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Epinephrine Auto-injectors: Is Needle Length Adequate for Delivery of Epinephrine Intramuscularly?

CONTRIBUTORS: Dawn Stecher, MD,^a Blake Bulloch, MD,^a Justin Sales, MD,^a Carrie Schaefer, MD,^b and Laine Keahey, MD^c

^aDepartments of Emergency Medicine, ^bRadiology, and ^cAllergy, Phoenix Children's Hospital, Phoenix, Arizona

KEY WORDS

anaphylaxis, epinephrine, epinephrine auto-injector, allergic reaction

ABBREVIATIONS

CI—confidence interval

ED—emergency department

CT—computed tomography

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Address correspondence to Dawn Stecher, MD, Phoenix Children's Hospital, Department of Emergency Medicine, 1919 E Thomas Rd, Phoenix, AZ 85016. E-mail: dstecher@phoenixchildrens.com

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WHAT'S KNOWN ON THIS SUBJECT: Epinephrine auto-injectors are used to treat anaphylaxis in the community. Experts now recommend that epinephrine be delivered intramuscularly instead of subcutaneously. The auto-injector needle length was not changed after this new recommendation was made.



WHAT THIS STUDY ADDS: This study shows that the needle on epinephrine auto-injectors is not long enough to deliver the medication intramuscularly in a significant number of children. These results suggest that the needle length should be increased to optimize the delivery of epinephrine.

abstract

OBJECTIVE: Studies show that intramuscular epinephrine results in peak plasma concentrations of epinephrine faster than the subcutaneous route, and therefore, epinephrine is recommended to be administered intramuscularly. The objective of this study was to determine if the needle length on epinephrine auto-injectors is adequate to deliver epinephrine intramuscularly in children.

METHODS: Patients between the ages of 1 and 12 years who presented to a children's hospital were enrolled in the study. Ultrasound was used to determine the depth from the skin to the vastus lateralis muscle. The patient's body mass index was recorded. The data were analyzed using simple descriptive statistics, and logistic regression was used to identify variables that might predict whether or not the needle length was exceeded.

RESULTS: A total of 256 children were enrolled. Of these, 158 children weighed less than 30 kilograms and would be prescribed the 0.15mg epinephrine auto-injector. Nineteen of these children (12%) had a skin to muscle surface distance of $> \frac{1}{2}$ " and would not receive epinephrine intramuscularly from current auto-injectors. There were 98 children weighing ≥ 30 kilograms who would receive the 0.3 mg epinephrine auto-injector. Of these 98 children, a total of 29 (30%) had a skin to muscle surface distance of $> \frac{5}{8}$ " and would not receive epinephrine intramuscularly.

CONCLUSION: The needle on epinephrine auto-injectors is not long enough to reach the muscle in a significant number of children. Increasing the needle length on the auto-injectors would increase the likelihood that more children receive epinephrine by the recommended intramuscular route. *Pediatrics* 2009;124:65–70

Anaphylaxis is defined as an “acute life-threatening reaction, usually but not always mediated by an immunologic mechanism, that results from the sudden systemic release of mast cells and basophil mediators” according to the Joint Task Force on Practice Parameters.¹ An anaphylactic reaction leads to a variety of symptoms involving multiple systems including cutaneous (urticaria, angioedema), cardiovascular (hypotension, dysrhythmias, myocardial ischemia), and gastrointestinal (nausea, abdominal pain, vomiting, diarrhea). Epinephrine has long been the treatment of choice for anaphylactic reactions. Recent studies have shown that in both children and adults, intramuscular epinephrine injected into the anterolateral thigh provides higher plasma concentrations of epinephrine faster than when using the previously recommended subcutaneous route.^{2,3} This quick spike of a high plasma concentration of epinephrine could be life-saving during an anaphylactic reaction. These findings led to a change in the practice of administering epinephrine subcutaneously for anaphylaxis. Expert consensus recommends injecting epinephrine intramuscularly into the anterolateral thigh at a dose of 0.01 mg/kg to a maximum of 0.5 mg, which may be repeated in 5 minutes if symptoms persist or worsen.⁴

Despite this recent change in the recommended administration route, the commercially available auto-injectors prescribed for emergency use in the community remain unchanged. The EpiPen (Dey, Napa, CA) auto-injector has a 22-gauge needle with a needle length of $\frac{5}{8}$ and $\frac{1}{2}$ in for the senior and junior pens, respectively. The TwinJect (Verus, San Diego, CA) auto-injector, which contains a second dose of epinephrine in case it is needed, has a 25-gauge needle with a needle length of $\frac{1}{2}$ in for the first injection and a length of $\frac{5}{8}$ in for the second injection, because the syringe and needle are re-

moved from the apparatus, exposing more of the needle for the second injection. The 0.3- and 0.15-mg versions of the TwinJect contain the same apparatus with the above-stated needle lengths.

