# *Painless Intradermal Delivery of Insulin: The Novel ClickSoft™ Microinjection Device*

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Improving the convenience and ease of administration of parenteral therapeutics is becoming a common practice to augment the product marketability in the biotechnology and pharmaceutical industries. The growth of the injectable market, increased competition in the industries, and requirements of end-user safety has driven product improvements and ease of administrations. In addition to diabetes treatment, injection therapy use is widespread in treatment of cancers, anemia, fertility, thrombosis, hormone replacements, obesity, etc. There are a number of devices in use today to deliver a drug like insulin, including syringes, insulin pens, jet injectors, and insulin pumps. No single device or type of device works well for everyone. The decision of which device to use may be based on a person's insulin regimen, ability to manipulate or operate a particular device, visual ability, insurance coverage or ability to afford a particular device, related supplies, occupation, and daily schedule or leisure-time activities. This means the customer-specific injection device needs for improved convenience will continue to increase in the future.

Diabetes affects approximately 177 million people worldwide and is increasing, with the World Health Organization predicting 370 million diabetics by 2030. It is the sixth most common cause of death as recorded on US death certificates.

FIGURE 1


Device With Drug Chamber (L); Actual Device Size (R)

Therapy for diabetes mellitus has developed and changed extensively since Banting and Best isolated insulin in 1921. Many people consider an injection (at best) unpleasant and (at worst) a painful encounter. This is because most shots are given subcutaneously or intramuscularly, reaching deep enough into the skin to hit nerves and cause pain along the way. In the beginning, syringes were the sole method of delivery of insulin therapy and even today remain a mainstay around the globe.

Each improvement in an insulin delivery system strives for two common goals: patient convenience and better glycemic control. Patients are seeking flexibility and convenience beyond the traditional syringe and vial system. As practitioners and patients seek to normalize glycemic control, insulin delivery injection devices are being developed that can help achieve this goal with improved comfort, convenience, and safety. Today, many different types of insulin administration devices are available, eg, insulin pump, insulin pens, jet injectors, etc.[1-11]

While newer insulin pumps are easier to use, many patients still find the overall insulin pump experience to be very complicated as it requires good maintenance and understanding of the operation. Moreover, the pumps are very expensive and are not affordable for everyone.

Insulin pen devices have some of the same limitations as syringes. Patients with impaired visual acuity or manual dexterity,

inability to cope with new technology, inability to manipulate the pen, or declining cognitive function will require the assistance and support of a caregiver. Pens, insulin cartridges, and pen needles are relatively much more expensive than the syringe and are not affordable by everyone.

The jet injectors have no needle, yet they can damage the skin if not adjusted properly. Many patients are bothered by the noise the injector makes upon delivery. Another deterrent for patients is the weekly maintenance and cleaning jet injectors require. Consequently, only a small percentage of patients use jet injectors.

Considering all of the aforementioned factors and in hope of improving the compliance and willingness for the exogenous insulin administration by diabetics around the world, PKA SoftTouch has developed a novel microneedle (ClickSoft™) with an ingenious mechanism for simple painless drug administration between the skin layers, ie, intradermal, painlessly insulin administration. The shallow delivery of drugs with this novel device actually causes no pain or much less pain and enhances the uptake.

This device (Figure 1) allows for the injection of drugs directly in between the epidermis and dermis (just under the stratum corneum), which avoids hitting nerves, and allows for rapid dispersal of the drug into the bloodstream via the interstitial fluid. Injection of the drug into the intradermal skin layers (between the epidermis and dermis) does not disturb the nerve junctions and thereby avoids the pain sensation. Thus, this device allows for the painless administration of insulin and many other therapeutics.

Furthermore, the proprietary technology is able to stabilize the insulin at room temperature. This is another milestone forward in the device as it will not require refrigeration for an extended period. It allows users to have a number of these devices in a pocket or purse and use them as required to control their insulin needs while they are away from their home or traveling. The different dosages will be indicated by various colored caps with large fonts on the devices. The following describes this novel ClickSoft device and its application in treatment of diabetes for a painless intradermal insulin administration.

