

# Drug Delivery Using the Endotracheal Tube: How Much Remains Inside the Tube?

T Moeller-Bertram, M Greenberg, G Schulteis, J Hayes, N Finer

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## Abstract

**Aim:** It is common practice in neonatal resuscitation to use an in-situ endotracheal tube (ETT) as a conduit for drug delivery when IV access is not available. However, depending on the volume used, fluid remaining in the ETT following drug delivery may significantly decrease the dose reaching the tracheobronchial tree mucosa and hence the circulation. We quantified the fluid volume that remains inside an ETT following its administration via a syringe in vitro.

**Materials and Methods:** In an attempt to simulate conditions in the delivery room, endotracheal tubes of internal diameter 2.5, 3.0 and 3.5 mm and five different fluid volumes (0.05 mL, 0.10 mL, 0.25 mL, 0.50 mL, 1.00 mL) were tested in an airway model.

**Results:** ANOVA confirmed that the percentage of fluid remaining inside the tube varied in direct proportion to the internal diameter of the ETT, and inversely with the volume injected. Calculation of 99% confidence limits revealed that an 1 mL volume of injection was the minimum required to ensure 95% injected volume injected is delivered to the infant.

**Conclusion:** Therefore, to ensure that greater than 90% of the required dose is delivered endotracheally, a diluent volume of at least 0.5 milliliter should be used.

**Implication:** This study demonstrates that medications given via an endotracheal tube for newborns requiring resuscitation should be diluted to at least 1 ml to ensure 95% of the drug is delivered to the patient.

**Conflicts of Interest:** There are no known conflicts of interest of any of the authors. No funding was required to complete the study

## INTRODUCTION

Epinephrine is the most important medication used in resuscitation of the newborn. The American Heart Association and The American Academy of Pediatrics in the The Neonatal Resuscitation Program (NRP) manual, recommend the endotracheal route for administering epinephrine initially during cardiopulmonary resuscitation as intravenous access is not usually available (<sup>1,2,3</sup>). This is based on previous data, which indicate that many drugs can be absorbed through the tracheobronchial tree mucosa into the systemic circulation (<sup>4,5,6,7</sup>), even in times of low pulmonary blood flow.

There is controversy as to what is the best method to deliver epinephrine to a neonate. To assure complete delivery of the

epinephrine, the NRP recommends considering the use of saline flush or the use of a feeding tube to deliver the medication directly to the distal end of the endotracheal tube (ETT). The efficacy of these methods is unproven. A recent study showed that there is little difference in whether or not a feeding tube is used to deliver the drug. (<sup>8</sup>)

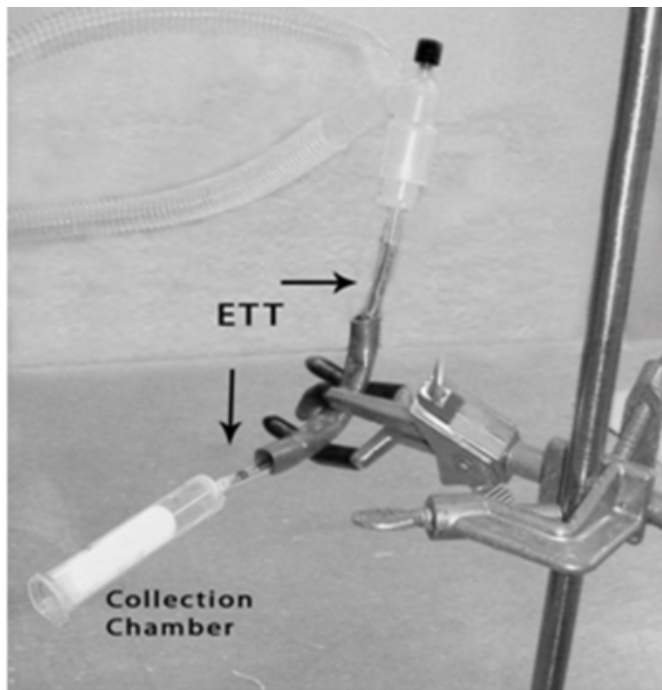
When using small volumes of drug, there is a possibility of some of it remaining inside the ETT, and thus not being delivered to the baby. We hypothesized that the amount of fluid remaining in the tube increases with decreasing volume injected, and that the internal ETT diameter directly influences the volume retained. The purpose of this study is to quantify this ratio for different volumes and ETT sizes. More importantly, we want to quantify the critical volume needed to assure 95% drug delivery after injection into an ETT independent of tested ETT size.

