

# Determination of safe sites of intramuscular arm injections and its relevance to the community

Surraj S<sup>1</sup>, Mrudula Chandrupatla<sup>1</sup>, Kusneniwar G N<sup>2</sup>

Departments of <sup>1</sup>Anatomy and <sup>2</sup>Community Medicine and Family Medicine, AIIMS Bibinagar, Hyderabad, Telangana, India

## ABSTRACT

**Background and Introduction:** Intramuscular injections are usually given in the arm or the gluteal region. Needle insertions done through the intramuscular route in the arm are almost always administered at a point 1 – 2 cm above the insertion of the deltoid. However, this site is not such an ideal one as found by certain other workers. Hence, this study was done to establish a series of safe determinant points in and around the arm in the South Indian population of the state of Telangana. **Materials and Methods:** The five proven safe injection points were tested through needle insertions by observing sterile aseptic precautions in the arms of 370 subjects at the outpatient department of a national level medical research institute after obtaining their consent following the universal safety protocol. **Results:** The points I [1 to 2 cm above deltoid insertion], II [a point midway between the midpoint of arm and insertion of deltoid] and III [midpoint between anterior acromion and deltoid insertion] were found to be safe for administering intramuscular arm injections in this subset of the population. **Conclusion:** This explains the erratic course of the anterior branches of the axillary nerve in different geographical populations. Hence, needle insertion points for arm intramuscular injections need to be determined according to the region.

**Keywords:** Deltoid, muscle, needle, point, population

## Introduction, Background And Objectives Of This Study

The branches of the axillary nerve that supply the various parts of the deltoid muscle have a lot of variation throughout their course, especially the nerve's anterior branch which is known to swerve off its linear path over the surface of the anterior portion of the deltoid. This anterior branch also has an erratic course that varies in different groups of people.<sup>[1-3]</sup> Although these variations exist, it is still mentioned in standard textbooks and literature that the point of insertion of a needle in the arm for intramuscular injection is 1 – 2 cm above the insertion of the deltoid.<sup>[1,2]</sup> There have been a few studies that have challenged

this perspective of administering an intramuscular injection and have recommended other individual safe points in and around the deltoid and axilla for the same. However, each of their proven findings has been challenged by certain other workers who still hold on to the conventional textbook view of administering an intramuscular injection.<sup>[4-9]</sup> Hence, the prime purpose of this study was to find out if those injection sites in and around the arm had been proven safe in other geographical populations by workers from other countries<sup>[3-8]</sup> were also found to be as safe and effective in this subset of the South Indian population in the state of Telangana, due to the fact that the anterior branch of the axillary nerve has an erratic course. Hence, the objectives of this study were – 1) To appreciate the anatomical importance of five safe injection point sites [as mentioned in literature<sup>[3,4,8]</sup> with relevance to the course of axillary nerve among the South Indian population during the ongoing vaccination and drug injections program that was held at a tertiary care center in South India. 2) To bring awareness among the community regarding the safer

**Address for correspondence:** Dr. Mrudula Chandrupatla, Additional Professor and Head, Anatomy, AIIMS Bibinagar, Hyderabad, Telangana, India.  
E-mail: drmrudula4@gmail.com

Received: 05-04-2022

Revised: 06-05-2022

Accepted: 10-05-2022

Published: 31-10-2022

### Access this article online

#### Quick Response Code:



Website:  
www.jfmpc.com

DOI:  
10.4103/jfmpc.jfmpc\_792\_22

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow\_reprints@wolterskluwer.com

**How to cite this article:** Surraj S Chandrupatla M, Kusneniwar GN. Determination of safe sites of intramuscular arm injections and its relevance to the community. J Family Med Prim Care 2022;11:6101-6.

anatomical intramuscular injection site areas in and around the arm. 3) To find out if such variations in axillary nerve had any symptomatic role in the general population and also to delineate those safer alternate sites of intramuscular injections in a vertical orderly manner. 4) To bring awareness among the health care workers regarding safe injection arm points using a circulated questionnaire

This study is also more relevant in terms of the ongoing vaccination against COVID-19, and to differentiate transient axillary nerve compression symptoms that arise solely due to needle insertion from those the side effects of the vaccine per se, which are often misunderstood by the patients or health care workers. These symptoms of axillary nerve compression include pain, tingling sensations, and numbness around the injection site that are often reversible.<sup>[1,6,8]</sup> Rarely difficulty in raising the shoulders is also noticed.<sup>[6,8]</sup> This study is different from other previously done studies on this topic, as it is the first one of its kind to establish a series of safe intramuscular injection points in an orderly manner in and around the arm from a proximal to distal fashion.

