JPPT | *In Vitro* Comparative Study

Comparison of Dosing Accuracy Between the ENFit LDT and a Neonatal-Specific ISO-Compliant Enteral Syringe

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OBJECTIVE To evaluate the dosing accuracy of 2 female enteral syringe types for use in neonates.

METHODS This was an *in vitro* study evaluating dosing accuracy of ENFit with low dose tip (LDT) and Nutrisafe2 (NS2) syringes. Acceptable dosing variance (DV) was +/− 10%. Outcomes included tests exceeding 10% DV and DV by syringe size, dispensing source, and intended dosing volume.

RESULTS A total of 300 tests were performed (LDT = 150, NS2 = 150) with 3 syringe sizes (0.5, 1, 3 or 2.5 mL). Compared with NS2, LDT had significantly more tests with unacceptable DV (48% vs 4.7%, $p < 0.0001$) and higher absolute DV (11.9% vs 3.5%, $p < 0.001$). Dosing variance was inversely proportional to syringe size, where the smallest syringes were least accurate (0.5 mL LDT 16.1% vs 4.6%, $p < 0.001$). The largest syringes had acceptable DV (3 mL LDT 8.8% vs 2.5 mL NS2 3.3%, $p < 0.001$). Bulk bottle with adapters demonstrated a higher DV with LDT compared with NS2 (13.3% vs 3.9%, $p < 0.001$). Medication cups without adapters were associated with acceptable DV for both LDT and NS2 (9.7% vs 2.9%, $p < 0.001$).

CONCLUSIONS The Nutrisafe2 syringe has greater dosing accuracy as compared with ENFit LDT syringe. Smaller syringes are associated with greater dosing inaccuracy, but this effect was within acceptable DV for the NS2 syringe. Bulk bottle adapters did not improve the accuracy of the LDT. More clinical evaluations are needed to determine if the ENFit can be safely used in the neonatal population.

ABBREVIATIONS DV, dosing variance; FDA, US Food and Drug Administration; ISO, International Organization for Standardization; LDT, low dose tip; NS2, Nutrisafe2

KEYWORDS dosing accuracy; enteral syringe; medication safety; neonate

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Introduction

Medication device misconnections between incompatible routes represent a small but preventable source of significant medication errors in the health care setting. Notably, inadvertent administration of enteral/oral liquids via the intravenous route can result in catastrophic consequences. Physical modifications have been implemented to syringes and tubing systems to prevent misconnections between the enteral and intravenous routes in accordance with recommendations from the International Organization for Standardization (ISO), an independent, non-governmental global organization for establishing national standards bodies. ISO launched standards for enteral systems (ISO 20695) and small-bore connectors (ISO 80369-1 and 3) that clearly delineate design criteria for the enteral route from other routes, similarly to the device standards recently applied to respiratory and neuraxial systems.[1,2]

Through the Global Enteral Device Supplier Association, manufacturers joined forces to create ENFit, a reverse orientation syringe and tubing design to decrease risk of misconnections, standardize enteral connections, and adhere to ISO-80369 criteria. Enteral-specific device systems evolved for the safe provision of nutrition, but their use has been extrapolated to medications as well. The standard female ENFit syringe has been proposed as the solution to enteral misconnections, but it has faced scrutiny by pediatric providers for dosing accuracy issues, especially with low volumes.[2–4] Contrary to traditional male slip tip syringes that are inserted in female enteral tubes, the female enteral syringe fits around the male enteral tube connection, creating a new physical space that may lead to inaccurate medication dosing. The standard ENFit syringe tip contains 0.2 mL of volume, which can result in significant over or underdosage if improperly used. The ENFit with low dose tip (LDT) feature has a small, internal male lumen inside the female syringe tip, which creates a moat that can serve as a reservoir for drug. Although the ENFit LDT was designed to overcome dosing inaccuracy seen with the standard ENFit syringe, computational fluid dynamics data and post-marketing clinical evaluation suggest that the LDT may still have unacceptable dosing variance (DV).[5–8] ISO standard 20695 reflects the inability of the LDT to reliably increase dosing accuracy compared with the standard ENFit syringe, delineating the LDT as an "alternative design." A recent US Food and Drug Administration

