Pharmacokinetic and Pharmacodynamic Assessment of Intradermal Insulin Delivery in a Rats: Microneedle vs. Conventional Needle vs. Subcutaneous Injection

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Introduction

Microneedles are novel and effective transdermal drug delivery system which facilitate drug delivery into the dermis layer of skin, with minimum pain [1]. To assess safety and efficacy, we tested microneedles in rats, comparing their pharmacokinetics and pharmacodynamics to conventional subcutaneous and intradermal administration.

Methods

Standardisation of Microneedle- various lengths of microneedles such 500 µ, 550 µ, 600 µ, 650 µ, 700 µ, 750 µ, 800 µ were tested and as per the skin thickness 750 µ microneedle was observed to be ideal for intradermal delivery in rats.

Total thirty male Sprague Dawley rats, aged 3-4 months and weighing 200-250 grams each, were included in the study. Rats received 3 IU/kg Actrapid (recombinant human insulin) via three methods: subcutaneously (SC) with 23G needle (n=10), intradermally (ID) with 26G needle (n=10), or intradermally with microneedle (MN) (n=10).

Blood samples collected via retro-orbital method over 3 hours. Insulin levels assessed using electrochemiluminescence assay, and blood glucose levels determined via autoanalyzer. Pharmacokinetic parameters, including AUC, C_{max}, T_{max}, and $T_{1/2}$, were calculated. Mean and standard deviation were used for statistical analysis, with p-values determined via ANOVA to ascertain significance.