## Materials and Methods

### Study design and plan of work

This study was carried out only after the approval of the Institute Research Council and the Ethics Committee of this institute of national importance where this research was conducted. This was a cross-sectional study designed for 6 – 8 months. The subjects for the study were chosen from the population that came to the outpatient department of this tertiary care institute from August 2021 to February 2022 either for therapeutic drug injections or for the administration of vaccine doses. The safe injection points were tested on the subjects only after a signed consent was obtained from them. Before the injection sites were tested, universal safety precautions and injection-safety measures were followed strictly. Before administering the vaccine or injection, the health care workers at the injection site were instructed and educated in their mother tongue regarding the safe anatomical injection sites and their clinical relevance to the community using a schematic diagram as shown in Figure 1.

The image shown [Figure 1] represents the collective pooling of safe points used in this study in comparison with previous studies.<sup>[4-9]</sup> In Figure 1, the safe points depicted are–I] a point 1-2 cm above the deltoid insertion, II] a point midway between the deltoid insertion and deltoid's midpoint, III] the point midway between anterior acromion and deltoid insertion which corresponds to the midpoint of the deltoid, IV] a point 5 cm below anterior acromion's midpoint, and V] the last one being the bisector point between the dropped imaginary bisector line from the posterior part of the lateral acromion and the anteroposterior upper axillary fold's imaginary line, respectively, as quoted in various previous studies.<sup>[3-8]</sup> This schematic diagram was given and explained to the nurses at the injection site and random allocation of each patient was made based on these points for administering

the vaccine. A total of 370 healthy subjects were selected for this study. This study included subjects aged 20 – 50 years only. It excluded subjects with neuropathies, skin diseases, subjects with a known history of diabetes mellitus, and those with muscular dystrophies or myopathies or muscular disorders.

### Sample size and methodology of study

The subjects' sample size was calculated by using the creative research systems survey software freely available to all online, licensed under the Creative Commons Distribution Act. Keeping a confidence level of 95 and confidence interval of 5, and for an estimated population aged 20 – 50 years which visited either the injection clinics or the vaccine o.p.d as per available turnover records from o.p.d, the sample size for 8 months was arrived at 370. This was also partly determined by the feasibility and also based on previous studies.<sup>[3-5]</sup> An alpha error (type 1 error) of 1% was used to arrive at this sample size keeping in mind the prevalence of symptomatic axillary nerve compression to be 5% (from previous studies<sup>[3-5]</sup>).

After administering the injections to the subjects by random allocation (as per the safe points depicted in Figure 1), they were then observed thrice for symptoms of axillary nerve compression at timely intervals on the same day, that is – 5 min after injection, the second observation being 15 min after the injection, and the third one being 30 min from the injection. That safe injection site point was then marked with a ballpoint pen, after obtaining the patient's consent for the same. Before marking the point site, it was ensured that at least three investigators observe that point independently for any mild symptoms of axillary nerve compression that might occur owing to the erratic course of the branches of the axillary nerve to eliminate observer bias. If such symptoms occurred, they were then noted and those patients were reassured, observed cautiously for the same, and local pain relief measures such as ice pack compression or warm water fomentation were then adopted along with physiotherapy measures which were later instituted to alleviate their numbness or pain and subsequently those safe injection points were then considered to be 'high risk' in this subset of the population. It was also decided based on the ethical guidelines of the institute that if more than five patients developed the same kind of symptoms at the same safe injection point, then those points were eliminated from the study after discussion with the investigators and the remaining subjects were then allocated the other safe points randomly. Meanwhile, the questionnaire was also circulated among the health care workers and their responses were also analyzed. The data were then pooled, analyzed, and stored in the computers of the investigators in the Department of Anatomy of the institute for future publishing.

