



What Should the Optimal Adrenaline Auto-Injector Needle Length Be?

Murat TÜRK¹ , Gamze TÜRK² , Ali KOÇ² , Özgür KARABIYIK² , İnsu YILMAZ¹ 

¹ Division of Allergy and Clinical Immunology, Department of Chest Diseases, Erciyes University School of Medicine, Kayseri, Turkey

² Department of Radiology, University of Health Sciences, Kayseri City Hospital, Kayseri, Turkey

Corresponding Author: Murat TÜRK ✉ mrttrk@gmail.com

This study was presented as a poster in "European Academy of Allergy and Clinical Immunology Congress, 2019, Lisbon, Portugal" and presented as an oral presentation in "25. National Allergy and Immunology Congress, 2018, Antalya, Turkey".

ABSTRACT

Objective: To identify the possible subcutaneous and peri/intraosseous injection risks with different needle lengths in adults using adrenaline autoinjectors (AAI) with different needle lengths. In addition, optimum needle lengths with the lowest injection failure risk were determined for both genders.

Materials and Methods: Skin-to-muscle distance (STMD) and skin-to-bone distance (STBD) were measured under minimal and maximum pressures at the anterolateral aspect of the thigh by ultrasound. Risks of *subcutaneous injection*, *peri/intraosseous injection*, and *total events* were calculated for both genders by taking a 15.2 mm needle length as reference for calculations. Possible *subcutaneous injection* and *peri/intraosseous injection* risks with different needle lengths were calculated and the most optimal needle lengths with the least total event risk were determined for each gender using different body mass index (BMI) threshold levels.

Results: A total of 208 adults (118 women, 90 men) with a mean age of 46.3 ± 15.7 were enrolled. BMI had the highest correlation with all ultrasonographic measures for each gender. STMD_{max} of 45 women (38%) and one man (1.1%) were longer than 15.2 mm. For men, *total event* risk was similar (3.3%) with needle lengths ranging from 12 to 18 mm. For women, considering two different BMI threshold levels with two different needle lengths (20 mm for 28 kg/m² and 26 mm for 32 kg/m²) reduced total event risk to 6.7% for both BMI thresholds.

Conclusion: The risk for inadequate intramuscular delivery is higher in women, especially those with higher BMI. Individualization of AAI needle lengths according to certain BMI values can improve the outcome, especially for obese women.

Keywords: Anaphylaxis, adrenaline, adrenaline auto-injector, needle length

Abbreviations: AAI: Adrenaline auto-injector, BMI: Body mass index, IM: Intramuscular, STBD: Skin-to-bone distance
STMD: Skin-to-muscle distance

INTRODUCTION

Despite the advances in understanding the underlying mechanisms of allergic diseases and the dazzling advances in the treatment of these diseases, the first drug of choice has never changed for one of the most severe allergic reactions. Adrenaline (epinephrine) is the initial drug of choice for anaphylaxis and delayed administration of adrenaline has been associated with increased risk of death (1-3). Nevertheless, it has been shown that

only 67% of cases of near-fatal anaphylaxis received prompt adrenaline. Besides prompt administration, an appropriate route of administration is also important for rapid adrenaline efficacy. Intramuscular (IM) injection of adrenaline into the vastus lateralis muscle has been shown to result in quicker time to peak plasma concentration (T_{max}) and higher peak plasma concentrations (C_{max}) when compared to intramuscular or subcutaneous injection into the upper arm (4, 5). Thus, The European Medicine Agency recommends an intramuscular injection

of adrenaline as the preferred route of administration in the case of anaphylaxis (6).

The administration of adrenaline before admission to the emergency room has been shown to reduce the likelihood of hospital admission when compared to the administration at the emergency room (7). Thus, adrenaline auto-injectors (AAIs) which enable self-administration outside the healthcare settings, have been developed (7). Different manufacturers have designed AAIs that basically differ in the drug dosage, trigger pressure and needle length. There are studies that show the needle length of these devices may be inadequate for IM injection, particularly in women and obese patients (8-11). It was shown that women were 6.4 times more likely than men to receive adrenaline in the subcutaneous tissue (11). In their study, Bhalla et al. showed that those patients with increased subcutaneous injection risk had higher body mass index (BMI) (11). Similarly, in a significant number of pediatric patients, it was shown that the needles of AAIs might not be long enough to reach the intramuscular area (12). Because of the significant effect of gender and anthropometric characteristics on adequate IM administration, the need for age, gender and/or BMI specific auto-injectors was reported (13).

