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Intramuscular vaccine administrations including the adoption of "Zeta-track technique" & "without aspiration slow injection technique" (ZTT & WASiT): a prospective review

Review

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Abstract: **Objective:** To review the current literature on the practice of intramuscular injections (IMIs), focusing on immunizations.
Methods: The present study comprises 2 reviews, characterized by high-quality evidence, pertaining to the deployment of the slow injection technique without aspiration (referred to in this paper as the without-aspiration slow injection technique [WASiT]) and combined with the Zeta-track technique (ZTT). The literature review is oriented toward the analysis of 2 features associated with IMIs techniques: safety and pain, integrating new evidence on vaccinee positioning for each muscle site and general relaxation techniques in the multi-parametric analysis.
Results: The rigorous and in-depth reviews in the current study reveal the usefulness of including, among the international guidelines for via intramuscular immunizations, the adoption of WASiT only for compliant vaccinees, and in combination with all validated techniques for IMIs, and the use of ZTT limitedly if specific well-developed muscles are indicated. All the technique's limitations are exposed.
Conclusions: Future research directions are presented by including the author's study designs to provide indirect evidence for the validity of the rationale of the slow injection technique using scientific methods, and for the conduction of future randomized controlled trials (RCTs) focused on revisiting the adoption of ZTT in a dynamic and integrated immunizations protocol in anterolateral thigh (ALT), ventrogluteal (VG), and also in the deltoid muscle, in the specific cases analyzed.

Keywords: *local reactogenicity • injection site reactions • injection technique safety • intramuscular injections • immunogenicity • vaccinal solution leakage • without-aspiration slow technique • Zeta-track technique*

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1. Introduction

In the scenario of the pandemic emergency, in which the immunization's procedure is involving several professions, it is legitimate to wonder whether the significant incidence rate of local adverse events recorded in recent anticovid and influenza immunisations[1–3] could have been avoided, or could still be avoided, by revising the international guidelines. Therefore, it is of paramount importance to review the general guidelines for

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the without-aspiration slow injection technique (WASiT) in cooperating subjects and, only in certain cases, advanced nursing procedures such as the Zeta-track technique (ZTT), which would therefore require the recruitment of a higher rate of retrained nurses in immunization campaigns.

1.1. Short review on techniques for intramuscular injections (IMIs)

This section briefly summarizes the IMI techniques that can be used to date until new scientific evidence is available, with a particular focus on vaccines injections.

(1) **The stretching technique,** or standard method, consists in spreading tightly the skin between thumb and forefinger isolating the muscle: it is recommended for immunizations to adults[4–6]; however, the pediatrician Cook and Murtagh[7,8] found in several randomized studies that stretching is also recommended for vaccinations of children, including infants aged 2 months, 4 months, 6 months, and 18 months; the validity of this indication is also attested by ultrasonographic studies conducted by the same author.[7]

(2) **The grasping technique**: it consists in grasping (i.e., compressing) the body of the muscle between thumb and fingers; this technique is more suitable if patient's muscle mass is small, with young children or cachectic/emaciated patients.[4,6,9]

(3) **The bunching up method**, i.e., pinching a skin fold, is indicated by the Centers for Diseases Control (Atlanta) (CDC) 2021 only for immunizations for pediatric and geriatric patients as an alternative to grasping.[6]

The first 3 mentioned techniques are associated with an increased risk of drug leakage along the needle tract infiltrating the subcutaneous tissue, compared to ZTT,[4,5,10–33] with a consequent increase in the incidence of signs of local irritation (redness, swelling, and indurations) and defined "injection site reactions" (ISRs); Diggle and Deeks[9] in 2000 focused on ISRs associated specifically with vaccines, documenting the local reactogenicity following superficial administrations.

Moreover, as emphasized by Poland et al.,[34] abscesses and granulomas, although rare, can occur when vaccine or medication intended for IMIs is inadvertently delivered into subcutaneous tissue. The choice of an injection technique associated with subcutaneous tissue infiltration may be compounded by the universal use of a 25 mm long needle, without calculating the body mass index (BMI) and consulting the reference tables for needle gauges and lengths[6] that are appropriate to the BMI of each single vaccinee. Such a needle may be too short, especially in subjects who have a more extensive subcutaneous fat layer.[34–39]

On the other side, cases of overpenetration have been reported in children[40]; moreover, regarding the importance of adequate needle length to BMI, Shankar[41] underlines how in a sample of 200 Indian subjects with a BMI mean of 24.2, the universal use of a 1 inch (25 mm long) needle caused overpenetration in 50% of the vaccinated subjects, hitting the bone or periosteum, despite the precaution of leaving outside 3 mm of the needle closest to the hub; thanks to ultrasound studies the author attested a high correlation between BMI and skin-to-muscle (SM) thickness, and in addition to this he demonstrated that SM thickness was significantly greater on the left side and in females.[41]

Superficial administrations or accidental injection of vaccine into the subcutaneous tissue of vaccines such as anticovid vaccines that, in contrast, have been formulated to be delivered into the muscle penetrated for ≥5 mm,[34] may be a cause of a partial dose administration[33] and therefore of failure to absorb the full dose vaccine solution at the appropriate site, compromising immunogenicity.[42,43] The bunching up technique, in particular, has the advantage of being easy to perform, but it presents a serious risk of more superficial injection such as the subcutaneous one, indicated for example, in the administration of insulin.

(4) **The ZTT** is an injection method that has the purpose of creating a disjointed puncture or interrupted injection pathway that locks the drug into the target muscle, almost completely preventing the phenomenon of drug outflow along the line of pathway traced by the needle that has the characteristic shape of a Z, i.e., allowing a statistically significant reduction in the dispersion of the injected solution along the subcutaneous tissue (and minimally on the skin) compared to the standard technique; vice versa, the stretching technique and even more so the bunching up one, increase indeed the risk of drug leakage into the needle track.

ZTT is mostly associated in the literature with the slow injection technique,[4,5,10–32,44,45–48] sometimes also associated with the air-lock technique,[33,49,50] and sometimes associated with both the air-lock and slow techniques.[11] Finally, it can also be associated with the rapid injection speed and rapid needle withdrawal, without waiting 5–10 s.[51]

1.2. The ZTT: The procedural algorithm

Pull the skin and subcutaneous layer about 2.5 cm[5] laterally to the side with the ulnar side of the non-dominant hand, i.e., third, fourth, and fifth fingers (if ZTT is combined with the slow needle's withdrawal, the skin will be kept displaced in this position by the same hand until 5–10 s after the drug solution administration). Thanks to a semi-experimental study[26] analyzed in Sections 4 and 5, it was clarified that even a skin displacement of only 1 or 2 cm could be sufficient to achieve significantly less drug loss than when the standard technique is used, minimizing irritation from the medication.

Once the displacement is applied, use the dominant hand to insert the needle at a 90° angle into the skin with a quick and smooth movement to alleviate client discomfort[5]; immediately after needle insertion, the thumb and index fingers of the non-dominant hand are ready to hold the syringe. At the same time that the dominant hand is slowly pushing the plunger of the syringe for injection, imparting a uniform motion of the solution (speed rate of 0.1 mL/s), the non-dominant hand, in addition to keeping the skin dislocated on the side opposite to the injection with the ulnar side, can continue to hold the syringe steady, thanks to the first and second fingers (as if holding a pen[5]). The latter technique may be indispensable to keep the syringe stable during the aspiration maneuver, which however has no rationale and is contraindicated[6,52] in the muscle sites suitable for vaccination (deltoid, anterolateral thigh [ALT], or ventrogluteal [VG] sites). "Holding the syringe steady minimizes discomfort."[5] If ZTT is combined with faster injection the nurse can use the entire non-dominant hand only for the displacement, simultaneously compressing the muscle on the side.

After possible waiting for 5–10 s holding the syringe in place to allow the drug to be absorbed (if also slow withdrawal is applied[4,5]), remove the needle gently and smoothly at the same angle it was inserted (90°). Traumatic removals could be another important cause of increased hematoma/ecchymosis rates. Note that after the needle's withdrawal, the skin can return to its original position, being relaxed.

1.3. The strengths of this technique are the *minimization* of the following risks

(1) Drug leakage in the subcutaneous tissue overlying the muscle along the needle track and backflow of the medication into the skin at the end of the injection. The rationale is that as a result of the slow injection time and efficient lock of the injected solution within the target muscle, a disjoint pathway with its characteristic Z-track is created, which allows the absorption, into the muscle site, of almost the entire full-dose calculated for the drug.