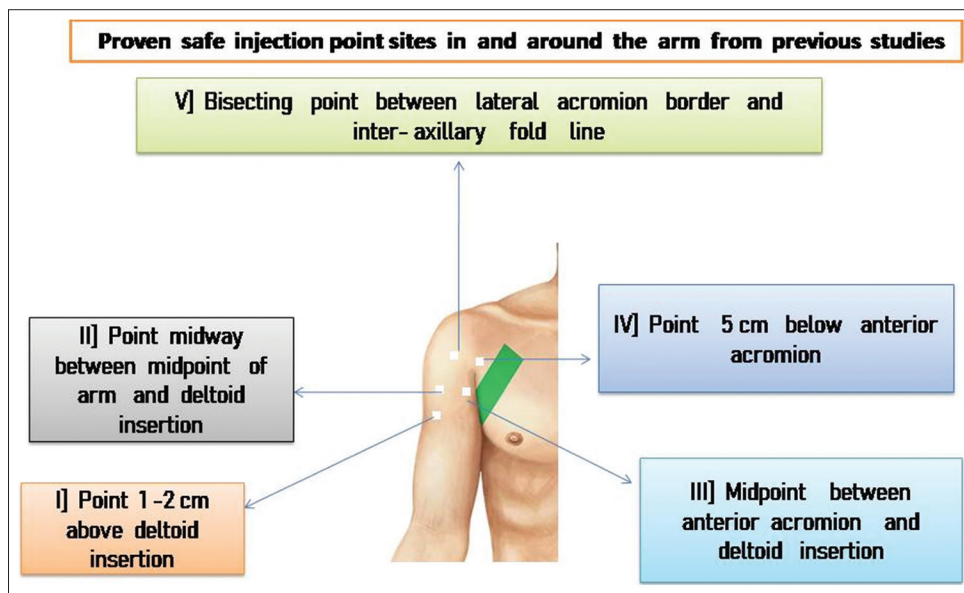
## Results

Table 1 shows the distribution of subjects based on the needle injections they received at their allocated safe points of the arm. It is evident from this table that 18.1% of subjects had willfully chosen points I and II over the other points. Only 1.4% of

**Table 1: Distribution of subjects based on the needle injections they received at their allocated safe points of arm**

Safe point number	Number of subjects who received needle insertions at this point at the end of the study		Total no of subjects (n=370)									
	n	Frequency	Subjects who were allocated this safe arm point initially		@Subjects who willingly chose this point		*Subjects who were allocated this point by the investigators		Subjects who defaulted from their originally allocated arm point		Subjects who had retained their originally allocated arm point for needle insertion	
			n	Frequency	n	Frequency	n	Frequency	n	Frequency	n	Frequency
I	136	36.7	74	20%	37	10%	25	6.8%	0	0%	74	20%
II	129	34.8	74	20%	30	8.1%	25	6.8%	0	0%	74	20%
III	95	25.7	74	20%	7	1.9%	24	6.5%	10	2.7%	64	17.3%
IV	5	1.4	74	20%	0	0%	0	0%	69	18.6%	5 <sup>#</sup>	1.4%
V	5	1.4	74	20%	0	0%	0	0%	69	18.6%	5 <sup>#</sup>	1.4%

<sup>#</sup>These were the subjects who willingly chose this point as alternative for needle insertion over their originally allocated arm point. \*These were the subjects who were randomly allocated this point by the investigators as alternative (rather than their originally allocated point) due to axillary nerve compression symptoms observed in previous five patients of another point group. <sup>#</sup>These were the first five subjects for each of the arm points IV and V, who developed transient axillary nerve compression symptoms that subsided within 30 minutes of needle insertion. Hence the points IV and V were rejected by the investigators and the subsequent subjects were allotted the points I or II or III randomly



