

CURRENT PERSPECTIVES AND FUTURE SCOPE FOR NEEDLE FREE INJECTION – A REVIEW ARTICLE

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Abstract

Needle free injection systems have been in use for more than 50 years to deliver drugs and vaccines. Many benefits have been reported in decreasing pain, anxiety among patients and needle prick injuries in healthcare workers. It deliver drug very fast as compared with conventional needles. As per immunization schedule, a baby must receive number of injections before reaching 2 years of age. Hence, this type of delivery system is a much-needed technology at this time. Already various ways of routes have been used for immunization like oral, nasal or transdermal. Other advances includes nasal spray, jet injectors, dry powder preparations, micro needles or Nano patches provide a promising alternative to conventional vaccination. Several clinical trials are going on globally. This article review various painless injection delivery system available especially for children and elderly population.

Keywords: Needle Free, Needle Free Injection Technology, Painless Drug Delivery Devices, New Vaccinations, Children.

INTRODUCTION

The most important primary prevention developed in history of medicine against several infectious disease is vaccination or immunization. Several developing countries including India currently faces reduction in childhood vaccination rates.¹

Despite major investments done by Govt of India for childhood vaccination for low and middle income countries. Vaccine-preventable illnesses such as pneumonia, diarrheal diseases, measles, and meningitis killed almost 400,000 children under the age of five in

India alone in 2015. Vaccination initiatives in India have boosted full vaccine coverage among children between 12 to 23 months from an estimated 62% in 2015-2016 to 76% in 2019-2020.²

In 1977, WHO implemented the expanded programme on Immunization (EPI) against six killer disease diphtheria, polio, TB, pertussis, measles and tetanus for all children under 5 years of age. Initially, it was adopted in India (1978) for BCG, DPT (0, 1, 2 dose) and typhoid vaccinations only. Later in 1979, oral polio vaccine (OPV) was included and further in 1985 vaccination for measles was also added. Additionally, Hep B, Hib included in the list.³

Recent policy implemented by Indian Government to boost childhood immunization “Mission Indradhanush”, a campaign to promote routine immunization, have increased complete coverage to an estimated 76%, however gaps remain due to both supply-side and demand-side reasons. Especially in Rural India while almost (94%) children got the bulk of immunizations in PHCs, continues to fall behind metropolitan regions in terms of all vaccines.⁴

The majority of vaccinations available in the market are in injectible form. As the child reaches 2 years of age, as per CDC guidelines he/she receives 18-24 doses of vaccination (injections). Although, oral vaccines for rotavirus, cholera, typhoid, and *Shigella flexneri* 2a are available in addition to the prototype oral Sabin polio vaccine. However, vaccine in the form of a nasal spray of Hib is available, Centre of disease control advisory committee backed out for using it during the 2016-2017 flu season.⁵

The WHO, has termed vaccine hesitancy "delay in acceptance or refusal of vaccination despite the availability of vaccination services". Available bulk of current vaccinations are aimed at children worldwide.⁶ Maximum children have phobia for needles. The most difficult aspect of vaccination as reported is fear of needles and pain during the injection. Despite the abundance of EBP available to reduce anxiety and discomfort during injection, these therapies are underutilized in the actual clinical practice. Persistent pain and anxiety related to needles produces inevitable suffering and dreadful encounter for children and their parents/caregivers while getting vaccination. Later, this post trauma leads to development of syringe phobia, unfavorable attitudes towards vaccination, and noncompliance with subsequent vaccinations.⁷

Study conducted by Singh M et.al showed that children majority 48% have significant anxiety and needle fear irrespective of presence of parents at the time of vaccination.⁸ Similar results reported by kenedy et.al where parents (44.2%) showed anxiety and concern related to needle fear and majority expressed needle phobia as main reason for non-compliance to immunization programme.⁹