Prompt and effective intervention is crucial in acute and life-threatening reactions such as anaphylaxis, which mostly occurs outside the healthcare settings. AAIs should be able to deliver the whole drug dose intramuscularly to all patients of different genders and anthropometric characteristics as rapidly as possible and without hesitation. In the present study, we aimed to identify the possible subcutaneous and peri/intraosseous injection risks with different needle lengths, taking a 15.2 mm needle length as the reference for calculations also, based on the ultrasonographic measurements in adult patients. In addition, optimum needle lengths with the lowest injection failure risk were determined for both genders based on the results.

MATERIALS and METHODS

Patients

This study was carried out in the two largest health facilities of Kayseri, Turkey (Erciyes University Hospital and Kayseri City Hospital) between 2017-2018. Patients older than 18 years of age, who were admitted to the radiology clinic for ultrasound/doppler ultrasonography and who agreed to attend the study were included. Written

informed consent was obtained from each participant. Patients with skin problems at the measurement area (pretibial edema, lymphedema or previous surgery of the leg) or with any neuromuscular problems that might cause muscle atrophy were excluded from the study. Age, gender, height, weight, and BMI of the patients were collected. The study was approved by the Erciyes University Ethical Committee, Kayseri, Turkey (Decision No: 2017/560).

Ultrasonographic Measures – Skin-to-Muscle Distance (STMD) and Skin-to-Bone Distance (STBD)

All measurements were done at the anterolateral aspect of the mid-right thigh using the Aplio-500 ultrasound system (Toshiba Medical Systems, Otawara, Japan) with 7,5 MHz linear probe by two radiologists. Both radiologists had similar measurements in 30 randomly selected patients. STMD and STBD were measured under minimal and maximum pressures. Minimal pressure (p_{min}) was defined as “just enough” pressure to obtain an adequate ultrasound image, and maximum pressure (p_{max}) was defined as the maximum pressure that can be performed by the radiologist and tolerated by the patient. The STMD was measured from the skin surface to the outer border of the vastus lateralis muscle, including the muscle fascia. The STBD was measured from the skin surface to the outer aspect of the periosteum of the femur.

Data Analysis

Risks of *subcutaneous injection* due to inadequate needle length, *peri/intraosseous injection* due to excessive needle length, and *total events* (sum of subcutaneous injection risk and peri/intraosseous injection risk) were calculated for both genders. Fifteen point two mm needle length of Epipen®, which is used worldwide, was taken as the reference for calculations. In addition, possible *subcutaneous injection* and *peri/intraosseous injection* risks with different needle lengths ranging from 12 to 28 mm were calculated in the same patient group. Finally, the anthropometric measurement that most correlated with the ultrasonographic measures was identified and *total event* risks were calculated for different threshold levels; then the most optimal needle lengths with the least *total event* risk were determined for each gender. Data were analyzed using SPSS software version 17 (SPSS Inc, Chicago, Illinois, USA). All measures were compared using the Mann-Whitney U-test. For all analyses, $p < 0.05$ was considered statistically significant.

RESULTS

Study Population

The general characteristics of 208 patients are shown in Table I. When compared to men, women had lower height (159±8 vs. 174±8 cm; p<0.001) and higher BMI values (29.9±9 vs. 26.4±5.1 kg/cm²; p<0.001).

Ultrasonographic Measures and Their Correlation with Other Anthropometric Measures

Table II shows the ultrasonographic measures and change rates during minimal and maximal pressures. STMD_{min}, STMD_{max}, and STBD_{max} were significantly higher in women. When maximum pressure was performed by the ultrasound probe, the mean change in STMD was found to be 1.3±1.6 mm (10.4%), and in STBD was found to be 11.7±4.3 mm (26.9%). The mean change in STMD was significantly higher in women (1.8±1.9 vs. 0.7±0.8 mm; p<0.001).

When we classified patients into 3 groups according to their BMI values (Group 1: 18.5-24.9 kg/m²; group 2: 25-29.9 kg/m² and group 3: ≥30 kg/m²), we found that when compared to men with the similar BMI cut-off values, women had longer STMD_{max} and STMD_{min} values.

According to univariate analysis, only gender and BMI were found to be the predictors of all four ultrasonic measures. Multivariate analysis revealed that BMI was an

independent risk factor for STMD_{max}, STMD_{min}, STBD_{max} and STBD_{min}; and gender was an independent risk factor for STMD_{max} and STMD_{min}.

When all parameters were taken into consideration, there was a strong correlation between STMD_{max} and STMD_{min} (r=0.971; p<0.001), STBD_{max} and STBD_{min} (r=0.874; p<0.001), and STBD_{max} and STMD_{max} (r=0.67; p<0.001) (Table III). Even though height had the highest correlation with STMD_{min} and STMD_{max}, this correlation was not present when each gender was analyzed separately. Finally, within all three anthropometric measures, BMI had significant correlation with STMD_{min}, STMD_{max}, STBD_{min}, and STBD_{max} for each gender (Table III).