Table. Testing Conditions

	ENFit LDT	NS2
Total tests, n	150	150
0.5-mL syringe, n	50	50
Bulk bottle, n	30	30
Medication cup, n	20	20
1 mL syringe, n	50	50
Bulk bottle, n	30	30
Medication cup, n	20	20
3/2.5-mL syringe, n	50	50
Bulk bottle, n	30	30
Medication cup, n	20	20

LDT, low dose tip; NS2, Nutrisafe2

(FDA) warning was released that cautions the potential for overdosage with the ENFit LDT.[9]

Preterm neonates often require extended duration of enteral tube use to meet their nutritional and medication needs until developmental maturity allows for safe oral administration.[10] Oral/enteral medication doses less than 1 mL are associated with higher risk of dosing errors in young children, and commonly result in need for hospitalization.[11] Enteral medication doses in the neonatal population are frequently low volumes (<1 mL) and require accurate dosages to help prevent unintended medication consequences.[6] Compared with adults, younger patients are 3 times more susceptible to medication overdoses and the associated complications.[12] Neonates are particularly vulnerable to medication errors, given wide intra- and interpatient variability in developmental pharmacokinetics and dynamics, relative lack of prospectively evaluated neonatal dosing literature, unavailability of population-specific dosage formulations, and higher propensity for significant morbidity and mortality.[13–15] Given these characteristics, dosing inaccuracy with enteral syringes in neonates likely represents a high-risk practice, since seemingly small variations in volumes delivered can result in clinically significant toxicity or treatment failure.[13–15]

In a previous publication, we demonstrated that DV exceeded 10% from the intended dose nearly 3 times more with ENFit LDT as compared with male oral syringes ($p = 0.003$).[6] In this study, we evaluated the performance of Nutrisafe2 (NS2), an ISO-compliant enteral syringe, that was designed specifically for neonatal patients and compared it to the ENFit LDT. Computational fluid dynamics evaluation suggests that the NS2 may decrease the potential for overdosage seen with the ENFit LDT from 0.12 mL to 0.029 mL due to its smaller syringe tip. There are no currently published clinical studies of the NS2 syringe to validate these findings. As health care systems move toward ISO compliant enteral systems, it is imperative that they understand the challenges related to dosing accuracy across the spectrum of available options to determine which is safest for neonatal patients. Given the lack of peer-reviewed clinical evaluation of these syringes, we sought compare the dosing accuracy of the NS2 to ENFit LDT.

Materials and Methods

An *in vitro* study was conducted at WakeMed Health and Hospitals. Two types of enteral syringes were evaluated. Methodology was based on a previous evaluation.[6] Based on previous studies showing the majority of DV in smaller volume syringes, 3 syringe sizes were selected (NeoMed ENFit LDT: 0.5 mL, 1 mL, 3 mL; Vygon NS2: 0.5 mL, 1 mL, 2.5 mL) for evaluation. For each syringe size, 2 intended volumes were evaluated: a low volume (low volume: 20% of syringe capacity) and a high volume (high volume: 80% of syringe capacity). For example, for a 1-mL syringe, the low volume was 0.2 mL while the high volume was 0.8 mL. FDA-approved instructions for use for each were followed.[16] The test liquid was dispensed from a bulk glass bottle with the corresponding adapter (ENFit or NS2) and directly from a medication cup.

To match previous methodology and to represent a common outpatient medication, brompheniramine maleate/dextromethorphan HBr/phenylephrine HCl oral liquid (Children's Dimetapp Cold & Cough; Pfizer, Inc, Sanford, NC) was used for all syringe tests. Volumetric measurement of dosages and confirmation of dose delivered via gravimetric assessment were completed in accordance with other clinical dosing accuracy studies.[6,17,18] A pre-weighed graduated cylinder and pipettor were used to determine density and specific gravity of the brompheniramine maleate/dextromethorphan HBr/phenylephrine oral liquid. An Ohaus Adventurer scale was used for measuring all tests (precision/accuracy = 0.001 g). A single investigator measured all doses for assessment. Dosing variance was calculated by dividing the difference between the actual and intended volume by the intended volume.