## FUNCTIONALITY, ATTRIBUTES & ADVANTAGES

ClickSoft is a spring-loaded microneedle intradermal injection system. Upon depressing the trigger, the device propels a fine stream of liquid medication from the drug chamber through an ultrafine needle in between the skin layers (intradermally). The pressure released on the trigger withdraws or retracts the needle completely into the device for a safe disposal (the device can be discarded without special handling). These steps are shown and explained in Figure 2. The attributes and advantages are listed in Table 1.

## PROOF-OF-CONCEPT DOG STUDY

The device was tested on two separate occasions for its effectiveness, efficacy, and safety measures in two specific studies as outlined further.

**OBJECTIVE:** The purpose of this study was to establish that the novel ClickSoft delivery device effectively delivers Atropine into the systemic circulation via shallow intradermal

**TABLE 1**

**Attributes & Advantages of the ClickSoft™ Microinjection Device**

- The product is aimed squarely at the vast type 1 market and growing type 2 market. ClickSoft has the dose range capabilities going up to 100+ units in a single dose (in 150-microliter volume), greater than any pen on the market or insulin syringe.
- Most suitable for twice- or once-a-day fixed dose basal insulin or premixed insulin.
- Very suitable for fast-acting insulins, eg, Lispro, Apidra, Actrapid, etc.
- Faster onset of action (rapidly absorbed via interstitial fluid), which is faster than any rapid insulins available today (refer to the data shown below).
- Reduces the injection force by 60% or more in comparison to other leading disposable pens or injection syringes (no pain or much less pain).
- Beneficial for all people with diabetes and in particular, for those with lower grip strength. It is estimated that up to 60% of individuals have limited joint mobility of the hand, needing very gentle operation.
- Prefilled, fixed-dose chamber (color coded for different doses).
- Single-use, completely disposable device prevents contamination from patient to patient. No fear of needle sticks after disposal (needle is retracted back into the device completely after use), non-hazardous disposal.
- Cost effective and affordable, price is very comparable to standard injection syringe price.
- Quality of life: the small size of the device makes it convenient to carry anywhere and to use comfortably in public.
- The device user stabilized insulin formulation, which can be stored at room temperature, thus no refrigeration needed.
- Uses thin needle (30 or 31 gauge) that can penetrate the skin to within a depth of 1 to 2 mm.
- Broad applicability: the device and formulation are more versatile for many injectable therapeutic deliveries in addition to insulin, eg, heparin, GLP-1, Jenuvia, Symlin, Exnatide, and vaccines.
- Can be used anywhere on the body (all over arms, legs, and stomach).

injection. The biologic effects of Atropine can be quickly observed by increased heart beats if it is absorbed in the blood stream.

**STUDY DESIGN:** This study was a randomized cross-over study in 20 healthy Beagle dogs, divided into 2 groups of 10 dogs each. The dogs were acclimatized to the study condition and stabilized for 7 days. They were given their regular dog chow and water as needed along with 12 hours lights on and 12 hours lights off. On the day of the study, the dogs were fasted for at least 10 hours prior to the dosing with Atropine. The dogs were implanted with the Polar M52 Heart Rate Monitor device with triple LED displays and memory functions to store information, and also with the standard ECG device to monitor ECG and pulse rate and oxygen levels along with the blood pressure. All data are reported as means ± SE. Heart rate variability was obtained using a Delta-Biometrics vagal tone monitor triggering the ECG R-R interval (Urbana-Champaign, IL). This device employs the time-series signal processing techniques as developed by Porges to estimate the amplitude of respiratory sinus arrhythmia (ie, increase in heart rates).

**TREATMENT 1:** Five dogs received Atropine administered via the microneedle (ClickSoft) device (0.03 mL total volume or ~ 0.044 mg/kg), and 5 dogs received Atropine (0.03 mL or ~ 0.044 mg/kg SC) via conventional needle (22 g) and plastic syringe (1 cc). The dogs were given rest for 48 hours to ensure complete washout of the drug, and they were then crossed over for the treatments.

