nuclear medicine
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26 department, used only for this purpose. No person other than the patient's parent
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28 and physician was allowed in the room. Radioactivity protection monitoring was
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30 carried out regularly and following each study, to ensure that no excess
31
32 radioactivity was present in the room following treatments. To avoid
33
34 contamination of the infant's chest and the environment during treatment, thus
35
36 interfering with lung gamma camera counting, the infant's chest and the VHC
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38 were enclosed in a special disposable large volume nylon wrap.
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43 The radiation dose of ^{99m}Tc aerosol used in this study was calculated according
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45 to the Medical Internal Radiation Dose Committee.[7] The dose of ^{99m}Tc to be
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47 given to each patient determined before the inhalation procedure was found to be
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49 $15\mu\text{Ci}/\text{kg}$. [8] As inhalation exposure is 0.05 RAD/mCi, (9) or 0.00075 RAD/Kg,
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51 the maximum exposure for a 20 kg child was 0.015 RAD. It was equivalent to
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53 the radiation received during cosmic-ray exposure of 3 weeks or a 12 hour flight
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3 and is much lower than the dose used in diagnostic imaging procedures. ^{99m}Tc
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5 is a pure gamma emitter and has a 6 hour physical half-life.[7]
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8 The deposition method suggested here has been in use clinically world-wide for
9
10 several decades and has been used in a number of previous paediatric
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12 studies.[6,10] It has regularly received ethical approval in the past and ethics
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14 approval was obtained for this study from the local research committee and the
15
16 Ministry of Health in Israel. Parents signed an informed consent.
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20 **Results**

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23 Thirteen infants were enrolled. Ten infants completed the study. Reasons for
24
25 non-completion were: One infant did not fall asleep during the observation
26
27 period; One infant awoke after completing aerosol administration and due to
28
29 excessive movement, image acquisition could not be undertaken, although
30
31 aerosol administration had apparently been achieved; The third infant was
32
33 subsequently found to be sick with a respiratory illness. She showed abnormally
34
35 high deposition in only one lung and was therefore excluded. All the infants
36
37 accepted the treatment without rejection and no leaks were observed reflecting a
38
39 good mask to face seal.
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44 A typical scintigram is shown in Figure 1. The individual deposition results of
45
46 the 10 patients are shown in Table 1.
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49 Right Lung deposition in all 10 infants ranged between 0.83 to 2.37 % of
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51 delivered dose with a mean value of 1.61 ± 0.56 %. The mean deposition in both
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53 lungs (which includes oesophageal and carinal deposition) was 4.17 %. The
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55 amount of drug deposited in the upper airway averaged 16.7% and in the
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3 stomach 1.4%. There was no correlation between deposition and age of the
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5 infants.
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10 11 **Discussion**

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14 The present study demonstrates that aerosol administration in infants during sleep
15
16 is a successful way to achieve potentially 'therapeutic' lung deposition when
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18 treatment is accomplished by means of a VHC attached to a calming and
19
20 relatively non-intrusive mask such as the SM. All of the infants readily accepted
21
22 the treatment with little difficulty and did not awaken, cry or demonstrate fear of
23
24 the mask or the subsequent aerosol therapy.
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28 Previous studies have stressed the difficulty of delivering inhaled medications to
29
30 infants. There are, potentially, both anatomic and physiological reasons for this.
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32 The epiglottis in infants is situated high in the upper respiratory tract (URT) very
33
34 close to the base of the infant's tongue,[11] The infant pharynx and supraglottic
35
36 tissue areas characteristically are less rigid compared to adults and thus more
37
38 susceptible to collapse and obstruction of the URT, particularly during
39
40 inspiration. Additionally, the airways of infants are narrower and are prone to
41
42 collapse, while tidal volume and flow velocity are relatively low. Currently
43
44 available conventional face masks are essentially miniaturized adult masks, with
45
46 a relatively large dead space, are poorly contoured, if at all, and require a
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48 considerable external force of more than 1 kg,[12] to apply them snugly to the
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50 infant's face, thus often upsetting the child.[13] The behavioural aspect of
51
52 aerosol therapy in infants is most important for achieving adequate delivery of
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54 aerosols to their lungs and they frequently refuse the application of a face mask
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3 by attempting to push it away as well as vigorously squirming and crying. Crying
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5 has been shown to greatly reduce lung deposition of inhaled medication to a
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7 negligible fraction of what is considered a therapeutic dose.[6,10,14,15]
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11 It was previously suggested, by several investigators, that sleep may provide a
12
13 non-threatening opportunity for aerosol administration to infants. Furthermore,
14
15 compared to the awake state, sleep is associated with slower and more regular
16
17 breathing, and a lower inspiratory flow velocity,[16-18] factors that have been
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19 shown to improve aerosol delivery to the lungs. Administration of inhaled drugs
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21 to infants during sleep may thus be a good alternative, particularly for
22
23 uncooperative young children. Murakami [14] demonstrated, in seven sleepy
24
25 infants, that scintigraphic deposition of nebulized aerosol appeared significantly
26
27 better than when they were wide awake. The mean deposition during sleep
28
29 appeared as good as that in co-operative older (3-14 years) awake children.
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31 However sleep was induced by means of sedation, and it was thus not a “real
32
33 life” study.
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39 In an aerosol ‘therapy’ study, Janssens et al [1] recorded the breathing patterns of
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41 awake and sleeping babies (age 11 ± 5.1 months), then applied the results by
42
43 means of a breathing simulator. They captured the delivered aerosol (generated
44
45 by MDI and delivered into a VHC) on filters located at the tracheal port of an
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47 infant airway model, the Sophia Anatomical Infant Nose-Throat (SAINT) model.
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49 They showed that treatment during ‘sleep’ greatly improved VHC aerosol
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51 delivery and almost doubled the dose compared to the ‘awake’ state; 11.3 ± 3.9
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53 compared to $6.5 \pm 3.2 \mu\text{g}$ of a $200 \mu\text{g}$ total delivered dose (5.5% vs 3.2%).
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3 These promising ‘in vitro’ results were somewhat contradicted during attempts to
4 translate them to real life conditions. Noble et al [19] showed that although mask
5 VHC aerosol administration during sleep was successful in most of the infants
6 and toddlers that he studied, a subgroup of 17% of the patients awakened during
7 the procedure. In a more recent study that assessed the effects of sleep on aerosol
8 delivery by VHC, it was found that 70% of infants awoke during application of
9 the mask and 75% of those became distressed and uncooperative. Not
10 surprisingly, the delivered dose in this study was only about half of that in awake,
11 cooperative infants.[2] Based on these disappointing studies, a recent Canadian
12 guideline discourages parents from delivering aerosols to their infants during
13 sleep.[3]

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28 The SM is a new face mask concept that integrates the infant’s own pacifier in
29 the treatment process. The mask has evidence-based facial contours and an
30 extremely small dead space (18.2 ml) resulting from 3D computerized face
31 analysis technology developed with the assistance of the Computer Science
32 department at Technion University.[20] Infants suck on their pacifier and the rim
33 of the mask is gently sealed to their face, mainly by suction on the pacifier. We
34 postulate that the very gentle touch of the contoured mask rim is thus not
35 considered as intrusive and frightening as currently available masks that require
36 application of considerable force in order to achieve a good seal and also fail to
37 provide the calming effect of the infant’s familiar pacifier. We have previously
38 shown adequate lung deposition when nebulized drug was administered to awake
39 infants through the SM.[21] Nebulization may require up to 15 min or more of
40 treatment which may, with current masks, be too long for the infant to tolerate.
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3 (taking into account preparation and cleaning) is considerably shorter (<5 min vs.
4 >20 min). It has been recently shown that no more than 2-3 breaths are necessary
5 following each puff to empty the VHC in young children [5] and thus actual
6 aerosol administration time, after application of the SM, can be as short as 10-15
7 seconds per puff. The current study is the first to employ the SM in combination
8 with a MDI+VHC.
9

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

16
17 Respiratory symptoms such as cough and breathlessness in infancy are common
18 during sleep.[22] The present study supports, not only the use of chronic anti-
19 inflammatory treatments (inhaled cortico-steroids) during sleep, but also suggests
20 that the use of acute treatments such as inhaled bronchodilators at the time of an
21 episode of nocturnal breathlessness and coughing may be rapidly effective,
22 possibly without awaking the child. Parents can be assured that using this
23 technique the infants will most likely accept and receive the necessary treatment.
24 Thus, the use of the SM is more likely than in the past to allow aerosol therapy to
25 be administered to infants during sleep without awaking them.
26

27
28 Furthermore, given the very high success rate with the SM approach,
29 paediatricians may now more confidently prescribe MDI+VHC+SM to achieve
30 more rapid and acceptable aerosol therapeutics, instead of providing more
31 expensive compressor+nebulizer systems and solution vials that involve about 20
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3 minutes of administration time from start to finish and the need to clean the
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5 nebulizer after treatment is finished. Use of nebulizers require that a mask be
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7 applied to the face for a much longer period of time which is more likely to
8
9 arouse the infant, further adding to the its distress, or the need to resort to the
10
11 ‘blow-by’ technique that provides a relatively small and unpredictable dose of
12
13 aerosol medication to the child.
14

15
16
17 A limitation of the present study stems from the fact that treatment was given
18
19 within 10 minutes of the commencement of sleep. Although we do not have
20
21 assessment of sleep stages, this may be a stage during which the child is less
22
23 likely to awaken if stimulated by such things as the application of a mask. We see
24
25 no reason, however, to suspect that the likelihood of awakening the child will be
26
27 greater at even a later stage of deep sleep, although this requires further ‘real-life’
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29 evaluation with sleep stage assessment. Another limitation may be our enrolment
30
31 only of infants who regularly use pacifiers and a study in non-pacifier users is
32
33 warranted. However, the virtually complete success rate in these ‘suckling’
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35 infants is exceptional and supports the use of sleep as a unique opportunity to
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37 deliver aerosol to infants, particularly to pacifier users by means of the SM.
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Table 1

Individual Deposition values (% of emitted dose)

<u>Pt. #</u>	<u>Rt.</u> <u>lung</u>	<u>Both</u> <u>Lungs</u>	<u>Stomach</u>	<u>Upper</u> <u>airway</u>
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

