



Contents lists available at ScienceDirect



Inadequacy of current pediatric epinephrine autoinjector needle length for use in infants and toddlers

Harold Kim, MD^{*,†}; Chitra Dinakar, MD[‡]; Paul McInnis, BSc[§]; Dan Rudin, MD^{||}; Xavier Benain, MD[¶]; William Daley, MD, MPH^{||}; Elke Platz, MD, MS[#]

^{*} Department of Medicine, Western University, London, Ontario, Canada

[†] Department of Medicine, McMaster University, Hamilton, Ontario, Canada

[‡] Department of Medicine, Stanford University, Stanford, California

[§] Department of Engineering, University of Waterloo, Waterloo, Ontario, Canada

^{||} Clinical and Exploratory Pharmacology, Sanofi US, Bridgewater, New Jersey

[¶] Sanofi, Montpellier, France

[#] Department of Emergency Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

ARTICLE INFO

Article history:

Received for publication November 29, 2016.

Received in revised form March 12, 2017.

Accepted for publication March 28, 2017.

ABSTRACT

Background: Epinephrine injection represents the standard of care for anaphylaxis treatment. It is most effective if delivered intramuscularly, whereas inadvertent intraosseous injection may be harmful. The needle length in current pediatric epinephrine autoinjectors (EAI) is 12.7 mm; however, the ideal needle length for infants and toddlers weighing less than 15 kg is unknown.

Objective: To determine the skin-to-bone distance (STBD) and skin-to-muscle distance (STMD) at baseline and after simulated EAI application in infants and toddlers (weighing 7.5–15 kg).

Methods: Study participants recruited from 2 North American allergy clinics underwent baseline and compression (10-lb pressure) ultrasonography of the anterolateral thigh with a modified ultrasound transducer mimicking the footprint and maximum pressure application of an EAI device. Ultrasound images, with clinical data masked, were analyzed offline for STBD and STMD in short-axis approach.

Results: Of 53 infants (mean age, 18.9 months; 54.7% male; 81.1% white; mean weight, 11.0 kg), 51 had adequate images for short-axis STBD measurements. In these infants, the mean (SD) baseline STBD was 22.4 (3.8 mm), and the mean (SD) STMD was 7.9 (1.7) mm. With 10-lb compression, the mean (SD) STBD was 13.3 (2.1) mm, and the mean (SD) STMD was 6.3 (1.2) mm. An EAI with a needle length of 12.7 mm applying 10-lb pressure could strike the bone in 43.1% of infants and toddlers in this cohort.

Conclusion: Our data suggest that the optimal EAI needle length for infants and toddlers weighing 7.5 to 15 kg should be shorter than the needle length in currently available pediatric EAIs to avoid accidental intraosseous injections.

© 2017 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Reprints: Harold Kim, MD, Western University, 525 Belmont Ave W, Ste 205, Kitchener, Ontario N2M 5E2, Canada; E-mail: hkimkw@gmail.com.

Disclosures: Dr Kim reported receiving consulting fees and speaker fees from Sanofi and Pfizer. Dr Dinakar reported receiving funding from the Food Allergy Research and Education as a Clinical Trials Network member. Drs Rudin, Benain, and Daley reported being employees of Sanofi and may own stock and/or stock options in the company. Dr Platz reported receiving consulting fees from Sanofi and Parexel. No other disclosures were reported.

Funding Sources: This work was sponsored by Sanofi. The sponsor of the study managed the data, and its representatives were involved in the data analysis and data interpretation. All final analyses were performed by the sponsor.

Previous Presentation: These data were presented in part at the American Academy of Allergy, Asthma, and Immunology Annual Meeting; March 7, 2016; Los Angeles, California.

<http://dx.doi.org/10.1016/j.anai.2017.03.017>

1081-1206/© 2017 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Anaphylaxis is a potentially life-threatening allergic reaction that can be caused by a number of different triggers, most commonly from ingested foods, insect stings, and medications.¹ The incidence of anaphylaxis is highest in young children up to 4 years of age, with a concomitant increase in the incidence of hospital admissions for anaphylaxis.^{2–4} Prompt administration of epinephrine is the treatment of choice for anaphylaxis. Current recommendations for self-treatment of food allergy causing anaphylaxis include strict avoidance of the food trigger and consistent availability of an epinephrine autoinjector (EIA) to treat reactions occurring at home or in community settings.¹

