

## Parenteral Injection Massage, Bioavailability and Adverse effects: A Systematic Review

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### ABSTRACT

Parenteral injections are important preventive and intervention modalities for children and adults. Pain issues during injection procedures need to be addressed to increase adherence to medications and vaccination. Although pain is a concern, so are the measures to allow increased bioavailability of injectates for the maximal use of the body and the prevention of adverse effects. The objective of this review is to find out whether massaging an injection site increases bioavailability of injectates, while at the same time decreasing the pain experience and adverse effects. The subjects included 327 infants whose ages are 2, 4 and 6 months and 165 adults (15 to 67) who received parenteral injections. There is insufficient evidence to recommend massage prior to or after an injection to decrease pain and increase the bioavailability of injectates. More experimental studies are recommended.

**Keywords:** *Parenteral Injection; Massage; Bioavailability; Adverse effects; Review.*

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## Introduction:

The parenteral administration of vaccines, medications and vitamins through the intramuscular or subcutaneous routes are important preventive and intervention modalities for diseases. However, it is a source of pain for those who receive these interventions, not only for children but also for adults. It cannot be avoided however as it is the best route for administering some interventions.

The pain experience from injections may come from the invasion of the needle to the body tissues and or the injectate itself. According to studies, the needle size, location of the injection<sup>1</sup>, the type (viscosity) and amount of injectate<sup>2</sup>, the length of time of administration and the “wobble” can all either mitigate or aggravate the pain experience.

Because of the pain experienced<sup>1,3,4</sup> during this invasive but necessary procedure, patients usually develop or experience distress (Jacobson, Swan, Adegbenro, Ludington, Wollan, & Poland, 2001; Taddio, et al., 2009; Uman, et al., 2008; Schechter, et al., 2007; and Parvez, Stinson, Boon, Goldman, Shah, & Taddio, 2010), anxiety (Uman, et al., 2008) and needle phobia (Taddio, et al., 2009; Uman, et al., 2008 and Ramponi & Sewickley, 2009) which can generally decrease compliance to treatment or non-adherence (Taddio, et al., 2009) among parents as well as the development of anti-vaccination sentiments (Jacobson, et al., 2001; and Ford, Yu, Pollard, & Diggle, 2007) especially during the current times where there is an increase in morbidity and mortality related to immunizable diseases as well as treatable diseases.

Pain issues during injection procedures need to be addressed to increase adherence to medications and vaccination, thus studies have been done to discover interventions for its reduction and control. Studies such as individual RCT's, SR's, meta-analyses and reviews have been done in an effort to develop an injection guideline, especially for immunizations.

Management of pain from injecting vaccines and medications include distraction (Cohen, et al., 2006; Cohen, Blount, & Panopoulos, 1997; Uman, et al., 2008; Schchter, et al., 2007; Berberich & Landman, 2009; Kristjánssdóttir & Kristjánssdóttir, 2011; and Cohen L. , 2002), hypnosis (Jacobson, et al, 2001; Berberich & Landman, 2009; Cohen L. , 2002; and Ramponi & Sewickley, 2009 ), breathing and coughing methods (Wallace, Allen, Lacroix, & Pitner, 2010) or bubble blowing (Sparks, 2001), giving the child breast milk (Sahebihag, Hosseinzadeh, Mohammadpourasl, & Kosha, 2011; and Shah, Aliwalas, & Shah, 2006), provision of oral sucrose (Jacobson, et al., 2001;