**Figure 1: Safe intramuscular arm injection points.**

subjects had received intramuscular injections at points IV and V. The prime reason for this low proportion of subjects at points IV and V is that the investigators decided to abandon points IV and V after five subjects in each of these points developed symptoms of axillary nerve compression that reversed back after half an hour. Only 2.7% of subjects had willfully defaulted from point III but none had defaulted from points I and II

Table 2 shows the reporting of symptoms of axillary nerve compression by the subjects after insertion of the needle at their allocated safe injection points of the arm. It is clear from the table that none of the subjects who were administered injections at points I and II of their arms had reported any symptoms of axillary nerve compression. Of the subjects who were administered injections intramuscularly at arm point III, only one subject had reported pain that subsided after 15 min of the institution of pain relief measures. Of the subjects who were administered at point IV, five of them developed symptoms among which four of them reported

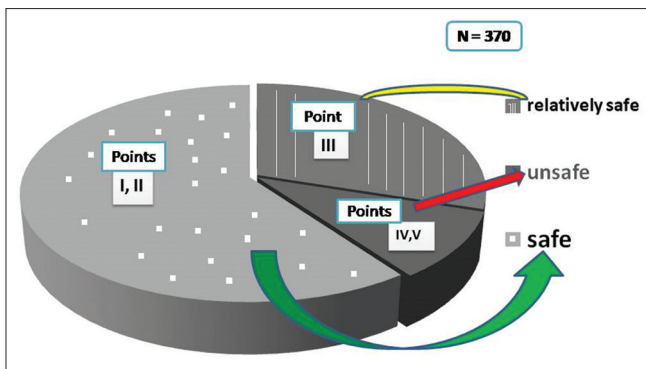
tingling sensations around the injection site and one of them reported numbness. However, each of their symptoms disappeared within 30 min after they were subjected to physiotherapy. A similar scenario was observed in another set of five patients who were administered injections at arm point V wherein all five of them developed numbness around the injection site that disappeared within 30 min of the onset of physiotherapy measures. Hence, based on the results of this study, the investigators decided that for this subset of the population, only points I and II were safe, points IV and V were unsafe, and point III was relatively safe (shown in Figure 2).

A simple questionnaire was circulated among the health care workers to assess their awareness regarding their knowledge of safe intramuscular arm injection points and safety in administering injections. This questionnaire was answered by only 1,200 participants from various hospitals both within and outside Telangana. The distribution of various types

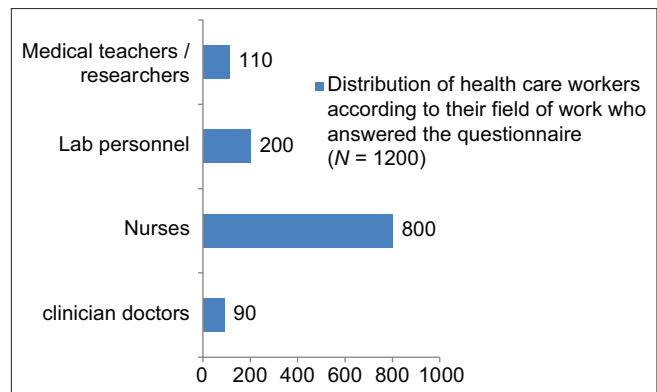
**Table 2: Reporting of symptoms of axillary nerve compression by the subjects after insertion of needle at their allocated safe injection points of the arm**

Safe point number	Reporting of symptoms of axillary nerve compression by the subjects (n=370)					
	No. of subjects who developed symptoms <sup>a</sup>	Within 5 min of inserting the needle	Within 15 min of inserting the needle	Within 30 min of inserting the needle	Recovery of symptoms within 30-45 min of inserting the needle (after physiotherapy and pain relief measures)	Non-recovery from symptoms
I	0	Nil	Nil	Nil	Not applicable	Not applicable
II	0	Nil	Nil	Nil	Not applicable	Not applicable
III	#1	No	Yes	No	Yes	No
IV	§5	Yes	No	No	Yes	No
V	^5	Yes	No	No	Yes	No

