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Original Contribution

Predictors of epinephrine autoinjector needle length inadequacy^{☆,☆☆,☆☆,★}Mary Colleen Bhalla, MD^{a,b,*}, Brad D. Gable, MD, MS^{a,b,c}, Jennifer A. Frey, PhD^a,
Matthew R. Reichenbach, MPH^d, Scott T. Wilber, MD, MPH^{a,b}^a Department of Emergency Medicine, Summa Akron City Hospital, Akron, OH, USA^b Northeast Ohio Medical University, Rootstown, OH, USA^c Ohio University, Athens, OH, USA^d Kent State University, Kent, OH, USA

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ABSTRACT

Background: Self-administered epinephrine is the primary out-of-hospital treatment of anaphylaxis. Intramuscular injection of epinephrine results in higher peak plasma concentration than subcutaneous injection. With the prevalence of obesity, autoinjectors may not have an adequate needle length for intramuscular injection.

Objectives: To measure muscle depth and evaluate predictors of autoinjector needle length inadequacy.

Methods: We performed a prospective cross-sectional study of a convenience sample of low acuity emergency department patients aged 18 to 55 years. We recorded demographic data, measured thigh circumference, and calculated body mass index (BMI). Using ultrasound, we took depth-to-muscle measurements of the vastus lateralis in a standing position, with and without gentle pressure to simulate muscle compression that occurs with correct autoinjector use. We conducted univariate analyses using χ^2 and t tests with $P \leq .05$ and 95% confidence intervals. We considered the patient a potential “failure” risk if his/her muscle depth exceeded 15.9 mm (longest available epinephrine autoinjectors needle).

Results: We enrolled 120 subjects with a mean BMI of 29.2 kg/m². Thirty-one percent (31%) of our sample were found to be failure risks (36/116; confidence interval, 22.6%–39.5%). Women were 6.4 times more likely than men to be a failure risk (54.4% vs 5% for men failure rate; $P < .001$). Failures were more likely to be shorter, have a higher BMI, and have larger thigh circumference ($P < .001$). We did not find any statistical difference in muscle depth for race, age, or weight.

Conclusion: The current epinephrine autoinjector needle length is inadequate for intramuscular injection, especially among women.

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1. Introduction

1.1. Background

Anaphylaxis is a serious allergic reaction that has a rapid onset and may cause death [1]. Self-administration of epinephrine during anaphylactic reactions is a lifesaving intervention [2,3]. Failure to inject epinephrine in a timely manner increases the risk of hypoxic-

ischemic encephalopathy and death [4]. Epinephrine autoinjectors have become the mainstay of therapy for the self-treatment of anaphylactic reactions outside the hospital [3]. Studies have shown that intramuscular (IM) administration of epinephrine results in higher peak plasma concentrations when compared with subcutaneous (SQ) administration [5]. In fact, a study by Simon et al [5] on adult volunteers found that there was actually no difference in plasma epinephrine levels between SQ epinephrine and SQ saline. Epinephrine concentrations were also found to be higher when injected into the vastus lateralis than the deltoid muscle [5]. The 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care recommend the IM route over SQ administration for epinephrine given for anaphylaxis [6]. The National Institute of Allergy and Infectious Diseases 2010 guidelines for the management of food allergy also recommends IM epinephrine injection with an autoinjector or a 1:1000 solution for the first-line treatment of anaphylaxis [1]. They recommend the epinephrine be injected into the anterior-lateral thigh [1].

There are several commercially available epinephrine autoinjectors available internationally. The 2 most commonly prescribed

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* Corresponding author. Department of Emergency Medicine, Summa Akron City Hospital, 525 East Market St., Akron, OH 44304-1619, USA. Tel.: +1 330 375 7530; fax: +1 330 375 7564.