(2) Local reactogenicity. Rationale: This is a direct consequence of the statistically significant reduction in the incidence of infiltration of the subcutaneous tissues both with irritant solutions[53–55] and with all pharmacological solutions that, on the contrary, are designed to be delivered in the muscle tissue.[4,5,10–33] Moreover, considering that pain receptors are present in the subcutis,[56] ZTT, reducing its infiltration with high statistical significance, should indirectly contribute to reducing the pain associated with IMIs.

(3) Reduction in drug response. Rationale: When a drug solution (such as a vaccine), formulated to be administered IMIs, is delivered at least at ≥5 mm in the muscle, the immunogenicity is best achieved[9,42]; muscle tissue is highly vascularized and consequently allows a faster mobilization and processing of the antigen than into the subcutaneous layer. Therefore, the ZTT, which is opposed to techniques associated with more superficial drug delivery, if associated with appropriate needle length/gauge, appropriate site and level of muscular activity, and proper positioning/relaxation of the vaccinee's muscle site, should theoretically also help to maximize the immunogenic response to vaccines. Regarding the needle to be chosen for ZTT, which can be conceived as a lateral stretching technique, it seems logical to use the same one indicated for the standard stretching between the first and second finger, rather than the needle used for bunching up, which on the contrary is on average 0.25 inches shorter.[6]

(4) Needle's movement. Rationale: stable positioning of the non-dominant hand during slow injection (or previous aspiration, if any) by the dominant hand. The positioning requires that the non-dominant hand pulls the skin laterally toward the side opposite the needle insertion site through the ulnar part (third, fourth, and fifth finger) and can simultaneously block the syringe cylinder with the first and second finger, keeping it stable: this implies high manual dexterity. In case of longer seconds of needle stay in the muscle (slow technique) the stability of the technique counterbalances the negative effect of wiggling (needle's shearing action).

Finally, also the individual's ability to have a steady and firm hand during IMIs administrations, varying between the operators, and the vaccinee's cooperation in remaining with a relaxed and immobile arm could

inevitably contribute to the overall stability of the injection procedure.

2. Research strategy

The following databases were used for the research from its inception, coinciding with the first mass administrations of anticovid vaccines, since September 2020: SCOPUS, Google Scholar, MEDLINE (OVID, Ebsco), and Science Direct.

Search terms were used to identify potential articles and the authors determined the eligibility of the studies with inclusion criteria.

The search terms comprised: IMI, injection technique safety, ZTT, rapid injection, injection speed, without-aspiration IMI, ISRs, drug leakage, local reactogenicity, systemic reactogenicity, randomized control trial, techniques for muscle relaxation, immunizations guidelines, muscle thickness measurements, and immunogenicity.

Search strategies were based on abstracts, keywords, and titles. The studies satisfying the following inclusion criteria were included in this prospective review:

(a) patients were administered IMIs in any setting (hospital or community);
(b) patients of all ages; and
(c) randomized controlled trial (RCT) or quasi-experimental study design where the effect of IMI's technique, injection site, positioning, and needle's characteristics on local/systemic safety and pain were examined, measuring at least 1 of the 2 following outcomes:

2.1. Safety improvement

Correlation between the intervention performed and the improvement in **safety** versus the compared technique, by measuring the following data: drug leakage immediately after injection, and signs of **local reactogenicity** (redness, swelling, indurations, bruising/hematomas) in the Δ**T** time interval up to 24 h/72 h after injection, with statistical significance expressed in Pearson's correlation coefficient *P*;

2.2. Pain reduction

Correlation between the intervention performed and the reduction of pain versus the comparative technique, by measuring pain in situ in the immediate time to injection and/or systemic reactogenicity (interference on activities of daily living [ADL], fever and irritability, and/or, in case of infants, persistent crying or screaming), in the 24 h/72 h following injection, with statistical significance expressed in Pearson's correlation coefficient *P*.

(d) analytical studies based on ultrasound findings were also included.[7,34–39,41,57]

3. The adoption of ZTT combined with WASiT in IMIs

3.1. The effects of the injection speed (rapid versus slow) on tissue trauma and pain

According to the international 2021 guidelines, vaccines must be rapidly injected without aspiration.[45]

These recommendations seem to be biased toward a fast injection guideline. The literature does not agree on the speed of injection: with the exception of vaccination of infants,[58] the vast majority of authors advocate that medicines be injected slowly.[4,5,10–32,44,45–48]

The ZTT is associated by definition with the slow injection technique from the most extensive body of the literature.[4,5,10–32,44] According to Hockenberry and Wilson,[45] a slow medication rate reduces pain and tissue trauma and also reduces the risk of medication's leakage back through needle track. This is in line with the recommendations of Ozdemir et al.,[48] who, following a study conducted in 2013 on the injection rate of methylprednisolone, had attested that a slow speed of drug delivery improves pain management IMIs.

Concerning the administration rate, Mitchell and Whitney[46] recommend plunger depression at a rate of 10 s/mL; by further slowing down the administration rate to 20 s/mL, they found no reduction in pain. This injection rate is still currently the reference rate for all IMIs including vaccines in the Fundamentals of Nursing books,[4,5] indicated with the corresponding rate of 0.1 mL/s.

The usefulness of administering the vaccine quickly is in particular referred in the literature for the immunizations of infants, for whom this seems to be a priority feature, given the need for the quick dissipation of immediate pain.[58]

Since the perception of pain is a subjective phenomenon, there cannot exist a wholly accurate scientific mechanism for discerning the exact degree of pain undergone in pursuance of various administration methods or rates, or variations in these. However, the study by Diggle and Deeks[9] in 2000 compared the rate of local reactions in 110 infants using 25 G 16 mm length needles versus 23 G 25 mm length needles, resulting in a significant reduction in local reactogenicity (pain in situ, redness, swelling, and indurations) through the adoption of the 23 G and 25 mm long needle. It is difficult to

state with certainty that the significant reduction in tissue trauma was attributable only to the larger diameter of the needle hole, allowing a reduction in the pressure of the injection jet, and not to the positive effects of a simultaneous greater length of the needle used (25 mm). However, it is very reasonable to assume this for the following reasons. The needle's length in vaccinations for infants from 2 months to 18 months that the literature has shown to be more suitable is 16 mm, and not 25 mm.[7,59–61]

The recommendations on injection speed provided by the scientific literature are postulated on the use of needle diameters between 21 G and 25 G (or even 20 G for oily solutions).[5] If we consider that the IMIs administration of vaccines involves the use of needles with a diameter between 23 G and 25 G,[6] and that the most widely used needle for the practice of immunizations is the 25 G, (i.e., the needle with a smaller diameter than those suitable for IMIs), these recommendations should even more reasonably be respected in the elaboration of international guidelines for immunizations: the smaller the diameter of the lumen through which a solution is pushed, the greater will be the injection jet on the target muscle or the subcutaneous tissue eventually infiltrated, and therefore the greater will be the tissue trauma, following the sudden distension of the tissues given by the rapid increase in pressure. This is a simple consequence of the continuity equation (Eq. [1]):

$$v = Q * A \quad (1)$$

where υ is the flow velocity of the fluid, *Q* is the flow rate, and *A* is the transverse section of the duct lumen. The principle of conservation of mass states that the volume of flow or flow rate of an incompressible fluid in a rigid duct that varies in amplitude must remain constant (Leonardo's principle or continuity equation).

The basis of the bibliography cited by the CDC to support the recommendation of rapid injection of vaccine solutions is represented by the RCT that was conducted by the pediatricians Ipp et al.[58] in 2007 on a sample of 113 infants 4–6 months of age receiving acellular Diphteria-Tetanus-Pertussis vaccine (DPTa) P-Hib immunization. Two pediatricians compared infants' pain response using slow injection, aspiration, and slow needle's withdrawal in the "standard group" versus using rapid injection, no aspiration, and rapid withdrawal in the other "pragmatic group." Based on behavioral and visual pain scales, the group that received the vaccine rapidly without aspiration experienced less pain. "No immediate adverse events were reported with either injection technique."