Based on our previous evaluation,[6] to detect a 15%

absolute reduction in unacceptable DV, a minimum of 104 samples in each arm would be needed for a desired power of 80% and a Type 1 error rate of 0.05. Statistical analysis was completed using JMP v16. Chi-square, *t* test, and analysis of variance were used as appropriate. The primary outcome was the comparison of the frequency of DV exceeding 10% of the intended dose for all NS2 syringes compared with the ENFit LDT. Secondary outcomes describe the overall dosing performance of the 2 female designs based on syringe size and nominal capacity.

Results

A total of 300 tests were completed (ENFit LDT= 150, NS2 = 150). The distribution breakdown is summarized in the Table. For each syringe size (n = 50), half the tests were completed at 20% (n = 25) and half at 80% (n = 25) syringe capacity. The LDT had significantly more tests with an unacceptable DV compared with the NS2 (48% vs 4.7%, $p < 0.0001$).

Absolute DV was significantly higher in theLDT group compared with NS2 (11.9% vs 3.5%, $p < 0.0001$). The overall distribution of DV for the 2 syringe types is described in Figure 1A. DV was inversely proportional to syringe size (Figure 1B), where 0.5 mL syringes demonstrated greater variance for both syringe types (16.1% vs 4.6%, $p < 0.001$ for LDT vs NS2, respectively). For 1 mL syringes, LDT had higher DV (10.7% vs 2.8%, $p < 0.0001$), but mean DV was within acceptable ranges for both syringes in the 3 mL/2.5 mL tests groups (8.8% vs 3.3%, $p < 0.001$). When assessing DV by syringe type and medication dispensing source (Figure 1C), LDT tests from bulk bottles with adapter caps had a higher DV compared with NS2 (13.3% vs 3.9%, $p < 0.001$). Medication cups were associated with acceptable DV for both ENFit LDT and NS2 syringes (9.7% vs 2.9%, $p < 0.0001$). The effect of syringe capacity on DV is presented in Figure 2. Accuracy and precision were improved with increasing dosing volumes for both syringe types.