E-mail addresses: bhallam@summahealth.org, mcmcquown@yahoo.com (M.C. Bhalla).

autoinjectors in the United States are EpiPen (Mylan Inc, Canonsburg, PA) and Twinject (Amedra Pharmaceuticals LLC, Horsham, PA). There is another autoinjector that is new to the market called Auvi-Q (Sanofi-Aventis U.S. LLC, Bridgewater, NJ). It has a 23-gauge needle with a length of 0.62-in. (15.7 mm). The needle of the EpiPen is a 22 gauge needle with a length of 5/8 in. (15.9 mm). The Twinject needle is a 2-needle injection system, with the first injection being given as an autoinjector with a 25-gauge needle with a length of 1/2 in. (12.7 mm) and the second being given as preloaded syringe with a 5/8-in. (15.9 mm) needle. Amedra Pharmaceuticals has a second product called Adrenaclick, which is the same autoinjector as the Twinject but is packaged without the second preloaded syringe. EpiPen is US Food and Drug Administration approved for IM injection [7]. Although SQ administration of epinephrine for the treatment of anaphylaxis is not recommended by the American Heart Association or the National Institute of Allergy and Infectious Diseases, Twinject and Adrenaclick are both US Food and Drug Administration approved for both IM and SQ administration [8].

1.2. Importance

Obesity is a growing problem in the United States. In 2009 to 2010, the overall prevalence for the country was 35.9% [9]. Obesity is defined as a body mass index ($BMI = \text{weight (kg)} / [\text{height (m)}]^2$) of at least 30 kg/m^2 , and overweight is defined as a BMI between 25 and 29.9 kg/m^2 [10]. In 2009 to 2010, the prevalence of adults in the United States who were overweight (and not obese) was 33.3% [11]. Given that 69.2% of adults in the United States are either overweight or obese, the currently available epinephrine autoinjectors may not have an adequate needle length to deliver an IM injection of epinephrine.

1.3. Goals of this investigation

Knowing a patient's muscle depth might predict those patients who would not get IM delivery of epinephrine using an autoinjector. Here, we propose to measure the muscle depth of adults via ultrasound at the position and location instructed by manufacturers of epinephrine autoinjectors. We hypothesize that (1) the currently available autoinjectors are insufficient for IM administration in many patients, (2) SQ soft tissue may be compressed and decrease muscle depth, and (3) muscle depth is dependent on sex, BMI, and thigh circumference. We also sought to determine if there is an ideal needle length.

2. Methods

2.1. Study design and setting

We performed a prospective, cross-sectional study in the emergency department (ED) of a large urban adult tertiary care center with more than 77 000 ED visits per year. Our institutional review board approved our study.

2.2. Selection of participants

Trained research staff recruited subjects. Patients were approached for participation after their initial ED evaluation was complete. Our initial screening for inclusion started with reviewing the current ED census on the computer for age and acuity level. (Acuity level is assigned by the triage nurse using Emergency Severity Index.) Then the attending caring for the patient was approached to see if the patient was well enough to stand for the study. The attending caring for the patients were blinded to the nature of the study. This was a convenience sample of all patients in the ED at the time the research assistant was available who were eligible for screening for inclusion and exclusion criteria. Once patients were

identified as being eligible for enrollment, every effort was made to enroll him or her before discharge to prevent selection bias. The only barrier to screening for enrollment was the availability of the research team, which typically occurred between 8:00 AM and 6:00 PM.

2.3. Inclusion criteria

Patients aged 18 to 55 years who presented to the ED when the research staff was present were eligible. We screened patients for inclusion only if they had been triaged as low or moderate acuity by the nursing staff. We chose the lower limit of 18 because we have a primarily adult population at our ED. We chose the upper limit of 55 because we wanted to focus on enrolling low acuity patients who could stand.

2.4. Exclusion criteria

We excluded patients with amputations or unformed limbs. In addition, patients unable to stand for measurements were excluded. We also excluded patients unwilling to participate, those for whom the measurement procedures are medically contraindicated in the opinion of the treating physician, those unable to speak or understand the English language, and those who previously participated in the same study.

2.5. Data collection

We collected demographic information including patient race, sex, age, measured weight, and self-reported height.