In the RCT, the researchers limited themselves to measuring the outcome, represented by infant pain exclusively in the immediate period of the injection, i.e., an immunization pain score within 15 s of the immunization, preceded by a baseline pain score 5 s prior to the vaccine injection, comparing the scores related to immediate crying among 56 infants receiving the rapid injection technique without aspiration and an equivalent group of infants receiving vaccination with both slow aspiration prior to injection (10 s) and slow injection, and needle removal 5–10 s after injection (slow withdrawal). Generally, most of the local and possibly also systemic adverse reactions such as fever and irritability are seen 48–72 h after injection.[8,60] However, the scores related to reactogenicity (signs of local inflammation and/or systemic reactions) in infants at home and the consequent psychological repercussions on parents caring for children in the post-injection phases, including at night, have not been measured.

Focusing on pain, it would be of paramount importance to distinguish the immediate pain, within 15 s from the injection, from that manifested in the following 72 h, measuring it at predetermined time intervals, and not only in infants, but in all age groups: this would allow detection of the real impact of a rapid injection technique compared with the slow one.

Moreover, an important confounding variable of the RCT is represented by having associated in a single intervention and relative observation, 3 variables: the slow injection, which is endorsed in all literature[4,5,10–32,44–48] with the exception of infant vaccination[58,61]; the 10 s aspiration, which has never been supported by scientific evidence demonstrating an increase in safety for IMIs in muscles suitable for immunization (deltoid, ALT, and VG sites); and the slow withdrawal, for which scientific evidence is not yet available, apart from a small study that seems to demonstrate its non-usefulness.[62]

The author himself,[58] in the limitations of the study, declares that it is "difficult to ascertain the relative contribution of injection speed versus aspiration on the observed overall reduction in pain," concluding that "the guidelines for recommending aspiration prior to IMIs and injection speed should have been re-examined."

Among limitations there are the exclusive detection of immediate pain, without monitoring its progression in the 72 h following the injection, and the non-identification of the differential effect of pain caused by protracted aspiration for 10 s in infants, compared with the hypothetical pain during the 10 s waiting prior to needle's removal, and also compared with slow injection, which remains, to date, an indication in the reference books of Fundamentals of Nursing[4,5]; on the contrary, 10 s aspiration has never been supported by the literature, but it represents, in itself, an incisive and objective factor of trauma for tissues, as demonstrated by the Stokes' equation concerning the effects of aspiration forces

(negative pressure), whose description is beyond the scope of this article.[63]

Moreover, considering how the physiopathology of the human body can be reproduced with the same mechanisms in the different body districts, in order to have a tangible idea of the effective and really visible tissue traumas that the suction forces (negative pressure) can cause on the tissues, more significant are the micro lesions, even bleeding ones, that a simple endotracheal suctioning maneuver can cause on the tracheal mucosa, and whose increase is associated in the literature to several factors, among which are the protraction of the suctioning time beyond 15 seconds, and the increase of the suctioning pressure.[64–66] Therefore, with the same physiopathological mechanisms of endotracheal suctioning, even in the suctioning maneuver for vaccinations (for which in addition very small caliber needles such as 25 G are used), the tissue trauma, and any related pain, is certainly produced.

On the other hand, however, it is worth noting that, besides the trauma of aspiration, even the slow injection technique in infants could represent in itself an additional risk for needle's shearing action (wiggling), regardless of the variable represented by the stability of the vaccinator's hand.

This objective risk of wiggling increase is inherent in the difficulty of keeping infants motionless during immunizations, particularly if distraction interventions are not adopted or there is maternal detachment (vaccine in ALT instead of VG, preventing infants from remaining prone in the lap of the mother's legs as in VG site,[7] and performing the vaccination procedure, instead, in ALT in front of the gaze of infants, resulting in their trauma and adverse effects on vital parameters.

Therefore, with regard to the variable "immediate pain" in relation to the speed of injection, the literature tends to consider that the slowness of the injection can contribute to increase it, only if the age group considered is represented by infants, without extending the usefulness of a rapid injection technique to all age groups.

After the study[58] in 2014 the researchers Girish and Ravi[61] reproduced an RCT with the same research design on a sample of 200 healthy infants, obtaining overlapping results but with the same limitations; these are analyzed in Table 1 of the current study.

Finally in adults, on the contrary, the literature agrees on the usefulness of performing the injection at a slow speed to minimize tissue trauma and therefore pain. Moreover, the increase in time needed to perform the injection with slow technique is negligible and this should not be considered as the real cause of any delays in vaccination. For example, according to Potter et al.,[4] who recommend a slow injection rate of 0.1 mL/s, the Pfizer anticovid vaccine solution (0.3 ml) should be injected slowly in only 3 s.

3.2. ZTT: the state of the art

The first researcher who invented and demonstrated the method of preventing flow-back, then called ZTT, was Shaffer, in 1929.

Only in 1984, more than half a century later, Shepherd and Swearington[10] focused on ZTT, pointing out that this technique could be performed in any appropriate muscle group provided that the overlying tissue can be displaced by at least 1 inch.

In 1986 Keen[11] compared ZTT combined, for the first time, with air-lock technique, with the standard method in 50 participating subjects who were prescribed analgesic therapy for pain related to sickle cell anemia or pancreatitis at scheduled hourly intervals of 3 h or 4 h for a total of 2–8 IMIs/die. Each subject received both types of intervention in the VG site, acting also as a control of himself, to control totally all the confounding variables. The evaluation of the degree of discomfort was based on the compilation of a 4-point Likert scale, while the monitoring of local adverse reactions was determined by visual observation of any redness and swelling and by palpation for the detection of any subcutaneous induration. The use of the ZTT resulted in a significant reduction in the incidence of local lesions at all selected time intervals, severity of discomfort at selected time intervals, and selected descriptors of discomfort (pain) at selected time intervals.

Kim[12] in 1988 conducted a subsequent study on a small sample (numbering 20) of participating subjects to compare the effect of the ZTT for IMIs with the effect of the standard technique on the severity of discomfort and lesions at the injection site. He found that there was no difference in the severity of subject discomfort between 2 groups, but the degrees of severity of subject discomfort following administration of IMI using ZTT tended to diminish; this suggested, according to the author, that ZTT could decrease the severity of discomfort in patients frequently receiving IMIs.

Erdal[13] conducted a study the following year, in 1989, which again compared the effect of the ZTT for IMIs with the effect of the standard technique in reducing pain and lesions, founding the superiority of ZTT in both outcomes.

Two authors, Keen[53] and Hahn,[54,55] in 1990 and 1992, respectively, pointed out that ZTT was particularly effective in administering irritating solutions, and so they claimed that waiting 5–10 s after completion of the delivery of the drug was necessary only if the drug was particularly irritating (iron preparation for example).

Study	Participants	Injection	Intervention	Comparison	Outcomes	Bias/limitations
Yilmaz et al.[33] Semi-experimental RCT	60 patients (surgery clinic) balanced for sex/age/BMI and randomized into 2 groups.	Diclofenac sodium 3 mL; Needle: 21 G, 38 mm length; Dorsogluteal site. Positioning: face up, internal rotation of femur both in intervention and in control group.	Technique used to improve safety: ZTT performed with a displacement of 1–2 cm and combined with air-lock technique (0.3 mL of air previously drawn into the syringe). It is not specified if the injection has been associated with standard speed of 0.1 mL/s or faster (21 G needle). Technique used to reduce pain: ZTT combined with air-lock technique.	Standard technique (stretching)	Statistically significant reduction in drug leakage ($P = 0.008$) (measurement of drug leakage by a different researcher with a ruler in millimeters, previous use of sterile absorbent paper on the injection site immediately after injection). Non-statistically significant reduction in pain ($P = 0.336$) (immediate pain measured through the 100 mm VAS assessed by a nurse blinded to the intervention).	One confounding variable: It is difficult to establish the differential contribution related to air-lock technique and ZTT, but the combination of the 2 techniques is also possible, and this publication has shown the effectiveness of ZTT along air-lock (0.3 mL). The sample is not very large for obtaining results' generalization.
Cook and Murtagh[8] RCT	566 children aged 2–18 months in good health; infants with neurological diseases/ history of severe immediate allergic or anaphylactic reaction to any vaccine antigen were excluded.	Vaccine solution: anti haemophilus influenzae B. Needle: 25 G, 16 mm length, fully entered at 90° to the skin surface using the stretching technique in infants rather than grasping/bunching up method in infants; on the contrary CDC [45] recommend 25 G 25 mm needle in infants (1–12 months). VG site, vaccine in VG site allowing the infant to remain on the mother's legs maintaining maternal contact (intervention) versus ALT site on the bed, observing vaccine administration in front of their eyes (control).	IMI (vaccine) in VG site (conversely CDC [6] recommend ALT site as preferred site in neonate/infants/toddlers).	Same injection and technique in ALT site	Safety improvement: Local reactions in the injection site were reduced with high statistical significance in the intervention group compared to the control one. Redness and swelling: $P < 0.0001$; bruising: $P = 0.0004$. Pain reduction: vaccinee irritability and fever, persistent crying or screaming were reduced with high statistical significance in the intervention group compared to the control one, and the reflected grade of acceptability of parents in relation to their sleep deprivation, etc. (e.g., due to children care in the delta T time interval up to 24 h following vaccine's injection) was at the same time greatly improved. Irritability: $P < 0.0001$; fever: $P = 0.0015$; persistent crying or screaming: $P = 0.0012$; parental acceptability: $P < 0.0001$.	No bias/limitations were detected. The outcomes demonstrate with high statistical significance the validity of the research hypothesis, despite the fact that the trial deviated from the CDC guidelines. The study by Junqueira et al.[60] confirms Cook's[8] outcomes with a sample of 580 newborns (0–6 months), detecting the same outcomes after the administration of hepatitis B vaccine in VG site.