Discussion

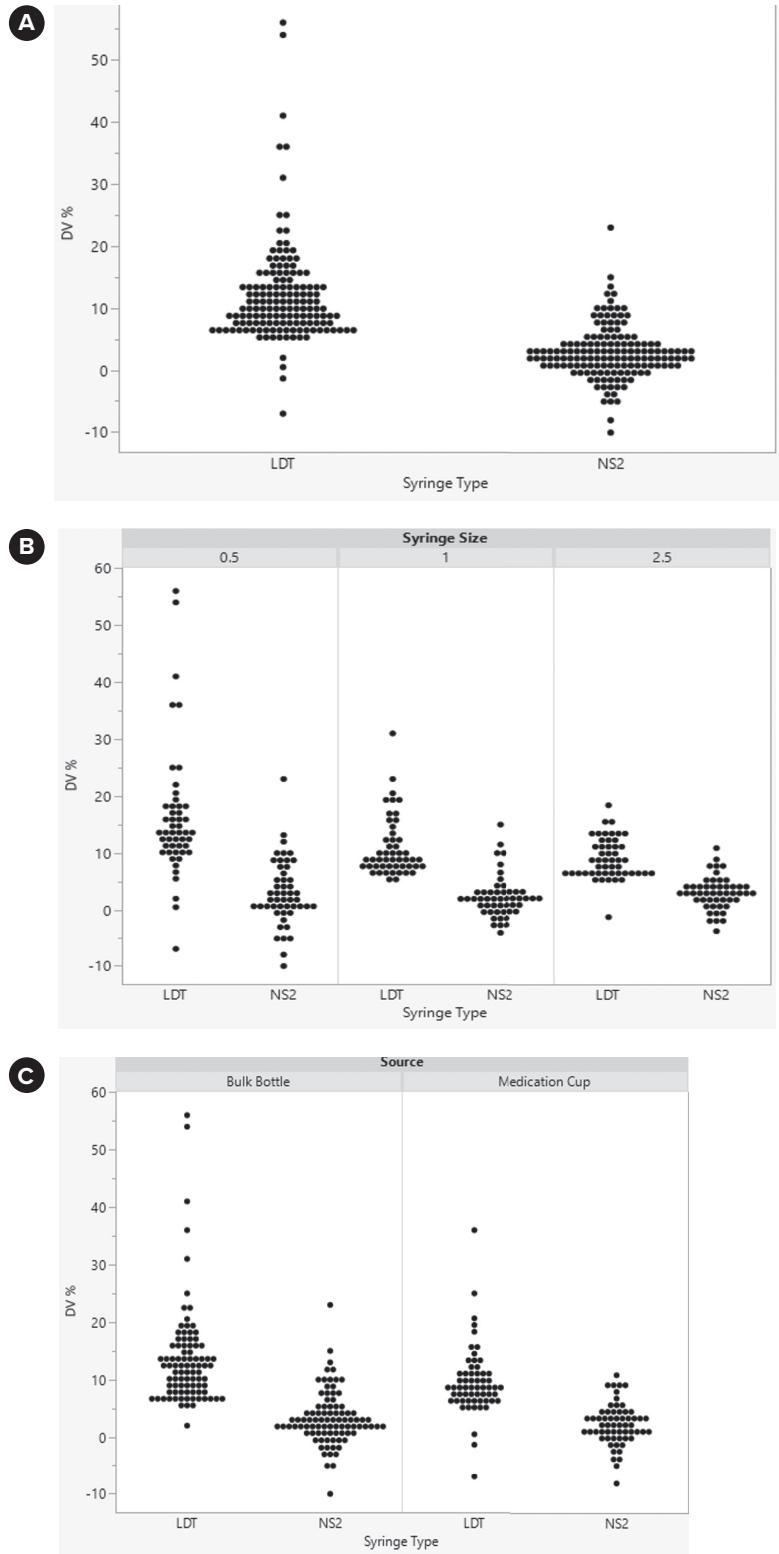
When choosing the appropriate enteral design for neonatal patients, the risk of compromised dosing accuracy must be considered in conjunction with the risk of device misconnection. Based on this evaluation, the neonatal ISO-compliant NS2 enteral syringe had significant greater dosing accuracy as compared with the ENFit LDT. The ENFit LDT was associated with a greater proportion of tests that fell outside of an acceptable DV, which is consistent with previous clinical evaluations.[6–8]

A recently published computational evaluation was completed that confirms the potential for the ENFit LDT to contribute to unintentional overdosage.[8] The authors predict that the LDT may overdose by as much as 34.7% when using a 0.5-mL syringe, which was comparable with experimental results showing a maximum overdosage of 39.6%.[6] For the 1 mL LDT, the calculated maximum overdose was 18.1%, which fell within the range of the previously published experimental values of 10.5 to 26.4%.[6] When fluid remained in the moat, the computation fluid analysis predicted overdosages as high as 300% of the intended dose with the 0.5 mL LDT and 148% with the 1 mL LDT. The 1 mL LDT was found to have up to 1.5 times higher maximal overdosage when compared with the legacy male slip tips. Overdosage potential was nearly 2-fold higher for 0.5 mL than 1-mL syringes of both types.

While this study adds to the currently sparse body of literature regarding enteral device dosing accuracy, several pertinent factors were not evaluated, including drug properties (i.e., viscosity and surface tension) that affect flow behavior, contribution of drug particulates from crushed medications, and the use of filling adapters (i.e., filling straw or bottle cap adapter). Published literature describes the effect of viscous liquid on dosing accuracy of oral syringes, where slow flow rates lead to bubbles in syringes and surface adhesion that results in volume loss.[19] Failure to account for the physical properties of liquid medications in this study significantly decreases its applicability to real-world device use. Additional considerations with this evaluation include the pressure dynamics within the syringe and fittings themselves, realistic characterization of uncertainties with respect to manufacturing tolerances and characterization of the dynamic transfer of fluids with varied compressibility (i.e., vacuum effects caused by air in the syringe or leakage into the fittings). In effect, the computational study identified a single source of inadequacy in the LDT syringe, namely the geometry of the syringe and fittings. However, it is quite possible that operational factors could lead to even greater inaccuracies. The failure of this dynamics model to replicate measurements achieved by real-world application of the syringes further underscores the inadequacy of a single variable evaluation, where actual volume measurements are the gold standard for how much drug reaches the patient. A comprehensive fluid dynamics evaluation of syringe application could shed light on the questions remaining after the initial analysis performed by Guha et al.[8] Additional studies including evaluation of adapters are greatly needed, instead of assuming their use reduces the degree of dosing inaccuracy to a clinically acceptable range with the LDT.

