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Excess subcutaneous tissue may preclude intramuscular delivery when using epinephrine autoinjectors in patients with anaphylaxis

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Abstract

Intramuscular epinephrine is the gold standard treatment for anaphylaxis. Intramuscular injection provides more rapid and higher plasma concentrations than subcutaneous routes. Given the increasing epidemic of obesity patients are at increased risk of subcutaneous delivery, we therefore assessed the depth of subcutaneous tissue in a population of patients with anaphylaxis.

Patients already prescribed epinephrine autoinjectors (EAIs) for anaphylaxis were examined with ultrasound and measurements of skin-to-muscle depth (STMD) at anterolateral thigh and anterior thigh were performed.

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28 patients (23 female, 5 male) with an age range of 18-75 took part in the study and in 68% the STMD was greater than EAI needle length (15.02mm) using the anterolateral thigh, the recommended administration site. The key predictors for increased STMD were female gender ($p = 0.0003$) and a BMI > 30 ($p = 0.04$). EAIs require longer needles to ensure intramuscular administration and ultrasound at point of prescription would aid needle length selection.

Keywords: Anaphylaxis, Autoinjector, Epinephrine, Skin-to-muscle depth

Introduction

Anaphylaxis is a life threatening allergic reaction causing around 20 deaths per year in the UK and is becoming more common (1). One UK study showed a rising incidence and prevalence, 19% and 51% respectively, between 2001 and 2005 and the 2013 EAACI Food Allergy and Anaphylaxis Group found an incidence of 1.5-7.9 per 100 000 person-years (2, 3).

Intramuscular epinephrine is the gold standard treatment for anaphylaxis and EAACI anaphylaxis guidelines recommend injection into the vastus lateralis muscle in the anterolateral thigh (4). Simmons *et al.* showed that intramuscular delivery produces faster and greater peak plasma epinephrine concentrations than subcutaneous delivery (5). Most episodes of anaphylaxis occur outside of medical facilities and therefore require the use of self-administered epinephrine autoinjectors (EAI). Early self-administration of epinephrine has been shown to improve outcomes including mortality (6).

Given the increasing obesity epidemic affecting adults and children in Europe, with 52.6% being either overweight or obese, there is growing concern whether current EAIs can reliably deliver intramuscular epinephrine (7). Song *et al.*, in a general population, demonstrated using CT scanning that they would not in 22% of adults and Stetcher similarly showed likely EAI failure in 30% of children over 30kg and 19% under 30kg, using ultrasound scanning (8, 9). Only one trial, a paediatric study by Bewick, has looked at allergy patients and showed, using ultrasound, just over 20% of children had a STMD greater than the EAI needle length (10). Therefore, we decided to look at a group of adult allergy patients attending a local allergy clinic and assess their STMD using ultrasound.

Methods

The study was an opportunistic sample of patients previously prescribed an EAI for a clinical history of anaphylaxis by a non-allergy specialist who subsequently attended our specialist allergy clinic at Worcester Royal Hospital during 2013.

A Sonosite ultrasound machine with 13.6mh probe was used to measure the STMD of the anterolateral thigh and anterior thigh. 3 measurements were taken at each site and the mean calculated. Measurements were taken by a single observer trained in the use of the ultrasound machine by a Consultant Radiologist. We also recorded age, sex and BMI.

The analysis was done on SPSS using an independent t-Test for age, Man Whitney U for BMI, Chi Squared for gender and Spearman's rho for correlation. A review by Schwartz found that the mean exposed needle length of the most commonly used EAI (EpiPen) was 15.02mm (11). We therefore compared the STMD to this.

Written consent was obtained from all patients and ethical approval was successfully obtained (12).

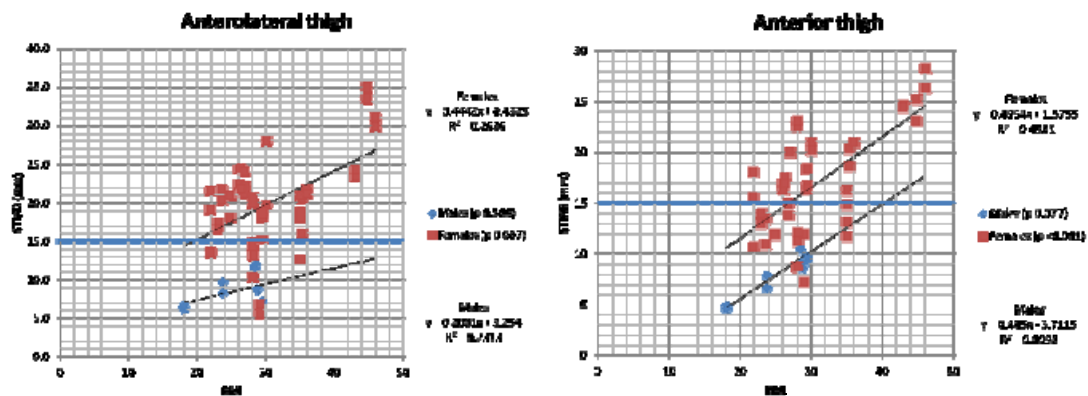
Results

28 patients took part in the study with female to male ratio 23:5, age range 18-75 and BMI 18-44. STMD for the anterolateral thigh ranged from 6.6mm to 33.5mm. In 19 patients (68%) the STMD was greater than EAI needle length. This number was reduced to 50% for the anterior thigh. This data is summarised in table 1.