**TREATMENT 2:** Five dogs received Atropine administered via the microneedle (ClickSoft) device (0.03 mL total volume or ~ 0.044 mg/kg), and 5 dogs received Atropine (0.03 mL or ~ 0.044 mg/kg, SC) via conventional needle (22 g) and plastic syringe (1 cc).

Dogs were monitored continuously by a heart monitor and ECG equipment to assess their well being and general health. In the case of excessive heart beats, the antidote was kept near by to terminate the experiment immediately. The heart rates, pulse rates, and blood pressures were monitored continuously by online ECG equipment attached to their legs by a regular ECG equipment strap bend. Upon injection of Atropine, the heart rates increased within minutes. The increase in heart rates is shown in Figure 3. At the end of the study, all dogs were returned to their normal life and were found in good health.

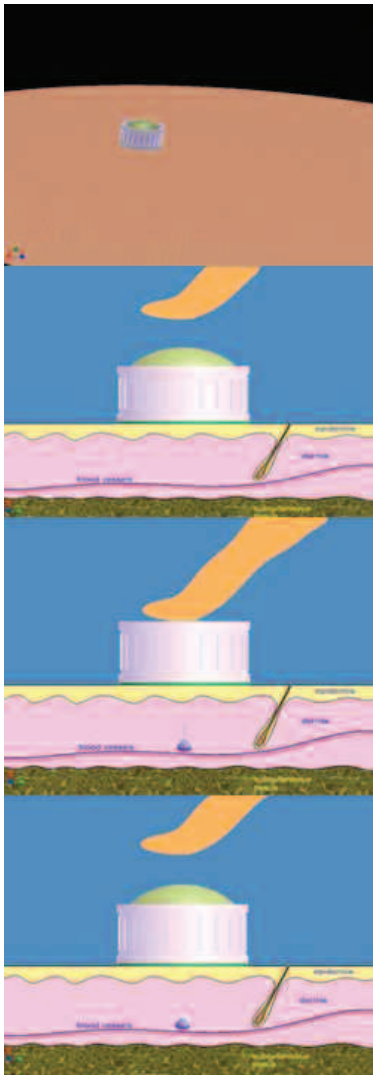
## RESULTS & CONCLUSION

The heart rate and the heart rate variability responses to two dosing methods, ie, SC injection versus intradermal injection with the ClickSoft device before and after the dosing are shown in Figure 4. The injection with the microneedle device elicited a significant increase in heart rate (time effect, $t = 10$, Heart Rates = 276, $P < 0.0001$ compared with SC injection, $t = 20$ min, Heart Rates = 235) with larger increases noted when compared with the same animals injected with the regular SC injection of the same dose. The average rates of percent change in the heart rates were significantly higher with the microneedle (210% from the baseline versus 76% SC injection). The recovery rates of returning heart beats to normal value was the same for the ClickSoft device and the regular SC injection with syringe. The novel device was proven safe and almost painless as the dogs never felt pricks when the device was placed and activated as opposed to injection, of which the dogs felt pain as assessed from their withdrawal behavior and sound emitted.

## PROOF-OF-CONCEPT HUMAN STUDY

**OBJECTIVE:** To compare the efficacy of the microneedle-based intradermal and epidermal drug delivery system with SC injection dose of human insulin after a standard meal at breakfast time in subjects with Type-1 diabetes.

**FIGURE 2**



**Device is positioned or placed on the body (1); device is activated by finger pressure, ie, device dome is pushed downward (2); the internal needle punctures the drug chamber and simultaneously enters the skin and delivers the dose intradermally within 5 seconds (3); when the finger pressure is released, the needle retracts back completely into the device and is now safe for disposal in any container (4).**

**STUDY DESIGN:** This was an open label, randomized, cross-over, comparative study of the microneedle device versus SC insulin injections involving 15 male or female volunteers with type 1 diabetes. All patients received the following two treatments in a randomized fashion on separate days.