To assure that measurements were obtained from the same anatomical position on all patients, we set up a standardized approach that would mimic the exact same location on the lateral thigh over the vastus lateralis indicated in the EpiPen visual instructions [12]. With the patient standing and arms at their side and supinated, we marked with a surgical marking pen the place where their index finger metacarpal-phalangeal joint rested against the thigh. We took 2 depth-to-muscle ultrasound measurements with a Siemens' Acuson X300 (Mountain View, CA) ultrasound using a wide-bandwidth linear transducer (VF8-3; 2.5–10.0 MHz). We obtained the first image with just enough pressure to get an adequate image and the second with tactile pressure mimicking the pressure provided with proper autoinjection (Fig. 1). The trained research staff visualized the soft tissue while performing the compression and froze the screen for measurement when the soft tissue was maximally compressed. We recorded the measurements for the subjects in both the minimal compression and the maximum compression views with the ultrasound in the frozen screen mode. Each image screen shot also included the femur for reference (Fig. 1). We trained the research staff on the use of the ultrasound on volunteers before enrolling any patients. All research staff were trained on the same ultrasound by the same member of the research team. The same ultrasound machine was used to enroll all patients. All research staff who enrolled patients were observed during the training and their initial enrollment period to assure they were taking all images and measurements correctly. All images were stored with deidentified subject study numbers assigned.

We then obtained thigh circumference measurements at the same body position as those used for the muscle depth. We used a body measuring tape that provided uniform tension to every measurement to allow for interuser reliability.

2.6. Power analysis

This was a pilot study, and depth prediction could not accurately be obtained before performing the study, which precluded us from calculating sample size. The statistical comparisons are thus for

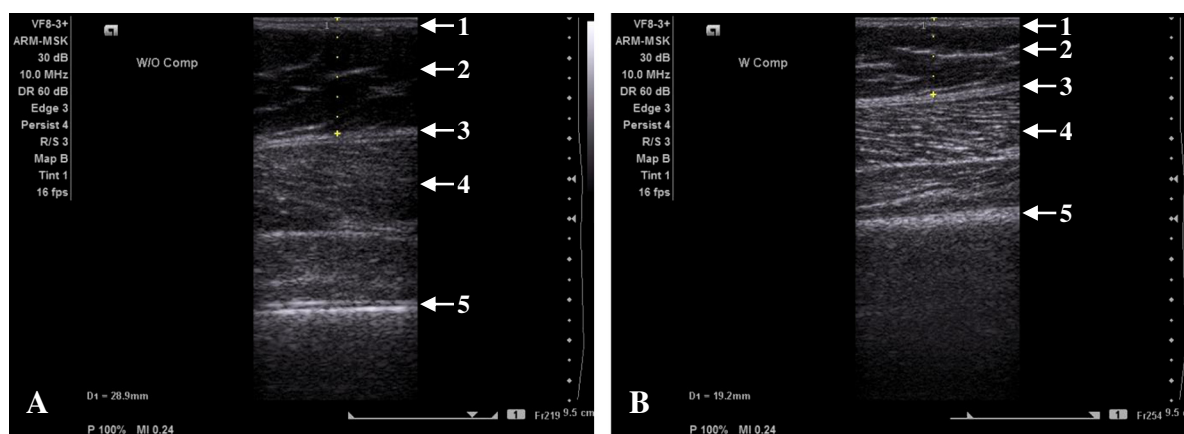


Fig. 1. Ultrasound images of muscles with anatomical labels. A, Uncompressed muscle. B, Compressed muscle. (1) Skin, (2) fat, (3) fat-muscle junction, (4) muscle, and (5) bone.

exploratory purposes because inferential comparisons may not be statically significant due to lack of power. We chose to enroll 60 men and 60 women a priori.

2.7. Outcome measures

Our primary outcome measure of interest was epinephrine autoinjector “failure,” which is whether or not adequate IM delivery of epinephrine would occur with self-administration of an epinephrine autoinjector. We categorized epinephrine autoinjector status as either a success or a failure risk if compressed muscle depth to a patient's vastus lateralis was less than or equal to 15.9 mm or was greater than 15.9 mm, respectively. We selected the value of 15.9 mm because it is the longest needle length of the currently available autoinjectors.