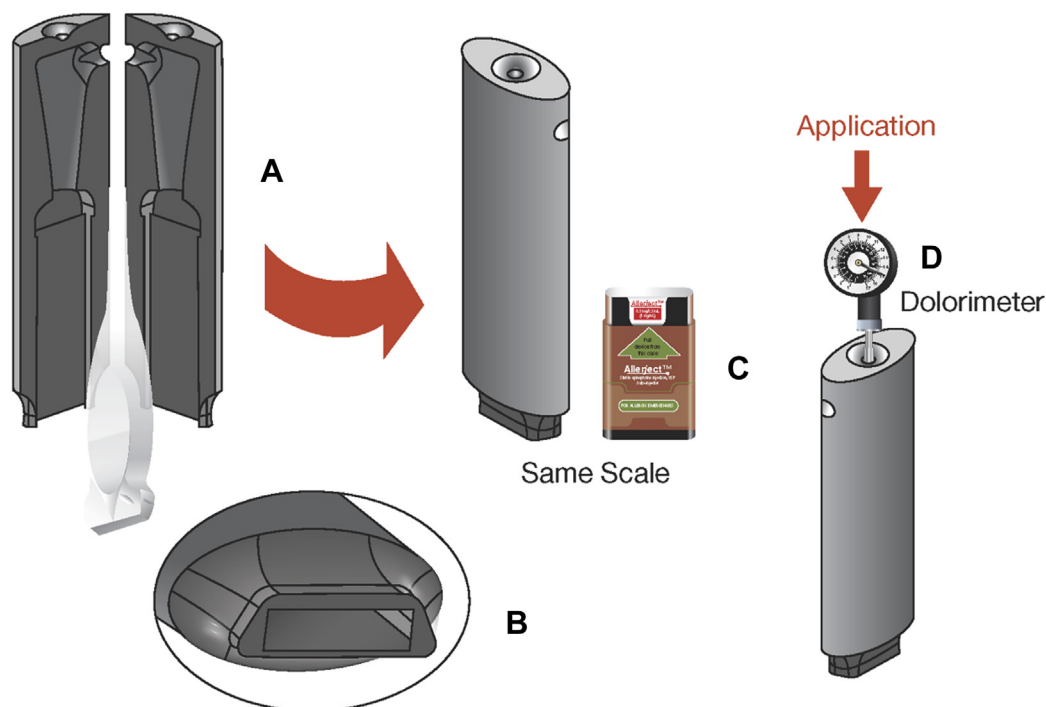


Figure 1. Modified ultrasound transducer mimicking the surface of an epinephrine autoinjector (Auvi-Q) with attached Dolorimeter. (A) Plastic shell surrounding ultrasound transducer. (B) Surface of plastic shell mimicking surface of the epinephrine autoinjector. (C) Plastic shell and epinephrine autoinjector side by side. (D) Dolorimeter attached to the plastic shell and embedded ultrasound transducer.

The US Food and Drug Administration–approved EAI in the United States and Canada (Auvi-Q/Allerject, EpiPen Jr) are indicated for use in children weighing 15 to 30 kg and administer 0.15 mg of epinephrine during intramuscular injections.^{5–7} The exposed needle length of these pediatric EAI is 11.43 to 13.97 mm (mean, 12.7 mm) for the Auvi-Q device (23-gauge needle) and 10.16 to 15.24 mm for the EpiPen Jr (22-gauge needle).⁸ Additional devices include Adrenaclick and a generic autoinjector, which are both available with 0.15 mg of epinephrine. Although epinephrine is used in the treatment of anaphylaxis in approximately 30% of young children, there are limitations and challenges with current strategies for prescribing epinephrine for young children, particularly for infants and toddlers weighing less than 15 kg.^{9,10} Because of the lack of a suitable alternative, the currently available 0.15-mg EAI are used in these younger children, based on recommendations from the Canadian Society of Allergy and Immunology and the Joint Task Force (American Academy of Allergy, Asthma, and Immunology and American College of Allergy, Asthma, and Immunology) on Practice Parameters.^{11,12} Given that the suggested dose of epinephrine is 0.01 mg/kg, using a 0.15-mg EAI for a child weighing 10 kg would deliver a 1.5-fold higher dose than recommended, and data on the effects of higher doses of epinephrine in very young children are lacking. On the basis of case reports, higher doses of epinephrine may cause ventricular dysrhythmias and cardiac ischemia.¹³ In addition, there may be a risk of injection of epinephrine into the bone in children weighing less than 15 kg given their current needle length based on prior reports of pediatric patients presenting to emergency departments with EAI needles embedded in the lateral thigh.^{14,15} Despite evidence from these studies suggesting that current EAI are not optimized to the weight of every patient, EAI are the preferred delivery method for non–health care professionals over using a vial and syringe to draw up and inject epinephrine in an emergency.^{9,16} In this study, we sought to use ultrasonography to measure the soft-tissue distances of the anterolateral thighs in infants and toddlers weighing 7.5 to

15 kg with a modified ultrasound transducer mimicking the surface and injection pressure of an actual EAI device (Auvi-Q).

Methods

Study Design and Setting

This was a prospective, observational study in infants and toddlers weighing 7.5 to 15 kg. The primary objective of this study was to determine the skin-to-bone distance (STBD) at baseline and at the time of simulated needle activation, as previously described, but using a modified ultrasound transducer.¹⁴ Secondary objectives were to determine the skin-to-muscle distance (STMD) at baseline and at the time of simulated needle activation, measuring thigh circumference and assessing safety of this approach. The modified device used in this study contained an ultrasound transducer that mimicked the footprint and maximum base activation force (10 lb) that an actual EAI device (Auvi-Q) would provide (Fig 1). This pressure was chosen based on the maximum activation force provided from the manufacturer. However, no needle was used and no medication was administered in this study; instead, only noninvasive ultrasound measurements were acquired with the modified transducer. This noninvasive approach was chosen to avoid discomfort to the study participants.