Schechter, et al., 2007; and Stevens, Yamada, & Ohlsson, 2004) or glucose that the child or adolescent can suck (Harrison, Yamada, Adams-Webber, Ohlsson, Beyene, & Stevens, 2011), putting or holding the patient in an upright position (Taddio, Ilersich, Ipp, Kikuta, & Shah, 2009 and Ramponi & Sewickley, 2009), cold application to the area of injection for 30 seconds with ice , “refrigerants” (Jacobson, et al., 2001 and Farhadi & Esmailzadeh, 2011), Vapocoolant spray (Reis & Holubkov, 1997; Cohen, et al., 2009; and Ramponi & Sewickley, 2009), Ethyl Chloride (Berberich & Landman, 2009), or Flouri-Methane (Hogan, Kikuta, & Taddio, 2010), applying local anesthetics like EMLA [combination of lidocaine and procaine (Jacobson, et al., 2001; Reis & Holubkov, 1997; and Hogan, Kikuta, & Taddio, 2010)] to the site of injection at least 60 minutes before the procedure or Liposomal lidocaine 4% (Ramponi & Sewickley, 2009) which has a faster effect at 20-30 minutes, the application of pressure to the area of injection prior to and after injection (Schechter, et al., 2007; Hogan, Kikuta, & Taddio, 2010; and Chung, Ng, & Wong, 2002) or touch (Sparks, 2001), the prophylactic use of analgesics and antipyretics (Ford, et al., 2007; Parvez, et al., 2010; and Prymula, et al., 2009), performing injection techniques of rapid injection without aspiration (bTaddio, et al., 2009; and Ipp, Taddio, Sam, Goldbach, & Parkin, 2007), a combination of the different forms of pain relief methods (Cohen Reis, Kraus Roth, Syphan, Tarbell, & Holubkov, 2003; and Reis & Holubkov, 1997), as well as local massage of the injection site after the procedure or stroking the skin close to the injection site (bTaddio, et al., 2009).

Health care providers who administer injections and see the patient in pain usually offer some form of intervention which is available at his/her disposal. These interventions maybe advising mothers to provide prophylactic use of analgesics or antipyretics, distraction, touch, and most commonly tactile stimulation or massage of the injection site. However, not all injectates are amenable to massage or even analgesic or antipyretic use due to adverse local reactions. Massage, for example, of heparin injection sites causes bruising or hematoma formation while prophylactic antipyretic use decreases the bioavailability of DPT for immune cell formation.

This means that during the administration of medications through parenteral routes, health care providers should remember that although pain is a concern, so are the measures to allow increased absorption or bioavailability of injectates for the maximal use of the body and the prevention of adverse effects.

Studies have shown that some interventions health care providers do, like provision of cold packs to ease pain, can actually prolong or delay the absorption of some injectates (Farhadi & Esmailzadeh, 2011) like DPT while increasing temperature increases bioavailability of unmodified insulin (Thow, Johnson, Antsiferov, & Home, 1989). On the other hand, massage has been demonstrated to increase immunogenicity (the ability of the body to provoke an immune response) of vaccines and bioavailability of medications aside from decreasing pain like in the case of insulin.

However, there has been no efforts to do a comprehensive systematic review of the efficacy of massage as an intervention to increase immunogenicity and at the same time decrease pain so that it can be included in guidelines for injecting vaccinations and medications in various body locations.

The objective of this review therefore is to find out whether to massage or not to massage an injection site to increase immunogenicity and bioavailability of injectates and at the same time, decrease the pain experience and adverse effects.

## Methods

Medline, Cochrane, PubMed, Joanna Briggs and Google Scholar were used to locate randomized control trials. Search terms used were immunization, vaccination, intramuscular injection, IM injection, subcutaneous injection, SC injections, massage, vitamin injection, injection site massage, immunization site massage, vaccination site massage, massaging injection site, vitamin absorption, absorption increased by massage, vitamin absorption increased by massage, and penicillin absorption when massaged. No restrictions were applied for the different searches. Additional studies were identified from reading the reference lists in the retrieved articles.

Studies were eliminated at several stages of the evidence review. The studies eliminated were those that were for procedures other than parenteral injections, animal studies, studies with no available full text, those that contained only teaching modules or materials, articles that addressed induration, panniculitis or lipoatrophy in patients with multiple sclerosis, guidelines as well as opinion articles. The remaining six (6) articles were then reviewed using the PEDro scale to note those that met the cut-off score of 6. Four of these 6 articles were included in this review with scores ranging from 5-7. Of these articles, two had negative results in one of their treatment arms. Because of the low scores of the articles retrieved,

caution is given to readers that the evidence to answer the question is weak.