**TREATMENT 1:** Subjects were given a bolus dose of insulin (Humalog, Lilly) 7 units at time 0 minutes.

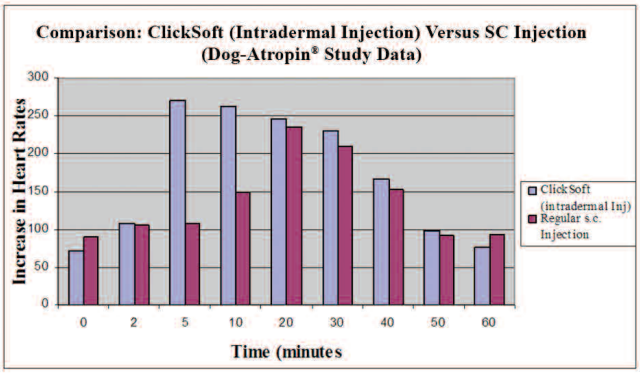
**TREATMENT 2:**Subjects were given an insulin dose (Humalog, Lilly) 7 units through the microneedle ClickSoft device at time 0 minutes.

Ten minutes after the dose, the subjects were asked to consume 360 calories from Boost or Ensure Plus liquid meals. Blood samples for plasma glucose and insulin were taken 30 minutes before the liquid meal (-30 minutes), just before the meal time (0 minutes), and after (15, 30, 60, 90, 120, 180, 240, and 300 minutes). At the end of the study period, the catheter was removed, and the subjects were permitted to leave the clinic after examination by a physician who declared them safe to leave the clinic.

## RESULTS & CONCLUSIONS

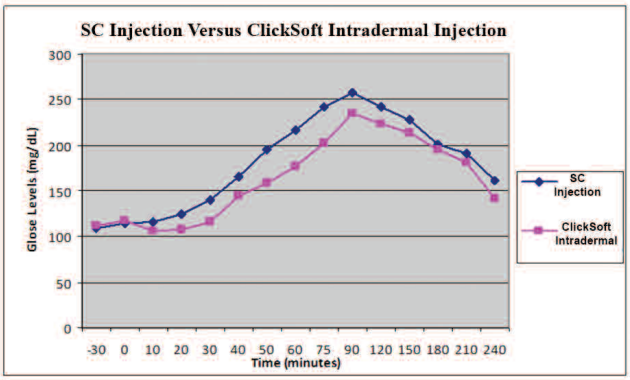
There was a significant difference in the glucose excursions at 30 and 60 minutes after a standard meal challenge as derived from the values of lower glucose levels in the microneedle device injection treatments when compared to the standard injection treatments. The 30 and 60 minutes post-prandial glucose levels were significantly lowered with the microneedle device versus the injection group (146 ± 5 mg/dL microneedle device versus 184 ± 7 mg/dL injection: 21% lower at 30 minutes and 192 ± 6 mg/dL microneedle device versus 236 ± 9 mg/dL injection: 19% lower at 60 minutes $p < 0.003$). The rises in serum insulin levels were significantly higher (Cmax = 93 ± 6 µU/ml for microneedle device at 20 minutes versus 78 ± 3 µU/ml injection treatment, 20% higher, $P < 0.001$). The absorption of insulin through the skin layers was significantly faster when compared to the SC-injected rapid-acting insulin (Humalog). The insulin delivered through the microneedle device was effective in lowering glucose when compared to the regular SC insulin injection. This was attributed to the much more rapid absorption of insulin through the skin layers (Tmax = 20 ± 3 minutes for microneedle device versus Tmax = 60 ± 10 minutes injection). There was no statistical difference in the variability of the absorption of insulin in the microneedle device versus SC