Selection of Participants

A total of 53 infants and toddlers were recruited from 2 allergy clinics in North America. The main inclusion criteria were male and female infants and toddlers weighing 7.5 to 15 kg regardless of a prior history of allergies. The main exclusion criteria were physical disabilities, specifically relating to leg function; evidence of thigh cellulitis, abscess, hematoma, lymphedema, or any skin disorder; prior thigh surgery; injection to the examined thigh (eg, vaccine) within 1 week of ultrasound assessment; withdrawal of consent during the screening process; and lack of cooperation or any

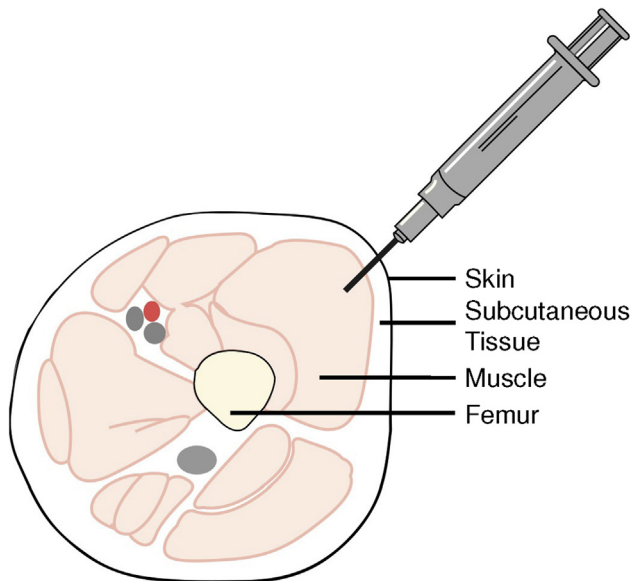


Figure 2. Cross-sectional anatomy of the anterolateral thigh indicating location for intramuscular injections.

condition that could potentially make the infant or toddler non-adherent to the study procedures. Written informed consent was obtained from the parents or legal guardians of all participants. Both study sites received approval from the applicable ethics committees (Western Institutional Review Board, Puyallup, Washington, and the Children's Mercy Hospital Pediatric Institutional Review Board, Kansas City, Missouri) through external institutional review board reliance for the conduct of this study.

Ultrasound Image Acquisition

The standardized ultrasound scanning location was identified by measuring half (midthigh) the distance from the greater trochanter to the lateral epicondyle of the femur. This location was determined with a tape measure on the infant's vastus lateralis muscle (Fig 2) of the anterolateral thigh and marked with a surgical

marking pen. Thigh measurements and calculations were recorded. Enrolled infants underwent unilateral thigh imaging with a standard ultrasound system used routinely in clinical practice for soft-tissue imaging with a high frequency (13–6 MHz) linear transducer (L25, SonoSite Nanomaxx, Bothell, Washington). The linear transducer was enclosed in a custom-made plastic case (Fig 1) that mimicked the footprint of the Auvi-Q device. A Baseline Dolorimeter (Fabrication Enterprises Inc, White Plains, New York) was attached to ensure appropriate pressure application of 10 lb (Fig 1), simulating the pressure that the actual EAI would apply. The modified ultrasound transducer was then placed on the pre-identified location on the study participant's thigh. A B-mode image was acquired by a trained investigator (physician or sonographer) without compression (Fig 3A) in short axis (transverse imaging plane) followed by 10-lb compression with the ultrasound transducer and synchronous ultrasound image capture (Fig 3B). The ultrasound transducer was then rotated 90°, and a long-axis image without compression and another image with compression were recorded in the same fashion. Infants underwent only one set of short- and long-axis measurement, unless the images were deemed of insufficient quality during analysis. In this case, repeat images were obtained if study participants' parents provided consent ($n = 5$ participants).

Ultrasound Image Analysis

All ultrasound images were sent for qualitative review and quantitative analysis, with the demographic and clinical data masked. Deidentified images underwent initial screening for overall image quality. If image quality was considered inadequate to ascertain measurements, additional measurements were obtained from the same infant and, if adequate, were used for analysis. Linear measurements were then performed by a single reviewer (E.P.) on all images of adequate quality for STMD and STBD as previously described.^{17,18} Intraobserver reproducibility of ultrasound measurements was assessed in approximately 10% of study participants' images using the intraclass correlation coefficient.¹⁹ The intraobserver correlation coefficients were 0.99 for STBD with and without compression and 0.93 for STMD with compression and 0.98 without compression.

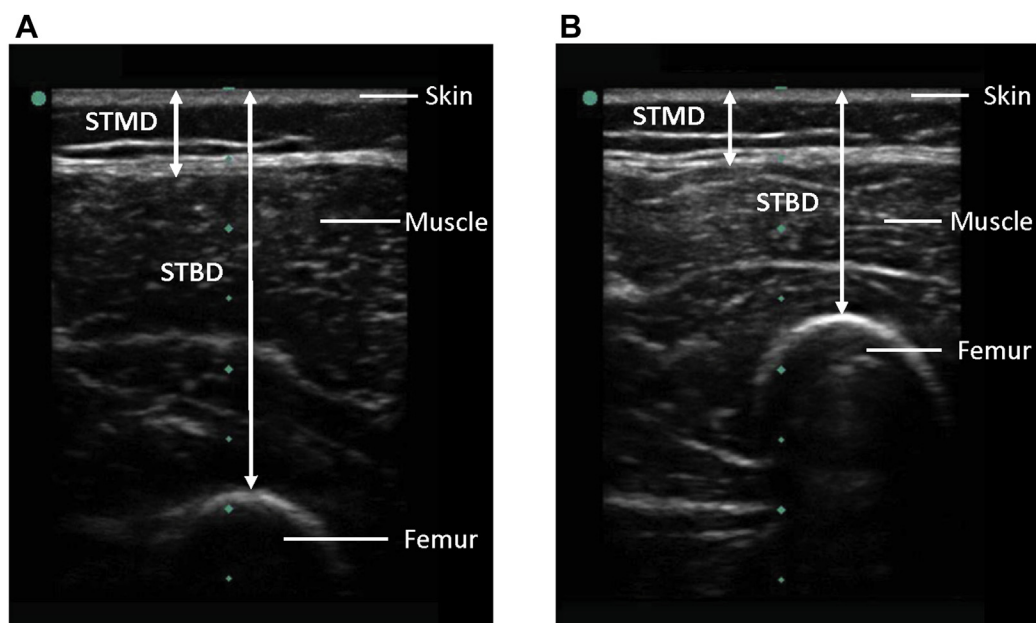


Figure 3. Short-axis ultrasound image of anterolateral thigh without compression (A) and with 10-lb compression (B). STBD, skin-to-bone distance; STMD, skin-to-muscle distance.