2.8. Statistical analyses

For all summary statistics and statistical analyses, we used the R2.14.1 software environment (R Development Core Team, 2011) [13]. We calculated the percentage of autoinjector failure with 95% confidence intervals (CIs). We used the Pearson χ^2 test to compare the prevalence of epinephrine autoinjector failures with and without tissue compression. We conducted univariate analyses of the relationships shared between our potential predictor variables of sex, BMI, and thigh circumference and epinephrine autoinjector status by using Pearson χ^2 tests and 2-tailed, independent t tests for categorical and continuous variables, respectively, at the 5% level of significance ($P \leq .05$) with appropriate 95% CI. We calculated Pearson correlation coefficients for the independent associations that compressed muscle depth shares with BMI and thigh circumference to assess whether or not these patient characteristics can serve as potential predictors of epinephrine autoinjector failure risk.

Lastly, we identified the epinephrine autoinjector needle length that would be needed to achieve a failure risk rate of 5% for epinephrine autoinjectors among the patients in the study.

3. Results

3.1. Characteristics of study subjects

Our study ($n = 120$) was composed of 60 men and 60 women, 60.8% of which were white (95% CI, 52.1–69.5), with an average age of 36 years (range, 18–55 years) and a mean BMI of 29.2 kg/m² (range, 17.3–61.5 kg/m²; Table 1). Seventy percent of our subjects were obese or overweight (95% CI, 61.8%–78.2%; BMI ≥ 25 kg/m²). Our study subjects had mean thigh circumferences of 58.2 cm (95% CI, 56.4–60.0

cm), a mean uncompressed muscle depth of 18.9 mm (95% CI, 16.3–21.4 mm), and a mean compressed muscle depths of 13.4 mm (95% CI, 11.6–15.2 mm).

3.2. Main results

Thirty-one percent (31%) of our sample (36/116; 95% CI, 22.6–39.5) were at risk for epinephrine autoinjector failure because these ED patients had compressed muscle depths exceeding 15.9 mm when intramuscularly delivered with pressure being applied to the injection site (Table 2). On the other hand, almost half of the ED patients (58/120) had uncompressed muscle depths exceeding 15.9 mm; thus, the prevalence of epinephrine autoinjector failures among ED patients is between 40.9% and 59.1% when injection is attempted without pressure being applied to the injection site. As such, there is no overlap between these 95% CIs; thus, application of pressure impacts epinephrine autoinjector status among ED patients ($P < .001$). However, even ED patients applying pressure during epinephrine autoinjector administration may not be adequate to allow successful IM delivery of epinephrine (Table 2).

Women in this sample were 6.4 times (95% CI, 3.1–15.5) more likely to be at risk for an epinephrine autoinjector failure in comparison with men ($P < .001$; Table 2). Men had a mean BMI of 28.8 kg/m² (95% CI, 27.2–30.4) and a mean thigh circumference of 56.0 cm (95% CI, 53.8–58.2). Women had a mean BMI of 29.6 kg/m² (95% CI, 27.6–31.7) and a mean thigh circumference of 60.5 cm (95% CI, 57.8–63.2). Subjects who were at risk for epinephrine autoinjector failures were more likely to be shorter, have a higher BMI and thicker thighs, and have a larger depth to thigh muscle compared with

Table 1
Characteristics of study population

Demographics	
Sex, n (%)	
Male	60 (50.0)
Female	60 (50.0)
Race, n (%)	
White	73 (60.8)
Nonwhite	47 (39.2)
Age (y), mean (SD)	36.0 (11.6)
Body composition, mean (SD)	
Height (in.)	67.0 (3.7)
Weight (lb)	187.2 (50.8)
BMI (kg/m ²)	29.2 (7.4)
Thigh measurements, mean (SD)	
Circumference (cm)	58.2 (9.8)
Uncompressed muscle depth (mm)	18.9 (13.9)
Compressed muscle depth (mm)	13.4 (9.9)