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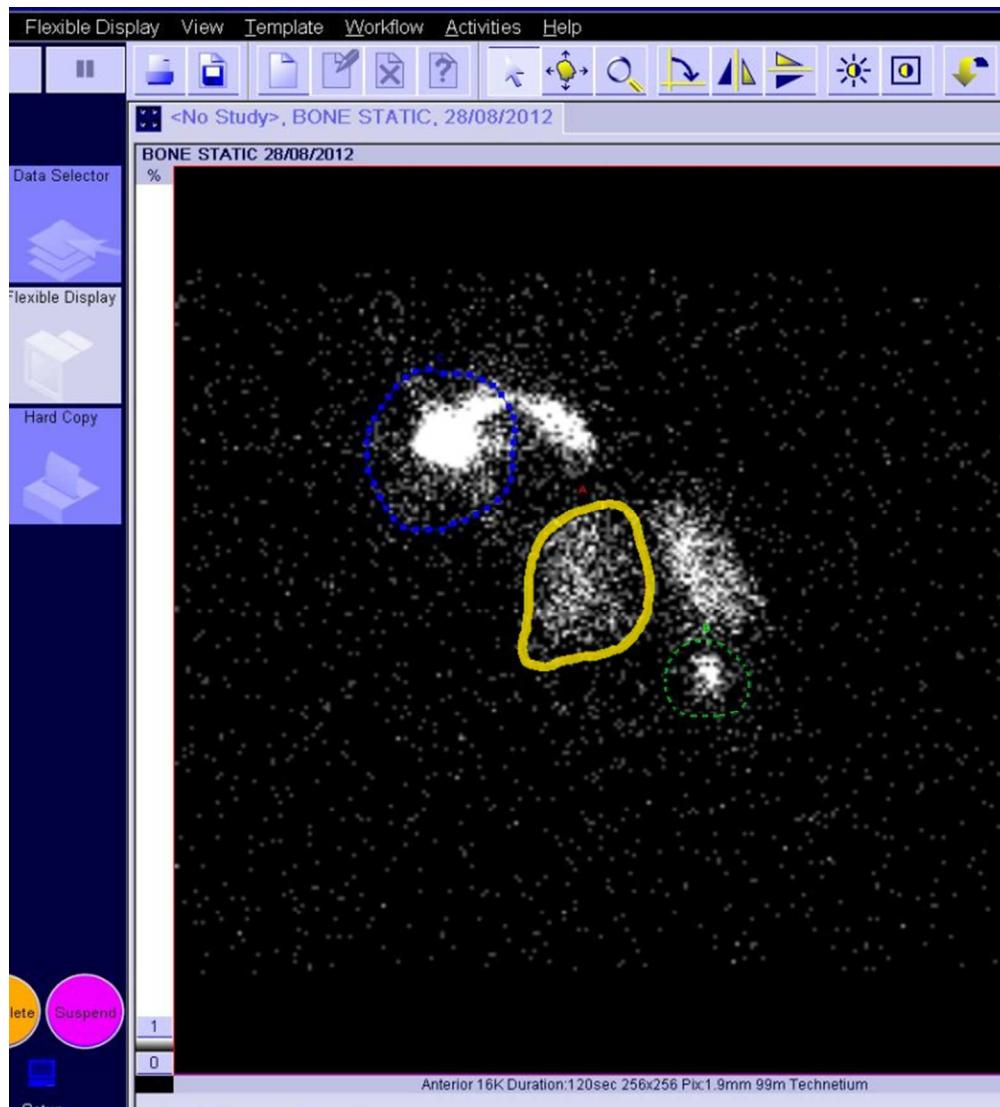
Figures Legend

Figure 1:

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

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Feasibility of Aerosol drug delivery to sleeping infants

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

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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 (\pm SD) averaged $1.6\pm 0.5\%$ 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 scintigraphy, 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 negligible 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

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3 sleeping infants who appear to regard it as being no different from their pacifier
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5 alone.
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8 The present study describes the feasibility of administering inhaled medications
9 during sleep using the SM. Infants, shortly after falling asleep, were given 99m
10 Tc in normal saline as placebo aerosolized medication using the SM attached to a
11 VHC and both right lung and total lung deposition were evaluated
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13 scintigraphically. Both acceptability of the treatment and fractional lung
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15 deposition served as the primary outcomes.
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21 **Methods**

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23 This was part of larger study that explored the relationship between use of
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25 pacifiers and reduction in sudden infant death syndrome mortality
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27 (NCT01120938). The infants received the Respimat- generated radiolabeled
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29 aerosol through a SootherMask attached to a valved holding chamber
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31 (InspiraChamber®[IC]) (InspiRx Inc, NJ USA) and their lung aerosol deposition
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33 was measured scintigraphically.
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38 Inclusion criteria: Infants (Age 0-12 months) who were prescribed intermittent or
39
40 regular inhaled therapy by a paediatric pulmonologist because of recurrent (>3x
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42 within the past 2 months) episodes of wheezing that responded to bronchodilator
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44 treatments, and who were regular users of pacifiers (at least two hours/day of
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46 pacifier use per parents' report). Patients had to be asymptomatic for at least 2
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48 weeks prior to the study. Demographic details are shown in Table 1.
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52 Exclusion criteria: Patients whose parents reported a history or symptoms of
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54 airway abnormalities (eg, previous airway surgery, tracheotomy, obstructive
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56 sleep apnoea, snoring, anatomical anomalies of mouth palate nose, pharynx and
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3 trachea) as well as those with chronic cardiopulmonary disease such as
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5 bronchopulmonary dysplasia, congenital heart disease, immune deficiency, or
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7 cystic fibrosis.
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10 Procedures:

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13 99mTc labelled aerosol generated by the Respimat SMI was administered to the
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15 infants via the IC+SM. The Respimat is powered by compressed air produced by
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17 means of a spring-driven piston within a small cylinder and generates a slowly
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19 moving aerosol bolus into the IC. The medication solution reservoir is a
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21 multidose plastic cartridge. We found the Respimat SMI preferable to
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23 pressurized metered dose inhalers (pMDI) because it is possible to readily radio-
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25 label the medication solution in the cartridge. As both pMDI and SMI, would, in
26
27 infants, be used with a VHC, the Respimat served as an ideal clinical surrogate.
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29 For each trial, the SMI cartridge was filled with 3.0 mL of 99m Tc-labelled
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31 normal saline. Addition of 99m Tc has no physical effect on aerosol
32
33 characteristics.[5]
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38 After priming the Respimat by discharging the inhaler 5 times to a hooded
39
40 exhaust system the emitted dose in terms of radioactive counts was measured by
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42 placing bacterial filters over the mouthpiece of the SMI and firing 5 puffs
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44 directly into the filter. The filters were immediately placed in a well counter
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46 (Capintec Ramsey New Jersey, USA) and were evaluated each morning (x4) for
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48 reproducibility.
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53 Infants arrived at the Nuclear Medicine department in the morning and were fed.
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55 The care-giver inserted the infants' pacifier into the SM which was then offered
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57 and accepted. They were put down to sleep sucking on the pacifier nipple in the
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1
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3 SM. Treatment commenced within 10 minutes after the infant fell asleep. The
4
5 average time from arrival to sleep in this strange environment ranged between
6
7 half and one and a half hour. The RespiMat was inserted into the back of the IC,
8
9 and the 'mouthpiece' of the IC was gently 'docked' into the orifice of the SM
10
11 sealed to the infant's face by its suction on the pacifier nipple. Two successive
12
13 'puffs' from the RespiMat, each followed by one minute of tidal breathing, were
14
15 then fired into the IC and the mask-VHC-inhaler combination was kept on the
16
17 infant's face, by the care giver, for one minute (see Figure 1 and Video1). This
18
19 ensured complete evacuation of the aerosol from the VHC.[6] The SM+VHC
20
21 were then removed.
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26 The infant was placed supine under a double (anterior and posterior) plate
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28 scanner (Symbia, Siemens GMBH, Munich, Germany) which enabled image
29
30 acquisition without moving the infant or the cameras. Scintigraphic scans of 60
31
32 seconds duration were obtained and gamma camera counts (corrected for decay
33
34 and tissue attenuation) of both the anterior and the posterior chest were measured
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36 as previously reported [7]. Similarly counts were measured for the VHC and
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38 mask to account for all the emitted dose. The tissue attenuation factor was
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40 determined based on our own experience with similar age infants (8). In brief, a
41
42 hollow acrylic disc, filled with a solution of a known amount of ^{99m}Tc (37–74
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44 MBq) served as the flood source. The square root of the ratio of transmission
45
46 scan counts obtained without the infant (N_0) to the geometric mean of the counts
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48 with the infant (N_t) provided the attenuation correction factor ($\sqrt{N_0/N_t}$).

49
50 The following regions of interest (ROIs) were evaluated: 1. Upper airway, 2.
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52 Stomach and 3. Lungs. Aerosol deposition in each of these regions was
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3 expressed as the percent of the total radioactivity previously emitted (2 puffs)
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5 from the Respimat.
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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 $15\mu\text{Ci}/\text{kg}$ [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

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3 (#0007-09-ZIV) and the Ministry of Health in Israel (#920090101). Parents
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5 provided written informed consent.
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8 **Results**

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11 Thirteen infants were enrolled. Ten infants completed the study. Reasons for
12 non-completion were: One infant did not fall asleep during the observation
13 period; One infant awoke after completing aerosol administration and due to
14 excessive movement, image acquisition could not be undertaken, although
15 aerosol administration had apparently been achieved; The third infant was
16 subsequently found to be sick with a respiratory illness. She showed abnormally
17 high deposition in only one lung and was therefore excluded. All the infants
18 accepted the treatment without mask rejection and no leaks were observed
19 reflecting a good mask to face seal. All infants were asleep flat and supine during
20 their scintigraphic image acquisition.
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34 A typical scintigram is shown in Figure 2. Lung deposition results for the 10
35 patients are shown in Table 1.
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39 Right Lung deposition in all 10 infants ranged between 0.83 and 2.37 % of the
40 total delivered dose with a mean of 1.61 ± 0.56 %. The mean deposition in both
41 lungs (which includes oesophageal and carinal deposition) was 4.17 %. The
42 amount of drug deposited in the upper airway averaged 16.7% and in the
43 stomach 1.4%. There was no correlation between deposition and age of the
44 infants.
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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 ± 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.