Outcome Measures

The primary study end point was the STBD of the anterolateral thigh in noncompressed and compressed states in short axis. The secondary end point was the STMD in noncompressed and compressed states.

Sample Size

The following assumptions were made to estimate the relative imprecision on the mean (SD) in children weighing 7.5 kg (16.5 lb) to less than 15 kg (33 lb). The mean (SD) STBD was assumed as 14.4 (2.4) mm.²⁰ The STBD was further assumed to be normally distributed. On the basis of these assumptions, with an assumed mean (SD) of 14.4 (2.4) mm in children weighing 7.5 kg (16.5 lb) to less than 15 kg (33 lb), a sample size of 50 would produce a relative imprecision of 4.7% on the mean and 16.5% on the SD.

Primary Data Analysis

Demographic and clinical characteristics, STBD, and STMD were summarized using descriptive statistics (mean [SD]) for continuous variables and number (percentage) for categorical variables. The STBD and STMD were analyzed within a mixed-effect model with fixed terms for axis (short and long axis), weight, and sex and a random term for participant. Axis and sex mean difference estimates and their associated 2-sided *P* values were provided within the mixed-model framework. Short-axis measurements were taken forward for further analyses because they are considered more accurate than long-axis measurements (due to potential off-axis measurements) and are the primary outcome of this study. The association between weight and STBD and STMD as measured by short axis was further explored using a linear regression model. Weight slopes and associated 2-sided 95% confidence intervals were provided. Because of a significant weight effect, STBD and STMD were adjusted for weight for children weighing 7.5, 11, and 15 kg. The percentage of children for whom a needle length would not strike the bone (estimated by 1-sided 95% tolerance intervals) and the percentage of children for whom a needle length would allow an intramuscular administration (estimated by 1-sided 95% tolerance intervals) were estimated for different needle lengths ranging from 6.5 to 13 mm and for different weights ranging from 7.5 to 15 kg. All analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc, Cary, North Carolina).

Results

Baseline Characteristics

A total of 53 infants and toddlers were enrolled at the study sites. Of these, 51 had complete short-axis compression data and were included in the main analyses. A subset of 50 participants had complete images for short and long axis, with and without compression. The baseline characteristics for all study participants and those included in the main analyses are given in Table 1.

STBD and STMD Measurements

Unadjusted measured and weight-adjusted estimated short- and long-axis measurements with and without compression are presented in Table 2. The measured mean (SD) STBD was 22.4 (3.8) mm at baseline and 13.3 (2.1) mm with compression in short axis. The measured mean (SD) STMD was 7.9 (1.7) mm at baseline and 6.3 (1.2) mm with compression. With compression, measurements performed in the long-axis approach were greater than short-axis measurements (15.7 vs 13.4 mm, *P* < .001 for STBD and 7.6 vs 6.4 mm, *P* < .001 for STMD). There was no significant difference in STBD and STMD based on sex (*P* = .08 for STBD and *P* = .25 for STMD). An EAI with a needle length of 12.7 mm applying 10-lb

Table 1

Baseline Characteristics of the Study Population

Characteristic	All participants (N = 53)	Participants with complete images (n = 51)
Age, mo	18.9 (9.7)	19.1 (9.8)
Male sex	29 (54.7)	29 (56.9)
Race or ethnic group		
White	43 (81.1)	42 (82.4)
Asian	4 (7.5)	4 (7.8)
Black	1 (1.9)	0
Other	5 (9.4)	5 (9.8)
Weight, kg	11.0 (2.0)	11.0 (2.0)
Weight group, kg		
7.5–11	29 (54.7)	28 (54.9)
11.1–15	24 (45.3)	23 (45.1)
Height, cm	80.1 (9.5)	80.2 (9.4)
BMI	17.2 (2.0)	17.1 (2.0)
Prior history of allergies	29 (54.7)	29 (56.9)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by square of height in meters).

Categorical data are reported as number (percentage) and continuous data as mean (SD).

pressure could strike the bone in 43.1% of infants and toddlers in this cohort.

Association Between Weight and Combined STBD and STMD Measurements

With increasing weight of study participants, STBD increased and STMD decreased (Fig 4). For short-axis compression data, plots of the estimated percentage of infants and toddlers for whom a needle would not strike the bone and of the percentage of those for whom a needle would allow an intramuscular administration are provided for infants and toddlers weighing 7.5, 11, and 15 kg (eFig 1). According to these weight-adjusted data, an EAI with a needle length of 12.7 mm could strike the bone in 54.9% of infants and toddlers weighing 7.5 kg, 37.9% of those weighing 11 kg, and 21.2% of those weighing 15 kg. Table 3 provides an overview of EAI needle length considerations with regard to both the risk of striking the bone and the EAI needle reaching into the intramuscular space. On the basis of these data, the optimal EAI needle length for this population would be between 7 and 8 mm.