With the previous recommendation to deliver epinephrine subcutaneously, all patients could use a similar needle length, because the needle only needed to traverse the epidermis and dermis. Because prompt delivery of epinephrine is potentially life-saving in an anaphylactic event, we need to ensure that children with anaphylaxis are being prescribed a medical device that will appropriately deliver the medication.⁵ With the new administration recommendation, it needs to be determined whether commercially available auto-injectors have sufficient needle length to deliver epinephrine intramuscularly to all users. In addition, the number of children who are overweight or obese has increased to an alarming 31.9% (95% confidence interval: 29.4%–34.4%) in recent years,⁶ which calls into question the ability of currently available auto-injectors to deliver epinephrine intramuscularly in many patients.

The objective of this study was to determine if the needle length on commercially available epinephrine auto-injectors is adequate for delivering the medication intramuscularly in children 1 to 12 years of age.

METHODS

This study took place in a freestanding, urban, tertiary care children's hospital in which the emergency department (ED) sees ~60 000 children per year. The hospital's institutional review board approved the study in July 2007. We used convenience sampling and enrolled patients when a research assistant or investigator was available. Patients between the ages of 1 and 12 years were prospectively obtained from 2 different areas. First, children who presented to the radiology department for an ultra-

sound, both inpatient and outpatient, were approached for enrollment. Second, ED patients were approached. Age was the only inclusion criterion. Children were excluded if they had a chronic disease that resulted in an abnormal growth pattern, including congenital heart disease, cystic fibrosis, failure to thrive, and autoimmune disorders. After obtaining informed consent, and informed assent for children aged 7 years or older, we used ultrasound to determine the depth from the surface of the skin to the surface of the vastus lateralis muscle. With the child in the supine position, the upper right leg was measured from the anterior superior iliac spine to the patella, and the midpoint between those landmarks on the lateral thigh was marked with a pen. The ultrasound probe was placed at this midpoint between the hip and the knee, over the lateral portion of the right midthigh, with minimal but enough pressure applied to obtain adequate images. This area is the recommended site for injection with an epinephrine auto-injector.⁴ Using the Phillips (Eindhoven, Netherlands) HDI 5000 12-5 linear array transducer, images were obtained in the sagittal plane, and the distance from the skin to the fascial layer of the muscle was measured in millimeters.

The patients' height and weight were recorded to calculate each patient's BMI. BMI percentiles were determined by using the 2000 clinical growth chart for children aged older than 2 years.⁷ For children younger than 2 years, BMI percentiles were determined on the basis of the National Health and Nutrition Examination Study standardized percentile curves for BMI.⁸ Each child's weight-status category was determined on the basis of the BMI percentile according to Centers for Disease Control and Prevention guidelines as follows: underweight, <5%; healthy weight, >5% and <85%; at risk of overweight, >85% and <95%; and

overweight, >95%.⁹ Additional patient information was collected, including age, gender, and ethnicity.

In a previous study using adults, it was found that only 1 of 50 men had a greater difference from skin to muscle than the EpiPen needle length, whereas 21 of 50 women had a greater difference.¹⁰ This represents a difference of 40% between the 2 genders. These results were used to estimate the statistical power needed to detect similar differences in our study population. To detect a 40% difference between boys and girls in our study at the .05 level of significance with 80% power, a sample of 32 boys and 32 girls would be needed. However, we were interested in examining male-female differences among 4 different age groups: 1 to 3, 4 to 6, 7 to 9, and 10 to 12 years. Therefore, 256 (128 boys and 128 girls) were enrolled, with 64 children in each age category. The data were analyzed by using simple descriptive statistics, and logistic regression was used to identify variables that might predict whether the needle length was exceeded. The Hosmer-Lemeshow test was used to assess the goodness of fit of the models.

RESULTS

A total of 256 children were enrolled: 128 (50%) girls and 128 (50%) boys. The ethnic backgrounds of our sample were Hispanic (47%), white (45%), black (4%), and other (4%). The age range was from 12 to 153 months, with a mean age of 82.7 months (6.9 years). When using the Centers for Disease Control and Prevention BMI percentiles for classification, a total of 70 (27.3%) children were found to be overweight, and 25 (9.8%) children were at risk for becoming overweight. A total of 158 children weighed <30 kg and likely would be prescribed the 0.15-mg epinephrine auto-injector, according to recommendations published in the package insert. The average distance from skin to muscle in

these children was 9.24 mm, with a range of 3.1 to 21.6 mm. Of these 158 children, 19 (12% [95% CI: 7%–17%]) had a skin to muscle surface distance of >½ in (Fig 1).