Risks of Subcutaneous or Peri/Intraosseous Injection

When an AAI with 15.2 mm needle length was taken as the reference in women, it was found that STMD_{max} of 45 women (38%) and STMD_{min} of 58 women (49.2%) were longer than 15.2 mm, resulting in inadequate penetration into the intramuscular area (Figure 1). Twenty-nine women (64.4%) with STMD_{max}>15.2 mm had BMI≥30. *Subcutaneous injection* and *peri/intraosseous injection* risks with different needle lengths for each gender are given in Table IV. Only one man (1.1%) had a STMD_{max} longer than 15.2 mm (Figure 2). There was no risk of *peri/intraosseous injection* with a 15.2 mm AAI needle length in women, whereas two men (0.9%) had *peri/intraosseous injection* risk with a 15.2 mm needle length.

Table I. Patient characteristics.

	Total (n=208)	Women (n=118)	Men (n=90)	p
Age; years				
Mean±SD	46.3±15.7	49.3±14.3	42.5±16.5	0.004
Median	47	50	42	
Range	34-58	39-59	27-58	
Height; centimeters				
Mean±SD	165±10	159±8	174±8	<0.001
Median	165	158	175	
Range	156-174	154-164	168-180	
Weight; kilograms				
Mean±SD	77±15.7	75±14.3	79.6±17.1	0.058
Median	76	73.7	80	
Range	65-86.7	65-84.9	68-87.3	
BMI; kg/m²				
Mean±SD	28.3±5.9	29.9±9	26.4±5.1	<0.001
Median	27.5	29.8	25.8	
Range	24.3-31.6	25.3-33.9	22.9-29.8	

SD: Standard deviation, BMI: Body mass index.

Table II. Results of the ultrasonographic measures and their change with different pressures.

	Total (n=208)	Women (n=118)	Men (n=90)	<i>p</i>
STMD_{min}; mm				
Mean±SD	12±6.3	15.8±5.5	7.1±3.1	
Median	11.1	15.3	6.4	<0.001
Range	6.5-16.6	12.4-19.1	5.2-8.5	
STMD_{max}; mm				
Mean±SD	10.7±5.5	14±4.8	6.5±2.7	
Median	10	13.3	6.1	<0.001
Range	6.3-14.6	10.9-17.7	4.3-7.8	
STBD_{min}; mm				
Mean±SD	43.7±8.8	44.9±9.1	42.3±8.3	0.051
Median	44.5	45.6	43.1	
Range	37.7-49.1	38.5-50.3	37.1-48.2	
STBD_{max}; mm				
Mean±SD	32±7.9	33.6±8.3	29.9±6.8	0.004
Median	31.8	32.6	30.8	
Range	26.8-36.9	27.8-38.9	25.7-34.6	
Change in STMD				
Mean±SD	1.3±1.6	1.8±1.9	0.7±0.8	<0.001
Percent	10.4	10.8%	9.8%	0.61
Change in STBD				
Mean±SD	11.7±4.3	11.2±4.2	12.3±4.3	0.07
Percent	26.9%	25.2%	29.2%	0.001

STMD: Skin-to-muscle diameter, STBD: Skin-to-bone diameter, SD: Standard deviation.

Table III. Correlation coefficient (r) matrix between different anthropometric and ultrasonographic measures.

Variables	Height	Weight	BMI	STMD _{min}	STMD _{max}	STBD _{min}
Weight						
General	0.29					
Men	0.39					
Women	0.15**					
BMI						
General	-0.36	0.78				
Men	-0.03**	0.87				
Women	-0.36	0.91				
STMD_{min}						
General	-0.53	0.13**	0.47			
Men	0.04**	0.4	0.43			
Women	-0.18	0.29	0.37			
STMD_{max}						
General	-0.51	0.15	0.48	0.97		
Men	0.08**	0.41	0.42	0.97		
Women	-0.16**	0.33	0.39	0.94		
STBD_{min}						
General	-0.06**	0.48	0.51	0.54	0.57	
Men	0.09**	0.5	0.51	0.43	0.48	
Women	0.03**	0.53	0.48	0.7	0.74	
STBD_{max}						
General	-0.15	0.38	0.47	0.61	0.67	0.87
Men	0.03**	0.36	0.38	0.49	0.53	0.86
Women	0.02**	0.5	0.46	0.7	0.79	0.88

STMD: Skin-to-muscle diameter; STBD: Skin-to-bone diameter; BMI: Body mass index. ** defines $p > 0.05$.

