[redacted]

(NEEDLE FREE DRUG DELIVERY SYSTEM)

HEALTH TECHNOLOGY ASSESSMENT SECTION
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MINISTRY OF HEALTH MALAYSIA

004/2013

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DISCLOSURE

The author of this report has no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

EXECUTIVE SUMMARY

Introduction

Since many years ago, conventional needles become primary method for delivery of drugs especially macromolecular drugs such as insulin and vaccine. Nowadays, there is needle-free drug delivery method that employs a high-speed stream of fluid that impacts the skin and delivers drugs intradermally, subcutaneously or intramuscularly. The device becomes the primary alternative to needle for delivery of macromolecules. In order to search for new, easy and safer ways to administer drugs, needle-free injection system have been explored as an alternative to conventional intra- or subcutaneous medication delivery devices. Consequently, one technology review was requested by Senior Principle Assistant Director of Medical Resource Unit of Ministry of Health (MOH) Malaysia to look into the performance of Injex (one of needle free drug delivery system) to deliver drugs or medications such as vaccine, insulin, anaesthesia and low molecular weight heparin (LMWH).

Objective/aim

To assess the safety, efficacy / effectiveness and cost-effectiveness of [redacted] (needle free drug delivery system) to deliver drugs or medication such as insulin, vaccine, anaesthesia and LMWH.

Results and conclusions

There was limited fair to good level of evidence retrieved to show that needle free drug delivery system was effective to deliver drugs or medications such as vaccine, anaesthesia and low molecular weight heparin (LMWH). However, there were also adverse event reported while using such device. Besides that, cost-effectiveness study retrieved was only on the use of needleless jet-injection system with Lidocaine for peripheral intravenous (IV) cannula insertion which incurred more cost compared to the use of conventional method (needle-syringe method). More clinical research is warranted.

Needle free drug delivery system ([redacted]) is recommended for research purposes in clinical setting to deliver drugs or medication such as vaccine, insulin, anaesthesia and low molecular weight heparin (LMWH).

Methods

Electronic databases were searched through Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present, EBM Reviews - NHS Economic Evaluation Database 4th Quarter 2012, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 2012 and EBM Reviews - Cochrane Central Register of Controlled Trials December 2012.

Searches were also run in PubMed, Horizon Scanning databases, FDA website and INAHTA for published reports. Only studies published within 1990s to 2000s were included in this technology review report.

[redacted] (NEEDLE FREE DRUG DELIVERY SYSTEM)

1. INTRODUCTION

Since many years ago, conventional needles become primary method for delivery of drugs especially for macromolecular drugs such as insulin and vaccine.[1] However, with concerns about the spread of disease around the world from needle stick injuries and the reuse of needles, the new invention on needle free drug delivery system is developed since sixties.[1,2]

Jet injection is a needle-free drug delivery method that employs a high-speed stream of fluid that impacts the skin and delivers drugs intradermally, subcutaneously or intramuscularly. Today, jet injections constitute the primary alternative to needle for delivery of macromolecules.[1]

The first patenting of jet injection technology was in 1936–1938 by Marshal Lockhart. During that period, few studies, which confirmed successful absorption of insulin following jet injection was published. The interest in jet injections increased substantially and several other drugs including penicillin, streptomycin, sulfones and vaccines against typhoid, diphtheria and tetanus, polio and smallpox were delivered using jet injectors. The interest in needle-free injectors, however, continued to rise. Consequently, several jet injectors were developed and commercialized for drug-delivery applications.[1]

In order to search for new, easy and safer ways to administer drugs, needle-free injection system have been explored as an alternative to conventional intra- or subcutaneous medication delivery devices.[2] Consequently, one technology review was requested by Senior Principle Assistant Director of Ministry of Health (MOH) Malaysia to look into the performance of Injex system of needle free drug delivery for vaccine, insulin, anaesthesia and low molecular weight heparin (LMWH).

2. OBJECTIVE/AIM

To assess the safety, efficacy / effectiveness and cost-effectiveness of [redacted] (needle free drug delivery system) to deliver drugs or medication such as insulin, vaccine, anaesthesia and LMWH.