Safety

There were no serious adverse events identified during the study. The only minor adverse event reported during the study was

Table 2

Mean (SD) Sonographic Thigh Measurements and Calculated Estimates Stratified by Weight in the 51 Study Participants

Variable	Sonographic measurements	Calculated estimates stratified by weight, kg		
		7.5	11	15
Thigh circumference, cm	26.2 (2.1)	-	-	-
Skin-to-bone distance, mm				
Short axis				
No compression	22.4 (3.8)	19.6 (3.5)	22.4 (3.5)	25.5 (3.5)
With compression	13.3 (2.1)	12.4 (2.0)	13.3 (2.0)	14.3 (2.0)
Long axis				
No compression	22.7 (3.3)	20.0 (2.9)	22.7 (2.9)	25.7 (2.9)
With compression	15.5 (2.5)	14.9 (2.5)	15.5 (2.5)	16.3 (2.5)
Skin-to-muscle distance, mm				
Short axis				
No compression	7.9 (1.7)	8.9 (1.6)	7.9 (1.6)	6.9 (1.6)
With compression	6.3 (1.2)	6.9 (1.2)	6.3 (1.2)	5.6 (1.2)
Long axis				
No compression	8.5 (1.9)	9.7 (1.8)	8.5 (1.8)	7.1 (1.8)
With compression	7.5 (1.7)	8.6 (1.6)	7.5 (1.6)	6.3 (1.6)

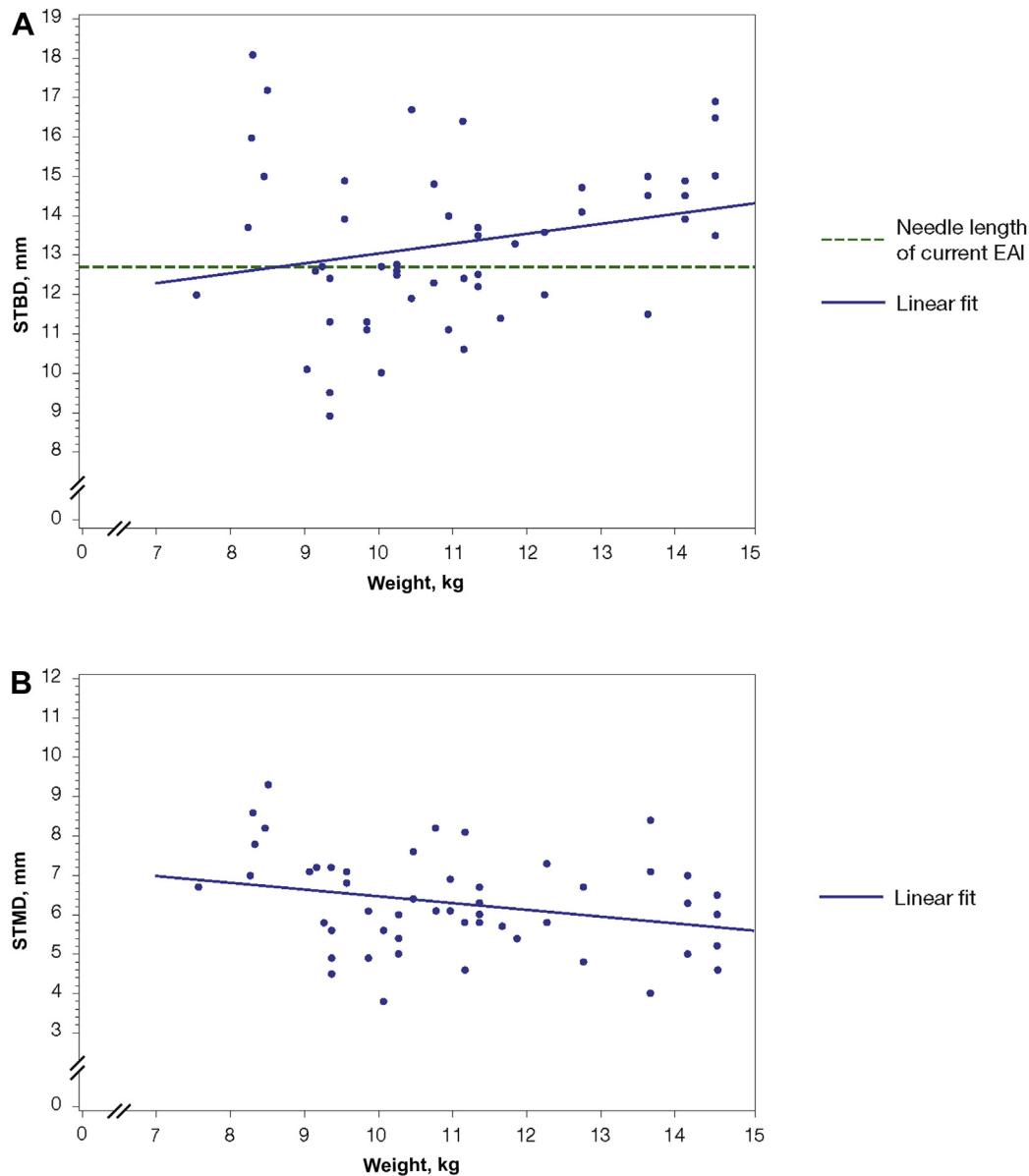


Figure 4. Sonographic thigh measurements with 10-lb compression according to weight. Short-axis skin-to-bone distance by weight (A) and short-axis skin-to-muscle distance by weight (B). EAI indicates epinephrine autoinjector.

pinching of the skin and mild discomfort during ultrasound image acquisition in 1 participant. As a result, the study participant's parents opted out of the study, and the study participant was discontinued from the study without completing the assessments.