<sup>a</sup>Symptoms of axillary nerve compression such as pain, tingling sensations and numbness at the site of injection that disappeared within 30 min. <sup>#</sup>Pain at injection site. <sup>§</sup>4 subjects reported of tingling sensations, one subject reported of numbness at injection site. <sup>^</sup>All five subjects reported of numbness at the site of injection



**Figure 2:** Intramuscular arm injection points in this study based on their safety



**Figure 3:** Distribution of the health care workers according to their field of work who answered this questionnaire

of health care workers who answered this questionnaire is depicted in Figure 3. Of the 1,200 health care workers who answered this questionnaire, clinician doctors constituted only 7.5% and medical teachers cum researchers constituted 9.2%. Nurses formed the major portion of those who answered the questionnaire (66.7%) and the remaining being lab personnel (16.7%).

This questionnaire focused on four primary elements that were – 1) Preference for arm over the gluteal region for intramuscular injections in adults. 2) Those who were aware of more than one safe intramuscular injection point in the adult arm. 3) Those who were aware of complications arising out of axillary nerve compression due to intramuscular injections in the adult arm. 4) Those who were aware of the need for monitoring the patients after an intramuscular arm injection. The distribution of responses by the health care worker participants who positively answered the four key parameters in the questionnaire is shown in Table 3.

The observations in Table 3 show that 83.2% of participants gave preference for arm over the gluteal region for intramuscular injections in adults. Only 33.3 and 16.8% of participants were aware of more than one safe injection point in the arm and the need for monitoring patients after intramuscular injection, respectively; 66.7% of participants were aware of the complications arising out of axillary nerve compression due to intramuscular injection in the adult arm.

## Discussion

The deltoid is the most commonly preferred site for intramuscular injections as quoted in standard literature.<sup>[1,2]</sup> It is preferred over the gluteal region because of the ease of administration of intramuscular injections in the arm. This muscle is the chief abductor of the arm and is supplied by the axillary nerve.<sup>[2]</sup> This axillary nerve that arises from the posterior cord of the brachial plexus splits into anterior and posterior divisions, respectively, after entering into the axilla. It is here in the axilla that the divisions of the axillary nerve are subject to a lot of variations, especially the anterior division. Despite there being a lot of variations, conventional standard textbooks still maintain the injection point site to be in the lower deltoid area or 1 – 2 cm superior to the insertion of the deltoid<sup>[1,2]</sup>

Some workers have suggested that there are multiple points in and around the arm that can be used as an alternative to the conventional one based on their safety with regard to the axillary nerve's course.<sup>[3-8]</sup> Nakajima *et al.*<sup>[3]</sup> suggested four such zone points from the mid-acromion apart from the conventional textbook point as reference points that have also been employed in our study. They have suggested the safest point to be the bisector point of the anteroposterior upper axillary fold line with the line dropped from the lateral margin of acromion.<sup>[3]</sup> The findings in this study do not fully agree with those of Nakajima *et al.* as this study suggests that the bisection point is unsafe



**Table 3: Distribution of health care worker participants who positively answered the four key parameters in the questionnaire**

Parameters analyzed	Total no. of participants (n=1,200)	
	No of participants who answered positively for this parameter (n)	Frequency
Preference of arm over the gluteal region for intramuscular injections in adults	998	83.2%
Those who were aware of more than one safe intramuscular injection point in the adult arm	400	33.3%
Those who were aware of complications arising out of axillary nerve compression due to intramuscular injections in the adult arm	800	66.7%
Those who were aware of the need for monitoring the patients after an intramuscular arm injection	202	16.8%

and so is the point 4-5 cm below the anterior acromion but the other three points that are proven to be safe by Nakajima *et al.* are also proven to be safe in this study, However Cook *et al.*,<sup>[4]</sup> have refuted two of the findings of Nakajima *et al.* and only agree with the bisector point method, but their findings are not well substantiated. According to Cook *et al.*,<sup>[4]</sup> the point below the anterior acromion and the point midway between the midpoint of the deltoid and its insertion are considered unsafe. This study, however, suggests that the point midway between the deltoid's insertion and its midpoint is safe that contradicts the view of Cook *et al.* However, the point 4-5 cm below the anterior acromion is found to be unsafe in this study too that matches with that of Cook *et al.*