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3 They showed that treatment during 'sleep' greatly improved VHC aerosol
4 delivery and almost doubled the lung dose compared to the 'awake' state; $11.3 \pm$
5 3.9 compared to $6.5 \pm 3.2 \mu\text{g}$ of a $200 \mu\text{g}$ total delivered dose (5.5% vs 3.2%).
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10 These promising 'in vitro' results were somewhat contradicted during attempts to
11 translate them to real life conditions. Noble et al [13] showed that although mask
12 VHC aerosol administration during sleep was successful in most of the infants
13 and toddlers that he studied, a subgroup of 17% of the patients awakened during
14 the procedure. In a more recent study that assessed the effects of sleep on aerosol
15 delivery by VHC, it was found that 70% of infants awoke during application of
16 the mask and 75% of those became distressed and uncooperative. Not
17 surprisingly, the delivered dose in this study was only about half of that in awake,
18 cooperative infants.[2] Based on these disappointing studies, a recent Canadian
19 guideline discourages parents from attempting to deliver aerosols to their infants
20 during sleep.[3]
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36 The SM is a new face mask concept that integrates the infant's *own* pacifier into
37 the treatment process. The mask has evidence-based facial contours and an
38 extremely small dead space (18.2 ml) resulting from 3D computerized face
39 analysis technology developed with the assistance of the Computer Science
40 department at Technion University [4]. When infants suck on the mask-
41 integrated pacifier, the rim of the mask becomes gently sealed to their face,
42 mainly by suction on the pacifier and with minimal, if any, additional applied
43 force.
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54 We postulate that the very gentle touch of the contoured mask rim is thus not
55 considered as intrusive and frightening as currently available masks that require
56
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3 application of considerable force in order to achieve a good seal [14] and also fail
4
5 to provide the calming effect of the infant's familiar pacifier. We have previously
6
7 shown adequate lung deposition when nebulized drug was administered to awake
8
9 infants through the SM [15]. Nebulization may require up to 15 min or more
10
11 which may, with current masks, be too long for the infant to tolerate. Treatment
12
13 by VHC+MDI is much faster and less expensive per dose than nebulisation and
14
15 the overall duration of therapy (taking into account preparation and cleaning) is
16
17 considerably shorter (<5 min vs. >20 min).
18
19

20
21 It has been recently shown that no more than 2-3 breaths are necessary following
22
23 each puff to empty the VHC in young children [6] and thus actual aerosol
24
25 administration time, after application of the SM, can be as short as 10-15 seconds
26
27 per puff. The current study is the first to employ the SM in combination with a
28
29 VHC.
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32
33 Respiratory symptoms such as cough and breathlessness in infancy are common
34
35 during sleep.[16] The present study supports, not only the use of chronic anti-
36
37 inflammatory treatments (e.g. inhaled cortico-steroids) during sleep, but also
38
39 suggests that the use of acute treatments such as inhaled bronchodilators at the
40
41 time of an episode of nocturnal breathlessness and coughing may be rapidly
42
43 effective, possibly without awaking the child. Parents can be assured that using
44
45 this technique the infants will most likely accept and receive the necessary
46
47 treatment. Thus, the use of the SM is more likely than in the past to allow aerosol
48
49 therapy to be administered to infants during sleep without awaking them.
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54 Furthermore, given the high success rate with the SM approach, paediatricians
55
56 may now more confidently prescribe VHC+SM to achieve more rapid and
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1
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3 acceptable aerosol therapeutics, instead of providing more expensive
4
5 compressor+nebulizer systems and solution vials that involve about 20 minutes
6
7 of administration time and the need to clean the nebulizer after the treatment is
8
9 complete. Use of nebulizers requires that a mask be applied to the face for a
10
11 much longer period of time which is more likely to arouse the infant, further
12
13 adding to the its distress, or the need to resort to the 'blow-by' technique that
14
15 provides a relatively small and unpredictable dose of aerosol medication to the
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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.

1
2
3 **Funding source:** None

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

7
8 **Conflict of Interest:** Israel Amirav and Michael Newhouse have patents rights for devices for
9 delivering aerosols to infants including those in the current study. The other authors have no
10 conflicts of interest relevant to this article to disclose.

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13 **Clinical Trial registry:** NCT01120938

14
15 **Data Sharing:** There is no additional data avai

16
17
18 **Contributors' Statement**

19
20 Israel Amirav: Dr. Amirav conceptualized and designed the study, coordinated
21 and supervised data collection, drafted the initial manuscript, reviewed and
22 approved the final manuscript as submitted.

23
24 Michael T. Newhouse: Dr. Newhouse was involved in the study design, reviewed
25 and approved the final manuscript as submitted.

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

29
30 Asaf Halamish: Mr. Halamish was involved in the study design, designed the
31 data collection instruments, and coordinated and supervised data collection. He
32 reviewed and approved the final manuscript as submitted.

33
34 Hamza Omar: Mr. Omar carried out the nuclear medicine studies and initial
35 analyses, reviewed and approved the final manuscript as submitted.

36
37 Miguel Gorenberg: Dr. Gorenberg was involved in the study design, designed the
38 nuclear data collection, reviewed and approved the final manuscript as submitted.

39
40
41 **List of abbreviations**

42
43 MDI- metered dose inhaler

44
45 VHC- valved aerosol holding chamber

46
47 DTPA-Diethylene Triamine Pentacetic Acid

48
49 SM- SootherMask

50
51 IC- InspiraChamber

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Table 1

Individual Deposition values (% of emitted dose)

<u>Pt. #</u>	<u>Age (m)</u>	<u>Gender</u>	<u>Rt. lung</u>	<u>Both</u>	<u>Stomach</u>	<u>Upper</u>
				<u>Lungs</u>		<u>airway</u>
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

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4 Figures and Video Legend
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6 Figure 1:
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8 Photograph illustrating the method of aerosol administration to a sleeping infant
9 showing the Respimat inhaler, InspiraChamber and SootherMask™
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14 Figure 2:
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16 A typical scintigram, the green dashed circle denotes the stomach, the blue dots
17 denote upper airways, and solid yellow- right lung.
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21 Video:
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23 Video illustrating the method of aerosol administration to a sleeping infant
24 showing the Respimat inhaler, InspiraChamber and SootherMask™
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Aerosol delivery to infants *without tears*- Back to Sleep!

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Asaf Halamish², Hamza Omar³, Miguel Gorenberg³MD

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Short title: Aerosol delivery during sleep

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.

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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 Pentacetic 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 (\pm SD) averaged $1.6\pm 0.5\%$ 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 scintigraphy, 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 negligible 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

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6 VHC with MDI ~~attached~~ or nebulizer rarely upsets the infant. Pilot observations
7
8 suggested a high degree of acceptance of the SM in sleeping infants who appear
9
10 to regard it as being no different from their pacifier alone. ~~Caregivers are advised~~
11
12 ~~to acclimatize the infant to the SM by routinely providing the pacifier in the SM~~
13
14 ~~instead of using the pacifier alone.~~

15
16 The present study describes the feasibility of administering inhaled medications
17
18 during sleep using the SM. Infants, shortly after falling asleep, were given 99m
19
20 Tc in normal saline as placebo aerosolized medication using the SM attached to a
21
22 VHC and both right lung and total lung deposition were evaluated
23
24 scintigraphically. Both acceptability of the treatment and fractional lung
25
26 deposition served as the primary outcomes.

27 28 29 **Methods**

30
31 This was part of larger study that explored the relationship between use of
32
33 pacifiers and reduction in sudden infant death syndrome mortality
34
35 (NCT01120938). The infants received the Respimat- generated radiolabeled
36
37 aerosol through a SootherMask attached to a valved holding chamber
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39 (InspiraChamber®[IC]) (InspiRx Inc, NJ USA) and their lung aerosol deposition
40
41 was measured scintigraphically. ~~d~~

42
43 Inclusion criteria: Wheezy ~~I~~infants (Age 0-12 months) ~~on who were~~
44
45 intermittent ~~prescribed intermittent~~ or regular inhaled therapy at home by a
46
47 paediatric pulmonologist because of recurrent (>3x within the past 2 months)
48
49 episodes of wheezing that responded to bronchodilator treatments, and who were
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51 regular users of pacifiers (at least two hours/day of pacifier use per parents’
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6 report). Patients had to be asymptomatic for at least 2 weeks prior to the study.

7
8 Demographic details are shown in Table 1.

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

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26 99mTc labelled aerosol generated by an MDIthe Respimat SMI (Respimat@,
27 Boehringer Ingelheim, Ingelheim, Germany) was administered to the infants via
28 the IC+SM. The Respimat is powered by compressed air produced by means of a
29 spring-driven piston within a small cylinder and generates a slowly moving
30 aerosol bolus into the IC. The medication solution reservoir is a multidose plastic
31 cartridge. We found the Respimat SMI preferable to pressurized metered dose
32 inhalers (pMDI) system ideal for this study because it is possible to readily
33 radio-label the medication solution in the cartridge. As both pMDI and SMI,
34 would, in infants, be used with a VHC, the Respimat served as an ideal clinical
35 surrogate. For each trial, the SMI cartridge was filled with 3.0 mL of 99m Tc-
36 labelled normal saline. Addition of 99m Tc has no physical effect on aerosol
37 characteristics.[45]
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50 After priming the Respimat by discharging the inhaler 5 times to a hooded
51 exhaust system the emitted dose, in terms of radioactive counts, was measured by
52 placing bacterial filters over the outlet mouthpiece of the inhaler-SMI and firing 5
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6 puffs directly into the filter. The filters were immediately placed in a well counter
7
8 (Capintec Ramsey New Jersey, USA) and were ~~tested-evaluated~~ each morning
9
10 (~~X4x4~~) for reproducibility.

11
12 Infants arrived at the Nuclear Medicine department in the morning and were fed.

13
14 The ~~care-care~~-giver inserted the infant's' pacifier into the SM, ~~the SM which~~ was
15
16 then offered and accepted. ~~and they~~ They were put down to sleep sucking on the
17
18 pacifier nipple in the SM. Treatment commenced within 10 minutes after the
19
20 infant fell asleep. The average time from arrival to sleep in this strange
21
22 environment ranged between half ~~to-and~~ one and a half hours. The Respimat was
23
24 ~~attached-inserted in~~ to the back of the IC, and the 'mouthpiece' of the IC was
25
26 gently 'docked' ~~into~~ the orifice of the SM ~~applied snuglysealed~~ to the infant's
27
28 face by ~~its~~ suction on the pacifier nipple. Two successive 'puffs' from the
29
30 Respimat, ~~each followed by one minute of tidal breathing,~~ were then fired into
31
32 the IC and the mask-VHC-inhaler combination was kept on the infant's face, by
33
34 the care giver, for one minute (~~see Figure 1 and Video1~~). This ensured complete
35
36 evacuation of the aerosol from the VHC.[56] The SM+VHC were then removed.