There were 98 children who weighed ≥30 kg. According to recommendations published in package inserts, these children would likely be prescribed the 0.3-mg epinephrine auto-injector. The average distance from skin to muscle in this group was 12.2 mm, with a range of 5.7 to 41.9 mm. Of these 98 children, a total of 29 (30% [95% CI: 21%–39%]) children had a skin to muscle surface distance of >½ in (Fig 2).

For each of the 2 weight groups (<30 and ≥30 kg), logistic regression analysis was performed to determine if age, BMI, gender, and/or race predicted whether the needle length was

exceeded. For both models, the Hosmer-Lemeshow test indicated that model fit was good. In the <30-kg group, both BMI and age had a statistically significant impact on the probability that needle length was exceeded. The higher the BMI, and the lower the age, the higher the probability that needle length was exceeded (Table 1). In the ≥30-kg group, only BMI had a statistically significant impact on the probability that needle length was exceeded. In this group, as well, the higher the BMI, the higher the probability that needle length was exceeded (Table 2).

LIMITATIONS

Convenience sampling of children presenting for ultrasound or to the ED may not be representative of children who use epinephrine auto-injectors. For prac-

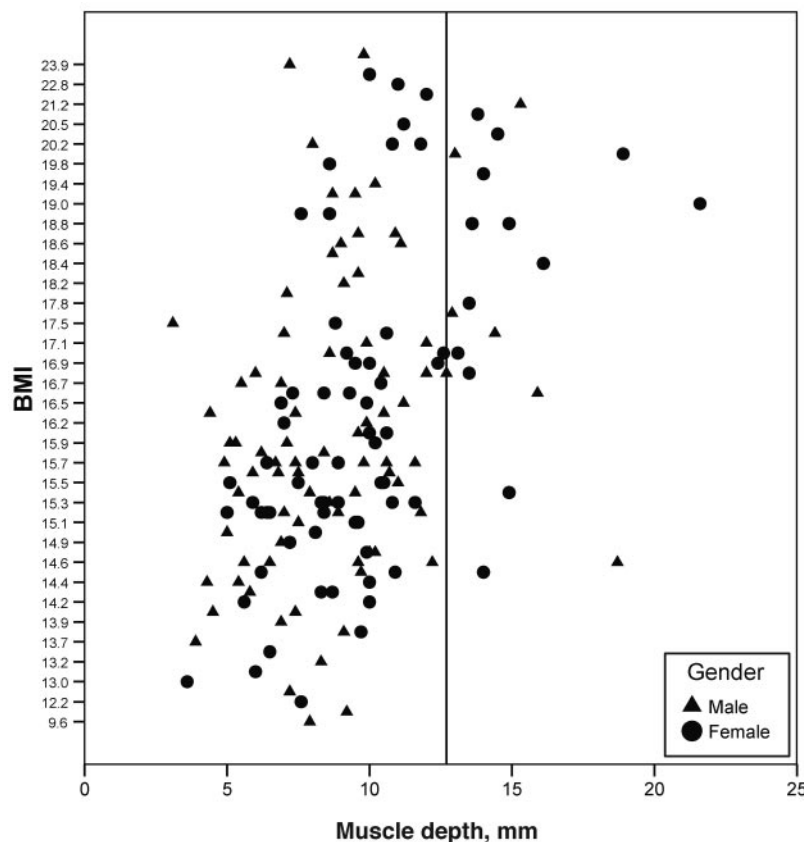


FIGURE 1

Scatter plot of depth to muscle from skin surface vs BMI (<30-kg group). The vertical line represents the length of the needle (12.7 mm).