Discussion

To our knowledge, this is the first study to assess the STBD and STMD in children weighing 7.5 to 15 kg with a modified ultrasound

transducer designed to mimic real-life delivery of epinephrine using a specific EAI (Auvi-Q). Our findings suggest that the optimal needle length for an EAI for infants and toddlers weighing 7.5 to 15 kg should be shorter than the needle length in current, commercially available pediatric EAIs to avoid inadvertent intraosseous injections.

Current recommendations favor the intramuscular injection of epinephrine into the vastus lateralis muscle over subcutaneous injection based on data from small studies in adults and

Table 3
Percentage of Children Estimated by 1-Sided 95% Tolerance Intervals in Whom EAI Needle Would Not Strike the Bone and Would Allow IM Administration

Weight, kg	6.5-mm needle length		7-mm needle length		7.5-mm needle length		8-mm needle length	
	Not striking bone	IM administration	Not striking bone	IM administration	Not striking bone	IM administration	Not striking bone	IM administration
7.5	>99	28.5	98.7	44.5	97.7	60.6	96.3	74.6
11	>99	47.9	>99	63.7	>99	77.0	98.5	86.8
15	>99	69.1	>99	81.1	>99	89.6	>99	94.8

Abbreviation: IM, intramuscular.

children.^{21,22} In these studies, intramuscular injection led to epinephrine levels that were superior to subcutaneous injections. There is concern that the needle length of EAI may be too short for some patients, resulting in subcutaneous rather than intramuscular injection.^{18,23} In a study of children weighing less than 30 kg, 12% of children were found to be at risk for subcutaneous injections.²⁴ However, this study did not specifically assess children weighing less than 15 kg. On the basis of our findings, an optimized needle length could be designed to increase the likelihood of intramuscular injection while avoiding striking the bone in most patients. In contrast to prior reports in adults, we did not find a significant sex-based difference in thigh measurements in our study population of infants and toddlers.^{18,23} This may be because of less pronounced anatomical differences in this young age group.

Although EAI is indicated for both intramuscular and subcutaneous injection, the disadvantages of subcutaneous injection must be weighed against potential concerns for intraosseous injection. Kim and colleagues¹⁴ measured STBD and STMD in 100 children with food allergies weighing less than 15 kg. The investigators used a conventional ultrasound transducer to apply maximal pressure, which was estimated at 8 lb. They found that the maximum STBD was less than 12.7 mm in 29% of children, suggesting that they were at risk of epinephrine injection into the bone. These findings are consistent with data from our study, which indicate that an EAI with a needle length of 12.7 mm could strike the bone with a range of 21% to 55% of children weighing between 7.5 and 15 kg. Our current study extends the methods and findings of prior investigations for several reasons. Apart from being a multicenter study, a modified ultrasound transducer closely resembling an actual EAI device was used to sonographically assess thigh distances. This novel device measured pressure application during simultaneous image acquisition. The ultrasound images obtained were assessed and analyzed by a single investigator masked to study participants' demographic and clinical data.

To our knowledge, no randomized clinical trial has been performed to determine the proper doses and needle length for pediatric patients with anaphylaxis.²⁵ However, the current recommended dose is 0.01 mg/kg. In adults, a large randomized study revealed that injection with the Auvi-Q and EpiPen led to similar serum levels of epinephrine.²⁶ The particular concern in young children is that if the needle of an EAI is too long and strikes the bone, it has the potential to penetrate the bone, possibly resulting in intraosseous delivery and absorption of epinephrine. Even in adults, injections through bone have been reported during unintentional EAI injection into a digit.²⁷ Injection of epinephrine in the intraosseous space leads to systemic absorption rates that are similar to intravenous administration of epinephrine.²⁸ In adults, inadvertent intravenous administration of an intramuscular or subcutaneous dose is associated with a higher risk of cardiovascular complications.^{13,29} Although empiric data on the extent of this cardiovascular risk in the pediatric population are lacking, ventricular dysrhythmias and myocardial ischemia have been reported previously.³⁰ Therefore, we believe that EAI needle length is a key clinical issue in young children at risk for anaphylaxis, and the findings from our study suggest that the needle length for EAI devices for this vulnerable population should be modified.³¹

Study Limitations

The modified ultrasound transducer used in this study was specifically designed to mimic the contact surface of the Auvi-Q device. Accordingly, differences in the surface area and applied pressure from other EAI devices or needles attached to a conventional syringe may result in distances different from those in our study. To assess STBD under the most conservative circumstances,