37
38
39 ~~The infant was placed supine under a double (anterior and posterior) plate~~
40
41 ~~scanner (Symbia, Siemens GMBH, Munich, Germany) which enabled image~~
42
43 ~~acquisition without moving the infant or the cameras.~~ Scintigraphic scans of 60
44
45 seconds duration were obtained ~~immediately after each treatment~~ and gamma
46
47 camera counts (corrected for decay and tissue attenuation) of both the anterior
48
49 and the posterior chest were measured as previously reported [67]. ~~Similarly~~
50
51 ~~counts were measured for the VHC and mask to account for all the emitted dose.~~
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53 ~~The tissue attenuation factor was determined based on our own experience with~~
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55 ~~similar age infants (8). In brief, a hollow acrylic disc, filled with a solution of a~~

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6 known amount of 99mTc (37–74 MBq) served as the flood source. The square
7 root of the ratio of transmission scan counts obtained without the infant (No) to
8 the geometric mean of the counts with the infant (Nt) provided the attenuation
9 correction factor ($\sqrt{No/Nt}$).

10
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13
14 ~~and~~ The following regions of interest (ROIs) were evaluated: 1. Upper airway,
15 2. Stomach and 3. Lungs. Aerosol deposition in each of these ~~areas~~ regions
16 ~~defined above~~ was expressed as ~~a~~ the percentage of the total ~~amount of~~
17 radioactivity previously emitted (2 puffs) from the Respimat.

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22 ~~Patients received the treatment~~ Treatments were administered in a special room
23 within the nuclear medicine department, used only for this purpose. ~~No person~~
24 ~~other than~~ Only the patient's parent and physician ~~was~~ were allowed in the room.
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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, ~~thus which would interfering~~ interfere with lung ~~gamma~~
~~camera scintigraphy counting~~, 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 ~~;~~ [79]. The dose of 99m Tc to
be given to each patient determined before the inhalation procedure was found to
be $15 \mu\text{Ci}/\text{kg}$ ~~;~~ [810]. 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

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6 weeks or a 12 hour flight and is much lower than the dose used in diagnostic
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8 imaging procedures. ^{99m}Tc is a pure gamma emitter and has a 6 hour physical
9
10 half-life.^[79]

11
12 The deposition method suggested here has been in use clinically world-wide for
13
14 several decades and has been used in a number of previous paediatric studies
15
16 ~~[-67,4011]~~. It has regularly received ~~ethical-ethics committee~~ approval in the past
17
18 and ~~ethics~~ approval was obtained for this study from the local hospital research
19
20 committee (#0007-09-ZIV) and the Ministry of Health in Israel (#920090101).
21
22 Parents ~~signed-anprovided written~~ informed consent.²³

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24 25 Results

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27
28 Thirteen infants were enrolled. Ten infants completed the study. Reasons for
29
30 non-completion were: One infant did not fall asleep during the observation
31
32 period; One infant awoke after completing aerosol administration and due to
33
34 excessive movement, image acquisition could not be undertaken, although
35
36 aerosol administration had apparently been achieved; The third infant was
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38 subsequently found to be sick with a respiratory illness. She showed abnormally
39
40 high deposition in only one lung and was therefore excluded. All the infants
41
42 accepted the treatment without mask rejection and no leaks were observed
43
44 reflecting a good mask to face seal. All infants were asleep flat and supine during
45
46 their scintigraphic image acquisition.
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49 A typical scintigram is shown in Figure ~~12~~. ~~The individual dLung~~ deposition
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51 results ~~of-for~~ the 10 patients are shown in Table 1.
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6 Right Lung deposition in all 10 infants ranged between 0.83 ~~to and~~ 2.37 % of the
7 total delivered dose with a mean ~~value~~ of 1.61 ± 0.56 %. The mean deposition in
8 both lungs (which includes oesophageal and carinal deposition) was 4.17 %. The
9 amount of drug deposited in the upper airway averaged 16.7% and in the
10 stomach 1.4%. There was no correlation between deposition and age of the
11 infants.
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21 Discussion

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24 The present study demonstrates that aerosol administration ~~in to~~ infants ~~during~~
25 ~~while asleep sleep~~ is a successful way to achieve potentially 'therapeutic' lung
26 deposition when treatment is accomplished by means of a VHC attached to a
27 calming and relatively non-intrusive mask such as the SM. All of the infants
28 readily accepted the treatment with little difficulty and did not awaken, cry or
29 demonstrate fear of the mask or the subsequent aerosol therapy.
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36 Previous studies have stressed the difficulty of delivering inhaled medications to
37 infants. ~~There are, potentially, both anatomic and physiological reasons for this.~~
38 ~~The epiglottis in infants is situated high in the upper respiratory tract (URT) very~~
39 ~~close to the base of the infant's tongue,[11] The infant pharynx and supraglottic~~
40 ~~tissue areas characteristically are less rigid compared to adults and thus more~~
41 ~~susceptible to collapse and obstruction of the URT, particularly during~~
42 ~~inspiration. Additionally, the airways of infants are narrower and are prone to~~
43 ~~collapse, while tidal volume and flow velocity are relatively low. Currently~~
44 ~~available conventional face masks are essentially miniaturized adult masks, with~~
45 ~~a relatively large dead space, are poorly contoured, if at all, and require a~~
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6 considerable external force of more than 1 kg,[12] to apply them snugly to the
7 infant's face, thus often upsetting the child.[13] The behavioural aspect of
8 aerosol therapy in infants is most important for achieving adequate delivery of
9 aerosols to their lungs and they frequently refuse the application of a face mask
10 by attempting to push it away as well as vigorously squirming and crying. Crying
11 has been shown to greatly reduce lung deposition of inhaled medication to a
12 negligible fraction of what is considered a therapeutic dose.[6,10,14,15]

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18 It was previously and it has been suggested, by several investigators, that sleep
19 may provide a non-threatening opportunity for aerosol administration to
20 infants~~them~~. Furthermore, compared to the awake state, sleep is associated with
21 slower and more regular breathing, and a lower inspiratory flow velocity,~~[16-~~
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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 ± 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.

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6 They showed that treatment during 'sleep' greatly improved VHC aerosol
7 delivery and almost doubled the lung dose compared to the 'awake' state; $11.3 \pm$
8 3.9 compared to $6.5 \pm 3.2 \mu\text{g}$ of a $200 \mu\text{g}$ total delivered dose (5.5% vs 3.2%).
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12 These promising 'in vitro' results were somewhat contradicted during attempts to
13 translate them to real life conditions. Noble et al [1913] showed that although
14 mask VHC aerosol administration during sleep was successful in most of the
15 infants and toddlers that he studied, a subgroup of 17% of the patients awakened
16 during the procedure. In a more recent study that assessed the effects of sleep on
17 aerosol delivery by VHC, it was found that 70% of infants awoke during
18 application of the mask and 75% of those became distressed and uncooperative.
19 Not surprisingly, the delivered dose in this study was only about half of that in
20 awake, cooperative infants.[2] Based on these disappointing studies, a recent
21 Canadian guideline discourages parents from attempting to deliver aerosols to
22 their infants during sleep.[3]
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35 The SM is a new face mask concept that integrates the infant's own pacifier into
36 the treatment process. The mask has evidence-based facial contours and an
37 extremely small dead space (18.2 ml) resulting from 3D computerized face
38 analysis technology developed with the assistance of the Computer Science
39 department at Technion University.[204]. When infants infants suck on their
40 mask-integrated pacifier, and the rim of the mask is becomes gently sealed to
41 their face, mainly by suction on the pacifier and with minimal, if any, additional
42 applied force.
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52 We postulate that the very gentle touch of the contoured mask rim is thus not
53 considered as intrusive and frightening as currently available masks that require
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6 application of considerable force ~~in~~ order to achieve a good seal [\[14\]](#) and also
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8 fail to provide the calming effect of the infant's familiar pacifier. We have
9
10 previously shown adequate lung deposition when nebulized drug was
11 administered to awake infants through the SM ~~in~~ [\[2115\]](#). Nebulization may require
12 up to 15 min or more ~~of treatment~~ which may, with current masks, be too long
13 for the infant to tolerate. Treatment by VHC+MDI is much ~~quicker~~ faster and
14 less expensive per dose than nebulisation and the overall duration of ~~the~~ therapy
15 (taking into account preparation and cleaning) is considerably shorter (<5 min vs.
16 >20 min).
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25 It has been recently shown that no more than 2-3 breaths are necessary following
26 each puff to empty the VHC in young children [\[56\]](#) and thus actual aerosol
27 administration time, after application of the SM, can be as short as 10-15 seconds
28 per puff. The current study is the first to employ the SM in combination with a
29 MDI+VHC.
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35 ~~Lung aerosol deposition in infants treated with MDI+VHC has been studied~~
36 ~~infrequently. Tal et al [10] studied 15 infants and young children with airway~~
37 ~~obstruction who were given inhaled medications via Aerochamber and mask.~~
38 ~~Seven of these were infants under the age of 12 months and their average lung~~
39 ~~deposition was 0.77%, approximately half of the present study (p<0.01).~~
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46 Respiratory symptoms such as cough and breathlessness in infancy are common
47 during sleep. [\[2216\]](#) The present study supports, not only the use of chronic anti-
48 inflammatory treatments (e.g. inhaled cortico-steroids) during sleep, but also
49 suggests that the use of acute treatments such as inhaled bronchodilators at the
50 time of an episode of nocturnal breathlessness and coughing may be rapidly
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6 effective, possibly without awaking the child. Parents can be assured that using
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8 this technique the infants will most likely accept and receive the necessary
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10 treatment. Thus, the use of the SM is more likely than in the past to allow aerosol
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12 therapy to be administered to infants during sleep without awaking them.
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14 Furthermore, given the ~~very~~ high success rate with the SM approach,
15
16 paediatricians may now more confidently prescribe MDI+VHC+SM to achieve
17
18 more rapid and acceptable aerosol therapeutics, instead of providing more
19
20 expensive compressor+nebulizer systems and solution vials that involve about 20
21
22 minutes of administration time ~~from start to finish~~ and the need to clean the
23
24 nebulizer after ~~the~~ treatment is ~~finished~~complete. Use of nebulizers requires that
25
26 a mask be applied to the face for a much longer period of time which is more
27
28 likely to arouse the infant, further adding to the its distress, or the need to resort
29
30 to the 'blow-by' technique that provides a relatively small and unpredictable
31
32 dose of aerosol medication to the child.
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35 The lack of control subjects using currently available masks is acknowledged as a
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37 limitation of the present study and a control group was originally incorporated.
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39 However, we felt that it would be unethical and unjustified to expose a control
40
41 group of infants, particularly since several historical scintigraphic studies are
42
43 available.
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46 ~~A limitation of the present study stems from the fact that treatment was given~~
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48 ~~within 10 minutes of the commencement of sleep. Although we do not have~~
49
50 ~~assessment of sleep stages, this may be a stage during which the child is less~~
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52 ~~likely to awaken if stimulated by such things as the application of a mask. We see~~
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54 ~~no reason, however, to suspect that the likelihood of awakening the child will be~~
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6 ~~greater at even a later stage of deep sleep, although this requires further 'real life'~~
7 ~~evaluation with sleep stage assessment.~~ Another limitation may be our enrolment
8 only of infants who regularly use pacifiers and a future study in non-pacifier
9 users is certainly warranted.
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14 This pilot study with the SM is, we think, clinically important as it demonstrates
15 a unique, innovative and apparently effective approach to providing infants and
16 toddlers with aerosol therapy during sleep. It has the potential for encouraging
17 pediatricians to use this technique in future clinical studies. However, the virtually
18 complete success rate in these 'suckling' infants is exceptional and supports the
19 use of sleep as a unique opportunity to deliver aerosol to infants, particularly to
20 pacifier users by means of the SM.
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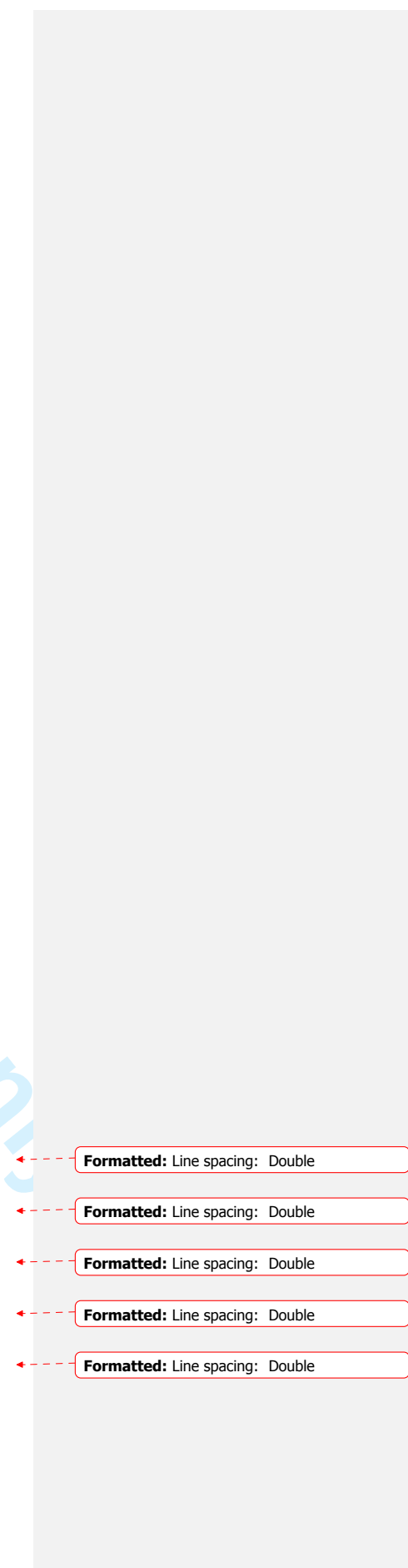
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Table 1