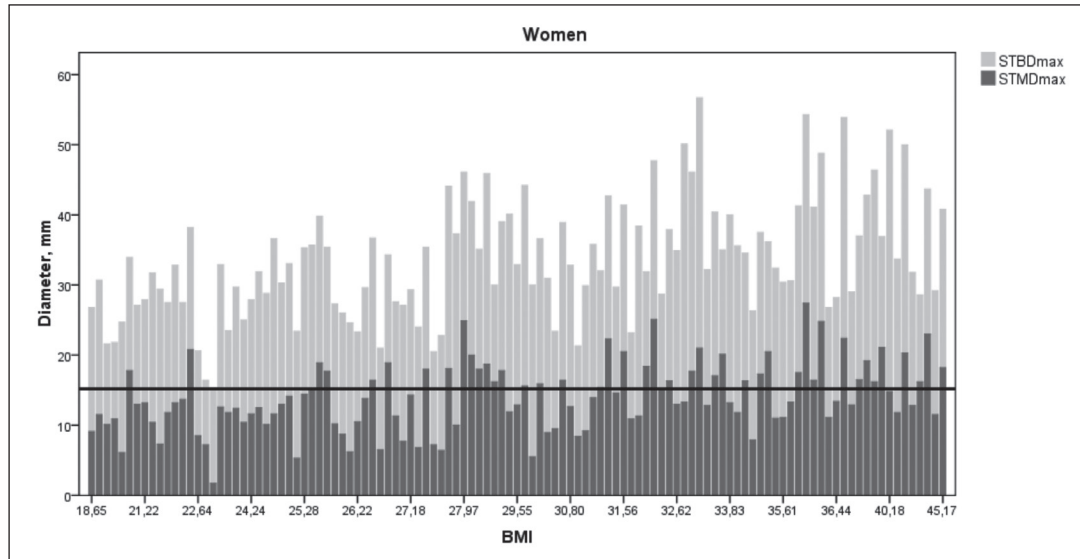


Figure 1. When an AAI with 15.2 mm needle length was taken as a reference in women, it was found that $STMD_{max}$ of 45 women (38%) were longer than 15.2 mm, resulting in inadequate penetration into the intramuscular area (Black line represents 15.2 mm).

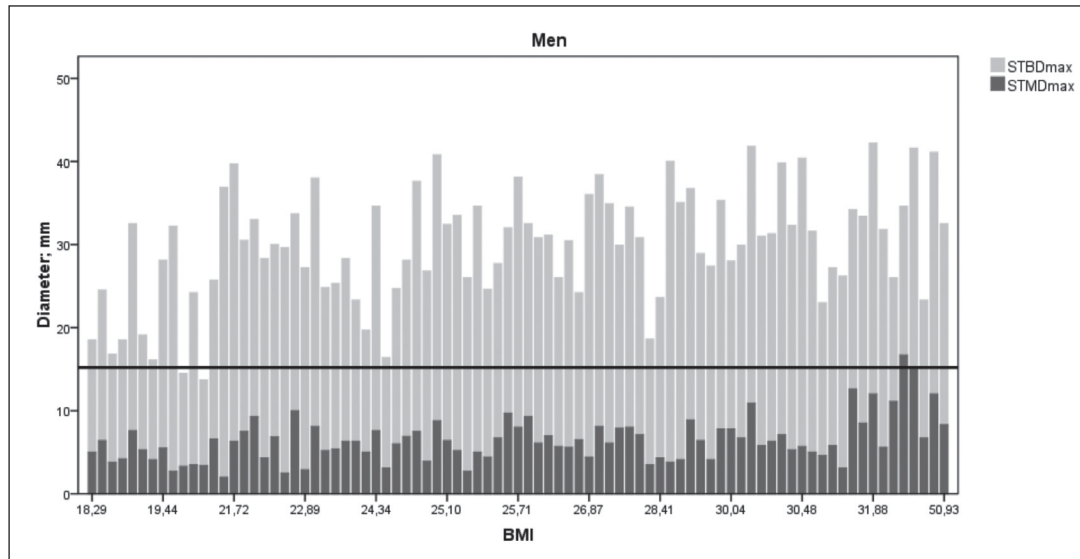


Figure 2. Only one man (1.1%) had a $STMD_{max}$ longer than 15.2 mm and two men (0.9%) had peri/intraosseous injection risk with a 15.2 mm needle length (Black line represents 15.2 mm).

Optimum Adrenaline Auto-Injector Needle Length for Men

For men, *subcutaneous injection* risk was very low with different needle lengths ranging from 12 to 28 mm. As expected, *peri/intraosseous injection* risk was expected to be higher with longer needles (Table IV). With needle lengths longer than 18 mm, the risk increment was significant (n=5 for 18 mm needle length vs. n=10 for 20 mm needle length; p=0.025). With needle lengths shorter than 12 mm, *subcutaneous injection* risk was expected to be significantly higher (n=5 for 12 mm needle length vs. n=9 for 10 mm needle length; p=0.046). *Total event*

number was similar with different needle lengths ranging from 12 to 18 mm (3.3% *total event* risk). Since the *total event* risk was very low within this needle length range, men were not further sub-grouped according to their anthropometric measurements.