Other workers have disagreed with Cook's findings and have supported a holistic approach to the Japanese studies including those of standard literature.<sup>[5-11]</sup> But the fallacy lies in the fact that the course of axillary nerve varies in populations, and the quest to find a single best injection point is irrelevant. Hence, the ultimate goal of this study was to establish a series of safe points considering the variant course of the anterior branch of the axillary nerve in this subset of the population, and so, the points I, II, and III (as depicted in Figure 1) were found to be safe in a series after analyzing the results. Many studies agree to the bisector point method as the safest<sup>[11-14]</sup> but population-based studies on the same are still lacking. Textbooks to date have not still included the other safe points apart from the usual one,<sup>[1,2]</sup> hence, this study would also serve as an eye-opener to other possible inclusion of safe points.

The axillary nerve being a typical peripheral nerve, is predominantly motor, and its myelination potential is quite adequate.<sup>[1,6,8]</sup> Hence, the risk of permanent damage due to risky injections is eliminated. A mild transient reversible paresthesia or compression may occur which will soon subside and patients can be properly reassured regarding the same.<sup>[10-13]</sup> Moreover, the type of injection needle chosen in this study and the angle of its insertion conform to those of the standard norms already established in previous studies.<sup>[11-13]</sup>

It is interesting to note that only 7.5% of doctors and 9.2% of medical teachers answered the questionnaire that was circulated by the workers in this study as compared to the nurses and lab personnel who formed the majority that answered the same [Figure 3]. This possibly reflects

upon the lack of positive attitude shown by clinicians and medical teachers for self-check on awareness regarding injection safety as compared to the active involvement shown by the nurses or lab personnel who being the front-line workers during injections or vaccinations in this subset of the population must have felt a dire need to answer this questionnaire. It was also surprising to find that only 33.3% of all the health care worker participants who positively answered the four parameters of the questionnaire were aware of more than one safe intramuscular injection point in the arm and only 16.8% of participants were aware of the need for monitoring the patients after an intramuscular arm injection [Table 3]. This could reflect upon the poor state of awareness among the health care workers in this region.

### Limitations

Some workers have compared the course of the posterior circumflex humeral artery via ultrasound to serve as a route to localize the axillary nerve's course.<sup>[14-16]</sup> However, there are still others who have suggested that the posterior circumflex humeral artery need not always accompany the nerve, especially regarding its anterior division as the artery enters the axilla from a posterior aspect.<sup>[15-17]</sup> These findings have also been further substantiated by cadaveric studies.<sup>[14-16]</sup> However, there has been a slight discrepancy between the findings established by sonographic studies and those of the cadavers, possibly because these studies have been done in different populations.<sup>[10-15]</sup> The present study, however, does not use ultrasound findings of the posterior circumflex humeral artery as a guide to course out the axillary nerve because the prime motive of the workers in this study is to establish an affordable cum accessible protocol of a series of safe injection points based on the results of this study for health care workers not only working in tertiary care hospitals with access to ultrasound but also for those workers who deal with vaccinations or therapeutic injections in rural health centers or community health centers where ultrasound is either not accessible or not affordable. Moreover, it is practically not possible for every doctor or nurse or lab personnel working in rural areas or community health centers in this region to use ultrasound every time to localize the branches of axillary nerve across the deltoid before administering injections owing to the large crowds of patients that visit outpatient departments of hospitals every day. This could also be considered a limitation of this study.

## Conclusions

Points I (1-2 cm above the deltoid insertion) and II (midway between the midpoint of arm and deltoid insertion) are found to be safe in this study. Point III (midway between the anterior acromion and deltoid insertion) is relatively safe and points IV (4-5 cm below anterior acromion) and V (bisector line point) were found to be unsafe. This could be due to the deviant non-linear course of the anterior branches of the axillary nerve that again varies with different geographical populations. Hence, the authors would like to suggest that the needle insertion points for intramuscular injections in and around the arm cannot be pointed toward a particular site and a series of points need to be determined according to the population of that region and protocols must be followed accordingly rather than a conventional textbook-based approach. It is deciphered from this study that in this subset of people of the state of Telangana in whom the study was done, intramuscular arm injections can be safely administered at a point 2 cm above the insertion of the deltoid, at a point midway between the insertion of the deltoid and the midpoint of the arm, and at the midpoint between the anterior acromion and deltoid insertion, respectively.