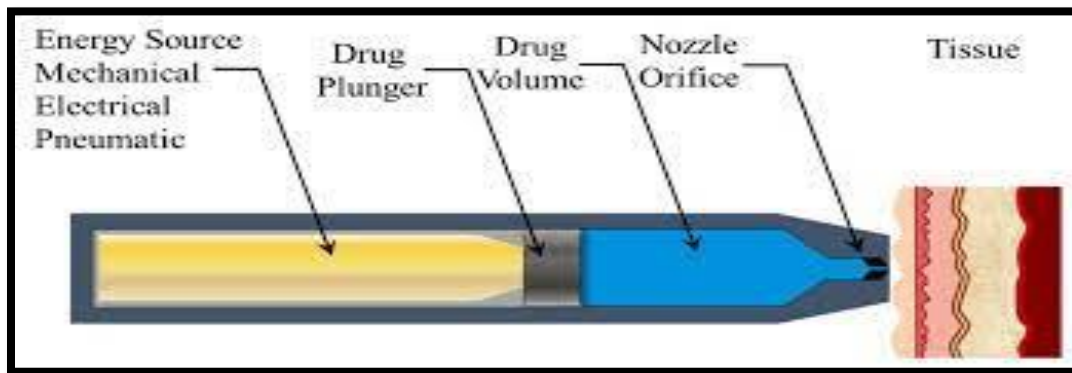


Figure 1: Needle Free Injection Technology

History of Needle Free Injections

Recently, it has been realized that there is a necessity to appropriately reduce pain and suffering associated with painful procedures. Based on empirical data, the WHO recommends implementing techniques that have been shown to be beneficial. Several approaches for assessing discomfort and pain related to invasive procedures are tested, including emotional aspects on how these influence child reaction.¹⁰

Supportive methods are strategies that attempt to provide social support, such as having presence of family while the procedure being done. Other approaches like therapeutic touch, skin stimulation with hot and cold substances, vibration and pressure, and so on.¹¹

Cognitive distraction, stimulating the use of imagination, positive self-instruction and changing recollections of past procedures are the key cognitive methods currently in use during immunizations among children.¹²

The above-mentioned interventions have shown significant decrease in the pain senses but the phobia for needles and the associated anxiety with the procedure definitely needs our attention as a health care provider. As the medical technology is getting advanced day by day, the need for the hour is to develop vaccination or drug administration a needle free way. The different types of drug delivery method available i.e painless are through oral and nasal route. Out of these, oral route is being most common and accepted to date. However, Intradermal and mucosal administration of drugs is broad classification. Topical administration of drugs can be administered through the skin by means of liquid jet injections and ballistic powder inoculation whereas, mucosal vaccination includes routes like ocular, oral, nasal, pulmonary, vaginal or rectal routes.¹³

This review investigates on the intradermal ways of drug administration which emphasis on liquid jet injections. All other routes have either penetration or breaking of skin barrier. These systems are unique methods of delivering medications into blood stream without piercing the skin with a traditional needle. Needleless injection is a quick and efficient method of administration for both liquid formulations and medications and vaccines in solid dose form.¹⁴

The first syringes that is hypodermic was invented in 1853 by physician Charles Gabriel Pravaz. Marshall Lockhart initially described needle-free methods in 1936. Then, in the early 1940s, Higson and others invented high-pressure guns that used a thin jet of liquid to puncture the skin and deposit the medicine in underlying tissue. These devices were widely used to immunize against infectious illnesses in large-scale vaccination drives.¹⁵

Working of Needle Free Injection

To understand the working principle behind the needle free injections, it is crucial to chalk out the structure of human skin, which is largest organ. It is made up of two layers i.e epidermis and the dermis. Under the dermis, there is another layer of skin i.e hypodermis or SC layer of fatty tissue. *Epidermis* layer is the outermost layer in the skin, which helps in creating waterproof barrier over the skin. It is made up of stratified squamous epithelium with lamina in the base. As epidermis is devoid of blood vessels, all the nourishment is provided by small capillaries present in deepest layers extending upto upper layer of dermis. *Dermis* layer present just under the epidermis has all the connective tissues, hair follicles and sweat glands. The blood capillaries present in the dermis helps in providing nourishment or excretion from the underlying cells. Hypodermis is the innermost subcutaneous tissues. It consists of fatty tissues and connective layer. The main purpose of hypodermis is to attach the skin with underlying bones and muscles. Additionally, helps in provision of blood vessels and nerves.¹⁶⁻¹⁷

Delivery of drug through needle free injection technique can be classified into the following:

- a. *Powder injections* –These injections are made up of a chamber that is loaded with content (in solid form) and a opening (nozzle) to eject particles of drugs into the skin using a power source that is commonly compressed gas. The drug chamber has an covering i.e a diaphragm which is few micron thick present on both sides.¹⁸ Because the drug is in powder form a little amount is injected through the skin hence the injection is painless. Using bioerodible carriers, slowly dissolving extracts particular, salts which are not completely soluble, or dissolution enhancers, the effect after releasing or performance of drug can be accomplished. Protein medications are extremely powerful and may be administered using a powder needle-free injection technique.¹⁹

Table 1: Working of Powder Injections

STEP BY STEP PROCESS OF POWDER INJECTION
<ul style="list-style-type: none">• The particles of drug exit from nozzles with the pass of gas stream.• There is a hole formed in the skin with the impact of injection from where the particles of drug goes inside the surface of skin.• At the end of the hole over the skin drug particles deposits in formation of a sphere and that penetrates across the stratum corneum.• As soon as the drug particles get penetrates into the skin, there is a complete distribution of the substance into stratum corneum and epidermis under the skin.