Table 2

Characteristics of subjects with regard to epinephrine autoinjector failure

	Success	Failure	URR or MD (CI)	P
Total	80	36		
Demographics				
Sex, n (%)				
Male	54 (91.5)	5 (8.5)	Reference	<.001
Female	26 (45.6)	31 (54.4)	64 (3.1 to 15.5) ^a	
Body type, n (%)				
Normal (BMI 18.5–24.9 kg/m ²)	30 (83.3)	6 (16.7)	0.4 (0.2 to 0.7) ^a	.009
Overweight (BMI 25–29.9 kg/m ²)	24 (75.0)	8 (25.0)	0.6 (0.3 to 1.1) ^a	.071
Obese (BMI 30+ kg/m ²)	26 (54.2)	22 (45.8)	Reference	
Race, n (%)				
White	49 (70.0)	21 (30)	Reference	
Nonwhite	31 (67.4)	15 (32.6)	1.1 (0.6 to 1.9) ^a	.77
Age (y), mean (SD)	36.8 (12.1)	34.3 (11.0)	−2.5 (−7.1 to 2.0) ^b	.28
Body composition, mean (SD)				
Height (in.)	68.1 (3.5)	64.6 (2.8)	−3.5 (−4.7 to −2.3) ^b	<.001
Weight (lb)	182.3 (45.3)	198.6 (62.3)	16.3 (−6.9 to 39.5) ^b	.16
BMI (kg/m ²)	27.6 (6.0)	31.8 (8.8)	5.8 (2.5 to 9.0) ^b	<.001
Thigh measurements, mean (SD)				
Circumference (cm)	55.2 (7.5)	64.9 (11.2)	9.7 (5.6 to 13.8) ^b	<.001
Uncompressed muscle depth (mm)	11.6 (6.6)	35.0 (12.2)	23.4 (19.0 to 27.8) ^b	<.001
Compressed muscle depth (mm)	8.4 (4.0)	24.6 (9.9)	16.2 (12.8 to 19.7) ^b	<.001

URR, unadjusted relative risk; MD, mean difference.

^a Values are presented URR (CI).^b Values are presented MD (CI).

subjects with predicted successes in this population ($P < .001$). Patients with normal BMIs are, on average, 60% less likely to be at risk for a failure in comparison with obese patients ($P = .009$; Table 2). We did not find statistically significant differences between epinephrine autoinjector successes and failures by race, age, or weight. There were missing data on thigh circumference from 4 patients and muscle depth from 5 patients, and thus, they were not included in those calculations.

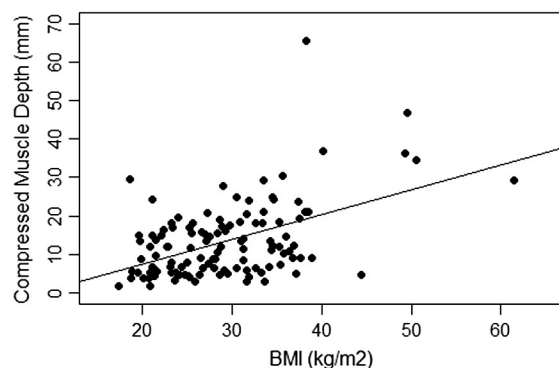
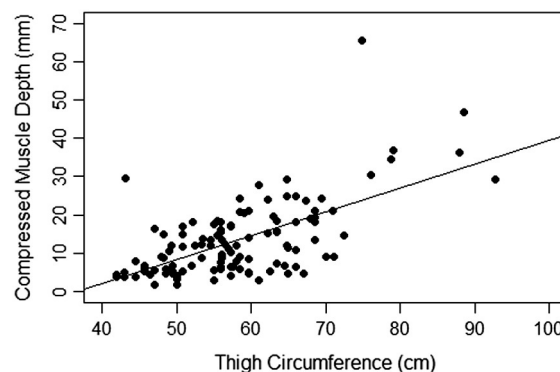
From our correlation analyses, we found significant associations between compressed muscle depth and BMI ($r = 0.48$; $P < .001$) as well as between compressed muscle depth and thigh circumference ($r = 0.62$; $P < .001$; Figs. 2 and 3). Thigh circumference and BMI account for 39% and 23%, respectively, of the variance in compressed muscle depth of ED patients in this sample.