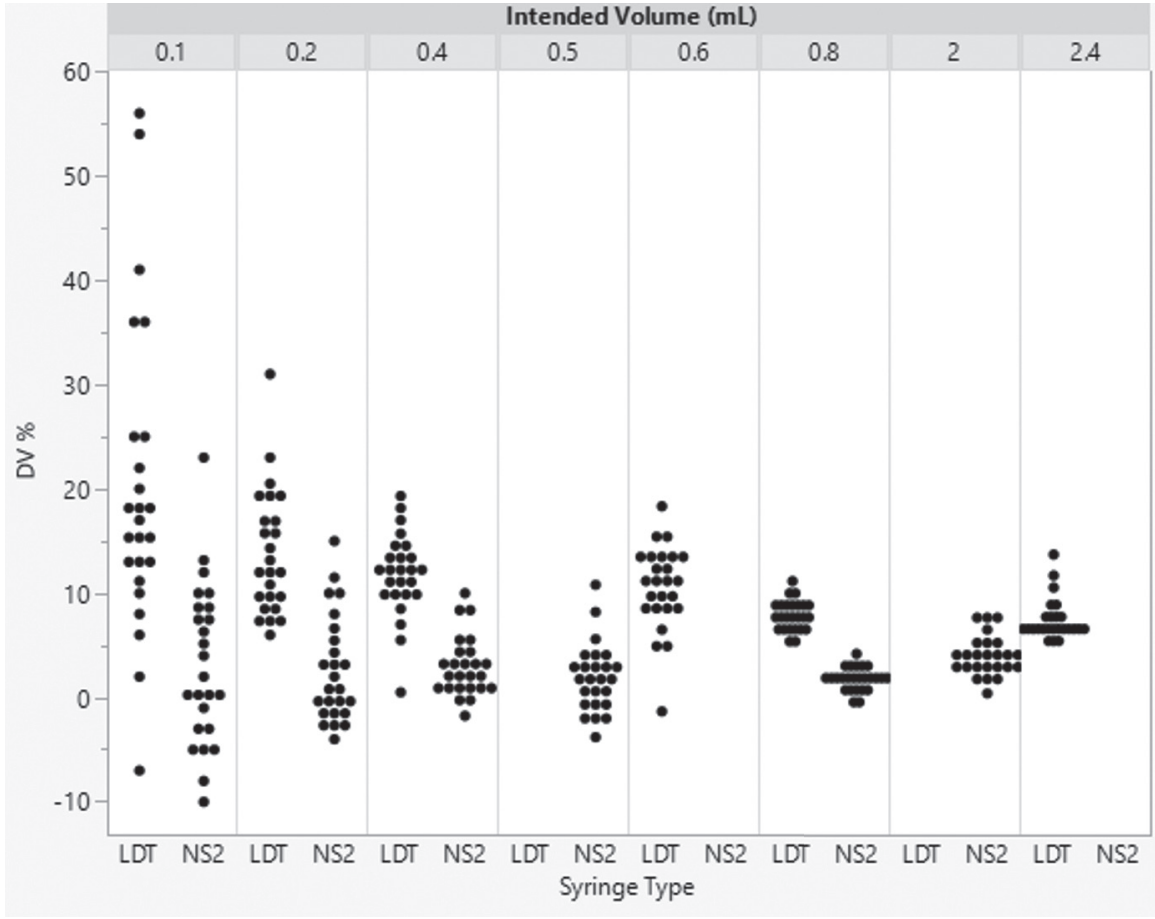
For health care systems who choose to use ENFit LDT syringes, mitigating the risk of overdosages is critical for safe medication delivery in neonatal patients. Despite not testing the effect of filling adapters on dosing accuracy, Guha et al[8] recommend their use to reduce DV to ≤ 10%. Our results using the ENFit bottle cap adapter reveal that dosing accuracy is not improved to ≤ 10%, so the end user must interpret this recommendation with caution. We did not test the accuracy associated with filling straws, but the use of a medication cup without a straw was found to be more accurate than the bottle