Individual Deposition values (% of emitted dose)

<u>Pt.#</u>	<u>Rt. lung</u>	<u>Both Lungs</u>	<u>Stomach</u>	<u>Upper airway</u>
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

<u>Pt. #</u>	<u>Age (m)</u>	<u>Gender</u>	<u>Rt. lung</u>	<u>Both Lungs</u>	<u>Stomach</u>	<u>Upper airway</u>
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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<u>5</u>	<u>5.4</u>	<u>F</u>	<u>1.47</u>	<u>4.51</u>	<u>1.26</u>	<u>9.76</u>	Formatted: Line spacing: Double
<u>6</u>	<u>11.7</u>	<u>M</u>	<u>2.37</u>	<u>6.33</u>	<u>0.8</u>	<u>32.81</u>	Formatted: Line spacing: Double
<u>7</u>	<u>5.0</u>	<u>F</u>	<u>2.29</u>	<u>4.88</u>	<u>1.58</u>	<u>16.5</u>	Formatted: Line spacing: Double
<u>8</u>	<u>10.8</u>	<u>F</u>	<u>1.4</u>	<u>4.02</u>	<u>1.13</u>	<u>8.37</u>	Formatted: Line spacing: Double
<u>9</u>	<u>5.4</u>	<u>M</u>	<u>1.19</u>	<u>2.41</u>	<u>2.52</u>	<u>15.01</u>	Formatted: Line spacing: Double
<u>10</u>	<u>5.4</u>	<u>M</u>	<u>2.23</u>	<u>4.75</u>	<u>0.72</u>	<u>18.95</u>	Formatted: Line spacing: Double
<u>Mean</u>	<u>9.28</u>		<u>1.61</u>	<u>4.17</u>	<u>1.42</u>	<u>16.75</u>	
<u>SD</u>	<u>0.68</u>		<u>0.56</u>	<u>1.27</u>	<u>0.97</u>	<u>7.81</u>	

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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 dots denote upper airways, and solid yellow- right lung.

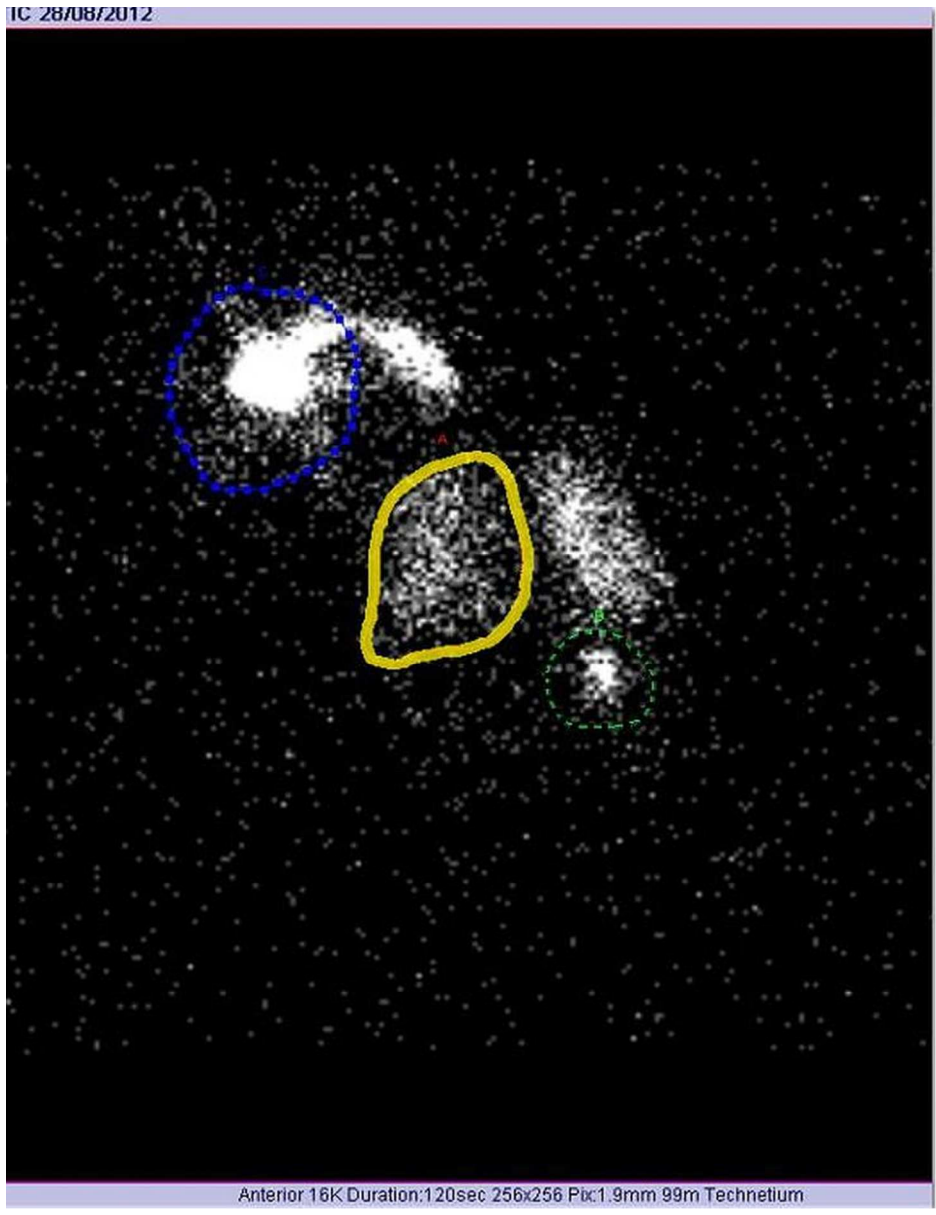
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Feasibility of Aerosol drug delivery to sleeping infants

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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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Total word count: 2479

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 technetium^{99m}DTPA-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 (\pm SD) averaged $1.6\pm 0.5\%$ 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

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3 conditions, in contrast to previous studies that resulted in frequent mask rejection
4 using currently available devices.
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7 Word count: 253
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14 **Strengths**

- 15 • Delivery of inhaled medications to infants is often associated with crying
16 and mask rejection. Treatment during sleep may be an attractive
17 alternative yet previous studies failed to confirm this approach as most of
18 the infants awoke during treatment.
19
- 20 • The present study describes a novel approach to overcoming these
21 problems during sleep.
22
- 23 • Treatment during sleep by means of a unique mask which includes the
24 infants' own pacifier, was accepted by all infants with no awakening and
25 improved lung deposition.
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31 **Limitations**

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

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3 sleeping infants who appear to regard it as being no different from their pacifier
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5 alone.
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8 The present study describes the feasibility of administering inhaled medications
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10 during sleep using the SM. Infants, shortly after falling asleep, were given 99m
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12 Tc in normal saline as placebo aerosolized medication using the SM attached to a
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14 VHC and both right lung and total lung deposition were evaluated
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16 scintigraphically. Both acceptability of the treatment and fractional lung
17
18 deposition served as the primary outcomes.
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21 22 **Methods**