	All Patients	Anterolateral thigh		P value	Anterior thigh		P value
		STMD > AAI needle length	STMD < AAI needle length		STMD > AAI needle length	STMD < AAI needle length	
STMD mm	18.39 (7.21) (anterolat) 15.29 (5.76) (ant)	22.26 (4.84)	10.2 (3.40)		19.61 (3.84)	10.29 (2.67)	
BMI	28.25 (25.1-33.75)	29.4 (26-35.3)	28.19 (22.8-28.85)	0.188	29.4 (26.8-36)	28 (23.25-28.85)	0.033
Age	49 (14.52)	47.68 (12.54)	52.25 (19.02)	0.55	47.73 (12.79)	50.67 (16.77)	0.62
Female:male	23:5	19:0	4:5	0.0003	15:0	8:5	0.008

Table 1 – Summary of data for anterolateral and anterior thigh divided into those where STMD was greater or smaller than the needle length with BMI, age and gender distributions for each category (Means and SD displayed for normally distributed data and medians and interquartile ranges for non-normally distributed data)

Female gender was significantly associated with an increased STMD with 87% of women having a STMD greater than the EAI needle at the anterolateral thigh compared to 0% of men (p 0.0003). There was a higher range of BMI for women (21.9-46) compared to men (18-29.4) but even patients with similar BMI's women still had greater STMD. Increasing BMI was also found to correlate with increasing STMD (see figure 1) with only 1 of 16 (p 0.04) with a BMI over 30 having a STMD smaller than the EAI needle in the anterolateral thigh group.



ey – Blue line equals the mean length of an EpiPen needle (15.02mm), Black line equals line of best fit

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Figure 1 - Scatter plots showing the relationship between STMD, BMI and gender for each anatomical site

Discussion

This is the first study looking at adult allergy patients and it shows that a significant number of patients (68%) have a STMD greater than that of an EAI needle. The patients at most risk of failure to deliver an intramuscular dose are females, even with a normal BMI, and patients with a BMI greater than 30. The anatomical site that had the highest proportion of patients with a STMD greater than an EAI needle was the current recommended injection site, the anterolateral thigh.

Studies by Simmons *et al.* have concluded that intramuscular administration results in a quicker time to peak plasma concentrations and it is widely held that this rapid peaking is responsible for the reversal of anaphylaxis induced hypotension and thus subsequent survival (6, 13). Unfortunately, due to ethical constraints, there is no experimental evidence confirming this. However, the fact that the median time from exposure to respiratory or cardiac arrest is 30 minutes for food, 15 minutes for venom, and 5 minutes for iatrogenic reactions, and the mean time for peak plasma levels of epinephrine with subcutaneous delivery being 34 minutes, compared to 8 minutes with intramuscular delivery, would suggest the theory has a sound basis (14).

Counter arguments suggesting that the force with which an EAI is used overcomes the discrepancy between STMD and needle length have mostly relied on animal cadaver studies or synthetic ballistics (10, 11). These studies only show EAI can deliver epinephrine deeper than the needle length but not cross fascia. A recent study by Dianco has confirmed that this is not possible meaning only subcutaneous delivery is possible when STMD is greater than needle length (15). Further to this, studies in children show the compression that occurs when using an EAI does not significantly reduce the STMD (16).

This study has limitations in that it uses opportunistic sampling, has a small sample size and high proportion of females and the diagnosis of anaphylaxis was made by a non-allergy specialist. Despite this we feel that our results are representative in view of the fact that the link between obesity and female gender to increasing STMD are in line with other studies.

Summary

We have shown that 68% of our allergy population have a STMD greater than the most common EAI putting them at potential risk of EAI failure. The key predictors for increased STMD were female gender and a BMI > 30. EAI require longer needles to ensure IM administration and ultrasound at point of prescription would aid needle length selection.

Conflict of interest

There are no real or perceived conflicts of interest for any of the authors of this research.

Contributions

Dr Johnstone – Dr Johnstone was the lead author on this research and was involved with concept development, ethics approval, data collection form design, data processing, literature review and article write up.

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Dr Hobbins – Dr Hobbins was responsible for data collection and was involved in data processing, literature review and article write up.

Dr Dhruv Parekh – Dr Parekh did the statistical analysis.

Prof. O’Hickey – Professor O’Hickey was responsible for the initial concept and oversaw the whole project. His department also provided limited funding for the project.

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