we standardized the pressure application to the maximum base activation force (10 lb) as provided by the manufacturer. We did not repeat measurements at lower pressures within the activation pressure range, which could potentially underestimate the STBD if lower pressures are used to activate the device. After completion of this study, the Auvi-Q device was temporarily removed from the market because of concerns of potential inaccurate dosage delivery. Although the device is scheduled to become available again in 2017, we believe that the findings of this study are important and may inform the optimization of EAI for infants and toddlers in the future. In addition, because ultrasonography cannot be performed through clothing, we could only perform measurements based on direct application of the modified ultrasound transducer to the skin. In the design of our study, we anticipated discrepancies between short- and long-axis measurements and, hence, used the more accurate short-axis measurements as the primary outcome. Differences between short- and long-axis measurements were likely attributable to off-axis movement of the ultrasound transducer in relation to the femur, especially during compression. Long-axis measurements were nevertheless obtained because it is unknown in which orientation (and with what imaging plane) caregivers would use the device in an emergency. In addition, we performed measurements at a standardized location on the mid-thigh based on the recommended injection site. Additional variability in measurements could have been introduced if measurements had been performed in more proximal or distal areas of the thigh.¹⁷ Since our study cohort was predominantly white, our findings should be verified in ethnically and racially diverse populations. Finally, because of the age group in which this study was performed, we measured the distance to the bone noninvasively as a proxy for the risk of the autoinjector needle striking the bone, which may not account for real-world variations in needle angle or the risk of intraosseous infusion.

Conclusions

Our data suggest that the optimal needle length for an EAI for infants and toddlers weighing 7.5 to 15 kg should be shorter (measuring approximately 7–8 mm) than the needle length in current, commercially available pediatric EAI to avoid unintentional intraosseous injections. These findings have important implications for the design of safe EAI for this vulnerable population.

Acknowledgments

Editorial assistance was provided by Hester van Lier, PhD, and Ingeborg Streng-Ouwehand, PhD, of Excerpta Medica, funded by Sanofi. We are grateful to Aterica Health Inc (Waterloo, Ontario, Canada) for the use of their 3-dimensional printer.

Supplementary Data

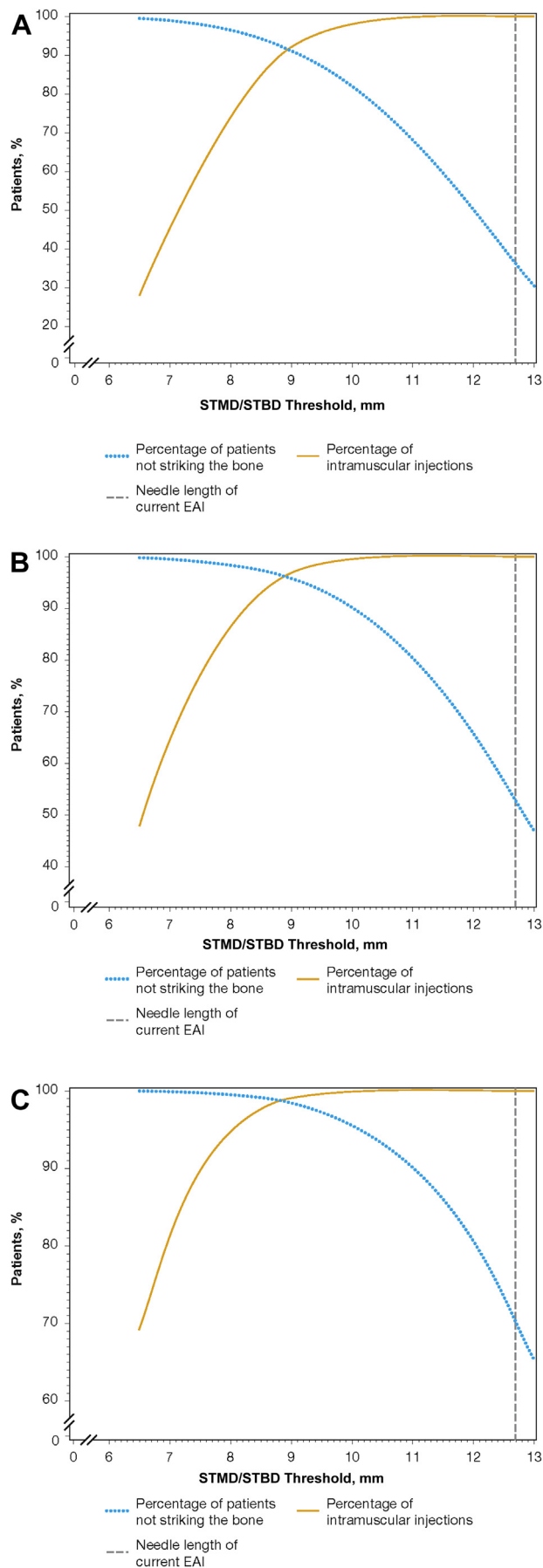
Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jana.2017.03.017>.

References

- [1] Simons FE, Arduzzo LR, Dimov V, et al. World Allergy Organization Anaphylaxis Guidelines: 2013 update of the evidence base. *Int Arch Allergy Immunol*. 2013;162:193–204.
- [2] Wasserman S, Watson W. Food allergy. *Allergy Asthma Clin Immunol*. 2011; 7(suppl 1):S7.
- [3] Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011; 128:e9–e17.
- [4] Rudders SA, Banerji A, Vassallo MF, Clark S, Camargo CA Jr. Trends in pediatric emergency department visits for food-induced anaphylaxis. *J Allergy Clin Immunol*. 2010;126:385–388.
- [5] AuviQ® Prescribing Information 2014. Bridgewater, NJ: Sanofi US, <http://products.sanofi.us/Auvi-Q/auvi-q.pdf>. Accessed March 2, 2016.