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24 This was part of larger study that explored the relationship between use of
25
26 pacifiers and reduction in sudden infant death syndrome mortality
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28 (NCT01120938). The infants received the Respimat- generated radiolabeled
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30 aerosol through a SootherMask attached to a valved holding chamber
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32 (InspiraChamber®[IC]) (InspiRx Inc, NJ USA) and their lung aerosol deposition
33
34 was measured scintigraphically.
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38 Inclusion criteria: Infants (Age 0-12 months) who were prescribed intermittent or
39
40 regular inhaled therapy by a paediatric pulmonologist because of recurrent (>3x
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42 within the past 2 months) episodes of wheezing that responded to bronchodilator
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44 treatments, and who were regular users of pacifiers (at least two hours/day of
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46 pacifier use per parents' report). Patients had to be asymptomatic for at least 2
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48 weeks prior to the study. Demographic details are shown in Table 1.
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52 Exclusion criteria: Patients whose parents reported a history or symptoms of
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54 airway abnormalities (eg, previous airway surgery, tracheotomy, obstructive
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56 sleep apnoea, snoring, anatomical anomalies of mouth palate nose, pharynx and
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3 trachea) as well as those with chronic cardiopulmonary disease such as
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5 bronchopulmonary dysplasia, congenital heart disease, immune deficiency, or
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7 cystic fibrosis.
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10 Procedures:

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13 99mTc labelled aerosol generated by the Respimat SMI was administered to the
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15 infants via the IC+SM. The Respimat is powered by compressed air produced by
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17 means of a spring-driven piston within a small cylinder and generates a slowly
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19 moving aerosol bolus into the IC. The medication solution reservoir is a
20
21 multidose plastic cartridge. We found the Respimat SMI preferable to
22
23 pressurized metered dose inhalers (pMDI) because it is possible to readily radio-
24
25 label the medication solution in the cartridge. As both pMDI and SMI, would, in
26
27 infants, be used with a VHC, the Respimat served as an ideal clinical surrogate.
28
29 For each trial, the SMI cartridge was filled with 3.0 mL of 99m Tc-labelled
30
31 normal saline. Addition of 99m Tc has no physical effect on aerosol
32
33 characteristics.[5]
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38 After priming the Respimat by discharging the inhaler 5 times to a hooded
39
40 exhaust system the emitted dose in terms of radioactive counts was measured by
41
42 placing bacterial filters over the mouthpiece of the SMI and firing 5 puffs
43
44 directly into the filter. The filters were immediately placed in a well counter
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46 (Capintec, Ramsey New Jersey, USA) and were evaluated each morning (x4) for
47
48 reproducibility.
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52 Infants arrived at the Nuclear Medicine department in the morning and were fed.
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54 The care-giver inserted the infants' pacifier into the SM which was then offered
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56 and accepted. They were put down to sleep sucking on the pacifier nipple in the
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3 SM. Treatment commenced within 10 minutes after the infant fell asleep. The
4
5 average time from arrival to sleep in this strange environment ranged between
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7 half and one and a half hour. The Respimat was inserted into the back of the IC,
8
9 and the 'mouthpiece' of the IC was gently 'docked' into the orifice of the SM
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11 sealed to the infant's face by its suction on the pacifier nipple. Two successive
12
13 'puffs' from the Respimat, each followed by one minute of tidal breathing, were
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15 then fired into the IC and the mask-VHC-inhaler combination was kept on the
16
17 infant's face, by the care giver, for one minute (see Figure 1 and Video1). This
18
19 ensured complete evacuation of the aerosol from the VHC.[6] The SM+VHC
20
21 were then removed.
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26 The infant was placed supine under a double (anterior and posterior) plate
27
28 scanner (Symbia, Siemens GMBH, Munich, Germany) which enabled image
29
30 acquisition without moving the infant or the cameras. Scintigraphic scans of 60
31
32 seconds duration were obtained and gamma camera counts (corrected for decay
33
34 and tissue attenuation) of both the anterior and the posterior chest were measured
35
36 as previously reported [7]. Similarly counts were measured for the VHC and
37
38 mask to account for all the emitted dose. The tissue attenuation factor was
39
40 determined based on our own experience with similar age infants (8). In brief, a
41
42 hollow acrylic disc, filled with a solution of a known amount of ^{99m}Tc (37–74
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44 MBq) served as the flood source. The square root of the ratio of transmission
45
46 scan counts obtained without the infant (N_o) to the geometric mean of the counts
47
48 with the infant (N_t) provided the attenuation correction factor ($\sqrt{N_o/N_t}$).

49
50 The following regions of interest (ROIs) were evaluated: 1. Upper airway, 2.
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52 Stomach and 3. Lungs. Aerosol deposition in each of these regions was
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3 expressed as the percent of the total radioactivity previously emitted (2 puffs)
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5 from the Respimat.
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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 $15\mu\text{Ci}/\text{kg}$ [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.

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 ± 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 ± 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.

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3 They showed that treatment during 'sleep' greatly improved VHC aerosol
4 delivery and almost doubled the lung dose compared to the 'awake' state; $11.3 \pm$
5 3.9 compared to $6.5 \pm 3.2 \mu\text{g}$ of a $200 \mu\text{g}$ total delivered dose (5.5% vs 3.2%).
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10 These promising 'in vitro' results were somewhat contradicted during attempts to
11 translate them to real life conditions. Noble et al [13] showed that although mask
12 VHC aerosol administration during sleep was successful in most of the infants
13 and toddlers that he studied, a subgroup of 17% of the patients awakened during
14 the procedure. In a more recent study that assessed the effects of sleep on aerosol
15 delivery by VHC, it was found that 70% of infants awoke during application of
16 the mask and 75% of those became distressed and uncooperative. Not
17 surprisingly, the delivered dose in this study was only about half of that in awake,
18 cooperative infants.[2] Based on these disappointing studies, a recent Canadian
19 guideline discourages parents from attempting to deliver aerosols to their infants
20 during sleep.[3]
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36 The SM is a new face mask concept that integrates the infant's *own* pacifier into
37 the treatment process. The mask has evidence-based facial contours and an
38 extremely small dead space (18.2 ml) resulting from 3D computerized face
39 analysis technology developed with the assistance of the Computer Science
40 department at Technion University [4]. When infants suck on the mask-
41 integrated pacifier, the rim of the mask becomes gently sealed to their face,
42 mainly by suction on the pacifier and with minimal, if any, additional applied
43 force.
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54 We postulate that the very gentle touch of the contoured mask rim is thus not
55 considered as intrusive and frightening as currently available masks that require
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3 application of considerable force in order to achieve a good seal [14] and also fail
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5 to provide the calming effect of the infant's familiar pacifier. We have previously
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7 shown adequate lung deposition when nebulized drug was administered to awake
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9 infants through the SM [15]. Nebulization may require up to 15 min or more
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11 which may, with current masks, be too long for the infant to tolerate. Treatment
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13 by VHC+MDI is much faster and less expensive per dose than nebulisation and
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15 the overall duration of therapy (taking into account preparation and cleaning) is
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17 considerably shorter (<5 min vs. >20 min).
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21 It has been recently shown that no more than 2-3 breaths are necessary following
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23 each puff to empty the VHC in young children [6] and thus actual aerosol
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25 administration time, after application of the SM, can be as short as 10-15 seconds
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27 per puff. The current study is the first to employ the SM in combination with a
28
29 VHC. Lung deposition in the present study was comparable to previous reports in
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31 infants (7,8,11,12,15) and is likely to exert comparable clinical efficacy.
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35 Respiratory symptoms such as cough and breathlessness in infancy are common
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37 during sleep.[16] The present study supports, not only the use of chronic anti-
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39 inflammatory treatments (e.g. inhaled cortico-steroids) during sleep, but also
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41 suggests that the use of acute treatments such as inhaled bronchodilators at the
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43 time of an episode of nocturnal breathlessness and coughing may be rapidly
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45 effective, possibly without awakening the child. Parents can be assured that using
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47 this technique the infants will most likely accept and receive the necessary
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49 treatment. Thus, the use of the SM is more likely than in the past to allow aerosol
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51 therapy to be administered to infants during sleep without awakening them.
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3 Furthermore, given the high success rate with the SM approach, paediatricians
4 may now more confidently prescribe VHC+SM to achieve more rapid and
5 acceptable aerosol therapeutics, instead of providing more expensive
6 compressor+nebulizer systems and solution vials that involve about 20 minutes
7 of administration time and the need to clean the nebulizer after the treatment is
8 complete. Use of nebulizers requires that a mask be applied to the face for a
9 much longer period of time which is more likely to arouse the infant, further
10 adding to the its distress, or the need to resort to the 'blow-by' technique that
11 provides a relatively small and unpredictable dose of aerosol medication to the
12 child.
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26 The lack of control subjects using currently available *conventional* masks is
27 acknowledged as a limitation of the present study and a control group was
28 originally incorporated. However, we felt that it would be unethical and
29 unjustified to expose an additional control group of infants to scintigraphy,
30 particularly since several historical scintigraphic studies are available. Another
31 limitation may be our enrolment only of infants who regularly use pacifiers and a
32 future study in non-pacifier users is certainly warranted. Similarly, the possibility
33 that sleep may be disturbed when infants are sick need to be also considered in
34 the future.
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47 This pilot study with the SM is clinically important as it demonstrates a unique,
48 innovative and apparently effective approach to providing infants and toddlers with
49 aerosol therapy during sleep. It has the potential for encouraging pediatricians to use
50 this technique in future clinical studies including more patients.
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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.

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.