Table 1. Continued

Study	Participants	Injection	Intervention	Comparison	Outcomes	Bias/limitations
Ipp et al.[58] RCT	113 infants aged 4–6 months, balanced for age and possible intake of oral analgesics before vaccination. Sample unbalanced by gender.	113 infants aged 4–6 months, balanced for age and possible intake of oral analgesics before vaccination. Sample unbalanced by gender.	113 infants aged 4–6 months, balanced for age and possible intake of oral analgesics before vaccination. Sample unbalanced by gender.	10 s aspiration performed before c + slow injection + slow withdrawal.	Safety outcome: no immediate adverse events were reported with either injection technique. Pain outcome: the immediate pain was greater in the standard versus pragmatic groups. • The immunization pain score was measured within 15 s/30 s of the immunization, preceded by a baseline pain score 5 s prior to the vaccine injection. Measurements (high statistical significance): • MBPS: $P < 0.001$; • Infant crying time assessed from videotape analysis (coder blinding): $P < 0.001$; • Percentage of crying infants $P < 0.001$; • Pain assessment from parents based on a VAS of 0–10: $P < 0.001$; • Pain assessment from physicians based on a VAS of 0–10: $P < 0.001$.	The high degree of confounding variables of the RCT is represented by having associated in a single intervention and relative observation, 3 variables in each randomized group: • Experimental group: no 10 s aspiration previous IMIs + rapid injection + rapid withdrawal; • Control group: 5–10 s aspiration performed + slow injection + slow withdrawal. Aspiration prior to injection has never been supported by scientific evidence in muscles suitable for immunization (deltoid, ALT, and VG sites): it was not recommended by nursing literature from 2001 [52], being independently associated with increased pain; total time's calculation is unclear. Exclusive detection of immediate pain, without monitoring its progression (fever and irritability/ persistent infants crying or screaming in the delta T home time interval up to 24 h following injection); also the scores related to local reactogenicity in the delta T time interval up to 72 h following injection have not been measured. No pediatricians/parents blinding. It is not possible to extend the results of the study conducted on infants to all age groups.

(Continued)

Study	Participants	Injection	Intervention	Comparison	Outcomes	Bias/limitations
Girish and Ravi[61]	200 healthy infants aged 1.5–18.0 months, with no significant differences in age, gender, and weight in the 2 randomized group of 100 infants; pre-vaccination analgesics were not used.	DTwP vaccine solution (0.5 mL) administered in ALT. Needle: 25 G, 25 mm length, inserted at 90° in in both groups. compressed muscle (grasping).	No 10 s aspiration previous IMIs + rapid needle's advancement into the muscle + rapid injection + rapid withdrawal: entire procedure completed in 1–2 s.	Slow advancement of the needle into the muscle + 5 s/10 s aspiration performed before IMIs + slow injection + slow withdrawal; entire procedure completed in 5 s/10 s.	Safety: no immediate adverse events were reported with either injection technique. Pain: Scores relative to pain were assessed using the MBPS compiled with the 2 clinical psychologist blind versus slow/rapid technique, observing videotapes from 5 s prior to immunization (baseline) up to 15 s later. Mean duration of cry were compared using Kaplan–Meier survival analysis: it was lesser in the interventions group (32.15 s with standard error 2.020) than in the comparison group (37.37 s with standard error 1.863), and pain in the intervention group was lower than that in the comparison group ($P < 0.001$).	Exclusive detection of immediate pain, without monitoring its progression in the 24 h following the injection (fever and irritability/ persistent infants crying or screaming in the delta T home time interval up to 24 h following injection); also the scores related to local reactogenicity in the delta T time interval up to 72 h following injection have not been measured. The high degree of confounding variables of the RCT is represented by having associated, in a single intervention and relative observation, 4 variables in each randomized group. The first 2 variables in the comparison are independently associated with increased pain rather than reduction of it, and they are not supported by the literature: • Berger and Williams[71] as early as 1992 advocated introducing the needle into the site at 90° using a dart-like motion to minimize pain, and recommended inserting the needle at a 90° angle into the skin using a quick and smooth motion, to attenuate the patient's discomfort[4,5]; • aspiration of 5–10 s performed before IMIs has never been supported by scientific evidence in muscles suitable for immunization[52]; total time's calculation is unclear.

(Continued)

Study	Participants	Injection	Intervention	Comparison	Outcomes	Bias/limitations
Abdelkhalek[44] Semi-experimental RCT	30 participants in the group I (shot blocker versus standard technique for IMIs) 30 participants in the group II (ZTT versus standard technique for IMIs) Adults aged 18–65 years, 60% of females in I group, 70% of females in II group, mean score of BMI was 26.33 ± 2.02 in I group, 26.63 ± 1.97 in II group. Surgical hospital.	Drug solution: neurovit 3mL, dorsogluteal muscle, 23 G (length not reported). Positioning: lateral position with knee slightly flexed.	Group I: shot blocker during IMIs. Group II: ZTT associated with WASiT (the aspiration prior to injection is not mentioned in the listed procedural algorithm, and the author states that the researcher has adopted the slow injection technique during IMIs).	Standard technique	The VDS, 6 pain descriptors) was compiled by the researcher who interviewed the patients in the immediate time after each injection: pain score was reduced both in groups I (shot blocker) and II (ZTT and WAST) compared to standard technique: $P = 0.000$ and $P = 0.020$, respectively. The level of anxiety as assessed using the "Beck Anxiety Inventory" (BAI, 21 items) was significantly reduced only in group II (ZTT and WAST) compared to standard technique ($P = 0.000$), but not using the shot blocker, probably seen as a new device by the patients ($P = 0.330$).	There is no mention of blinding with respect to the technique adopted for both the patients and the researcher administering the IMIs, as well as for the researcher administering the questionnaires. Despite proper positioning the administration of IMIs was not performed in the VG site.[72,73] The total sample was not very large.
Kara and Yapucu Gunes[50] RCT (crossover design), double blinding.	86 randomized patient in postoperative care, with mean age of 46.4 ± 15.1 years;, and 38.7% of women and 46% of men; not homogeneous for BMI (mean BMI was 27.1 ± 6.08).	Diclofenac sodium (3 mL), needle: 21 G, inserted at 90°; length associated with BMI not reported. Dorsogluteal site (I injection in right side, II in left side, and III again in right site).	Technique improving safety: internal rotation of foot (B) 3 interventions in the same patient (crossover study) chosen in a random sequence with intervals of 8 h used to estimate pain: (A) Positioning: prone with toes pointing down during injection with standard technique (not declared); (B) Positioning: prone with internal rotation of 1 foot (relaxation) during injection with standard technique (not declared); (C) Same positioning in A combined with ZTT with displacement of 2.5 cm along air-lock (0.2 mL of air), and with slow technique both in injection and in needle's withdrawal. All 3 interventions was preceded by aspiration.	(A) versus (B) versus (C)	VAS was used to assess the level of pain associated with varying BMI and with each intervention: The influence of BMI on pain was significant in A ($P = 0.006$) and C ($P = 0.007$) (the minimum common denominator was the positioning). In B (safer positioning) BMI's influence was not significant. There was significant difference between the 3 techniques in affecting pain ($P = 0.009$). The patient reported less pain with (C) in comparison with (A), but less pain with B (safer positioning) in comparison with (C). The results supported the following hypothesis: "If ZTT along air-lock and slow ZTT technique is combined with the prone position with the foot internally rotated, the pain should be significantly reduced compared to the standard technique with the toes pointing down."	In addition to injection pain, participants were already experiencing postoperative pain; moreover, both aspiration[52] prior to injection and dorsogluteal site[72] are independently associated with increased pain and reduction in safety. It is hypothesized that this is counterbalanced by safer positioning (internal rotation of the thigh, which is accompanied by movement of the femoral neurovascular bundle,[74] reducing but not eliminating the probability of the needle passing through it causing injury, and consequently pain). Also, relaxation from correct positioning reduces pain. Missing data: needle length not reported. The sample was not very large.