3. TECHNICAL FEATURES

[redacted] (Needle Free Drug Delivery) System[3]

[redacted] system consists of a spring-loaded variable-dose injector to which a disposable plastic ampoule containing the medication is attached. When activated the trigger releases the spring propelling a liquid drug with high velocity through a micro-orifice (diameter 0.17mm) in the tip of the ampoule. The jet

stream of medication traverses the skin (140cm) and the drug disperses subcutaneously. Spring pressure and orifice diameter are designed for a depth of penetration of about 3-9mm at the usual subcutaneous injection sites.[4]

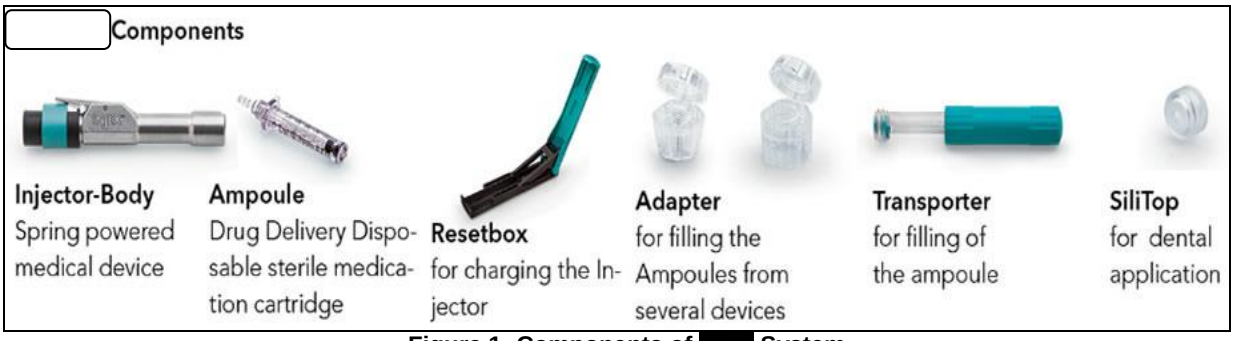

Figure 1: Components of [redacted] System

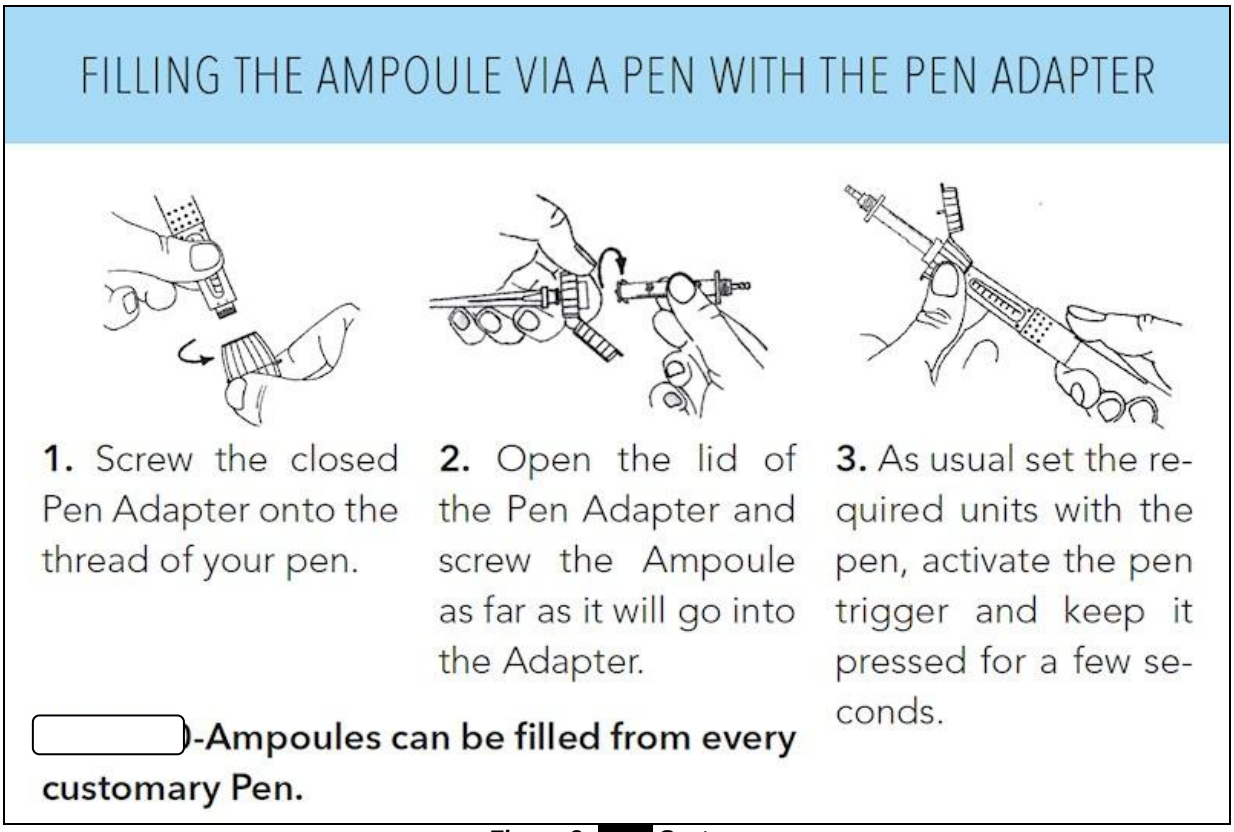

Figure 2: [redacted] System

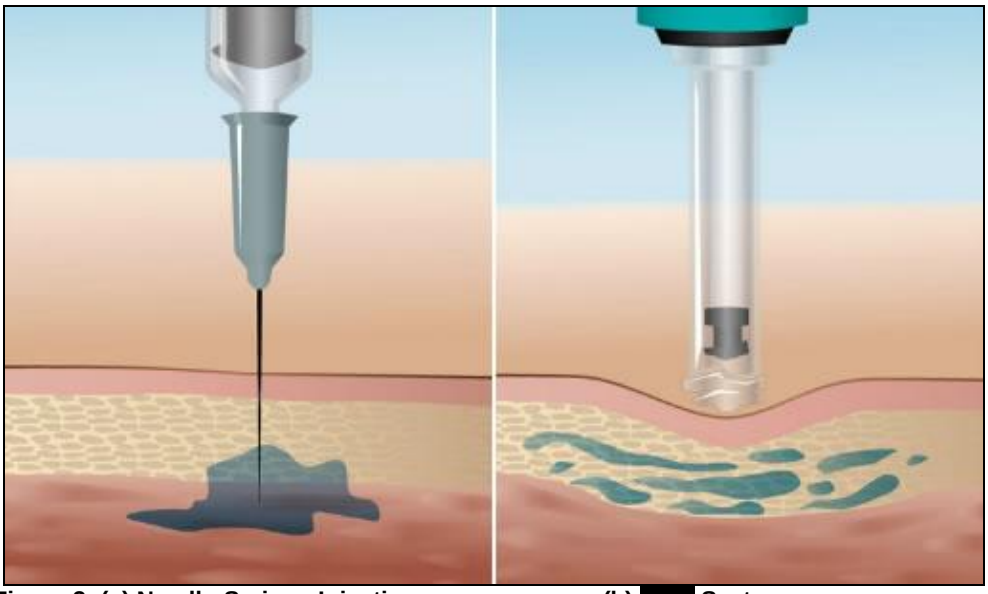

Figure 3: (a) Needle-Syringe Injection (b) [redacted] System

Review by Baxter J. and Mitragotri S. in 2006 stated that needleless injector or needle free drug delivery system can be used for vaccines, insulin, growth hormone and other macromolecules drugs (such as Heparin) and small molecules (such as Lidocaine, and penicillin).[1]

4. METHODS

4.1. Searching

Electronic databases were searched through Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present, EBM Reviews - NHS Economic Evaluation Database 4th Quarter 2012, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 2012 and EBM Reviews - Cochrane Central Register of Controlled Trials December 2012. Searches were also run in PubMed, Horizon Scanning databases, FDA website and INAHTA for published reports.

Search was limited to studies published within 1990s to 2000s. Google and Google Scholar were also used to search for additional web-based materials and information about the technology. Besides, additional articles from reviewing the references of retrieved articles also included.

Appendix 1 showed the detailed search strategies.

4.2. Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection.