**FIGURE 3**



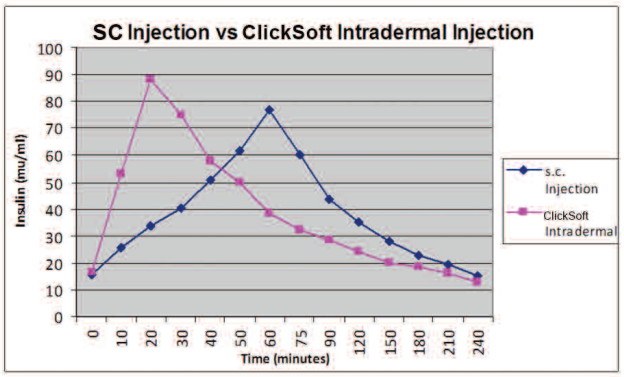

**Comparison of ClickSoft (Intradermal Injection) Versus SC Injection (Dog-Atropin Study Data)**

**FIGURE 4**




**Average Blood Glucose Levels (ClickSoft Versus SC Injection)**

**FIGURE 5**




**Average Serum Insulin Level (ClickSoft Versus SC Injection)**

injection as estimated from the individual data of each treatment, and both treatments were comparable to each other in absorption characteristics ($p > 0.751$). See Figures 4 and 5.

The absorption of insulin through the intradermal route was significantly faster when compared to the subcutaneously injected rapid-acting insulin (Humalog). The 30 minutes and 60 minutes post-prandial glucose levels were rapidly lowered with the microneedle device versus the injection group. The Humalog peaked faster (approximately 50%) within 20 minutes of intradermal injection (Tmax = 20 minutes) as opposed to regular SC-injected Humalog (Tmax = 60 minutes). This was attributed to the much more rapid absorption of insulin through the intradermal interstitial fluid with microneedle injection. There was no pain associated with the microneedle device injection as patients never felt the pricking pain that is associated with the SC injection.

Experts agree that interest and developments in novel insulin injectors are needed, especially toward the ease of administration and reduction in pain during the injection process. The pain reduction and the ease of administration will add substantial value to injectable products. Pharma partners now strongly recognize that the development and selection of the optimal injection device can have a significant impact on product success, and view single-dose, disposable technology as an interesting and rapidly changing market segment. In conclusion, based on its simplicity, cost-effectiveness, and its ability to reduce or eliminate pain in most cases, the Microneedle (ClickSoft) device will help initiate early insulin therapy to prevent dreadful future complications of diabetes and may help increase patient compliance to take insulin doses when needed. ◆

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## BIOGRAPHIES

**Mr. Maneesh Khanna** is Partner and Director at PKA. He has over 21 years of industrial experience with key exposure in the field of product development leading from an initial concept to the final product development. His vast international experience and technical skills for the design and manufacturing of precision products and assemblies have provided him a strong background for the innovative development of microneedle devices. His contributions in the field of medical devices include the development of IV Cannula, the Blood Collection Bag system, an Endotracheal Tube, and other IV therapy products for a medical company in India. Mr. Khanna earned his MEng in Design and Manufacturing and Micro Machining from McMaster University in Canada.

**Dr. Marko Mihic** is a Physician and Surgeon at the Diabetes Research Institute, St. Joseph Hospital in Toronto, Canada. Dr. Mihic is also Co-Founder of the Institute (Center, University Clinic) of Diabetes in Zagreb as a central institution for the organization of healthcare, education, and research in the field of diabetology in Croatia. He has authored several key publications in the field of Diabetes and Metabolic Syndromes. Dr. Mihic earned his MD from the University of Toronto with specialization in Diabetes.

**Dr. Pankaj Modi** is the Founder and President of PKA. He has over 23 years of experience in developing novel drug delivery systems and non-invasive medical devices for various therapeutics. Dr Modi is author of 30 US and 175 worldwide patents on various drug delivery systems. He has published over 35 papers and book chapters in leading medical and biotechnology journals. Dr. Modi is an Editorial Board Member for many drug delivery and medical journals. Dr. Modi earned his PhD in Biomedical Sciences from the University of Toronto, Postdoctoral Fellowship from McMaster University, and Doctorate in Internal Medicine with specialization in Endocrinology and Diabetes.