### MATERIALS AND METHODS

Standard neonatal ETTs (Mallinckrodt, Inc, St Louis, MO) with internal diameters of 2.5 mm, 3.0 mm and 3.5 mm were used. The experiment was designed to simulate clinical practice. The experimental apparatus is shown in figure 1.

#### Figure 1

Figure 1: Photograph of the experimental apparatus. A copper tube bent in a 90 degree angle to resemble the oropharynx-tracheal pathway was mounted on a stand. The endotracheal tube (ETT) was inserted and a plastic collecting device filled with cotton attached to the ETT end with parafilm. A ventilator was connected to the ETT via pediatric tubing after each fluid volume injected for standardized 5 breath ventilation.



Each ETT was held at a 90 degree angle to replicate its anatomical position by placing it through a copper cylinder bent to simulate the oropharyngeal-tracheal pathway. All ETTs were inserted to 12 cm to assure standardization of the ETT curvature. A plastic collecting device was connected to the end of the ETT with parafilm (American National Can, Chicago, IL). It consisted of a tube where the distal end was filled with cotton to absorb the fluid leaving the ETT. A 1mL syringe (Becton, Dickinson and Co., Franklin Lakes, NJ) containing different volumes of water were used to administer each trial. Ten trials each were performed for five different fluid volumes (0.05 mL, 0.10 mL, 0.25 mL, 0.50 mL, 1.00 mL). The syringe was weighed before and after administration of the fluid in order to obtain the exact amount delivered. All weights were obtained using a Mettler

At250 scale (Mettler Toldeo Inc, Heightstown, NJ), which is accurate to 0.1 mcg.

After administering the fluid into the ETT, the ETT was connected to an Ohmeda 7000 ventilator and five breaths of 50 ml tidal volume at a rate of 40 breaths/min were given. Following the ventilation, the collector was carefully taken off the ETT and weighed to determine the amount of fluid that left the ETT. Direct observation was used to ensure that no fluid was lost from the ETT or the collecting device. This was repeated for each trial. The ETT and collector were dried with free-flowing air, and the cotton in the collector was replaced between each trial.

Values obtained were the following:

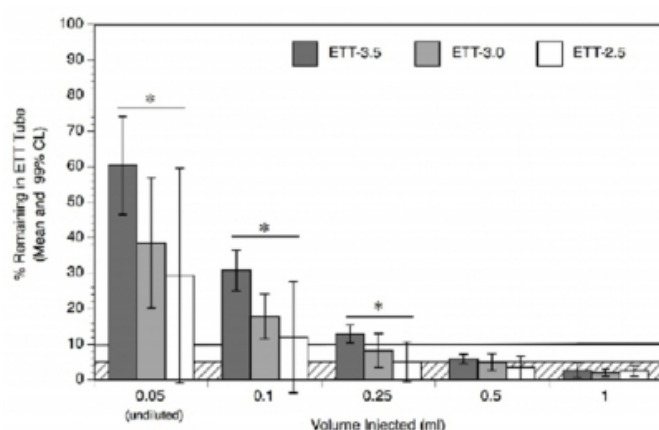
- A) Fluid administered: (weight of filled syringe before fluid delivered) – (weight of syringe after fluid delivered)
- B) Fluid collected\*: (weight of collector after fluid delivered) – (weight of collector before fluid delivered)
- C) Amount left in ETT: A-B

### RESULTS

The results of the experiment are shown in Figure 2.

