

a.

b.

Figure 2a. Skin to bone distance, STBD min (grey filled circles, Y-axis) versus weight using low pressure on the ultrasound probe. **2b.** The skin to muscle distance using low pressure, STMDmin versus weight, applying the variation in needle length of Epipen®, 5 mm [9].

Table 2. Estimated needle lengths.

Needle\Weight class	0-10 kg	10-15 kg	15-30 kg	30-50 kg	50-80 kg	>80 kg	Figure number
HPEAI							
STBD _{max} Longest needle Naked skin	8	8	8	8	15	21	1a
STMD _{max} = STBD _{max} - 2 mm							
STMD _{max} Longest Needle Naked skin STBD = STMD - 2 mm	6	6	6	6	13	19	1b
STMD _{max} Shortest Needle Naked skin - (2 mm + 2.5 mm) = -4.5 mm	3.5	3.5	3.5	3.5	10.5	16.5	
STMD _{max} Shortest Needle Thick clothes STBD - (2 + 2.5 + 3) = -7.5 mm	0.5	0.5	0.5	0.5	7.5	13.5	
LPEAI							
STBD _{min} Longest needle Naked skin	15	15	20	22	30	36?	2a
STMD _{min} = STBD _{min} - 2 mm							
STMD _{min} Longest needle Naked skin STBD = STMD - 2 mm	13	13	18	20	28	34	2b
STMD _{min} Shortest needle Naked skin STBD - (2 + 2.5) = 4.5	10.5	10.5	15.5	17.5	25.5	31.5	
STMD _{min} Shortest Needle Thick clothes STBD - (2 + 2.5 + 3) = 7.5 mm	7.5	7.5	12.5	14.5	22.5	28.5	

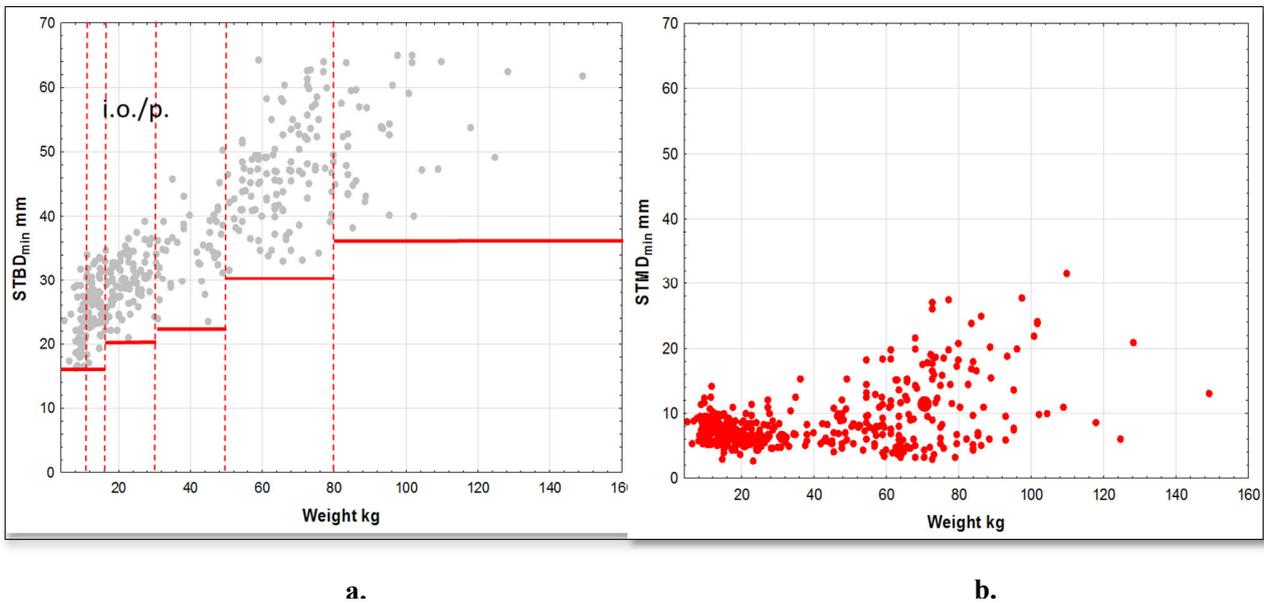


Figure 3a. illustrated the proportion of patients likely to receive a SC injection. **3b.** Illustrated the effect of applying the LPEAI Emerade® variation in needle length.