The inclusion and exclusion criteria were:

Inclusion criteria

Population	Patient/general population who needed administration of pharmaceutical preparations (insulin, vaccine, low molecular weight heparin and anesthesia)
Interventions	Jet-injector (needle free drug delivery system / needleless injection)
Comparators	Needle-syringe injection
Outcomes	Pain and efficacy (drug distribution, seroconversion)
Study design	RCT, non-randomized controlled trials, and Cross-sectional studies
	English article

Exclusion criteria

Study design	Animal studies and laboratory studies
	Non English article

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and evidence graded according to the US / Canadian Preventive Services Task Force (Appendix 2).

5. RESULTS AND DISCUSSION

There were four full texts articles and one abstract included in this technology review report. The full text articles consist of three randomized controlled trials, and one non-randomized controlled trial and the abstract consist of a cross-sectional study. Those studies discussed about the effectiveness and the technical issue of needle free drug delivery system or jet-injector compared with conventional needle-syringe injection. There was no study retrieved on the administration of insulin using [redacted]. One of the articles also reported on cost-effectiveness.

5.1. EEFICACY/ EFFECTIVENESS

The five studies looked into the effectiveness and patients tolerability towards needleless injector compared with conventional needle-syringe methods.

Lysakowski C et al. conducted a randomized controlled trial in 2003 to evaluate the efficacy, safety and cost-effectiveness of jet-injector with lidocaine for

insertion of peripheral IV cannula compared with jet-injector without treatment. Insertion of an IV cannula is generally considered to be painful. Often, patient perceive it being extremely uncomfortable; some may even develop a needle phobia so different methods have been proposed to alleviate the pain including development of innovative analgesic methods that are simple to use, painless, effective with minimal delay, without adverse effects and cost-effective. Four hundred adults from surgical unit were involved in the study. All patients were randomly assigned (computer-generated random) into four groups. Group 1 was no treatment group where a Jet-Injector was applied to the patient's skin in the usual manner but without injection; however the noise of the Jet-injector was simulated by a second Jet-Injector. The no-treatment group control was chosen for 3 reasons; first no gold standard analgesic treatment in the setting, second the researchers aimed to estimate baseline pain of cannula insertion without any analgesic treatment and third in the hospital setting, analgesic is not routinely used for cannula insertion in adults. Group 2 was jet with 0.5mL saline; the reason of Group 2 was to exclude the idea that the saline injection was analgesic (by comparison with Group 1). Group 3 was jet with 0.5mL lidocaine 1% and Group 4 was jet with 0.5mL lidocaine 2%. Data from the saline, lidocaine 1%, and lidocaine 2% groups were used to test for dose-responsiveness with lidocaine. All patients received midazolam 7.5mg orally 30 minutes before procedure and were blinded (unaware treatment allocation). [5, Level 1]

The first anaesthesiologist only involved in preparation of the jet-injector according to patients allocation, and the second anaesthesiologist was blinded regarding patients' assignment and the content of jet in all group except in Group 1. Then the second anaesthesiologist interviewed the patients for pain related to treatment and cannula insertion. Patients were asked to rate pain intensity using a Numerical Verbal Scal (NVS) ranging from 0 (no pain) to 10 (excruciating pain). The researcher estimated the average pain intensity on cannula insertion to be on average 5 on an 11-point NVS. To demonstrate a 50% reduction in pain, 25 patients per group were required ($\alpha = 0.05$; $\beta = 0.8$; anticipated SD, 3.5). There were three *pre-hoc* decisions; first a NVS ≤ 1 was minimal pain. Second, a NVS ≤ 3 represented less than moderate pain; this degree of discomfort was regarded as acceptable. Third, a NVS > 5 was unacceptable. Sensitivity analyses were performed for predefined NVS values (for instances, all patients reporting a NVS ≤ 3. The percentage of patient having NVS ≤ 3 which was considered as acceptable was 42.4%in Group 1, 39.3% in Group 2, 60.7% in Group 3 and 86.7% in Group 4. In Group 3 (Lidocaine 1%) compared to no treatment, the relative risk [RR] was 0.70; 95% CI, 0.53-0.93), and in Group 4 (Lidocaine 2%) the RR was 0.49; 95% CI, 0.38-0.62).[5, Level 1]