(Continued)

Study	Participants	Injection	Intervention	Comparison	Outcomes	Bias/limitations
Shankar et al.[41] cross sectional, analytical study	400 arms of 200 adult Indians balanced for gender, without scars and/or certain systemic diseases with varying age and BMIs (mean BMI of 24.2); radiology department.	Deltoid side, both left and right sides (in the sample all participants stated that the right arm corresponded to the dominant one). 23 G, length 25 mm, inserted at 90°, leaving outside 3 mm of the needle.	Safety improvement: to make subsequent protocols for IMIs on the deltoid side safer. Thickness measurement (in cm) by ultrasound probe of: • SM, • MB, and • SB at the deltoid IMI site on both sides of the participants' arms; needle's insertion (standard IMIs) to participants.	Comparison between gender and side differences in the SM and MB thickness at the deltoid site for IMIs.	Assuming a standard needle length of 25 mm, the prevalence of overpenetration in Indian adults was 50% (both male and female), while under-penetration was 1%. Correlation of SM thickness with the BMI, age, and gender: Females with the same medium BMI had a significantly higher SM thickness: $P < 0.001$ (subcutaneous layers thicker), and lower MB thickness: $P < 0.001$ (thinner muscle layer) in comparison with males. The mean thickness of the male deltoid (1.69 ± 0.4 cm) was greater than that of the female deltoid (1.48 ± 0.52 cm): $P < 0.001$ Right muscle thickness was significantly greater in both men (mean of measurements: 1.74 cm; side differences: $P = 0.001$) and women (mean of measurements: 1.52 cm; side differences: $P = 0.014$). When side and gender differences were considered together there was greater side differences in the SM thickness (greater subcutaneous layer) among females ($P = 0.024$) in comparison with males ($P = 0.380$). Deduction: The technique of IMIs needs to be dynamically adapted to each individual.	Missing data: It was not reported which solution was injected, but it is supposed there was performed only needle's insertion in the deltoid site. Cook's[75] protocol for safer landmarking was not used.

Note: CDC, Centers for Diseases Control (Atlanta); ALT, anterolateral thigh; BMI, body mass index; IMI, intramuscular injection; MB, muscle-to-bone; MBPS, Modified Behavioral Pain Scale; RCT, randomized controlled trial; SB, skin-to-bone; SM, skin-to-muscle; VAS, visual analog scale; VDS, Verbal Descriptor Scale; VG, ventrogluteal; WASiT, without-aspiration slow injection technique; WAST, without-aspiration slow technique; ZTT, Zeta-track technique.

Table 1. Study characteristics.

Presenting inferences aligning with those of Keen,[11] Newton et al.[14] in 1992 and Berman et al.[5] in 1993 suggested that ZTT should be used with the full range of IMIs medications, as it is believed to reduce pain as well as the incidence of solution leaks.

In 1996 MacGabhann[67] conducted a research study comparing ZTT with the air-bubble (air-lock) technique, rather than the standard technique, and reported more pain and bleeding using ZTT than the air-lock technique.

In 2010 Najafidolatabad et al.[68] undertook a quasi-experimental study comparing the pain severity, drug leakage, and ecchymosis rates caused by IMI of tramadol 0.5 mL using air-lock technique versus ZTT. The sample is comprised of 90 female patients aged 18–60 years, with a mean BMI of 26.5 ± 4.2 in the air-lock group, and a mean BMI of 26.5 ± 4.3 in the ZTT group.

The drug leakage was measured immediately after the injection; the possible presence of ecchymosis was detected by interviews with patients and pain was evaluated by a 10 cm visual analog scale (VAS).

The study outcomes showed significant reduction both in complications and in pain using air-lock technique versus the comparison one (ZTT): ecchymosis ($P < 0.05$), drug leakage ($P < 0.05$), and pain severity ($P < 0.05$).

The study's biases are the following:

- there are no data concerning the timing of ecchymosis and VAS assessment;
- there is no blinding of the patients to the treatment received;
- there is no blinding of the researcher in data collection; and
- the site for IMIs was not reported.

Neither MacGabhann's study[67] nor Najafidolatabad's[68] compared the use of ZTT and air-lock t. with the standard t., while D. Yilmaz's later study[33] was diriment about this important comparison, because it compared for the first time, in 2016, both ZTT along with air-lock technique, and the standard technique along with air-lock t., showing that the air-lock with ZTT was more effective than ZTT alone, and also with respect to the standard technique associated with the air-lock one.

In 1996 Beyea and Nicoll[16] argued and explained in detail how ZTT created a disjoint perforation or broken injection pathway that locks medication into the target muscle, while the standard technique increased the risk of drug leakage into the needle track.

In addition, Beyea and Nicoll[15] in agreement with Berman et al.[5] and Smith and Duell[69] argued that, after completion of delivery of the entire volume of drug solution, the needle should be left inserted into the muscle for 5–10 s before removal. This indication was subsequently confirmed by numerous authors.[4,5,24]

In 1997 Hasani and Alizadeh[17] conducted a quasi-experimental study to examine the effect of ZTT on severity of pain, bruises, and drug leakage at the injection site. The study's sample was constituted by 60 adult medical-surgical patients, and subjects served as their own controls by receiving both ZTT and standard IMIs. Data collection pertaining to techniques used in the administration of injections was carried out during 1996, following both a subjective measure (assessing the pain reported by each patient, which was reported by them as lesser, equal, or greater corresponding to each injection) and objective ones (measures of injection site drug leakage and bruises [as longest diameter size, recorded in millimeters]). Data were analyzed by parametric (paired *t*-test and one-way analysis of variance) and bi-parametric (chi-squared test and sign test) statistical tests, demonstrating that the ZTT significantly decreased the incidence of selected descriptors of the 3 variables of pain ($P < 0.001$), bruises ($P < 0.05$), and drug leakage ($P < 0.001$) at injection site and its superiority was supported with respect to standard technique.

Subsequently in 2000, Rodger and King[19] stated that "ZTT was recommended for all injection sites." In line with Keen's findings,[11,53] they found a significant decrease in both pain and injection site lesions using ZTT. This requires the overlying skin and subcutaneous tissue to be displaced by 2.5–3.75 cm before injection and released immediately after. It prevents leakage of the drug and locks it into target muscle tissue.

Jacobson et al.[70] in 2001 valuated, in a scientific paper focused on "making vaccines more acceptable," that "ZTT could be effected in decreasing injection pain in children."

In 2007 Floyd and Meyer[22] emphasized the use of ZTT, with the indication of stretching the skin of "2–3 cm" to the side, prior to injection insertion, to lock the medication in the muscle by "distorting the needle pathway."

In 2008 Barron and Cocoman[23] lecturers at the School of Nursing in Dublin, claimed that the "Z tracking (ZTT) was endorsed in all literature related to IMIs with the exception of infant vaccination." In addition, their contribution was fundamental to redeeming uncertainties in the literature regarding the minimum skin and subcutis displacement in centimeters sufficient to allow the execution of ZTT in children, emphasizing at the same time, as the literature was very focused on immunizations in young children aged <2 years, rather than in children and adolescents, and as the correct execution of "a good track" was a nursing responsibility. To use ZTT in IMIs, "the children's nurse should use their non-dominant hand to displace the skin and subcutaneous

tissue 1/2 inch (1.25 cm) or 1 cm laterally to the injection site before injecting."

Only Yilmaz later,[33] in 2016, confirmed with a semi-experimental study how, even in adults, a lateral displacement of only 1–2 cm could be sufficient to obtain a statistically significant reduction of drug leakage, going beyond the previous concept of Rodger and King,[19] regarding the need for overlying skin and subcutaneous tissue to be displaced by 2.5–3.75 cm before injection.