## Result

The subjects of the study included 327 infants whose ages are 2 months, 4 months and 6 months and 165 adults whose ages range from 15 to 67 who received parenteral injections. Three of the studies were through intramuscular while one is by subcutaneous injection. The injectates varied as to content (DPT vaccination, immunoglobulin, antibiotic and insulin injections) and amount. Two studies gave injections at the gluteal muscle, one at the lateral middle thigh and one was subcutaneous abdominal injection. Outcome data from three studies used the VAS to rate pain (one is through the mothers of the immunized children) and two utilized biochemical measures that include the serum glucose levels (through the Otthotoluidine method), the total and free insulin (through the Nakagawa method) and the blood and serologic studies for anti-FHA, anti-PT and tetanus titers measured by enzyme-linked immunosorbent assay with the reference serum JN1H10.

In one study, the application of massage to the DPT vaccine site caused adverse effects notably pain and fever of  $>38^{\circ}\text{C}$  most commonly reported within 48 hours. There is however an increase in two titers (anti-FHA and anti-PT titers) at 6, 7, 18, and 19 months and 18 and 19 months respectively. Tetanus titers did not show any difference between the groups (Hsu, Huang, Lee, Lin, Lee, & Chen, 1995). Acupressure, a type of massage was done in another study to note pain experience when penicillin is injected to the gluteal muscle. This study showed a mean score of those who received acupressure as  $3 \pm 2$  as compared to those who did not receive it with a score of  $5 \pm 2$  which is significant at  $p < 0.000$ . Males (2.1 as compared to females 3.7) and older individuals have lower pain sensation (Alavi, 2007) as compared to younger subjects ( $r=0.3$  at  $p 0.02$ ).

The two other methods are manual pressure application and the use of an electric vibrator to massage the area after administering an injection. For the manual application of pressure, one study showed a significant difference in the rating for pain for the experimental (13.6mm with range of 0.0-57.0 mm) as compared to the control group (21.5mm with range of 0.0-59.0mm) with a  $p$  value of 0.04. In the study on the use of an electric vibrator to massage insulin site injection for 3 minutes, the study showed that the effects were significant only at the "0" ( $3.77 \pm 4.84\mu\text{U/ml}$ ) and "30" minutes time intervals but not significant in the "15" minute interval. The most significant findings in the "30" minute elapse time after

massage is in the free insulin (BS  $4.5 \pm 1.8$  against PM  $14.7 \pm 3.7$ ) and the fall in the serum glucose (BS  $90.5 \pm 2.5$  against PM  $99.2 \pm 1.7$ ) which is significant at  $p < 0.05$ .

## Conclusions

Two of the studies utilized the conventional massage (light strokes and acupressure) while two used different methods which are manual pressure and electric vibrator. The study on massaging the site of DPT injection requires that this be done in one minute. This study revealed that there is an increase in adverse effects specifically pain, fever and swelling. Conversely, there is an increase in immunogenicity due to the increase in the bioavailability of the injectate which can be explained by the wider dispersal caused by the manipulation and thus better absorption of the vaccine. There is however a need to clarify the "massage" as conceptualized by the authors since pressure and manner of massage maybe different from one person to another.

Massage of the gluteal area prior to the injection with penicillin on the other hand has shown a beneficial effect to more severe types of pain only, especially among the older and male subjects. However, acupressure, to be done correctly, has to be done by trained practitioners or like in the study, one who was trained by a practitioner. The study has also mentioned that in the provision of the interventions, the subjects were standing up and it may not be applicable to those in other positions.