Another controlled trial was conducted by Arapotathis KN et al. in 2010 to look into the efficacy of needleless anesthesia using needle free drug delivery system, Injex, in dental and to compare children's acceptance and preference for one type of needleless jet injection compared with classical local infiltration anesthesia. Forty one girls and 46 boys between ages of six to eleven years old

involved in this study. They were selected among non-fearful children with no previous experience of dental anesthesia using split-mouth design. The first dental procedure was performed with the classical infiltration anaesthesia. The same amount of anaesthetic was administered using the Injex needleless device in a second session 1 week later, during which a second dental procedure was performed. Patients rated their acceptance and preference for the two methods, and the dentist recorded data about the need for additional anaesthesia. The results showed that 50% ($p<0.001$) of children were significantly reported negative experiences during administration with Injex needleless anaesthesia. Most (73.6%) of the children preferred the traditional method. Among the 87 treatment procedures attempted following the use of Injex, 80.5% required additional anaesthesia, compared with 2.3% of those attempted following traditional infiltration. The authors then concluded that traditional infiltration was more effective, acceptable and preferred compared with the Injex.[6, Level II-1]

Hollingsworth SJ et al. conducted a single-blind randomized controlled trial to look into the pain score of using needle free drug delivery system (J-tip) compared with pre-filled needle-syringe method and to look into plasma distribution of LMWH after administered using needle free system. Sixty patients from surgical wards of Middlesex Hospital, London involved in this study. They were randomized by coin-toss and should received LMWH 2500IU/day as prophylaxis against DVT either through J-tip method or pre-filled needle-syringe method. For each patient their age, gender, pain score on injection, bruising at the site of injection and plasma anti-factor Xa levels were recorded to allow comparison between LMWH delivered by needle-syringe and by the J-tip device. Twenty nine patients received the LMWH through J-tip method and 31 patients received through needle-syringe methods. For both methods, each patient received 2500IU of Dalteparin sodium, which was delivered subcutaneously in total volume of 0.2ml solution. Following the injection, pain was scored by each patient using analogue system rated from '0' = no pain to '4' = very painful. After the observation, the authors found that in term of pain scores, J-tip was significantly more comfortable for patient, with median pain score of 0 (range, 0 to 2; n = 28) versus score of 2 (range, 0 to 3; n = 18) for the needle-syringe group ($P < 0.001$). Meanwhile for levels of plasma for anti-factor Xa, both methods gave similar levels of LMWH in the peripheral blood of the subjects. The mean ± SEM values for plasma anti-factor Xa was 0.154 ± 0.010 U/mL in the J-tip group (n=29) versus 0.18 ± 0.030 U/mL for the needle-syringe group (n=28); $P < 0.42$). From the results, the authors claimed that J-tip or needleless injection had several potential benefits over needle-syringe method. The potential benefits include needleless injection eliminate anxiety induced by fear of needles, no special skills were required by the healthcare staff to learn how to use the needleless injection device, short time training, painless drug delivery, eliminated needle-prick injection, J-tip delivered medication with high velocity and high-pressure delivery to permeate through the subcutaneous space rather than being delivered as liquid depot as would occur with a needle and syringe. However, J-tip could not be used to deliver medication intravenously and intra-arterially.

There is also a potential problem if involve high molecular weight medication.[7, Level 1]

Williams J et al. conducted randomized controlled trial in 2000 to compare needle free drug delivery system (Biojet) with needle-syringe method and to determine a significant different between these needleless and needle-syringe method in seroconversion rates or geometric mean titers (GMT) of anti-Hepatitis A Vaccine (HAV) antibody occurs at day 15, 30 and 210 days after vaccination. The trial was conducted in Alaska involving 206 females and 115 males from Alaska Native Medical Caner (ANMC). All patients were randomized to receive vaccine HAVRIX 1440 EL.U via jet or traditional needle syringe using computer generated randomization code. Vaccinated with Biojet group consisted of 109 females and 52 males meanwhile vaccinated with needle syringe group injection consisted of 97 females and 63 males. The authors reported that there was a significant increase in HAV antibody GMT in Biojet group at day 15 ($z = 2.39$, $P<0.02$), at day 30 ($z = 4.19$, $P<0.0001$) and 7 month ($z = 2.37$, $P<0.01$) compared to needle-syringe group. Participants in the Biojet group had a greater proportion of persons with an anti-HAV level ≥ 20 at day 15 and day 30 than the needle method and this was significant ($P=0.002$) at day 30. In conclusion, Jet-injection method of HAV vaccine delivery provided significantly higher HAV GMT at 3 points in time (day 15, day 30 and at 7 month) and significantly higher seronconversion of $\geq$ 20MIU at day 30.[8, Level 1]