Optimum Adrenaline Auto-Injector Needle Length for Women

In women, there was a 46% *subcutaneous injection* risk with 14 mm needle length, whereas, this risk was expected to decrease to 0.8% with 28 mm needle length (Table IV). However, *peri/intraosseous injection* risk was also expected to increase with longer needles.

The lowest *subcutaneous injection* and *peri/intraosseous injection* risks were expected between the needle lengths 20 to 26 mm in women. *Total event* risks were significantly higher when the needle was longer than 26 mm or shorter than 20 mm [(n=20 for 26 mm needle length vs. n=32 for 28 mm needle length; p=0.002) and (n=28 for 18 mm needle length vs. n=17 for 20 mm needle length; p=0.001), respectively]. A minimum of 15 and a maximum of 20 total events were expected within this range.

Since the *total event* risk was still very high for women, the effect of anthropometric measures on the results

was evaluated. Mean BMI was significantly higher in women with $STMD_{max} \geq 15.2$ mm compared to those with $STMD_{max} < 15.2$ (32.4±5.5 vs. 28.3±5.8 kg/m²; p<0.001). BMI also had the highest correlation with $STMD_{max}$. Therefore, women were divided into subgroups according to their BMIs. *Subcutaneous injection* and *peri/intraosseous injection* risks with different needle lengths and different BMI threshold values are given in Table V.

When each of five different BMI threshold values was evaluated separately, for women with higher BMI, the optimal needle length with the lowest *total event* risk was 26

Table IV. Subcutaneous injection and peri/intraosseous injection risks with different needle lengths for both gender (risks are based on $STMD_{max}$ and $STBD_{max}$ values).

	Needle lengths								
	14 mm	15.2 mm	16 mm	18 mm	20 mm	22 mm	24 mm	26 mm	28 mm
Subcutaneous injection risk; n (%)									
Total (n=208)	56	46	43	26	15	7	4	1	1
Men (n=90)	2 (2.2)	1 (1.1)	1 (1.1)	0	0	0	0	0	0
Women (n=118)	54 (45.8)	45 (38)	42 (35.6)	26 (22)	15 (12.7)	7 (5.9)	4 (3.4)	1 (0.8)	1 (0.8)
Peri/intraosseous injection risk; n (%)									
Total	1	2	3	7	12	18	29	46	67
Men	1 (1.1)	2 (2.2)	2 (2.2)	5 (5.5)	10 (11)	10 (11)	14 (15.4)	27 (29.7)	36 (39.6)
Women	0	0	1 (0.8)	2 (1.7)	2 (1.7)	8 (6.8)	15 (12.7)	19 (16.1)	31 (26.3)
Total event risk*									
Total	57	48	46	33	27	25	33	47	48
Men	3 (3.3)	3 (3.3)	3 (3.3)	5 (5.5)	10 (11)	10 (11)	14 (15.4)	27 (29.7)	36 (39.6)
Women	54 (45.8)	45 (38)	43 (36.8)	28 (23.7)	17 (14.4)	15 (12.7)	19 (16.1)	20 (16.9)	32 (27.1)

* Sum of the subcutaneous injection and peri/intraosseous injection risks.

Table V. Subcutaneous injection and peri/intraosseous injection risks with different needle lengths and different BMI threshold values (risks are based on $STMD_{max}$ ve $STBD_{max}$ values) for women.

N=118	18 mm		20 mm		22 mm		24 mm		26 mm		28 mm	
	SIR	P/IIR	SIR	P/IIR	SIR	P/IIR	SIR	P/IIR	SIR	P/IIR	SIR	P/IIR
>26 (n=82), n (%)	24 (20.3)	0	14 (11.9)	0	7 (5.9)	3 (2.5)	4 (3.4)	8 (6.8)	1 (0.8)	8 (6.8)	0	18 (15)
≤26 (n=36), n (%)	2 (1.7)	2 (1.7)	1 (0.8)	2 (1.7)	0	5 (4.2)	0	7 (5.9)	0	11 (9.3)	0	13 (11)
>28 (n=67), n (%)	20 (16.9)	0	13 (11)	0	6 (5.1)	1 (0.8)	3 (2.5)	3 (2.5)	1 (0.8)	3 (2.5)	0	6 (5.1)
≤28 (n=51), n (%)	6 (5.1)	2 (1.7)	2 (1.7)	2 (1.7)	1 (0.8)	7 (5.9)	1 (0.8)	12 (10.2)	0	16 (13.6)	0	25 (21.2)
>30 (n=58), n (%)	17 (14.4)	0	12 (10.2)	0	6 (5.1)	1 (0.8)	3 (2.5)	3 (2.5)	1 (0.8)	3 (2.5)	0	6 (5.1)
≤30 (n=60), n (%)	9 (7.6)	2 (1.7)	3 (2.5)	2 (1.7)	1 (0.8)	7 (5.9)	1 (0.8)	12 (10.2)	0	16 (13.6)	0	25 (21.2)
>32 (n=42), n (%)	15 (12.7)	0	10 (8.5)	0	5 (4.2)	0	3 (2.5)	0	1 (0.8)	0	0	2 (1.7)
≤32 (n=76), n (%)	11 (9.3)	2 (1.7)	5 (4.2)	2 (1.7)	2 (1.7)	8 (6.8)	1 (0.8)	15 (12.7)	0	19 (16.1)	0	29 (24.6)
>34 (n=28), n (%)	10 (8.5)	0	7 (5.9)	0	4 (3.4)	0	2 (1.7)	0	1 (0.8)	0	0	2 (1.7)
≤34 (n=90), n (%)	16 (13.6)	2 (1.7)	8 (6.8)	2 (1.7)	3 (2.5)	8 (6.8)	2 (1.7)	15 (12.7)	0	19 (16.1)	0	29 (24.6)