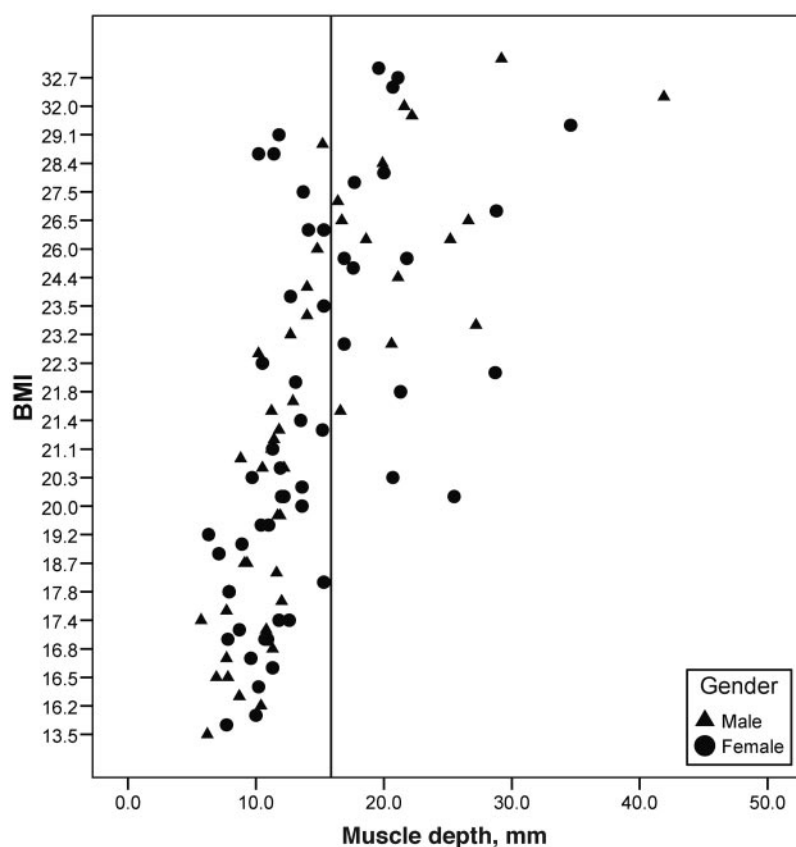


FIGURE 2 Scatter plot of depth to muscle from skin surface vs BMI (>30-kg group). The vertical line represents the length of the needle (15.8 mm).

tical reasons, this method of sample collection was deemed acceptable.

Using ultrasound with minimally applied pressure to the lateral thigh may not be accurate when considering that auto-injectors require application of some pressure to the overlying tissues. This pressure would result in a shorter distance from the skin to the muscle. For this reason, we measured only to the fascial layer of the muscle and assumed the added pressure would allow the needle to enter into the muscle compartment and guarantee intramuscular delivery of the medication. In addition, we analyzed our data by using an estimate of 25% for displacement of tissue with applied pressure from a previous adult study that originally used computed tomography (CT) to measure depth from skin to muscle. In a CT scan, there is no

pressure being applied to the lateral thigh. In this study, the ultrasound requires application of some pressure to obtain images. Therefore, this estimate of 25% displacement is likely an overestimate in this study.

Without randomized, controlled trials comparing efficacy and safety of intramuscular versus subcutaneous epinephrine during anaphylaxis, we assume that administration via the

intramuscular route is superior, because it leads to peak plasma levels of epinephrine much faster than when using the subcutaneous route.

DISCUSSION

In this study, it was found that the needle length on the commercially available epinephrine auto-injectors used on children with anaphylaxis is not long enough to reach the muscle in a significant number of children. Results showed that the higher a child's BMI, the less likely the needle length would be sufficient to deliver the medication intramuscularly.

On the basis of available data, no exact incidence for anaphylaxis can be established. However, it is reasonable to assume that 0.05% to 2% of the population may be affected.¹¹ In addition, there is underreporting of episodes, and the incidence of anaphylaxis seems to be increasing.^{11–13} Although anaphylaxis is not very common, it is a life-threatening disorder for which treatments are available.

A previous study was performed on adults by using CT scans of the lower extremity to measure distance from the skin to the vastus lateralis muscle.¹⁰ The investigators inferred from their CT findings that although the needle length was adequate to reach muscle in almost all (49 of 50) men, a number (21 of 50 [44%]) of women were found to have a greater depth to their muscle than the needle would allow for adequate administration.¹⁰ However, because the epinephrine auto-

TABLE 1 Logistic Regression Model Results for Children <30 kg in Weight

Variable	Odds Ratio			P
	Lower Confidence Limit	Point Estimate	Upper Confidence Limit	
Age	0.954	0.975	0.997	.027
Nonwhite ^a	0.675	1.999	5.921	.211
Gender ^b	0.119	0.358	1.077	.068
BMI	1.024	1.266	1.566	.030

Dependent measure = probability that needle length was exceeded. Hosmer-Lemeshow test of model fit: $\chi^2 = 5.98$ ($P = .650$).

^a Coded as 1 for nonwhite, 0 for white.

^b Coded as 1 for male, 0 for female.

TABLE 2 Logistic Regression Model Results for Children ≥ 30 kg in Weight

Variable	Odds Ratio			P
	Lower Confidence Limit	Point Estimate	Upper Confidence Limit	
Age	0.984	1.014	1.045	.360
Nonwhite ^a	0.155	0.516	1.711	.279
Gender ^b	0.335	1.114	3.705	.860
BMI	1.274	1.494	1.752	.001

Dependent measure = probability that needle length was exceeded. Hosmer-Lemeshow test of model fit: $\chi^2_2 = 5.72$ ($P = .679$).