In 2010 Kara and Gunes[50] conducted an RCT to determine the effect on pain of 3 different combinations of techniques/positionings for IMIs and elaborating, based on the outcomes, the following deduction: "if ZTT along air-lock and slow technique is combined with the prone position with the foot internally rotated, the pain should be significantly reduced compared to the standard technique with the toes pointing down"[50]; this stance is analyzed in Table 1.

In 2016, Shehata[51] conducted a study to measure the effects of skin tapping and ZTT on pain intensity among hospitalized adult patients who received IMIs. The study revealed that the pain score was reduced when IMIs were administered using ZTT associated for the first time with rapid injection and withdrawal (second and third time of injection) rather than routine standard technique (first time of injection) and there was highly significant decreasing of total pain in second and third times of injection for study group II itself. These findings were in line with those of Keen.[11]

In 2016 Yilmaz[33] conducted a semi-experimental, randomized, and controlled study to compare the effects on pain and drug leakage determined by the use of ZTT combined with the air-lock technique versus the standard one, for IMIs; the study[33] is analyzed in Table 1.

The researcher[33] compared the effects on pain and drug leakage determined by the use of ZTT combined with the air-lock technique versus the standard one, for IMIs of the same drug (diclofenac sodium) on a sample of 60 participating subjects, balanced for sex and age and randomized into 2 intervention groups. In both intervention groups the air-lock technique was performed at the same time with 0.3 mL of air previously drawn into the syringe. The ZTT was performed with a displacement of approximately only 1–2 cm. The needle used, for both groups, was 38 mm length and 21 G (this diameter allows independently a reduction of the pressure of the injection jet compared to gauge of smaller diameter, such as 22–25 G).

The framework used for the evaluation of pain was the VAS, and the data were assessed by a blinded nurse with respect to the intervention: the pain was detected only during the injection, without considering the subsequent pain at intervals in the following 72 h and/or in subjects subjected to repeated injections. The diameter of the leak was measured by a different researcher, with a millimetric ruler, after the use of sterile absorbent paper compressed on the needle entry site. The results of his study confirmed those obtained by Keen[11] in 1986, combining ZTT with the air-lock technique. Moreover, Hasani and Alizadeh,[17] who conducted a similar study in 1997, demonstrated, in the group of subjects receiving IMI with ZTT associated with air-lock technique, a statistically significant reduction in drug leakage (P = 0.008), and a non-statistically significant reduction in pain (P = 0.336).

However, the results of Yilmaz's study[33] are not generalizable in the indication of ZTT both because of the small sample and because it is difficult to establish the differential contribution related to air-lock technique and ZTT.

In 2019 Abdelkhalek[44] conducted a quasi-experimental randomized controlled study on a sample of 60 patients balanced for BMI and without significant differences on demographic data, finding that pain score was reduced when IMIs were administered using ZTT and WASiT, as well as using shotblocker (an innovative and patented device), rather than using the standard technique. Moreover ZTT was also revealed to be effective, for the first time, in minimizing the level of anxiety.

Finally, a very recent application of ZTT seems to be the extension of its use not only to IMIs but also to subcutaneous insulin administrations. According to the results of a study conducted by Demirhan et al.[76] in the sample of participants receiving insulin with ZTT, the liquid leakage was 0 mm, i.e., completely absent, compared to the group receiving the standard 10 s waiting for needle's withdrawal technique, reporting a liquid leakage of 0.4 ± 0.5 mm.

It is not possible to extrapolate/generalize the results of this study both because it does not concern IMIs and because, owing to the limited sample, the possibility of avoiding a longer post-injection needle dwelling time caused by the slow withdrawal is very significant; however, according to these results, it would be enough to associate ZTT only with slow injection, and not also with a slow needle withdrawal, together with the positive effects on drug leakage remaining unchanged.

4. Table of selected papers basing on inclusion criteria

The effect of IMI's technique, injection site/positioning, and needle's gauge/length on local and systemic safety and pain, measured in the immediate time peri-injection and/or in the time interval up to 24 h/72 h after injection.

The reported results are focus on safety improvement and pain reduction.

The **outcomes** include:

- correlation between the intervention performed and the improvement in **safety** versus the compared technique, by measuring the following data: drug leakage immediately after injection, and signs of **local reactogenicity** (redness, swelling, indurations, bruising/hematomas) and/or **systemic reactogenicity** (fever and irritability and/or, in case of infants, persistent crying or screaming) in the Δ**T** time interval up to 24 h/72 h after injection, with statistical significance expressed in Pearson's correlation coefficient *P*; and
- correlation between the intervention performed and the reduction of **pain** versus the comparison technique, by measuring the effects in the **immediate time** to injection and/or **systemic reactogenicity** (fever and irritability and/or, in case of infants, persistent crying or screaming) in the time Δ**T** interval up to 24 h/72 h after injection, with statistical significance expressed in Pearson's correlation coefficient *P*.

The third frame concerning the injection protocol comprises: injected solution (including vaccines), needle's gauge (G) and length, patient's positioning, injection side (left or right, if reported), and muscle site, e.g., deltoid site, or VG and ALT sites for intramuscular injections (IMIs).

5. Discussion

The table highlights how the iatrogenic causes of local and/or systemic reactogenicity in IMIs are multifactorial since the decision algorithm focused on vaccinee safety involves not only the choice of the technique associated with greater safety but also the following parameters:

- the choice of the right needle (gauge and length)[34,41,35–39];
- the choice of a suitable injection technique associated with a correct injection rate, preventing that the drug solution is seaped through the subcutaneous tissue to the external skin, minimizing irritation (considering that pain receptors are present in the subcutaneous tissue[56] this should, indirectly, help to reduce the pain associated with IMI);
- the adoption of the correct muscle relaxation techniques, which facilitate, at the same time, the exposure of the muscle in the bonymarking process, allowing the nurse to identify the correct landmarks for deltoid,[1,2,75,77,78] VG,[4,5,79,72] and ALT sites.[4,5,59,60] This increases patient safety; on the contrary, injecting the vaccine without referring to the updated guidelines for vaccinee positioning[76] (and probably also adopting the univocal position of the vaccinator standing and the vaccinee sitting,[2] not ergonomic for the operator) is associated with increased adverse damage and pain of such intensity that it can interfere with ADL, and/or even cause the failure to process the antigen, when, for example, injected in a joint or in the subacrominal bursa, "too high" in the arm, preventing immunogenicity[1,2];
- the application of universal techniques for anxiety reduction,[70,80–86] which are positively reflected not only in the reduction of pain, but also in the reduction of muscle stiffening, increasing safety also for IMIs;
- the choice of the suitable muscle site, whose contributory weight is certainly among the most incident in the total. It is influenced not only by standardizable factors such as the age, the drug, and volume of injectate but also by criteria customized for each client, such as the degree of individual development/activity relative to each of the usable muscles with respect to the literature (deltoid, ALT, and VG sites).[4,5,25,87]

Considering that the injection of a vaccine formulated to be absorbed into the muscle tissue, which is highly vascularized, allows a faster mobilization and processing of the antigen than into the subcutaneous layer, and that "increased muscle warmth and activity have been equated with higher absorption,"[88] it is evident how a correct and dynamic injection protocol might be a healthy strategy for the vaccinee. If the nurse realizes that the deltoid muscle in children or in those aged ≥19 years, is underused or underdeveloped, and/or there are any limitations present/objective difficulties in bonymarking (obese patients), the decision to dynamically opt for the ALT side may result in positive effects on the degree of immunogenicity developed.

Although the deltoid site is the preferred one for vaccine administrations in adults/children,[6] and although it is the most easily accessible site, uncovering only the arm, the choice of the ALT site is however easily feasible, especially in home vaccines, at the patient's bedside. Regarding the choice of the VG site, in contrast to the ALT one, it would be desirable to conduct further trials to confirm an efficient immune response at this site for the anticovid vaccine in all age groups, in addition to the studies already conducted for other vaccines.[8,60]

These studies represent the first 2 extensive trials comparing the use of certain vaccines in the VG site versus ALT and have already have proven that the use of the VG site up to 18 months guarantees, in each of the specific vaccines tested, an immunogenicity overlapping that of the ALT site, while minimizing local and systemic reactogenicity.

Even though an individual may present with hypodevelopment of the deltoid muscle due to reduced physical activity with the arms, and/or other disabling conditions,

the VG and ALT muscles are, indeed, proportionally thicker in millimeters than the deltoid muscle at all ages; at the same time ultrasound findings show that the deltoid muscle in males and in the right arm of both genders offers a greater thickness in millimeters for immunization (on the contrary, the immunization guidelines recommend using the non-dominant arm, with the priority of minimizing the risk of soreness/functional limitation of the dominant arm in the days following immunization).