We found that we would need a needle length of 29.6 mm to successfully deliver epinephrine via the IM route with only a 5% failure risk rate (95% CI, 1%–9%). This is almost double the length of the longest available epinephrine autoinjector needle. We also found that the needle length would need to be 17.6 and 34.5 mm for men and women in this study sample, respectively, to achieve an epinephrine autoinjector failure risk rate of approximately 5% for each sex.

4. Limitations

Our study is limited because we only theorized which patients would have failed to achieve an IM injection of epinephrine. A true but impractical method of evaluation would have been to inject the patients and measure their plasma concentrations levels. Further studies are needed to determine the plasma concentrations of epinephrine in patients with different muscle depths or to investigate alternative sites for injection in those patients with deep muscles. Other limitations include the fact that this study enrolled a convenience sample that was done when the research team was available. We attempted to enroll all patients who were eligible for screening for inclusion and exclusion criteria when the research team was available to prevent selection bias. We do feel that from a body habitus standpoint, our patients were representative of a general population because nationally, 69.2% of adults are overweight or obese [9,11]. This study was also conducted on patients in an ED, so it is unknown if our results can be generalized to a non-ED population.

Another limitation was the use of an ultrasound transducer to compress the soft tissue rather than an actual epinephrine autoinjector. It is possible that using the actual autoinjector would result in

**Fig. 2.** BMI and compressed muscle depth.**Fig. 3.** Thigh circumference and compressed muscle depth.

more or less tissue compression than with the ultrasound. We were unaware that ultrasound probes were available with that depth of penetration that would be similar to the size of an autoinjector tip, so we were unable to compare. The research team found no difficulty in maximally compressing the soft tissue, and we did not receive patient complaints that we were pushing too hard, so we feel that the results are valid. Another study could be conducted with a newly created ultrasound transducer that attaches to an autoinjector to see the exact depth the needle can penetrate with compression from only the autoinjector. In real life, there would be variability in how much pressure an individual applies when using the autoinjector on oneself or another person, but we obtained all of our measurements using ultrasound to indicate maximal soft tissue compressibility.

5. Discussion

Timely IM injection of epinephrine is the standard of care for treatment of anaphylaxis [1]. In cases of anaphylaxis with respiratory or cardiac arrest, the median time from exposure to arrest is 30 minutes for food, 15 minutes for venom, and 5 minutes for iatrogenic reactions [14]. If an epinephrine autoinjector needle is too short to reach the muscle, the medication may be injected subcutaneously. A study performed in children found that time to mean maximum plasma epinephrine concentrations was 8 ± 2 minutes for IM injection and 34 ± 14 minutes for SQ injection [15]. Giving epinephrine subcutaneously instead of intramuscularly could, in theory, result in death owing to the time to maximum plasma concentration of epinephrine.

Two studies have previously looked at muscle depth to evaluate the adequacy of epinephrine autoinjector. One previous study performed on children measured muscle depth using ultrasound. They found that 30% of pediatric patients weighing greater than 30 kg had a skin-to-muscle depth greater than the EpiPen needle length of 5/8 in. (15.9 mm) and 12% of patients weighing less than 30 kg had a skin-to-muscle depth greater than the EpiPen Junior needle length of 1/2 in. (12.7 mm) [16]. Their protocol placed the ultrasound probe on the skin with only enough pressure to obtain quality images [16]. Only one study thus far has attempted to measure muscle depth for purposes of evaluation of autoinjector needle length in adults. Song et al [17] used computer tomography scan of the thigh to measure depth. They compared muscle depth to a needle length of 14.3 mm and found that 2% (1/50) of men and 42% (21/50) of women studied had a skin-to-muscle depth that exceeded 14.3 mm [17]. They estimated the affect of soft tissue compression on muscle depth using ultrasound on 1 woman and 1 man and found a compressibility of 25% on the woman and 19% on the man. Using that estimate to the overall results would predict 2% of men failing (1/50, no change) and 28% of women (14/50, 7 fewer failures). They did not test the compressibility on any other subjects, however, and it is therefore unknown if this is a truly generalizable compression percentage. Both of these studies measured muscle depth of the lateral thigh with the patient in the supine position. The EpiPen manufacturer instructions state that the device is to be swung and firmly pushed against the outer thigh so the unit is perpendicular to the thigh [12]. The accompanying photographs on the instructions show a subject standing to use the autoinjector [12]. The instructions also state that the autoinjector is designed to work through clothing [12]. If one were giving it through clothing, it might make the needle reach a shallower depth.