## Acknowledgements

The authors would like to acknowledge the research council and ethics committee of AIIMS Bibinagar, Telangana for granting them permission to conduct the study. The authors would also like to acknowledge the nursing officers at the injection's clinic of the out-patient department of AIIMS Bibinagar, Telangana for helping them in this study.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## References

- Greenway K. Rituals in nursing: Intramuscular injections. *J Clin Nurs* 2014;23:3583-8.
- Rodger MA, King L. Drawing up and administering intramuscular injections: A review of the literature. *J Adv Nurs* 2000;31:574-82.
- Nakajima Y, Mukai K, Takaoka K, Hirose T, Morishita K, Yamamoto T, *et al.* Establishing a new appropriate intramuscular injection site in the deltoid muscle. *Hum Vaccin Immunother* 2017;13:2123-9.
- Cook IF. An evidence based protocol for the prevention of upper arm injury related to vaccine administration (UAIRVA). *Hum Vaccin* 2011;7:845-8.
- Van Mulder TJ, de Koeijer M, Theeten H, Willems D, Van Damme P, Demolder M, *et al.* High frequency ultrasound to assess skin thickness in healthy adults. *Vaccine* 2017;35:1810-5.
- Marshall HS, Clarke MF, Evans S, Piotto L, Gent RJ. Randomized trial using ultrasound to assess intramuscular vaccination at a 60° or 90° needle angle. *Vaccine* 2013;31:2647-52.
- Hirsch L, Byron K, Gibney M. Intramuscular risk at insulin injection sites--measurement of the distance from skin to muscle and rationale for shorter-length needles for subcutaneous insulin therapy. *Diabetes Technol Ther* 2014;16:867-73.
- Taddio A, Ilersich AL, Ipp M, Kikuta A, Shah V; HELPinKIDS Team. Physical interventions and injection techniques for reducing injection pain during routine childhood immunizations: Systematic review of randomized controlled trials and quasi-randomized controlled trials. *Clin Ther* 2009;31(Suppl 2):S48-76.
- Jackson LA, Peterson D, Nelson JC, Marcy SM, Naleway AL, Nordin JD, *et al.* Vaccination site and risk of local reactions in children 1 through 6 years of age. *Pediatrics* 2013;131:283-9.
- Nakatani T, Sanada H, Sugama J, Nagakawa T, Konya C, Ohkuwa M. Appropriate site for intramuscular injection in the deltoid muscle evaluated in 35 cadaverous arms. *Memoirs Health Sci Med Kanazawa Univ* 2000;24:27-31.
- Cook IF. Best vaccination practice and medically attended injection site events following deltoid intramuscular injection. *Hum Vaccin Immunother* 2015;11:1184-91.
- Cocoman A, Murray J. Intramuscular injections: A review of best practice for mental health nurses. *J Psychiatr Ment Health Nurs* 2008;15:424-34.
- Zaizi A, Dellero O, Rouijel B, Amrani A. Neurotization of isolated axillary nerve palsy in a teenage patient. *Int J Surg Case Rep* 2020;77:222-4.
- Steinmann SP, Moran EA. Axillary nerve injury: Diagnosis and treatment. *J Am Acad Orthop Surg* 2001;9:328-35.
- Probst DT, Mackinnon SE, Prather H. Isolated axillary nerve injury in an Elite high school American football player: A case report. *Sports Health* 2019;11:550-3.
- Nerve Compression Syndrome. 2011. p. 4-15. Available from: <https://www.healthline.com/health/nerve-compression-syndrome#symptoms>.
- Gibney MA, Arce CH, Byron KJ, Hirsch LJ. Skin and subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: Implications for needle length recommendations. *Curr Med Res Opin* 2010;26:1519-30.