A light gas cannon is used to inject the powder. It achieves the desired particle velocity by employing an accelerating piston that both accelerates and transports particles. Particles exit the piston surface via a deceleration mechanism that slows the piston. This causes particles to be ejected, which act on the target tissue region.²⁰

b. *Injections in liquid form*- The fundamental of liquid injection is to get the drug in close contact with the skin surface so as to generate enough pressure to disseminate the drug by punching a hole in the skin. The device consists of gas or spring pistons, drug loaded chambers and nozzles with opening with the size ranging from 150-300 μm . However, gas injections also work on similar principle, but actual difference is there in design and working of the injection devices.²¹

Table 2: Working of Liquid Injections

STEP BY STEP WORKING OF LIQUID INJECTIONS
<ul style="list-style-type: none">• There is pressure build up caused by impact of piston on liquid reservoir that causes jet to shoot out the drug at very high velocity 100m/s.• Due to high-pressure impact of jet, there is a formation of hole on the skin.• The depth of the hole in the skin grows deeper as the jet continues to impact. If the volumetric rate of hole creation is smaller than the volumetric rate of jet impingement on the skin, some liquid will splash back towards the injector.• The liquid accumulates in the hole due to a deeper hole in the skin, which slows down the incoming jet. Then there is the continuing growth of a hole.

c. *Depot or projectile injections*- These injections deliver drug directly into the muscles. By the mechanism of slow delivering of medication into muscles over a period of time.

Parts of Needle Free Injections

- Injection device:** It is made up of plastic and has a drug chamber to maintain sterility of the procedure.
- Nozzle:** The function of nozzles in injection is to pass the drug when the nozzle touches the surface of skin. It has a flat surface with an opening. Speed is controlled by the diameter through which drug is passed. Diameter of a standard nozzle is 100 μm , where drug particles are fired with speed of 100 μm and depth of 2mm. Hence, the entire injection procedure is painless. However, patient experience a gush of air/ gas over the skin which actually feels like finger flicking against the skin.²²
- Drug reservoir:** To hold the amount of drug to be administered.
- Pressure source:** It can be mechanical, storing energy into the spring and then releasing it through moving a plunger that generates required pressure. It is very important for administering medicine into the blood stream via the skin. Carbon dioxide and nitrogen are the most often utilized gases in electronics.²³⁻²⁴

Process of Needle Free Injection

The mechanism creates force by propelling the medication through an opening at high speed using gas compressed in nature (such as CO₂ or NO₃). While the medicine is administered through the device, an ultrafine stream of fluid penetrates the epidermal

layers, delivering the drug into the systemic circulation quickly. An injection takes less than a third of a second to administer and happens in three stages:

STEP 1: This step is known as stage of peak pressure, as exact pressure is exerted to puncture the skin (0.025 sec).

STEP 2: (0.2 sec) this stage involves actual delivery of drug into skin.

STEP 3: (0.05 sec) this stage is termed as drop-off phase. The pressure exerted with each vaccine is same to ensure tissue depth is similar with each injection. This needleless technique of administering drug enhances distribution of medicine into the skin tissue. With the pressure the fluid flows into skin tissue with least resistance.²

Table 3: Different Types of Needle Free Injections

<i>Basis of working</i>	<i>Type of load used</i>	<i>Basis of drug delivery</i>	<i>As per site of drug delivery</i>
Spring loaded powdered	Liquid	Micro needle	Intradermal injectors
Energy propelled	Powder	Nano patches	Intramuscular injector
Lorentz force actuator	Projectile	Sandpaper assisted	Subcutaneous injector
Shockwave assisted		Iontophoresis	
Gas propelled			

Category as Per Working of Needle Free Injection

Spring loaded system- It is considered as the simplest method as it easy to administer and pain free. It utilizes the energy storage with the help of spring mechanism within to provide the force to eject the drug portion to desired distance. The spring helps in maintaining the elasticity and helps in prolong usage of device.

Laser propelled systems of injection - In this maneuver, desired force is achieved with the help of erbium doped yttriumgarnet laser to eject ultra-fine as well as exact amount of drug into skin. It consist of two chambers to hold the desired drug amount in place and other to help drive the drug into the skin.

Energy propelled systems of injection- The energy is generated to eject the desired drug into the skin.

Lorentz force actuator systems of injection- The drug is administered in this type of injection system with the help of piston to shoot drug desired with pressure that is very high and speed exactly matching the speed of sound present in air.

Gas propelled system of injection- This type of injections are either single use or needs cartridge replacement frequently. It has high scope as it provides high energy density similar to metal spring, which helps in gas combustion.

Shock wave assisted system of injection- As there is sudden release of energy, shock waves are generated. Explosive materials are use to ignite the prototype.²⁶

Category as Per Type of Load used for Needle Free Injection

Liquid based injection system- This type of injection involve the utilization of power of liquid jet to puncture skin and fat tissues present under it for better absorption of drug. There is least harm to the underlying skin. The force of liquid punch a hole in to the skin to administer desired drug at very high pressure.