The study by Barnhill, et al. (1996) suggested that pressure application be used as part of the IM injection procedure while Dillon (1983) posits that the application of a three (3) minute massage on the insulin injection site may be beneficial in improving the bioavailability of conventional insulin in the postprandial state of patients receiving insulin.

Since there is a wide variance in the methods and applications of massage in the reviewed articles as well as a very minimal number of subjects used in each of the studies, there is insufficient evidence to recommend massage prior to or after an injection to decrease pain and increase the bioavailability of vaccines and medications for the uptake of the body. It is therefore recommended that more stringent studies be made on the bioavailability and immunogenicity of vaccines when massaged or not massaged as well as its adverse effects and pain mitigation.

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## Appendix A

Review of Evidence: To Massage of not to massage an injection site

Review of evidence	Number	Reason
Abstracts Matching search terms	6620	
Articles identified through alternate means	18	
Articles rejected at title stage	5783	Animal studies and other painful procedures like venipunctures were removed
Articles rejected at abstract stage	821	Animal studies, those which were abstract only, teaching modules and materials, as well as massage to improve or repair induration/panniculitis/lipoatrophy in Multiple Sclerosis injection treatments were eliminated
Articles retrieved and copied for review	18	
Articles rejected at first reading	12	Since RCT's are the best evidence, opinions were eliminated
Articles scored	6	
Articles meeting cut-offs	4	

The Scored articles were graded as follows:

Number of articles	Score
2	3
2	5
1	6
1	7

## Appendix B

Evidence Table Template

Author, Date	Population	Intervention (#studied)	Control (# studied)	Outcome	Critical Appraisal
Review of evidence	Number	Reason			
Hsu, et al., 1995	Age: 2 months - 125 4 months - 100 6 months - 102	175 infants massaged for 1 minute at the injection site	152 infants with standard care	Massage adverse effects: Pain and fever within 72°, mostly 48° with temperature of >38°C Increase in the anti-FHA and anti-PT titers at 6,7,18, 19 months and increase in pertussis agglutination titers at 18 and 19 months Tetanus – no difference	- 19 month follow-up - Biochemical measures Study confirmed that local manipulation soon after vaccination augments the antibody responses but at the same time increases the adverse events
Alavi, N.M., 2007	Age: 15 to 59 years old with Mean of 28 years	64 subjects (cross-over design with intrasubject comparison Each subject – 1 buttocks with acupressure for 1 minute, other buttocks with no massage 50 patient injected Penicillin 6.3.3 14 patient injected Penicillin G plus procaine		Mean score of pain: with Accupressure - 3±2 Without Accupressure – 5±2 @ p <0.000 Gender- more effective in males Male – 2.1 Female – 3.7 Age – lower pain sensation among older individuals at r - 0.3 and p 0.02	-First of few studies on topic -Blinding of those giving intervention  Study suggestive that acupressure is more effective in more severe pain
Barnhill, et al.; 1996	Age: 18-60 years old Gender: Male - 18 Female - 30	48 manual application of pressure	45 no pressure	Mean pain score: Experimental-13.6mm with range of 0.0-57.0 mm Control – 21.5mm with range of 0.0-59.0mm Significant at p 0.04	-Randomization -Acknowledged limitations of the study Study suggests that pressure application be used as part of procedure for IM injection
Dillon, R., 1983	Age: 15-67 Gender: Male – 2 Female - 6	8 patients with control day and experimental day Experimental day – 3 minutes massage with an electric vibrator Control day – no massage		With Massage values at 0,15,30 minutes 0 – 3.77±4.84µU/ml 15 – not sig 30 – a. Free insulin: BS4.5±1.8 PM14.7±3.7 b. Fall in serum glucose: BS90.5±2.5 PM99.2±1.7 Significant p<0.05	-Follow-up of patients included 10 additional -Use of biochemical measures  Study suggests that massage may improve conventional insulin therapy and increase bioavailability of insulin in postprandial states

Legend:

BS – Baseline

PM – Post Massage