It is inferred from the literature that in individuals aged ≥18 years, all 3 immunization sites (VG, ALT, and deltoid) can be used.[4] Accordingly, placing safety as the primary criterion for the choice of the administration site, the VG site should also be included in immunization guidelines as indicated in the literature,[4] in all cases in which neither the deltoid nor the ALT site can be used, and reporting the corresponding needle size according to BMI or at least weight, age, and sex, as well as for the deltoid and ALT sites.[6]

If the data in future trials should prove efficient immunogenicity in the VG site for anticovid vaccine as well, we anticipate that, under such circumstances, the use of the VG site would be allowed not merely as a third protocol option, but rather the routine use of the VG site would allow the combination of the choice of muscle site associated with greater safety (in fact, in addition to the dorsogluteal site, the deltoid and ALT sites are also associated with possible neurovascular complications[89,90]) with the ZTT and WASiT injection technique, which is strongly recommended by the larger body of literature, when placing the parameter of the injection technique's safety as a priority.

Conversely, regarding the reduction of immediate pain associated with the injection technique, ZTT does not reach levels of statistical significance.

Focusing on the discomfort or the possible reduction of pain related to the injection techniques, the literature is not in agreement: a few authors[49,51] have demonstrated ZTT's superiority compared to the standard technique. Abdelkhalek[44] investigated the effects of this technique on anxiety, showing ZTT to be effective even also in anxiety reduction, in contrast to the standard technique.

Najafidolatabad et al.,[68] comparing ZTT with the air-lock technique instead of the standard technique, reported more pain and bleeding using the ZTT than the air bubble technique.

Tambunan and Wulandari[49] demonstrated the efficacy of ZTT in reducing pain when combined with the air-lock technique.

Whereas the standard IMI technique, and even more the lifting of a skin fold (bunching up), is associated with drug leakage and irritation of the subcutaneous tissue, the ZTT, creating a disjointed pathway with the characteristic Z shape, allows a significant reduction of the dispersion of the drug solution in the subcutaneous tissue. It efficiently seals the drug in the target muscle, while the air-lock technique seems to allow to almost completely seal the drug in the muscle, thanks to the additional injection of 0.1–0.5 mL of air (previously added in the syringe) at the end of the delivery of all the drug available. Obviously, to inject the air last in the end, according to physical laws, the syringe must be kept in a vertical position.

However, there is no evidence in the literature of the safety of injecting 0.5 mL of air into the muscle at the end of the IMI, since the muscle tissue, unlike the subcutis, is heavily supplied with blood vessels, and so it is not possible to exclude other risks related to the air-lock technique. This is confirmed by the fact that the literature predominantly recommends expelling all the air before the execution of IMIs, also with reference to vaccines.[4–6]

Moreover, it would be desirable to repeat the studies already performed on ZTT associating it with WASiT technique in suitable sites, rather than associating it with the aspiration maneuver in the dorsogluteal site (such a muscle site presents more subcutaneous fat compared with the VG one). In fact, the dorsogluteal site is independently associated with neurovascular complications, including also the ecchymoses highlighted in the study.[68]

However, it was not possible to include the study by Najafidolatabad[68] showing the superiority of air-lock technique with respect to ZTT in the table, because the injection site (listed among the inclusion criteria of the current review) was not reported; moreover, the outcomes of the study[68] appear to be non-generalizable because of the high degree of the listed bias. More studies would be needed for more accurate results.

Based on this prospective review, by performing the advanced nursing technique of ZTT and WASiT in IMIs, it is expected that pain can be reduced at 72 h after injection or after repeated injections, in comparison with performing the standard technique and performing a significantly reduced variant thereof, versus the bunching-up technique. In fact, considering that pain receptors are present in the subcutis,[56] ZTT & WASiT should indirectly contribute to reducing the pain associated with IMI.

The literature shows that ZTT is associated with an efficient reduction of drug infiltration in the subcutaneous tissue allowing an almost total drug expulsion in the target muscle when compared to the standard technique/bunching up. On the contrary, if ZTT is compared to the air-lock technique in the dorsogluteal site, it is associated with a higher incidence of pain/local adverse damage.

5.1. Limitations of the study

The number of studies that could be fully analyzed in the table is very limited because studies not providing access to the full text in English or not providing information on the data reported in the inclusion criteria were excluded; moreover, in most of the studies analyzed, double blinding was not present (patient to the treatment and executor to the treatment).

At the same time, the multifactorial nature of the variables affecting the safety of IMIs, as well as the possible pain associated with them, makes it clear that it is necessary to weigh up the contributory effect of each of them, both independently and associated in the same patient (crossover study) in comparison with the standard technique.

Therefore, a high degree of accuracy in calculating the best combination of variables could be made possible only by designing a cross-testing framework for rigorous measurement of the outcomes.

5.2. Z-track's limitations

Although the literature,[4,5,10–33] with certain exceptions,[67,68] endorses and advocates the use of ZTT, the statistically significant results obtained by Yilmaz[33] by performing this technique with a lateral skin displacement of even only about 1–2 cm are not generalizable, due to the limited sample size (60 participating subjects), and the concomitant use of the air-lock technique.

According to Shepherd and Swearington,[10] ZTT can be applied in any appropriate muscle group provided that the overlying tissue can be displaced by at least 1 inch, i.e., 2.5 cm.

This last limitation prevents therefore the use of the ZTT in muscles of reduced size, or even, paradoxically, in muscles that are too tight, such as those of athletes with muscular hyperplasia, for which the overlying skin and subcutaneous tissue cannot be easily displaced by at least 2.5 cm ZTT in IMIs.

Potter et al.[4] recommend ZTT for all IMIs but "preferably" applied in a wide and deep muscle, for example, in the VG muscle.

Moreover Berman AT et al.[5] advocate the use of the ZTT in all IMIs without limitations, and pose, for example, as an emblematic image of its use, the middle third of the vastus lateralis muscle, which, like the VG, is a deep and wide muscle, and in children, in particular, is highly developed.

According to Pullen[21] ZTT should be used in all adult IMIs: this limitation implicitly expresses reservations about using this safety technique in children, probably because on average the deltoid muscle, which even in many adults is not well developed, may have extremely small dimensions.

However, as explained, if only one simple measure is taken, namely displacing overlying muscle tissue laterally on the side of injection by only 1 cm or 1/2 inch (1.25 cm), ZTT can be adopted in immunizations of all children in ALT[23] with the exception of infant vaccinations[9]; this is in line with the results of Yilmaz,[33] who demonstrated statistically significant reduction of drug leakage and local adverse reactions due to minimal displacement of only 1–2 cm.

Barron and Cocoman[23] also reiterate that the preferred site for IMIs is ALT not only for infants and toddlers, but also for young children, in whom it is well developed.

Finally the debate on the possibility of using ZTT in children is still open, as well as the emphasis given in the literature on the need of a "good ZTT"[23] or on the deficit of retraining regarding this technique.[91]

6. Conclusions

Based on this literature review on ZTT and WAST in IMIs and on the significant percentage of local adverse reactions to vaccines IMIs recorded during anticovid/influenza immunizations,[1–3] the adoption of ZTT associated with WAST in vaccination practices should be re-evaluated in specific cases, considering that its inclusion among the vaccination techniques (particularly in adults and muscles uniformly considered suitable for ZTT by the evidence-based practice, i.e., ALT and VG sites), would necessarily involve the recruitment of a higher rate of registered nurses (RNs) in vaccinations, implying mature nursing skills.

Specifically, WASiT should be re-evaluated in all vaccinations with the exception of infants, and in general in non-cooperative subjects. Despite the fact that the largest body of literature agrees on an injection rate of 0.1 mL/s with the exception of infants, scientific evidence attesting with maximum accuracy a reduction of pain with slow technique cannot exist, since pain is a subjective perception. However, more studies are needed to prove this.

As future research direction it is proposed to conduct an RCT comparing the reduction of tissue trauma and pain related to it, in a sample homogeneous for BMIs range, age, and gender, using for immunizations IMIs needles 23 G and 25 mm length versus needle 25 G and 25 mm length, and without aspiration (i.e., changing only the gauge, and keeping unchanged the length of the needle, to avoid the confounding variable arising from the simultaneous variation of the length of the needles in the 2 groups). The result of a possible

reduction of the variable "pain" in the group vaccinated with a needle with a larger diameter, would be an objective scientific evidence of the positive effect of the reduction of the injection jet on the tissues, providing indirect evidence of the validity of the rationale of the method of slow injection.