^a Coded as 1 for nonwhite, 0 for white.

^b Coded as 1 for male, 0 for female.

injectors require somewhere between 2 and 8 lb of pressure to trigger the auto-injector, it was felt that these results might be erroneous. If the pressure applied to the leg displaces the subcutaneous fat, the distance to the muscle could possibly be reduced enough for the needle to reach the muscle. They then took 1 representative male and 1 representative female and performed an ultrasound with 0 and 8 lb of pressure to determine how much it decreased the depth of the muscle. They found that with the added pressure, the depth to the muscle was decreased by 25% in women and 19% in men.¹⁰ When correcting for this reduction in depth with applied pressure for the patients in the study, needle length was still insufficient in 14 (28%) women and 1 (2%) man.¹⁰

Obviously, when using an auto-injector in real life, the patient would apply some pressure to the tissues, which would effectively decrease the distance from the skin to the muscle. For this reason, we measured only to the fascial layer without any additional pressure applied to the probe, assuming that the tissue deformation that occurs when some pressure is applied would allow the needle to penetrate into the muscle fibers and deliver the medication intramuscularly. In our study, when reducing the depth from the skin to the muscle by 25%, the number of children in whom the needle would not reach the muscle was

reduced to 3 (2%) in the <30 -kg group and 13 (13%) in the >30 -kg weight group. However, extrapolating the amount of reduction in depth from skin to muscle with applied pressure from an adult population is likely inaccurate for children.

Recent changes in the recommendation to deliver epinephrine intramuscularly in the anterolateral thigh came from studies that showed that intramuscular epinephrine delivery is faster than subcutaneous.^{2,3} In children, intramuscular injection leads to a faster spike in plasma epinephrine levels (8 + 2 minutes intramuscular versus 34 + 14 minutes subcutaneous; $P < .05$) in addition to a higher peak plasma concentration (2136 + 351 pg/mL intramuscular versus 1802 + 214 pg/mL subcutaneous; P not significant).² The results from this study led to the recommendation of administering epinephrine intramuscularly instead of subcutaneously. In addition, studies have shown that a delay in administration of epinephrine is associated with an increased risk of fatality.⁵

The 2 commercially available auto-injectors in the United States and Canada are the TwinJect and EpiPen. Currently the needle length on the 0.3 mg EpiPen auto-injectors is 1.58 cm ($\frac{5}{8}$ in), while it is 1.27 cm ($\frac{1}{2}$ in) on the 0.15 mg EpiPen auto-injectors. The 0.15-mg TwinJect auto-injector has the same needle length as the EpiPenJr and would produce the same results in children

weighing <30 kilograms. In children weighing ≥ 30 kilograms, the 0.3 mg TwinJect would reach the muscle in fewer children than the EpiPen as it has a shorter needle ($\frac{1}{2}$ in).

We determined needle lengths for the different BMI categories to ensure that 95% of children would receive the medicine appropriately. A needle length of 2 cm would reach the muscle in 95% of children weighing ≥ 30 kg and with a BMI of $<85\%$. Ninety-five percent of children with a weight of ≥ 30 kg and a BMI of $>85\%$ would require a needle length of 3 cm to reach the muscle. Comparing these data with those from the adult study, it seems that these needle lengths would reach 95% of adults in their respective BMI categories as well.¹⁰

For the children weighing <30 kg and requiring the 0.15-mg auto-injector, a needle length of 1.5 cm for children with a BMI of $<85\%$, and a needle length of 2 cm for children with a BMI of $\geq 85\%$, would ensure that the needle is reaching the muscle in 95% of children.

On the other hand, if all 0.15-mg auto-injectors were made with a needle length of 2 cm and all 0.3-mg auto-injectors were made with a needle length of 3 cm, that would ensure intramuscular injection of epinephrine for $>95\%$ of all patients.

Another option would be to dispense epinephrine ampules/syringes/needles to caregivers with varying needle lengths on the basis of BMI. However, when this approach was studied, it was found that parents took a significantly longer time to draw up the dose when compared with controls, which included physicians and nurses ($P < .05$). There was also a problem with caregivers drawing inaccurate doses.¹⁴

CONCLUSIONS

The needle on the current epinephrine auto-injectors is not long enough to reach the muscle in a significant number

of children. Increasing the needle length on the currently available auto-injectors would ensure that children are receiving epinephrine by the recommended route.

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