Figure 1. (A) Overall DV by syringe type. (B) DV by syringe size. (C) DV by medication dispensing source. ENFit LDT 3 mL is presented with NS2 2.5-mL syringes.



DV, dosing variance; LDT, low dose tip; NS2, Nutrisafe2.

Figure 2. DV by syringe capacity. NS2 2.5-mL syringes (20% capacity = 0.5 mL, 80% capacity = 2 mL), ENFit LDT 3-mL syringes (20% capacity = 0.6 mL, 80% capacity = 2.4 mL).



DV, dosing variance; LDT, low dose tip; NS2, Nutrisafe2.

cap adapter. Additionally, the authors did not evaluate the use of adapters for oral use, which adds another layer for potential over and underdosage. Of note, the FDA-approved instructions for use of the ENFit LDT do not currently require the use of either adapter type (filling or oral administration), so these remain optional accessories. ENFit manufacturer recommendations suggest that use of such adapters is intended to improve dosing accuracy for both the standard and LDT syringes, but publicly available clinical data to prove or disprove this recommendation are lacking. Based on the results of this study, it does not appear that the risk of overdosages is universally mitigated by the use of bulk bottle adapters.

This study confirms prior computational fluid dynamic analysis of the NS2 syringe, which suggested lower potential for overdosage compared with the ENFit LDT.[5] The NS2 syringe performance is likely due to its design, where the syringe tip is smaller and has less potential volume available for displacement when connected to an enteral tube.[5] This syringe may provide an ISO-compliant option for health care systems with neonatal patients to provide both dosing accuracy and reduced risk of misconnections. The drawback to this design compared with ENFit LDT is that there would not be one enteral system for all patients. While this may not be problematic for standalone children's hospitals, it may have significant effects for larger health systems that care for adults, pediatrics, and neonates.

There are several limitations to this study, including that tests were completed with a single manufacturer of ENFit LDT syringes. Differences in manufacturing may affect device performance, so the results of this study may not be able to be extrapolated to all available devices.[20] Each test was performed by a single experienced evaluator, so it is not possible to determine the effect of interuser technique variability on DV. The effect on DV by less experienced users, such as parents or other non–health care professional caregivers, should be evaluated, especially given previously published reports that parents often struggle with oral liquid medication

administration.[21–23] Only 1 liquid medication formulation was used in this study, which may limit the ability to predict the effect of drug characteristics, such as viscosity and particle size, on syringe performance. Enteral straw and oral adapters were not evaluated in this analysis, so there can be no conclusion drawn regarding their ability to improve dosing accuracy.

Conclusion

This study further validates that ENFit LDT syringes have a higher risk of dosing inaccuracy compared with other available designs, even when used with bulk bottle adapters.[4–7] The Nutrisafe2 syringe may have a dosing accuracy advantage over the ENFit LDT in the neonatal population given its smaller syringe tip, which decreases the maximal volume that may be unintentionally delivered with medication administration. Smaller syringes are associated with increased dosing inaccuracy, underscoring the need for development of oral medication formulations with appropriate concentrations and dosing volumes for neonates. As new enteral devices enter the market, it is imperative that they are tested for safety as well as precision and accuracy, particularly when they are to be used in patients who may be at high risk of therapeutic failure or toxicity. Clinical evaluations are critical to validate experimental conditions modeled in computational fluid dynamic studies. Given the inability of bulk bottle adapters to improve dosing accuracy to ≤ 10% in this study, further clinical studies are needed to evaluate the FDA statement supporting their use to overcome LDT syringe performance issues. The ENFit LDT should be used cautiously in neonatal patients until more data are available to ascertain how they may be safely used in this population.

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