To date, our study is unique for several reasons. First, no previous study has looked at using ultrasound in adults to measure muscle depth of the lateral thigh. Second, we took measurements on all of the adults to mimic the soft tissue compression and found that 22 of the 120 study patients had a muscle depth less than 15.9 mm only with soft tissue compression and exceeded this muscle depth without compression. We also used a failure length of 15.9 mm, which is the length of the longest available epinephrine autoinjector needle,

whereas Song et al [17] used a length of 14.3 mm. Both the study by Song and the pediatric study measured the patient in a supine position, which may change the distribution of SQ tissue over the lateral thigh when compared with a standing position. We obtained our depth-to-muscle measurements in the position described by the autoinjector manufacturers.

We found our results interesting and comparable with the failure rates found with the pediatric and adult populations previously studied. However, what was most striking was the failure rate of women compared with men. The study by Song et al [17] also found that women are more likely to have a greater muscle depth than men. In our study, there was no statistical difference between men and women for their mean BMI or thigh circumference. The disproportionate failure rate may be caused by the differences of adipose tissue distribution in men and women. Premenopausal women tend to have “gynoid” obesity or lower body adiposity more frequently than men who tend to have “android” obesity [18]. The lower body adiposity may be a lower risk for cardiovascular disease but has a disadvantage for IM injections in the thigh. In our study, we found a mean thigh circumference of 58.2 cm for our entire study population, which is larger than the mean thigh circumferences of 52.9 and 53.8 cm found in women and men, respectively, 20 years and older described by the US National Health Statistics Reports [19]. These data were from 2003 to 2006, and it is possible that the average person now has a larger thigh because obesity is increasing. Our percentage of study subjects who were overweight or obese (70%) was very similar to the percentage of the population of the United States (69.2%) [9,11].

In the study of Song et al [17], there was no difference in BMI between failure and success (28.1 vs 26.9 kg/m²); however, in the pediatric study of Stecher et al [16] for the group weighing more than 30 kg, the higher the BMI, the higher the probability that the needle length was exceeded. We did find a mean difference in BMI between our successes and failures. We did not find a mean difference in weight between our successes and failures, despite a difference of 14 lb. It may be that BMI is a better predictor of body habitus and muscle depth because it accounts for height.

We can conclude that the current needle length is far from adequate, across this sample, especially among women. We believe that an increase in sample size for both sexes would likely identify an even greater need for a change in the standard “one size fits all” needle length for IM delivery of epinephrine via autoinjectors among adult ED patients experiencing anaphylaxis. It would be impractical for one needle length to work for all patients. For our sample, a needle length of 34.5 mm would be needed to achieve IM delivery in 95% of women studied. This length would be far too long for some of our patients and would actually hit the femur. (Measuring distance to bone was not part of our original research plan; however, every measurement image was stored and every image included the femur. We randomly reviewed a few of the images and the femur depth.) One solution would be to have autoinjectors available in several different needle lengths. Prescribing may be difficult, however, if one does not have access to an ultrasound. Doing a study with a bigger sample size would be needed to develop a regression model to predict muscle depth with other measurements and may overcome this prescribing limitation. We did find that no patient with a thigh circumference greater than 80 cm or a BMI greater than 40 kg/m² had a muscle depth less than 15.9 mm, but this only applied to a handful of patients in our study sample (Figs. 2 and 3). An alternative would be an autoinjector that senses the change from SQ to muscle tissue during needle advancement and stops at the correct depth. Further research and development is needed to produce an improved and effective out-of-hospital epinephrine delivery system.

In conclusion, we found that currently available autoinjectors are inadequate for IM injection in the population studied, especially among women.

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