RESULTS

The results are illustrated in **Figures 1 and 2**. The $STBD_{max}$ is illustrated in Figure 1a, and the $STBD_{min}$ in **Figure 2a** (red horizontal lines). They have been constructed to approximately show how long the penetrating part of an EAI needle can be without hitting the bone.

The next step was to describe the influence of needles of the above-mentioned lengths using the brand-specific data on the variation of needle length. Using needles of the lengths in **Figures 1a and 2a** (minus 2 mm) for injection into the muscle using the variation of needle length as illustrated in **Figures 1b** for HPEAIs (Epipen®/ Epipen Jr® and Auvi-Q®), and in **Figure 3b** for, the LPAI: s (Emerade®). The length is reduced by 2 mm to adjust for the fascia findings by Diacono et al. (10).

In **Figures 1b and 2b** is illustrated the proportion of patients likely to receive a SC injection. Using the variation in needle length accepted by the manufacturer of Epipen®/Epipen Jr®, it appears that even the longest accepted needles would cause SC injection in many patients and the shortest accepted needles would cause SC injection in all patients weighing less than 40 kg wearing winter clothes.

In **Figure 2b** is illustrated the effect of using low pressure on the optimal needle length not causing any i.o./p. injection, injected with the shortest needle approved and through thick clothing, IM injection will be achieved in most patients.

In summary, starting out with the ideal to not cause any i.o./p. injection, then using the longest needle accepted for lot release for IM injection many patients will get SC injections if using HPEAIs. The LPEAIs will compress the

muscle less and have longer needles leading to most patients receiving IM injection.

DISCUSSION

In recent years the risk of SC or i.o./p injection of epinephrine using EAIs has been widely discussed. This paper is based on data from the three original studies completed by Dr. Harold Kim’s group [3-5]. These studies represent the most extensive investigations published on the relationships between the STMD, and the STBD versus weight. Distances were determined by ultrasound at the mid anterolateral aspect of the thigh, the recommended area for IM injection of epinephrine using EAIs [13].

In the original series of studies [3-5], we used 8 pounds or about 35 Newtons (N) as “high pressure” and applied a minimal pressure, referred to as “low pressure”, to mimic the pressure required to release the needle of HPEAIs and LPEAIs, respectively. The declared variation in pressure that is accepted by companies for release of new lots of EAIs has been presented elsewhere [7] and summarized in **Table 1**. This data was not known by us at the time of the original studies. There are instruments available that can apply a specified pressure to the ultrasound probe [14,15] that should be used in all future trials using ultrasound imaging for the study of STBD and STMD. Also, the pressure applied to the probe was not sufficiently well defined in the original studies. Therefore, we did not present any risk data for any specific EAIs currently available. Instead, we illustrated the principle that by avoiding i.o./p. injection in all patients, by using short enough needles, there would be SC injections occurring frequently when using HPEAIs and less often if using LPEAIs.

Our results suggest that the risk of SC injection is very high if using a needle length that would definitely not cause i.o./p. injection if using high pressure on the probe/auto injector. This risk is reduced when requiring a lower pressure to trigger the auto injector as the lower pressure would allow a longer needle to be used. This occurs because less pressure compressing the muscle will provide a greater STBD and therefore allow the use of longer needles. Then, we believe more patients will receive IM injections. Using this qualitative approach to this important issue, we were able to estimate the needle lengths for EAI designs that would deliver the epinephrine to the IM compartment. These findings should be useful in future studies and future EAI designs.

The findings from our study should be confirmed in well-designed prospective studies. With future larger studies, the chance of avoiding i.o./p. injection could be calculated by z-scores for different weight classes, age classes, pubertal stages etc. in children and adolescents and z-scores for weight classes and possibly BMI classes, in adults. Currently, 15 kg and 30 kg are the weight thresholds most often used for EAI prescribing. But we propose the intervals of 10, 50 and 80 kg be used for estimating successful IM injection based on our data.

In closing, if we have the primary goal of avoiding i.o./p. injections, an LPEAI design for EAI designs is more likely to result in successful IM drug delivery. Therefore, when designing future EAI designs or modifying currently available EAI designs, we recommend devices that require less force to release the needle and drug. This lower force will allow for the designers to find the proper needle lengths for different weight ranges that will deliver the epinephrine properly.

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