Data Sharing Statement: No additional data

List of abbreviations

MDI- metered dose inhaler

VHC- valved aerosol holding chamber

DTPA-Diethylene Triamine Pentacetic Acid

SM- SootherMask

IC- InspiraChamber

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Table 1

Individual Deposition values (% of emitted dose)

<u>Pt. #</u>	<u>Age (m)</u>	<u>Gender</u>	<u>Rt. lung</u>	<u>Both</u>	<u>Stomach</u>	<u>Upper</u>
				<u>Lungs</u>		<u>airway</u>
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

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4 Figures and Video Legend
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6 Figure 1:
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8 Photograph illustrating the method of aerosol administration to a sleeping infant
9 showing the Respimat inhaler, InspiraChamber and SootherMask™
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14 Figure 2:
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16 A typical scintigram, the green dashed circle denotes the stomach, the blue dots
17 denote upper airways, and solid yellow- right lung.
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21 Video:
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23 Video illustrating the method of aerosol administration to a sleeping infant
24 showing the Respimat inhaler, InspiraChamber and SootherMask™
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6 **Feasibility of Aerosol Drug Delivery to Sleeping Infants**
7 **Aerosol**
8 **delivery to infants *without tears* – Back to Sleep!**
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35 **Short title:** Aerosol delivery during sleep

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

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38
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42

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45 authors have no conflicts of interest relevant to this article to disclose.
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47 **Clinical Trial registry:** NCT01120938
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8 Contributors' Statement
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10 Israel Amirav: Dr. Amirav conceptualized and designed the study, coordinated
11 and supervised data collection, drafted the initial manuscript, reviewed and
12 approved the final manuscript as submitted.
13

14 Michael T. Newhouse: Dr. Newhouse was involved in the study design, reviewed
15 and approved the final manuscript as submitted.
16

17 Anthony S. Luder: Dr. Luder reviewed and approved the final manuscript as
18 submitted.
19

20 Asaf Halamish: Mr. Halamish was involved in the study design, designed the
21 data collection instruments, and coordinated and supervised data collection. He
22 reviewed and approved the final manuscript as submitted.
23

24 Hamza Omar: Mr. Omar carried out the nuclear medicine studies and initial
25 analyses, reviewed and approved the final manuscript as submitted.
26

27 Miguel Gorenberg: Dr. Gorenberg was involved in the study design, designed the
28 nuclear data collection, reviewed and approved the final manuscript as submitted.
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31 List of abbreviations
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33 MDI- metered dose inhaler
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35 VHC- valved aerosol holding chamber
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37 DTPA-Diethylene Triamine Pentacetic Acid
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39 SM- SootherMask
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41 IC- InspiraChamber
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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 (\pm SD) averaged $1.6\pm 0.5\%$ in the right lung.

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

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

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10 The present study describes the feasibility of administering inhaled medications
11 during sleep using the SM. Infants, shortly after falling asleep, were given 99m
12 Tc in normal saline as placebo aerosolized medication using the SM attached to a
13 VHC and both right lung and total lung deposition were evaluated
14
15 scintigraphically. Both acceptability of the treatment and fractional lung
16
17 deposition served as the primary outcomes.
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23 **Methods**

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25 This was part of larger study that explored the relationship between use of
26
27 pacifiers and reduction in sudden infant death syndrome mortality
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29 (NCT01120938). The infants received the Respimat- generated radiolabeled
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31 aerosol through a SootherMask attached to a valved holding chamber
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33 (InspiraChamber®[IC]) (InspiRx Inc, NJ USA) and their lung aerosol deposition
34
35 was measured scintigraphically.
36

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38 Inclusion criteria: Infants (Age 0-12 months) who were prescribed intermittent or
39
40 regular inhaled therapy by a paediatric pulmonologist because of recurrent (>3x
41
42 within the past 2 months) episodes of wheezing that responded to bronchodilator
43
44 treatments, and who were regular users of pacifiers (at least two hours/day of
45
46 pacifier use per parents' report). Patients had to be asymptomatic for at least 2
47
48 weeks prior to the study. Demographic details are shown in Table 1.
49

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

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12 Procedures:

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15 99mTc labelled aerosol generated by the Respimat SMI was administered to the
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17 infants via the IC+SM. The Respimat is powered by compressed air produced by
18
19 means of a spring-driven piston within a small cylinder and generates a slowly
20
21 moving aerosol bolus into the IC. The medication solution reservoir is a
22
23 multidose plastic cartridge. We found the Respimat SMI preferable to
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25 pressurized metered dose inhalers (pMDI) because it is possible to readily radio-
26
27 label the medication solution in the cartridge. As both pMDI and SMI, would, in
28
29 infants, be used with a VHC, the Respimat served as an ideal clinical surrogate.
30
31 For each trial, the SMI cartridge was filled with 3.0 mL of 99m Tc-labelled
32
33 normal saline. Addition of 99m Tc has no physical effect on aerosol
34
35 characteristics.[5]

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38 After priming the Respimat by discharging the inhaler 5 times to a hooded
39
40 exhaust system the emitted dose in terms of radioactive counts was measured by
41
42 placing bacterial filters over the mouthpiece of the SMI and firing 5 puffs
43
44 directly into the filter. The filters were immediately placed in a well counter
45
46 (Capintec, Ramsey New Jersey, USA) and were evaluated each morning (x4) for
47
48 reproducibility.

49
50 Infants arrived at the Nuclear Medicine department in the morning and were fed.
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52 The care-giver inserted the infants' pacifier into the SM which was then offered
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54 and accepted. They were put down to sleep sucking on the pacifier nipple in the
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6 SM. Treatment commenced within 10 minutes after the infant fell asleep. The
7
8 average time from arrival to sleep in this strange environment ranged between
9
10 half and one and a half hour. The Respimat was inserted into the back of the IC,
11
12 and the 'mouthpiece' of the IC was gently 'docked' into the orifice of the SM
13
14 sealed to the infant's face by its suction on the pacifier nipple. Two successive
15
16 'puffs' from the Respimat, each followed by one minute of tidal breathing, were
17
18 then fired into the IC and the mask-VHC-inhaler combination was kept on the
19
20 infant's face, by the care giver, for one minute (see Figure 1 and Video1). This
21
22 ensured complete evacuation of the aerosol from the VHC.[6] The SM+VHC
23
24 were then removed.

25
26 The infant was placed supine under a double (anterior and posterior) plate
27
28 scanner (Symbia, Siemens GMBH, Munich, Germany) which enabled image
29
30 acquisition without moving the infant or the cameras. Scintigraphic scans of 60
31
32 seconds duration were obtained and gamma camera counts (corrected for decay
33
34 and tissue attenuation) of both the anterior and the posterior chest were measured
35
36 as previously reported [7]. Similarly counts were measured for the VHC and
37
38 mask to account for all the emitted dose. The tissue attenuation factor was
39
40 determined based on our own experience with similar age infants (8). In brief, a
41
42 hollow acrylic disc, filled with a solution of a known amount of ^{99m}Tc (37–74
43
44 MBq) served as the flood source. The square root of the ratio of transmission
45
46 scan counts obtained without the infant (N_0) to the geometric mean of the counts
47
48 with the infant (N_t) provided the attenuation correction factor ($\sqrt{N_0/N_t}$).

49 The following regions of interest (ROIs) were evaluated: 1. Upper airway, 2.
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51 Stomach and 3. Lungs. Aerosol deposition in each of these regions was
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6 expressed as the percent of the total radioactivity previously emitted (2 puffs)
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8 from the Respimat.
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11 Treatments were administered in a special room within the nuclear medicine
12 department, used only for this purpose. Only the patient's parent and physician
13 were allowed in the room. Radioactivity protection monitoring was carried out
14 regularly and following each study, to ensure that no excess radioactivity was
15 present in the room following the treatments. To avoid contamination of the
16 infant's chest and the environment during treatment, which would interfere with
17 lung scintigraphy—, the infant's chest and the VHC were enclosed in a special
18 disposable large volume nylon wrap which was removed immediately prior to
19 imaging.
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29 The radiation dose of ^{99m}Tc aerosol used in this study was calculated according
30 to the Medical Internal Radiation Dose Committee [9]. The dose of ^{99m}Tc to be
31 given to each patient determined before the inhalation procedure was found to be
32 $15\mu\text{Ci}/\text{kg}$ [10]. As inhalation exposure is 0.05 RAD/mCi, or 0.00075 RAD/Kg, the
33 maximum exposure for a 20 kg child was 0.015 RAD. This is equivalent to the
34 radiation received during normal cosmic-ray exposure of 3 weeks or a 12 hour
35 flight and is much lower than the dose used in diagnostic imaging procedures.
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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](#)

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6 committee (#0007-09-ZIV) and the Ministry of Health in Israel (#920090101).

7
8 Parents provided written informed consent.

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11 **Results**

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13 Thirteen infants were enrolled. Ten infants completed the study. Reasons for
14 non-completion were: One infant did not fall asleep during the observation
15 period; One infant awoke after completing aerosol administration and due to
16 excessive movement, image acquisition could not be undertaken, although
17 aerosol administration had apparently been achieved; The third infant was
18 subsequently found to be sick with a respiratory illness. She showed abnormally
19 high deposition in only one lung and was therefore excluded. All the infants
20 accepted the treatment without mask rejection and no leaks were observed
21 reflecting a good mask to face seal. All infants were asleep flat and supine during
22 their scintigraphic image acquisition.
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34 A typical scintigram is shown in Figure 2. Lung deposition results for the 10
35 patients are shown in Table 1.

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38 Right Lung deposition in all 10 infants ranged between 0.83 and 2.37 % of the
39 total delivered dose with a mean of 1.61 ± 0.56 %. The mean deposition in both
40 lungs (which includes oesophageal and carinal deposition) was 4.17 %. The
41 amount of drug deposited in the upper airway averaged 16.7% and in the
42 stomach 1.4%. There was no correlation between deposition and age of the
43 infants.
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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 ± 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.