SIR: Subcutaneous injection risk, P/IIR: Peri/intraosseous injection risks.

mm. For all five BMI threshold levels, *total event* number with a 26 mm needle length was lower than that with 24 mm and 28 mm, but the difference was not significant. Similarly, for women with lower BMI, the optimal needle length with the lowest *total event* risk was 20 mm. For all 5 BMI threshold levels, *total event* number with 20 mm needle length was lower than that with 18 mm and 22 mm, but the difference was not significant.

Our results showed that in women with BMI>28 kg/m², with a 26 mm AAI needle length, *subcutaneous injection* risk was 0.8% and *peri/intraosseous injection* risk was 2.5%; whereas in women with BMI≤28 kg/m², with a 20 mm AAI needle length, *subcutaneous injection* risk was 1.7% and *peri/intraosseous injection* risk was 1.7% (6.7% *total events* in all women). In women with BMI>32 kg/m², with a 26 mm AAI needle length, *subcutaneous injection* risk was 0.8% and *peri/intraosseous injection* risk was 0%; whereas in women with BMI≤32 kg/m², with a 20 mm AAI needle length, *subcutaneous injection* risk was 4.2%, *peri/intraosseous injection* risk was 1.7% (6.7% *total events* in all women). Considering 28 kg/m² as threshold level would increase *peri/intraosseous injection* risk but decrease *subcutaneous injection* risk; whereas taking 32 kg/m² would do the opposite.

DISCUSSION

Our results highlight that the risk for inadequate IM delivery is higher in women, especially those with BMI>32 kg/m². *Total event* risk was much lower in men compared to women. In addition, two different AAI needle lengths and BMI cut-off values had been identified for the lowest *total event* risk in women.

Since designing a study to evaluate the IM delivery ratio and bioavailability of adrenaline in patients with anaphylaxis in real-life settings would be unethical and probably not possible, the present study, like previous studies, was performed on healthy subjects. Previous studies aiming to present IM delivery rates of different commercially available AAIs have shown that most of the auto-injectors available on the market might fail to reach the right compartment due to insufficient needle lengths (8, 10, 12, 14-18). In a preliminary study where STMD was calculated on computed tomography scans, Song et al. found that mean STMD of women was nearly twice that of men (0.66±0.47 cm for men and 1.48±0.72 for women). STMD was longer than Epipen® autoinjector needle length in only one obese man, and 21 women (21%), 11 of whom

were obese (8). Tsai et al. found that 28% of women (19/69) and none of the men had STMD_{max}>15.2 mm (10). They also showed that women with STMD_{max}>15.2 mm had higher BMI compared with STMD_{max}≤15.2 mm (33±8 vs. 25±4 kg/m², p<0.001). Another recent study using ultrasonographic measures also found that 33% and 10% of adults had subcutaneous injection risks with high-pressure AAI (with 15 mm needle length) and low-pressure AAI (with 23 mm needle length), respectively (15). In another study, the same investigators also showed that obese women had higher subcutaneous injection risk with Epipen® (17).

For the proper activation of trigger mechanisms of the AAIs, there is a certain amount of pressure that needs to be performed on the skin. This pressure compresses the subcutaneous tissue and makes it thinner. Therefore, while calculating the optimum needle length, this factor should be taken into consideration. As far as we know, ultrasound is the best imaging tool that can imitate and show the changes in the subcutaneous tissue at the same time by probe compression (19). The change in STMD under minimum and maximum pressures has been reported as 11% in literature (19), whereas in our study it was 10.4%. Another study measured the difference in subcutaneous tissue diameter between the minimum and maximum pressures and found 14.1 mm change (range 3.7 – 31.0 mm) (15). Dreborg et al. presented the data that pressure applied to release the needle for different AAIs may vary and the mean pressures needed to trigger different devices varied between 15-28 newtons. Even though the ultrasound probe surface area is much larger than AAIs, we believe that the maximum pressures applied in our study would be enough, and probably much more higher than, to activate the trigger mechanisms and can be adapted in all commercially available AAIs (15).