**Figure 2**

Figure 2: Mean percentage ( $\bar{X} \pm 99\%$  confidence interval) of injected volume remaining in the ETT varied inversely with the injection volume, but directly with ETT diameter. A significant difference in % remaining as a function of ETT diameter was noted for dilution volumes up to 0.25 ml (\* $p < 0.01$ , significant main effect of ETT diameter at a given dilution volume). As a visual aid, the top horizontal line facilitates identification of injection volumes where the upper limit of the 99% confidence interval falls below 10% remaining (ensuring 90% delivery at volumes of 0.5 ml and above regardless of ETT diameter). The lower horizontal line (at the upper limit of the shaded area) similarly facilitates identification of the 1.0 ml injection volume as ensuring at least 95% delivery (note that upper limit of 99% confidence limit does not extend outside the shaded region regardless of ETT diameter). ETT = endotracheal tube.



For 0.05 mL delivered volume, the mean percentage of injected volume remaining was 60% for the 3.5 mm diameter ETT, 38% for the 3 mm ETT and 28% for the 2.5 mm ETT. As injection volume was increased, the percentage remaining in an ETT of given diameter decreased, but the relationship between ETT diameter and % remaining was preserved until a dilution volume of 0.5 ml was reached (10-fold dilution). Two-factor ANOVA confirmed this pattern of results, with a significant main effect of ETT diameter ( $F[2,60] = 21.42$ ,  $p < 0.0001$ ), significant main effect of injection volume ( $F[4,60] = 58.88$ ,  $p < 0.0001$ ), and a significant ETT diameter x injection volume interaction ( $F[8,60] = 5.50$ ,  $p < 0.0001$ ). Separate follow-up comparisons at each injection volume of percent remaining as a function of ETT diameter revealed a significant influence of ETT diameter on fluid retained in the tube at injection volumes of 0.05, 0.10, and 0.25 ( $p < 0.01$  following Bonferroni correction for multiple comparisons), but not at volumes of 0.5 or 1.0 ml.

The upper limit of the 99% confidence interval for percent

volume remaining in the ETT tube fell below a critical volume remaining of 10% with an injection volume of 0.5 ml for all ETT diameters examined (Figure 2). Moreover, the upper limit of the 99% confidence interval fell below a critical volume remaining of 5 % with an injection volume of 1.0 ml for all ETT diameters examined.

## DISCUSSION

Current recommendations for the use of epinephrine in newborn infants are based only on evidence derived from animal models and human adult literature. There are no randomized controlled trials addressing the issues of optimum dosage and route of administration of epinephrine in the neonate (9). The International Guidelines of Neonatal Resuscitation do not explicitly state whether a diluent should be used, and the evidence supporting these recommendations has not been rigorously scrutinized. In this study we show that very small volumes delivered via an ETT result in highly varying amounts actually leaving the ETT with a significant amount of it potentially remaining in the ETT. Increasing the volume delivered to at least 0.5 mL will confidently result in 90% of the fluid leaving the ETT and a volume of 1 mL delivered will result in 95% leaving the ETT for ETT sizes of 2.5 mm, 3.0 mm and 3.5 mm internal diameter.

The International Liaison Committee on Resuscitation (ILCOR) produced a revised consensus document on resuscitation in 2000 to address changing physiology of the newborn, and techniques for providing advanced life support. This document recommends epinephrine to be administered intravenously or intratracheally if the heart rate remains  $< 60$  bpm despite 30 seconds of effective assisted ventilation and chest compression circulation. Regarding endotracheal administration of medications, it acknowledges that the tracheal route leads to a more variable response to epinephrine than the intravenous route, but also states that neonatal data is insufficient to recommend a higher dose of epinephrine for tracheal administration (10). The newest available NRP recommendations now state that epinephrine should be given preferentially by the intravenous route to assure adequate patient delivery, but that intratracheal administration should be performed when there is no vascular access or prior to establishing an umbilical venous line (3).