Furthermore, there is a lack of literature indicating exactly how much the injection rate should be reduced or increased with respect to the general indication of 0.1 mL/s when varying the needle bore's diameter (gauge) which, for immunizations, is generally even narrower than that used for other common IMIs.

The use of ZTT, when compared to the standard technique (stretching) or bunching up, is associated, in current studies, with a significant reduction in the incidence of local adverse reactions (redness, swelling, induration, and other lesions), representing the best practice when safety is considered the priority.[4–5,10–33]

On the contrary, as regards the effects of ZTT on the perception of discomfort and/or possible pain after IMI, the literature is discordant.

However, Kim's[12] hypothesis that ZTT could decrease the severity of discomfort in persons receiving frequently IMIs is very significant.

If future RCTs prove the validity of this hypothesis, this would at the same time suggest that the safety itself associated with ZTT may in turn influence the reduction of pain over time: this would not be observed in the 15 s immediately following injection, but in the at least 72 h following frequent injections in the same enrolled subject.

Finally, studies on the efficacy of the innovative device "shot blocker" are still few, but increasing.

Both the positive effects of shot blocker and tapping with the palmar aspect of fingers in IMIs arise from the application of pressure on the skin. It can stimulate non-nociceptive Aβ fibers, which do not transmit pain signals, and which can interfere with signals from pain fibers, thereby inhibiting pain (gate control theory). Similarly, also the ZTT, during the dislocation procedure, determines the application of pressure, although only laterally with respect to the needle's insertion site, and also influenced by variability in the degree of force imparted by the nurse's hand; therefore it is reasonable to assume that this may represent one of the intrinsic features of ZTT that could contribute in reducing pain, but there are no studies demonstrating this.

Abdelkhalek's study[44] shows a statistically significant reduction in the pain score as well as using ZTT and WAST rather than using the standard technique, even in the immediate post-injection period in adults.

The literature review also shows that, regarding the reduction of the immediate pain's perception, rather than the comparison between ZTT and WAST versus standard technique, there are other factors that influence it, and that, on the contrary, are uniformly supported by the literature. These factors are the use of correct gauge and length of the needle correlated to BMI (avoiding both hypopenetration and hyperpenetration), the correct volume of solution to be injected with respect to the muscular site,[4,5] the choice of the suitable muscle site and the positioning favoring both the muscle relaxation of the patient and, at the same time, the bony marking by the nurse for deltoid site,[1–3,75,77,78] VG site,[4,5,72,79] and ALT site.[4,5,59,60] That prevents also neurovascular complications, in particular in deltoid[89] and ALT sites.[90]

In addition to the execution of the correct IMI procedure based on the listed parameters, additional techniques to the IMI procedure itself are also of relevant importance and therefore should be the focus of future attention. These techniques are: rhythmic tapping,[51,92] manual pressure,[86,92] or shot blocker; [44,93] application of a cold surface; and, in particular in infants, distraction, breastfeeding, or in general the administration of anything that imitates it and the non-maternal detachment during the injection.[53,81–83]

Finally, concerning music therapy based on melodies associated with the sweetest reminiscences of each individual and/or the Mozart effect, despite strong evidence on the uniqueness of its role in reducing anxiety as recorded in the literature,[81–84] as assessed based on levels of perceived pain amelioration (and having been demonstrated to produce a beneficial outcome in terms of stimulation of many other precious skills, including problem-solving skills or open-mindedness, which would unquestionably be useful for the ideal attitude needed in hospital settings), there is a lack of meta-analyses that include them among the data related to the procedures aiming for reducing the pain associated with IMIs, despite music's immense level of anxiolytic efficacy demonstrated by the data.

In addition is the fact that music improves the vital parameters[85] up to the reduction of muscle tension,[94] which is directly correlated to the injection's pain, generating also better compliance with treatments.[95]

Finally, regardless of the injection technique adopted, the multifactorial nature of the variables affecting the safety of IMIs, as well as the possible pain associated with them, makes it clear that it is necessary to weigh up the contributory effect of each of them, both independently and associated, comparing to the standard technique.

Author's suggestions of combinations for future studies include, e.g.:

- combining ZTT along air-lock in the right VG site instead that in the dorsogluteal one;
- ZTT and WASiT in ALT site in older children; and

- ZTT with only 1 cm dislocation and WASiT in dominant deltoid site.

The combinations are multiple, but all trials should include the correct positioning for each muscle site according to literature and the specific and general relaxation techniques reported in the current study.

Regarding the extension of the adoption of ZTT for IMIs vaccines in the deltoid, a muscle that in most adults and in almost all children is not as wide and deep as the VG and vastus lateralis muscles, the margin of error in land marking is narrower, and being an advanced nursing procedure that requires a higher manual dexterity, an RCT with a large sample of participants would be necessary to demonstrate its increased safety with respect to the standard technique in immunization practices.

It would be of paramount importance to ensure, both in the intervention and comparison group, the correct application of Cook's[75] new protocol concerning the specific vaccinee positioning for deltoid IMIs, by prioritizing the patient's safety.

Specifically, Cook's[75] protocol has not yet been included in the CDC guidelines,[45] but its full application, which includes positioning the vaccinator's hand on the ipsilateral hip and consequent 60° arm abduction, is critical for safety.
This simple abduction, for example, allows:

- easy visualization of the deltoid tuberosity for muscle attachment (otherwise this is particularly difficult in obese patients), and the acromion, speedier recognition of the midpoint between these 2 anatomical landmarks, that is the right site for injection; [1–3,75,77,78]
- relaxation of the vaccinees and consequently pain reduction;
- the movement of the anterior branch of the axillary nerve proximally toward the mid-acromion by 1.3–1.4 cm, avoiding injection into the nerve in all probability.[75]

Moreover, in the pilot studies, it would be reasonable to start the experimentation from the immunization in the deltoid site of the dominant arm of the male subjects, as it results in having a greater thickness in millimeters thanks to the few descriptive studies based on the ultrasound findings available in the literature.[41,57]

Therefore, it would be similarly urgent to conduct descriptive observational studies focused on the measurement in millimeters of the thickness of each muscle site through studies focused on ultrasound findings, which are extremely scarce in the literature.[7,34–39,41,57,96,97] This would be fundamental to enable it to be stated with certitude whether in children, or whether in children and adults both, the dislocation of skin and subcutaneous tissue of only 1 cm could be sufficient for an efficient ZTT.[23,33]

Based on this literature review it would be very useful to address the research on the conduction of a double-blind and randomized trial comparing ZTT and WASiT versus standard stretching in full adherence to the CDC 2021[6] and versus bunching up (or possibly also versus grasping technique) in deltoid site vaccinations, comparing the results obtained within 3 groups of male adult participants, homogeneous for BMI and age, all participants with normal/well developed deltoid muscle site (neither emaciated people nor athletes with muscle hyperplasia), by measuring the 2 fundamental outcomes analyzed in the table of the current study (safety and pain).

The intervention in the pilot study could include a combination of:

(a) ZTT and WASiT with only 1 cm dislocation;
(b) Cook's[75] new protocol for landmarking in the deltoid muscle site; and
(c) general relaxation techniques (e.g., Mozart effect: concerto No. 21 in C Major, K 467, Pollini-Muti; concerto No. 23 in A Major K 488, A. Brendel, and many others).[81]

The collection of results should include the measurement of:

- the drug leakage immediately after injection, using the method adopted in the study of Yilmaz[33]
- the other signs of local reactogenicity (redness, swelling, induratio, pain in situ, ecchymosis/hematoma) after highlighting the site of IMI with surrounding tracing of a 5 cm radius circle with a skin pen for the visualization and direct palpation of the site by the nurse;
- systemic reactogenicity (fever, fatigue, cephalea, or ADL impairment) by administration of questionnaires, VAS, or videotape analysis with coder blinding for pain detection; and
- the antibody level by blood sampling between 45 d and 60 d after the vaccine to assess any potential variation in immunogenicity.[60]

Based on the current literature review, the measurements for the assessment of reactogenicity should not be limited to the immediate peri-injection period, but extended to the time interval ΔT up to 72 h after the IMIs.

Finally, the high degree of accuracy in defining the best combination of variables could only be made possible by designing a cross-testing framework for a rigorous measurement of the outcomes.

Ethical approval

Ethical issues are not involved in this paper.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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