Other than needle length and tissue compression, another factor affecting the depth of injection into the right compartment is the propulsion force of the AAI. Tightly coiled spring inside the Epipen® delivers a force of 22.7 pounds (20) which causes a mean maximum injection depth of 29.68±2.08 mm in ballistic gelatin (21). This propulsion force may enable the drug to reach wider areas than the needle length. However, Diacono et al. clearly presented that the deep fascia of the thigh prevents fluid traveling from the subcutaneous tissue into the underlying muscle in animal tissues (22). The results of this study showed that the whole needle orifice

of the AAI needles must pass completely into the muscle. Therefore, in previous similar studies, while calculating the possible IM delivery ratios over STMD measurements, the needle length was reduced by 2 mm when estimating the $STMD_{max}$ (14, 15, 17). Since *subcutaneous and peri/intraosseous injection* risks are separately calculated for needle lengths from 14 to 28 mm, this reduction was not done in our study.

What Should be the Optimal Needle Length for Men and Women?

According to our results, with a 15.2 mm needle length, *subcutaneous injection* risk was 1.1%, *peri/intraosseous injection* risk was 2.2% (*total event* risk 3.3%) in men. Since this result was found to be the same for both 14 and 16 mm needles, when the 2 mm orifice length was also considered for fascial penetration, we may propose 16 mm needle length is optimal for men.

On the other hand, there is not a single optimal needle length for women. Compared to men with the same BMI, STMD was higher in women. With 15.2 mm long needle length, *total event* risk was 38% in women, and it was all formed by *subcutaneous injection* risk. Between 20-26 mm needle lengths, *total event* risk was expected to lower to 12.7%. Since the percentage was still high, we tried to find different optimal needle lengths for women with different BMIs, which had the highest correlation with all ultrasonographic measures. As shown in Table V, it was possible to lower the *total event* risk to 6.7% with a needle length of 26 mm for women with higher BMI ($BMI > 28$ or 32 kg/m^2) and 20 mm for women with lower BMI ($BMI \leq 28$ or 32 kg/m^2). Even though taking these two BMI thresholds did not affect the *total event* possibility, since *peri/intraosseous injection* risk was lower with 32 kg/m^2 , we suggest the optimal needle length should be 20 mm for women with $BMI \leq 32 \text{ kg/m}^2$ and 26 mm for women with $BMI > 32 \text{ kg/m}^2$. However, there were not many patients with very extreme BMI levels in our study, therefore, we think needle length should be individualized for these patients.

Besides optimizing needle lengths, there are other subjects that should be improved in AAIs available on the market. Dreborg et al. showed that needle lengths may show variations between two devices of the same manufacturer, and this variation was greatest for Epipen® at 5 mm (17). Also, as we noted before, the needed trigger pressure may also vary among the same brand devices (19) and these variabilities should also be minimized by

the manufacturers. Lastly, in a recent study, Duvauchelle et al. claimed that needle length or IM injection may not be absolutely required for auto-injector efficacy (23). They showed that in 11 of 12 overweight women in whom the administered AAI's needle length failed to reach the muscle, the magnitude of the first plasma peak of adrenaline in terms of Tmax and Cmax did not differ from that observed in normal-weight men. They also observed a sequential, immediate and larger second peak in these patients which resulted in a significantly higher total bioavailability than in normal-weight men. However, this study only included a limited number of healthy subjects. Decreased vascular tone, capillary leakage, and intravascular volume loss occur during anaphylaxis. These changes in micro and macrovascular environment may result in changes in the tissue vascularization. Therefore, it is controversial whether the findings of this study can be adapted to patients with anaphylaxis. Also, if this study is ever supported by similar studies in the future, an additional question emerges as to whether adrenaline should be administered subcutaneously.

The present study has some limitations. Even though measurements showed no significant difference in 30 randomly selected patients, interobserver variation may be present among the two radiologists. Secondly, maximum pressure was defined as the maximum pressure performed by the radiologist and tolerated by the patient; but the exact pressure amount was not measured. Thirdly, in real life, patients usually use the AAIs with their clothes on. Since standardization is not possible, the effect of clothes on subcutaneous tissue compression and the possible increase in the distance could not be evaluated. Fourthly, the surface area of the ultrasound probe is wider than that of AAIs, and it is not possible to estimate how this affects our results. Lastly, even though our results are similar to studies from different countries, we cannot generalize our findings for other populations for certain.