Powder based injection system- The principle of this type is usage of non-reactive helium gas that produces enough density and velocity to penetrate the drug into the skin of desired dosage.²⁷

Projectile system of injection- This type of injection involves drug to be administered into muscles directly. Inside the muscle these create storage, through which drug is administered continuously over a specific period of time.²⁸

Category as per mechanism of delivery of drug into tissues

Nano patches- This type of injectors uses nano patches to deliver drug into skin with the help of nano patch projections. This system is not visible through naked eyes. The entire procedure is painless; however, drug is directly injected into key immune cells under the skin.

Sandpaper assisted delivery- This type of drug delivery involves using a “sand paper” kind of substance to produce erosion/ abrasion of superficial skin. It is proved successful in providing skin permeability for different vaccines.

Iontophoresis enabled drug delivery system- This type of drug delivery system consists of passing approx 0.5 mA/cm² of electric current to force drug molecules into the skin. There are two electrodes, which are placed on the skin to complete the circuit. One of the electrode has drug reservoir and it is positively or negatively charged based on drug used.

Micro-needle patches drug delivery system- In this type of system, thousands of micro needles are employed around 750-μm long into the skin avoiding the blood vessels. It is pain free as pain receptors are also avoided while the needles are placed in the skin. Thus, it has better drug compliance.²⁹

Category as per mechanism of delivery of drug into tissues

Intradermal injector –This type of injector system involves DNA based vaccines into intradermal layer with very shallow depth between the layer of skin.

Intra muscular injector- The drug delivery system is considered as deepest among all, commonly used for delivery of vaccination

Subcutaneous injector- Commonly growth hormones are administered with desired dose into fat layer of the skin.

Table 4: Different Types of Products Available in Market for Needle Free Injections

PRODUCT	USAGE
<i>Serojet</i>	Subcutaneous administration of drug
<i>lject (Bioject company)</i>	Subcutaneous or intramuscular injections
<i>Injex</i>	For local anesthesia
<i>Bioject@ Zetaject</i>	Subcutaneous or intramuscular injections
<i>Cool click</i>	For hormone replacement
<i>Vitajet</i>	For insulin subcutaneously
<i>Mhi-500</i>	For insulin subcutaneously
<i>Madajet</i>	For dentistry local application

Way Ahead For Needle Free Injections

Around the world: A company manufacturers based on needle free injection technology has launched Pharmajet® in the year 2021. As per the announcements by the company enrollment of the patients has already started for phase -1 in Australia against SARS-CoV-2. A French- Thai Pharmaceutical company BioNet-Asia in collaboration with Biotech Technovalia developed this DNA based vaccine. ³⁰

In India: A patch of plaster that is stucked on the skin of young children to provide pain free injection experience has been launched by Serum Institute of India. A manufacturer company known as Micron Biomedical actually tested the measles and rubella (MR) vaccine among young children upto 9 months of age. The study showed that patches were well tolerated and safe with no allergic reactions or adverse events. Patches is being developed for COVID-19, flu and Hep B whereas, HPV, rotavirus and typhoid needle free patches have already completed initial research and development stages in India. ³¹

Especially for COVID-19 pandemic outbreak vaccine with name of ZyCoV-D known as “needle free” covid vaccine has been given green signal for use among children in India. This vaccine will be given 28 days apart and used only in emergency situation. The manufacturer company Zydus Cadila has got approval from Drug general center of India (DGCI). ³²

A similar study has been conducted by ICMR, (Sep 2023) among the rhesus macaques against SARS-COV-2 with the title “Advancing vaccine delivery”. The study hypothesized that needle free injection technology has potential for advancing immunization technology as it shows better immune response and more viral clearance from the body. ³³

CONCLUSION

Since the breakthrough development in needle free vaccination for children around the world. This technology is definitely making immunization easy to administer and store in the field. Various studies have been in process right now to prove that needle free vaccine technology is far more better, easy, safe and effective than conventional jabs especially among children. Needle free technology is widely accepted by children, parents making it best method for administering injections to the mass population. The future application has proved to be key to success to deliver vaccines, insulin, certain proteins, genes and

other drugs. As a healthcare provider, we need to be aware about advancement in technology as well as provide training to others. With growing rate of infection, needle prick injuries, pain and anxiety among children due to injection. Hence, there is needle free technology has bright way ahead in reducing injuries and to deliver painless medication delivery in all age groups.

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Author Contributions

All the authors have been actively involved in this review from conception, design, data acquisition, interpretation, drafting of article or scrutinizing it thoroughly and finally agreeing on submitting the content in journal to be published. Here, all the authors are eligible to become an author as per the guidelines of international committee of medical journal editors (ICMJE).

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Conflicts of Interest

Nil

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