Another controlled trial conducted by Baer CL et al. in 1996 compared the effectiveness of needle free drug delivery system (Biojet) with conventional needle and syringe injection in administering intramuscular (IM) morphine and subcutaneous (SC) heparin in 2 different groups of healthy adults. Forty subjects involved in morphine study where about 8mg morphine was used. IM morphine was given 24 hours apart with jet injector and with a needle-syringe to 30 subjects at the deltoid site and 10 subjects at the dorsogluteal site. Blood samples for plasma concentrations of the morphine were drawn at 15, 30, 45, 60, 120 and 240 minutes post injection and were analyzed using radioimmunoassay. Meanwhile for the SC heparin study, about 3500U heparin was used in 29 subjects. The SC heparin was administered at abdominal area every 8 hours for 5 days with both injection methods; 48 hours between the 2 series of injection. Daily blood samples for plasma heparin were analyzed by calorimetric assay for antifactor Xa activity. At the end of both studies, they found that the mean morphine concentration, peak value and area under the curve (AUC) did not differ between the Biojet and the conventional needle injection. Similar results were shown in heparin administration. The authors concluded that the plasma drugs concentration by Biojet were equivalent to those provided by conventional needle and syringe when administering either IM Morphine and or low-dose subcutaneous heparin.[9]

5.2. SAFETY

Few types of needle free drug delivery systems had receive 510(k) pre-market notification by United State Food and Drug Administration such as Injex Needle Free Injection System by Rosch Ag Medizintechnic in 2002. The safety aspects of needleless free injection were reported by the following studies which also reported on effectiveness.

Lysakowski C et al. also looked into adverse events of needleless injector in their study. About 13.5% patient from Group 2, 3 and 4 experienced local skin redness, and 16.9% had minor local bleeding. All the problems however, resolve after 24 hours without any recurrent. Failure to insert cannula in 17.6% patients who received jet treatment also occurred compared with without treatment (10.1% patients). However, the difference was not significant. The authors stated three major drawbacks of Jet device. First, treatment with Jet was not painless because one-fifth of the patients reported moderate pain. A second drawback was a large number of technical failures which was one-tenth of all applications, including the device could not be used which require further improvement of the device and well trained personnel. The third drawbacks was due to the thought that insertion of cannula was more difficult after use of the device, which was probably due to high pressure injection of local anesthetic with subsequent local edema and minor bleeding.[5]

Williams J et al. also observed the adverse events of needle free drug delivery (Biojet) compared with needle-syringe. The study showed that Biojet had greater local reactions compared to needle-syringe methods, 151 diary cards from Biojector group and 150 diary cards from needle-syringe group. The local reactions included redness, swelling and bruising. Besides, cross-contamination was a major concerned as Jet-injection created multiple openings into tissue and caused a blood and serous fluid leakage. Another issue highlighted with used of jet-injector was the safety design of the jet. The authors stated that needle used to draw medication should be used once and discard, then the cartridge aperture was held firmly on skin should contact only with one patient and disposed. Additional to that, the cartridge aperture size must chose according to patient's individual body mass and fat distribution, any wrong size will caused deposited medication in subcutaneous tissue rather than in deep muscle.[8]

In Araposthatis et al study, the authors reported the needleless injection (Injex) method resulted in significantly more bleeding ($P<0.001$) compared to the conventional needle-syringe methods.[6]

5.3 COST/COST-EFFECTIVENESS

There was no retrievable evidence on the cost-effectiveness of needle-free injection system used for vaccine, heparin and anaesthesia administration.

However, there was one cost-effectiveness study using needleless injection for IV cannula insertion included in this technology review report.