In conclusion, intramuscular injection of adrenaline with an effective dosage is very important for the efficient treatment in anaphylaxis. Since BMI may differ among people, individualization of AAI needle lengths according to certain BMI values may be appropriate. Our results show the optimal needle lengths with the lowest *total event* rate as 16 mm for men independent from BMI, as 20 mm for women with $BMI \leq 32 \text{ kg/m}^2$, and 26 mm for women with $BMI > 32 \text{ kg/m}^2$ — underlining the necessity of individualized AAIs according to these reference intervals.

Conflict of Interests

All authors declare that they have no potential conflict of interests regarding any aspect of this study.

Financial Support

None.

REFERENCES

1. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol Pract* 2001;107:191-3.
2. Simons FE, Ebisawa M, Sanchez-Borges M, Thong BY, Worm M, Tanno LK, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. *World Allergy Organ J* 2015;8:32.
3. Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernández Rivas M, et al. Anaphylaxis: Guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy* 2014;69:1026-45.
4. Simons FE, Gu X, Simons KJ. Epinephrine absorption in adults: Intramuscular versus subcutaneous injection. *J Allergy Clin Immunol* 2001;108:871-3.
5. Simons FE, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol* 1998;101:33-7.
6. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Adrenaline auto-injectors Art. 31 - Assessment report for publication. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Adrenaline_31/WC500192305.pdf. Accessed at 28.07.2019.
7. Fleming JT, Clark S, Camargo CA, Jr., Rudders SA. Early treatment of food-induced anaphylaxis with epinephrine is associated with a lower risk of hospitalization. *J Allergy Clin Immunol Pract* 2015;3:57-62.
8. Song TT, Nelson MR, Chang JH, Engler RJ, Chowdhury BA. Adequacy of the epinephrine autoinjector needle length in delivering epinephrine to the intramuscular tissues. *Ann Allergy Asthma Immunol* 2005;94:539-42.
9. Johnstone J, Hobbins S. Excess subcutaneous tissue may preclude intramuscular delivery when using adrenaline autoinjectors in patients with anaphylaxis. *Allergy* 2015;70:703-6.
10. Tsai G, Kim L, Nevis IF, Dominic A, Potts R, Chiu J, 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.
11. Bhalla MC, Gable BD, Frey JA, Reichenbach MR, Wilber ST. Predictors of epinephrine autoinjector needle length inadequacy. *Am J Emerg Med* 2013;31:1671-6.
12. 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.
13. Song TT. Epinephrine needle length in autoinjectors and why it matters. *J Allergy Clin Immunol Pract* 2018;6:1264-5.
14. Dreborg S, Wen X, Kim L, Tsai G, Nevis I, Potts R, et al. Do epinephrine auto-injectors have an unsuitable needle length in children and adolescents at risk for anaphylaxis from food allergy? *Allergy Asthma Clin Immunol* 2016;12:11.
15. Dreborg S, Kim L, Tsai G, Kim H. Epinephrine auto-injector needle lengths: Can both subcutaneous and periosteal/intraosseous injection be avoided? *Ann Allergy Asthma Immunol* 2018;120:648-53.
16. Duong M, Botchway A, Dela Cruz J, Austin R, McDaniel K, Jaeger C. Skin to intramuscular compartment thigh measurement by ultrasound in pediatric population. *West J Emerg Med* 2017;18:479-86.
17. Dreborg S, Tsai G, Kim H. Implications of variation of epinephrine auto-injector needle length. *Ann Allergy Asthma Immunol* 2019;123:89-94.
18. Kim L, Nevis IF, Tsai G, Dominic A, Potts R, Chiu J, 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.
19. Dreborg S, Kim H. Authors' response. *Ann Allergy Asthma Immunol* 2018;121:644-5.
20. Song TT, Lieberman P. Epinephrine auto-injector needle length: What is the ideal length? *Curr Opin Allergy Clin Immunol* 2016;16:361-5.
21. Schwirtz A, Seeger H. Comparison of the robustness and functionality of three adrenaline auto-injectors. *J Asthma Allergy* 2012;5:39-49.
22. Diacono D, Pumphrey RS, Sharma V, Arkwright PD. The deep fascia of the thigh forms an impenetrable barrier to fluid injected subcutaneously by autoinjectors. *J Allergy Clin Immunol Pract* 2015;3:297-9.
23. Duvauchelle T, Robert P, Donazzolo Y, Loyau S, Orlandini B, Leher P, et al. Bioavailability and cardiovascular effects of adrenaline administered by anapen autoinjector in healthy volunteers. *J Allergy Clin Immunol Pract* 2018;6:1257-63.