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6 They showed that treatment during 'sleep' greatly improved VHC aerosol
7 delivery and almost doubled the lung dose compared to the 'awake' state; $11.3 \pm$
8 3.9 compared to $6.5 \pm 3.2 \mu\text{g}$ of a $200 \mu\text{g}$ total delivered dose (5.5% vs 3.2%).
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12 These promising 'in vitro' results were somewhat contradicted during attempts to
13 translate them to real life conditions. Noble et al [13] showed that although mask
14 VHC aerosol administration during sleep was successful in most of the infants
15 and toddlers that he studied, a subgroup of 17% of the patients awakened during
16 the procedure. In a more recent study that assessed the effects of sleep on aerosol
17 delivery by VHC, it was found that 70% of infants awoke during application of
18 the mask and 75% of those became distressed and uncooperative. Not
19 surprisingly, the delivered dose in this study was only about half of that in awake,
20 cooperative infants.[2] Based on these disappointing studies, a recent Canadian
21 guideline discourages parents from attempting to deliver aerosols to their infants
22 during sleep.[3]
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35 The SM is a new face mask concept that integrates the infant's *own* pacifier into
36 the treatment process. The mask has evidence-based facial contours and an
37 extremely small dead space (18.2 ml) resulting from 3D computerized face
38 analysis technology developed with the assistance of the Computer Science
39 department at Technion University [4]. When infants suck on the mask-
40 integrated pacifier, the rim of the mask becomes gently sealed to their face,
41 mainly by suction on the pacifier and with minimal, if any, additional applied
42 force.
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51 We postulate that the very gentle touch of the contoured mask rim is thus not
52 considered as intrusive and frightening as currently available masks that require
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6 application of considerable force in order to achieve a good seal [14] and also fail
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8 to provide the calming effect of the infant's familiar pacifier. We have previously
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10 shown adequate lung deposition when nebulized drug was administered to awake
11
12 infants through the SM [15]. Nebulization may require up to 15 min or more
13
14 which may, with current masks, be too long for the infant to tolerate. Treatment
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16 by VHC+MDI is much faster and less expensive per dose than nebulisation and
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18 the overall duration of therapy (taking into account preparation and cleaning) is
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20 considerably shorter (<5 min vs. >20 min).
21

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23 It has been recently shown that no more than 2-3 breaths are necessary following
24
25 each puff to empty the VHC in young children [6] and thus actual aerosol
26
27 administration time, after application of the SM, can be as short as 10-15 seconds
28
29 per puff. The current study is the first to employ the SM in combination with a
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31 VHC. Lung deposition in the present study was comparable to previous reports in
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33 infants (7,8,11,12,15) and is likely to exert comparable clinical efficacy.
34

35
36 Respiratory symptoms such as cough and breathlessness in infancy are common
37
38 during sleep.[16] The present study supports, not only the use of chronic anti-
39
40 inflammatory treatments (e.g. inhaled cortico-steroids) during sleep, but also
41
42 suggests that the use of acute treatments such as inhaled bronchodilators at the
43
44 time of an episode of nocturnal breathlessness and coughing may be rapidly
45
46 effective, possibly without awaking the child. Parents can be assured that using
47
48 this technique the infants will most likely accept and receive the necessary
49
50 treatment. Thus, the use of the SM is more likely than in the past to allow aerosol
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52 therapy to be administered to infants during sleep without awaking them.
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6 Furthermore, given the high success rate with the SM approach, paediatricians
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8 may now more confidently prescribe VHC+SM to achieve more rapid and
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10 acceptable aerosol therapeutics, instead of providing more expensive
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12 compressor+nebulizer systems and solution vials that involve about 20 minutes
13
14 of administration time and the need to clean the nebulizer after the treatment is
15
16 complete. Use of nebulizers requires that a mask be applied to the face for a
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18 much longer period of time which is more likely to arouse the infant, further
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20 adding to the its distress, or the need to resort to the 'blow-by' technique that
21
22 provides a relatively small and unpredictable dose of aerosol medication to the
23
24 child.

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26 The lack of control subjects using currently available *conventional* masks is
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28 acknowledged as a limitation of the present study and a control group was
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30 originally incorporated. However, we felt that it would be unethical and
31
32 unjustified to expose an additional-control group of infants to scintigraphy,
33
34 particularly since several historical scintigraphic studies are available. Another
35
36 limitation may be our enrolment only of infants who regularly use pacifiers and a
37
38 future study in non-pacifier users is certainly warranted. Similarly, the possibility
39
40 that sleep may be disturbed when infants are sick need to be also considered in
41
42 the future.

43
44 This pilot study with the SM is ~~we think~~ clinically important as it demonstrates
45
46 a unique, innovative and apparently effective approach to providing infants and
47
48 toddlers with aerosol therapy during sleep. It has the potential for encouraging
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50 pediatricians to use this technique in future clinical studies including more
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52 patients.

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Table 1

Individual Deposition values (% of emitted dose)

<u>Pt. #</u>	<u>Age (m)</u>	<u>Gender</u>	<u>Rt. lung</u>	<u>Both Lungs</u>	<u>Stomach</u>	<u>Upper airway</u>
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

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7 Figures and Video Legend
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9 Figure 1:

10 Photograph illustrating the method of aerosol administration to a sleeping infant
11 showing the Respimat inhaler, InspiraChamber and SootherMask™
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16 Figure 2:

17 A typical scintigram, the green dashed circle denotes the stomach, the blue dots
18 denote upper airways, and solid yellow- right lung.
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22 Video:

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

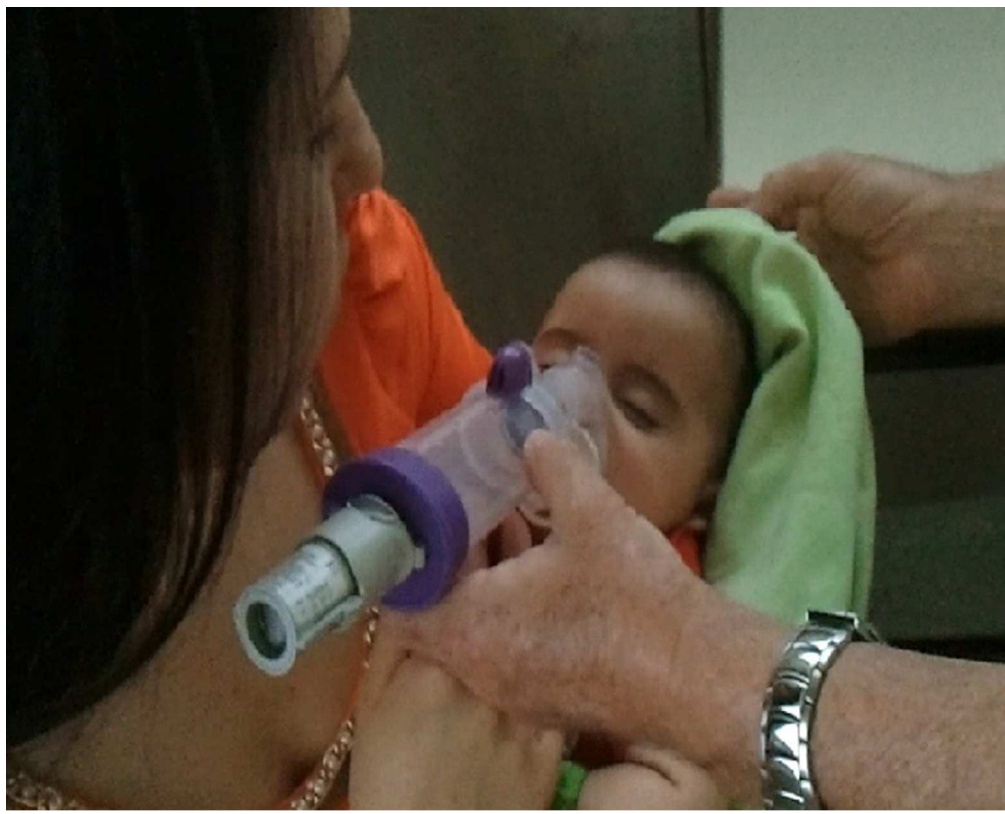
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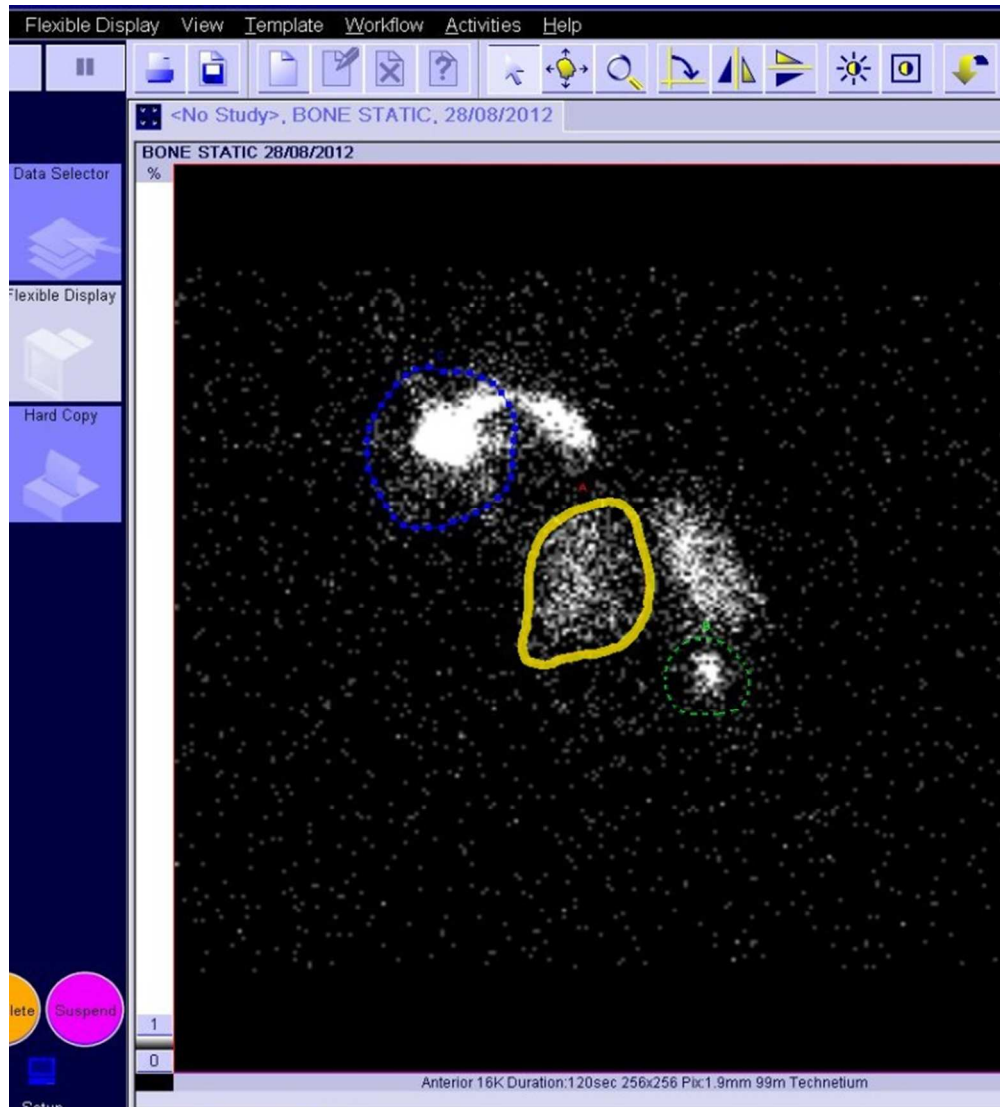
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178x143mm (96 x 96 DPI)

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207x228mm (96 x 96 DPI)