The study was conducted by Lysakowski C et al. Annual cost for peripheral vein cannulation was estimated assuming that the hospital decided to insert all with a Jet and cost in generating one gainer, in example, a patient who profited from a change in clinical practice from doing nothing (no analgesia for IV cannulation, as is the routine in the hospital) to use the Jet with Lidocaine 1% or 2% was quantified. Meanwhile direct and indirect costs considered were the acquisition costs, syringe needle to fill the device, lidocaine ampoules and IV cannula. However, labour cost was not taken into account. ICERs were calculated as ratio of the difference in cost between two strategies and the difference in health effects between the strategies. Health effect was considered as number of patients who reported pain intensity on cannula insertion that was equal to or less than predefined NVS value. Then the sensitivity analysis performed for different pain scores, different jet acquisition cost and different failure rates. Two assumptions were made; first it was assumed that second device was used for subsequent cannula insertion if there was a technical failure. Second assumption was in case of cannula insertion failure, second cannula and a second Jet had to be used for a subsequent essay. The third assumption was second attempt was always successful.[5]

The authors reported that the incremental cost of Jet with lidocaine 1% compared with no treatment was $4.1. Meanwhile the incremental cost of Jet with lidocaine 2% compared with no treatment was $4.3. Thus the annual costs for Geneva University Hospitals (120,000 cannula/year) estimated at $492,000 for Jet with lidocaine 1% and $516,000 for Jet with lidocaine 2%. Based on pain scale, for minimal pain (NVS ≤ 1), the ICER was $18 for Jet with lidocaine 1% compared with no treatment and $11 for Jet with lidoacaine 2% compared with no treatment. When no more than moderate pain (NVS ≤ 3) was the end-point, ICER was $23 for Jet with lidocaine 1% compared with no treatment and $10 for Jet with Lidocaine 2% compared with no treatment. After considered the efficacy, cost and safety, the authors finally concluded that, the Jet device could be used selectively in certain patients such as children, needle phobic or patient with frequent cannula insertion.[5]

Based on proposal from the company, the price for Injex system is about RM1, 000 for the device and RM5 for the insulin ampoule. Other drug ampoules were not stated.

5.4 LIMITATIONS

This technology review has several limitations. The selection of studies was done by one reviewer. Although there was no restriction in language during the search but only English articles were included in this report. Only studies published within 1990s to 2000s were included in this technology review report.

6. CONCLUSION

There was limited fair to good level of evidence retrieved to show that needle free drug delivery system was effective to deliver drugs or medications such as vaccine, anaesthesia and low molecular weight heparin (LMWH). However, there were also adverse event reported while using such device. Besides that, cost-effectiveness study retrieved was only on the use of needle-free jet-injection system with Lidocaine for peripheral intravenous cannula insertion which incurred more cost compared to the use of conventional method (needle-syringe method). More clinical research is warranted.

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9. APPENDIX

9.1. Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1948 to present

1 Pharmaceutical Preparations/
2. Injections, Jet/
3. from 2 keep 1-2,5-7,9-11,13,15-16,22,25,27-28
4. Drugs administration.tw.
5. (Pharmaceutic# adj1 preparation$).tw.
6. Drug$.tw.
7. Needleless injection.tw.
8. (Injection$ adj1 jet).tw.
9. Free needle injection$.tw.
10. 2 or 4
11. 2 and 4
12. 4 or 7
13. 6 or 7
14. 6 and 7
15. Drug Delivery Systems/
16. 2 and 15
17. 2 or 15
18. From 16 keep 1-4,6-21,23-29,31-32

OTHER DATABASES	
EBM Reviews - Cochrane Central Register of Controlled Trials	Same MeSH, keywords, limits used as per MEDLINE search
EBM Reviews - Database of Abstracts of Review of Effects	
EBM Reviews - Cochrane database of systematic reviews	
EBM Reviews - Health Technology Assessment	
PubMed	
NHS economic evaluation database	Needleless injection, Injex system
INAHTA	Injex, needleless injection
FDA	Needleless injection system
Horizon scanning database	Needle free injection, needleless injection
Others (Google Scholar, Google)	Injex, Needleless injection

9.2. Appendix 2

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)