The NRP manual mentions that 0.5 to 1.0 mL of normal saline may be used to flush the epinephrine down the ETT, or the dose may be diluted with the same volume of saline. It

also recognizes that ETT administration may result in the small volume being stuck inside the collector (3). We show a significant inverse relationship between volume injected and percentage remaining inside the ETT ( $p = 0.0001$ ). This is important in the event of neonatal resuscitation because the patient would only receive a fraction of the injected dose if it were not diluted. In addition, from our study it was possible to estimate that 0.5 and 1 mL volume result in 90% and 95% of the dose being delivered to the patient (with 99% confidence), respectively, with no influence of ETT diameter selected for intubation and drug delivery with these 10-20-fold dilution volumes. Conversely, up to 60% will be lost when an undiluted volume of 0.05 mL is injected. It should be noted that although these confidence interval calculations are based upon a relatively modest sample size of 10 volume measurements for each ETT diameter/injection volume combination tested, we conservatively used 99% rather than 95% confidence intervals to estimate injection volume needed to ensure 90% or 95% delivery of total dose administered via the ETT tube. Therefore, we feel that our estimates are sufficiently conservative in recommending the use of simple 10-fold (90% delivery) or 20-fold (95% delivery) dilutions.

This study highlights an expected relationship between volume delivered and volume remaining in the ETT. It must be noted that this data was generated under artificial experimental conditions. Limitations of our design include the following:

First, the study was accomplished using a collecting device that did not have the compliance that a test lung or patient would have. However, during instillation of epinephrine in the delivery room, the infant's ventilation is interrupted and there is no positive airway pressure in the airway during such instillation. This can be avoided using an inline adapter, but such adapters are not standard of care during neonatal resuscitation. Subsequent to instillation manual ventilation is resumed. Second, the tidal volume that we used (50cc) was larger than a normal neonatal tidal volume, using an estimate of 7cc per kilogram body weight. This was done because of the large dead space in the ventilator setup used to standardize ventilation. The use of such large volumes may force more of the administered fluid into the lung, and thus our recommendation is always to use 1 ml as a minimum diluents for intratracheal epinephrine instillation. Third, although the ETT was passed through a rigid artificial oropharyngeal-tracheal pathway, removal of the collecting device possibly resulted in minimal movement of the ETT.

This movement could have altered the path of the fluid, affecting the amount of liquid left inside the tube. However, movement happens clinically during chest compressions, thus the experimental conditions may correlate to the clinical situation. Finally, although each tube was inserted into the same rigid oropharyngeal-tracheal pathway to 12 cm, the angle of the tube may not have been identical in each trial. Again, in clinical practice, the tube will also not be in the same position in each patient secondary to varying anatomy. Therefore, we believe that the findings of this laboratory experiment can be considered consistent with those encountered during a neonatal resuscitation.

## CONCLUSIONS

We have shown that administration of small volumes of fluid via an endotracheal tube sized for neonates may result in significantly less fluid being delivered than anticipated. Based on our findings we recommend administering drugs like epinephrine in at least 1.0 ml volume via an ETT to assure a minimum of 95% of the drug being delivered to the infant.

## CORRESPONDENCE TO

Mark Greenberg, M.D.  
UCSD Medical Center  
200 W. Arbor Drive, San Diego 92103  
Ph: 619.543.1999  
Fax: 619.543.5424

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**Author Information**

**Tobias Moeller-Bertram, M.D.**

Assistant Clinical Professor of Anesthesiology, Department of Anesthesiology, University of California San Diego

**Mark Greenberg, M.D.**

Associate Professor of Anesthesiology and Pediatrics, Department of Pediatrics, and Anesthesiology, University of California San Diego

**Gery Schulteis, Ph.D.**

Associate Adjunct Professor of Anesthesiology, Department of Anesthesiology, University of California San Diego

**Jennifer Hayes, M.D.**

Resident in Anesthesiology, Department of Anesthesiology, University of California San Diego

**Neil Finer, M.D.**

Professor of Pediatrics, Department of Pediatrics, University of California San Diego