- [6] *Allerject™ Prescribing Information* 2013. Bridgewater, NJ: Sanofi US, <http://products.sanofi.ca/en/allerject.pdf>. Accessed March 2, 2016.
- [7] *EpiPen® Prescribing Information* 2012. Canonsburg, PA: Mylan, https://www.epipen.ca/sites/default/files/pdf/hcp/en/English_PL.pdf. Accessed March 13, 2016.
- [8] Center for Drug Evaluation and Research: Application 201739Orig1s000 (Intelliject). 2011. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/201739Orig1s000MedR.pdf. Accessed February 23, 2017.
- [9] Sicherer SH, Simons FE. Section on Allergy and Immunology, American Academy of Pediatrics. Self-injectable epinephrine for first-aid management of anaphylaxis. *Pediatrics*. 2007;119:638–646.
- [10] Fleischer DM, Perry TT, Atkins D, et al. Allergic reactions to foods in preschool-aged children in a prospective observational food allergy study. *Pediatrics*. 2012;130:e25–e32.
- [11] Halbrich M, Mack DP, Carr S, Watson W, Kim H. CSACI position statement: epinephrine auto-injectors and children < 15 kg. *Allergy Asthma Clin Immunol*. 2015;11:20.
- [12] Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis—a practice parameter update 2015. *Ann Allergy Asthma Immunol*. 2015;115:341–384.
- [13] Campbell RL, Bellolio MF, Knutson BD, et al. Epinephrine in anaphylaxis: higher risk of cardiovascular complications and overdose after administration of intravenous bolus epinephrine compared with intramuscular epinephrine. *J Allergy Clin Immunol Pract*. 2015;3:76–80.
- [14] Kim L, Nevis IF, Tsai G, et al. Children under 15 kg with food allergy may be at risk of having epinephrine auto-injectors administered into bone. *Allergy Asthma Clin Immunol*. 2014;10:40.
- [15] Brown JC, Tuuri RE, Akhter S, et al. Lacerations and embedded needles caused by epinephrine autoinjector use in children. *Ann Emerg Med*. 2016;67:307–315.e8.
- [16] Simons FE, Chan ES, Gu X, Simons KJ. Epinephrine for the out-of-hospital (first-aid) treatment of anaphylaxis in infants: is the ampule/syringe/needle method practical? *J Allergy Clin Immunol*. 2001;108:1040–1044.
- [17] Bewick DC, Wright NB, Pumphrey RS, Arkwright PD. Anatomic and anthropometric determinants of intramuscular versus subcutaneous administration in children with epinephrine autoinjectors. *J Allergy Clin Immunol Pract*. 2014;1:692–694.
- [18] Bhalla MC, Gable BD, Frey JA, Reichenbach MR, Wilber ST. Predictors of epinephrine autoinjector needle length inadequacy. *Am J Emerg Med*. 2013;31:1671–1676.
- [19] *SAS/QC® 9.3 User's Guide* 2011. Cary, NC: SAS Institute Inc, <https://support.sas.com/documentation/cdl/en/qcug/63964/PDF/default/qcug.pdf>. Accessed March 2, 2016.
- [20] Kim L, Nevis IF, Tsai G, et al. Do epinephrine auto-injectors have an unsuitable needle length for young children? *Allergy Asthma Clin Immunol*. 2014;10:A19.
- [21] Simons FE, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *J Allergy Clin Immunol*. 2001;108:871–873.
- [22] Simons FE, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol*. 1998;101:33–37.
- [23] Tsai G, Kim L, Nevis IF, et al. Auto-injector needle length may be inadequate to deliver epinephrine intramuscularly in women with confirmed food allergy. *Allergy Asthma Clin Immunol*. 2014;10:39.
- [24] Stecher D, Bulloch B, Sales J, Schaefer C, Keahey L. Epinephrine auto-injectors: is needle length adequate for delivery of epinephrine intramuscularly? *Pediatrics*. 2009;124:65–70.
- [25] Sheikh A, Simons FE, Barbour V, Worth A. Adrenaline auto-injectors for the treatment of anaphylaxis with and without cardiovascular collapse in the community. *Cochrane Database Syst Rev*. 2012;8:CD008935.
- [26] Edwards ES, Gunn R, Simons ER, et al. Bioavailability of epinephrine from Auvi-Q compared with EpiPen. *Ann Allergy Asthma Immunol*. 2013;111:132–137.
- [27] Schintler MV, Arbab E, Aberer W, Spindel S, Scharnagl E. Accidental perforating bone injury using the EpiPen autoinjection device. *Allergy*. 2005;60:259–260.
- [28] Sapien R, Stein H, Padbury JF, Thio S, Hodge D. Intraosseous versus intravenous epinephrine infusions in lambs: pharmacokinetics and pharmacodynamics. *Pediatr Emerg Care*. 1992;8:179–183.
- [29] Kanwar M, Irvin CB, Frank JJ, Weber K, Rosman H. Confusion about epinephrine dosing leading to iatrogenic overdose: a life-threatening problem with a potential solution. *Ann Emerg Med*. 2010;55:341–344.
- [30] Davis CO, Wax PM. Prehospital epinephrine overdose in a child resulting in ventricular dysrhythmias and myocardial ischemia. *Pediatr Emerg Care*. 1999;15:116–118.
- [31] Song TT, Lieberman P. Epinephrine auto-injector needle length: what is the ideal length? *Curr Opin Allergy Clin Immunol*. 2016;16:361–365.

Supplementary Data



eFigure 1. Estimated percentages of infants and toddlers in whom a given needle length would not strike the bone and estimated percentage of intramuscular administration according to weight in children weighing 7.5 kg (A), 11 kg (B), and 15 kg (C). EAI indicates epinephrine autoinjector.