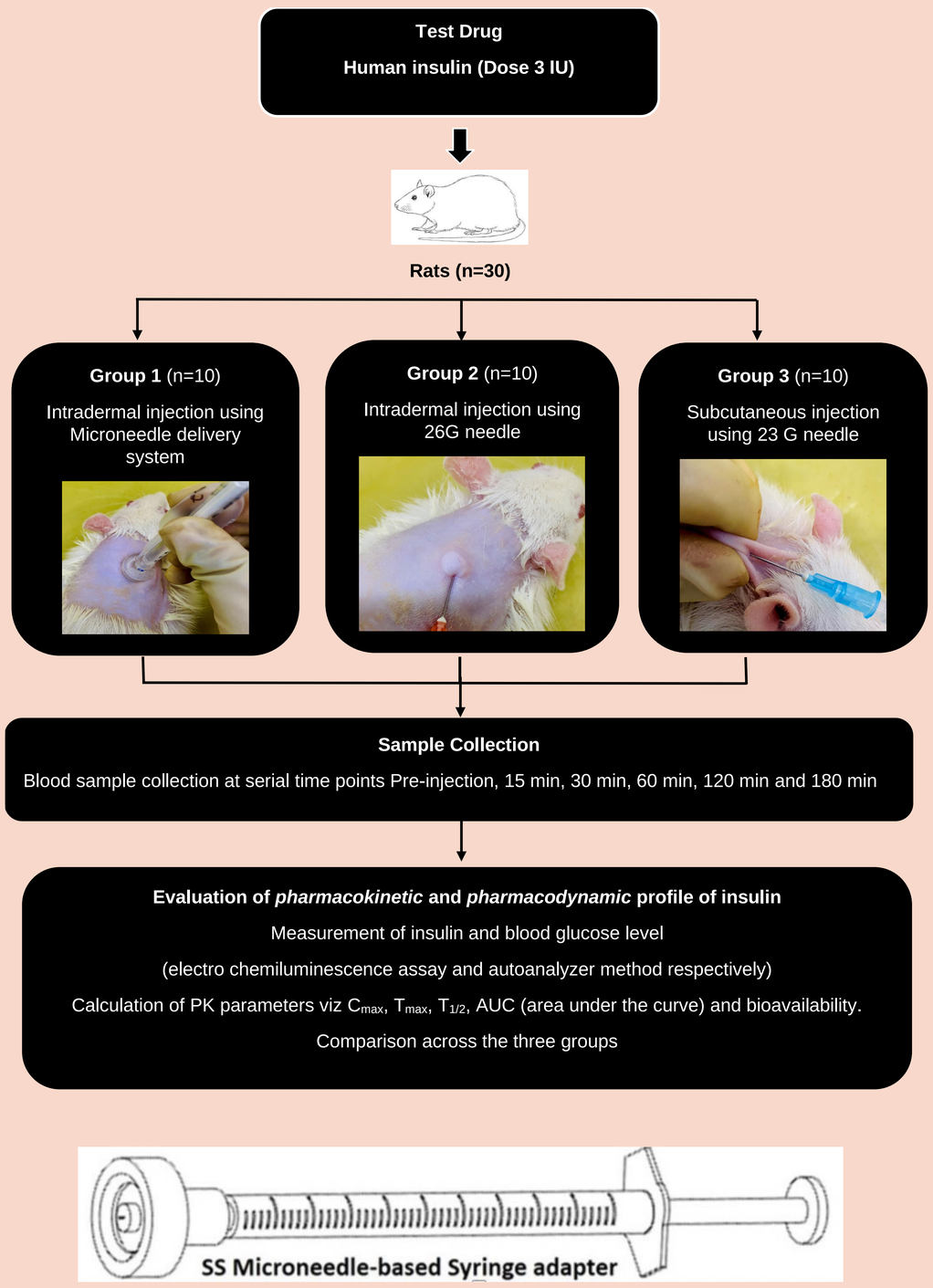


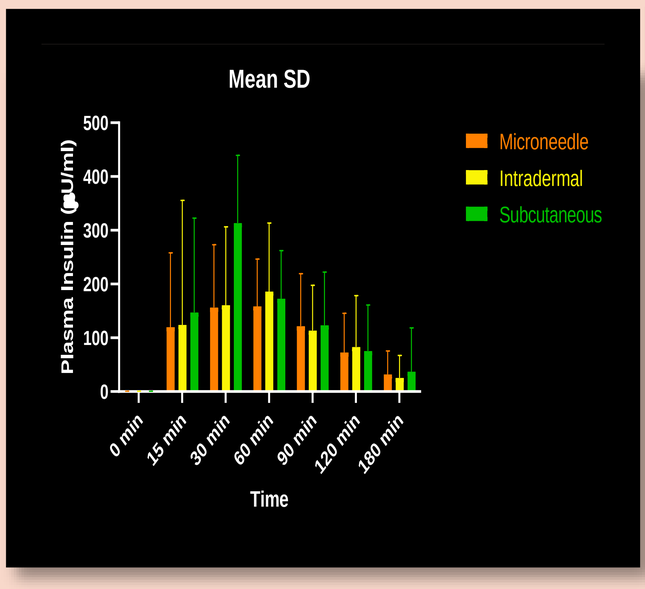
Figure : (1) Flowchart representing the detailed methodology, (2) Microneedle used 750 µm length and 200 µm diameter .

Result

The drug was effectively delivered via microneedles without adverse effects such as bleeding, erythema, swelling, or pain, confirming its safety.

Mean±SD and N, analyzed using two-way ANOVA followed by Tukey's test for post hoc comparisons. There is no significant difference between, AUC of plasma insulin for MN vs ID (p value=0.93); and for ID vs SC (p value=0.068); and for MN vs SC (p value=0.069). Similarly, there was no significant difference, plasma glucose levels for MN vs ID (p value=0.92); for MN vs SC (p value=0.98); and for ID vs SC (p value=0.85).

Mean (SD) bioavailability via AUC by trapezoidal method was 272.97(±202 SD) ng.h/ml, 288.48 (±241.72 SD) ng.h/ml, and 349.01 (±215.68 SD) ng.h/ml for MN, ID and SC injection respectively. The respective mean (SD) Tmax values were 48.33 (±23.45 SD) min, 46.67 (±20.46 SD) min, 28.33 (±5.00 SD) min.



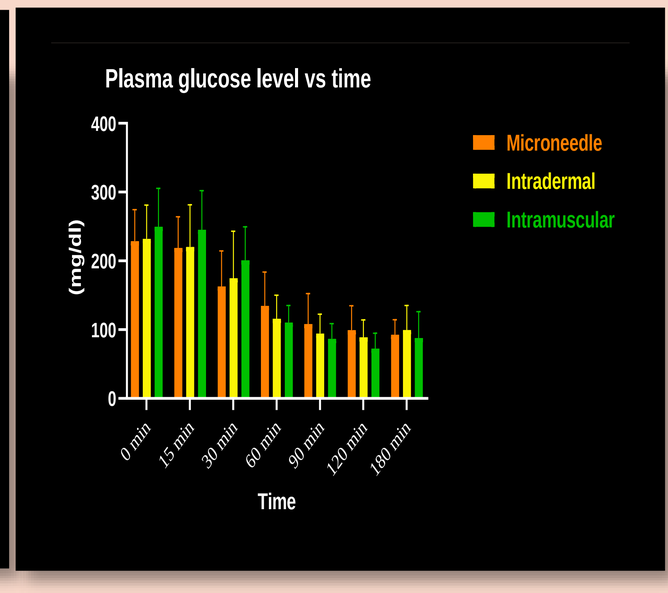


Figure 1: Graphical representation of Mean and SD of the 3 groups (MN, ID & SC). Bars representing the mean plasma insulin levels and error bars representing the standard deviation

Figure 2: Graphical representation of Mean and SD of the 3 groups (MN, ID & SC). Bars representing the mean plasma glucose levels and error bars representing the standard deviation

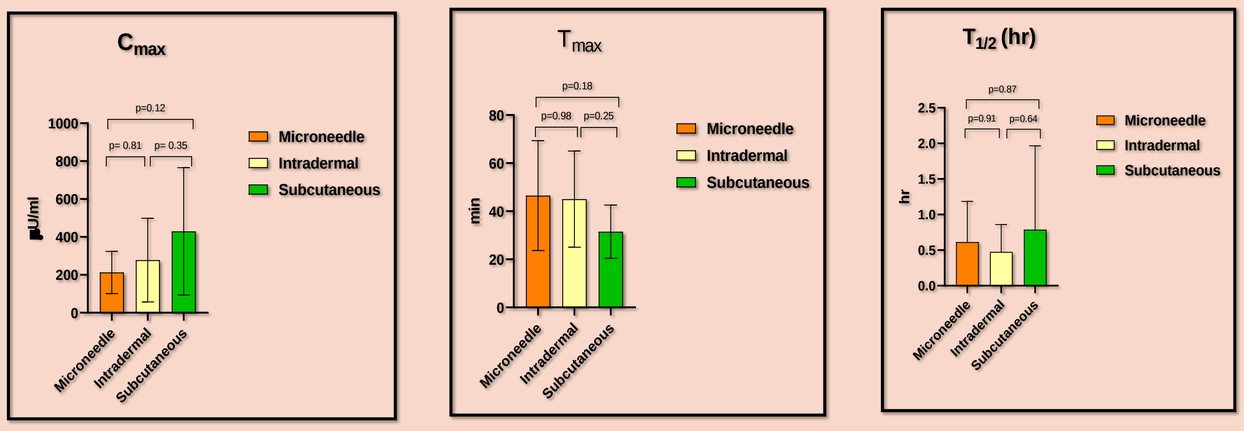


Figure 3, 4, & 5 representing the pharmacokinetic profile of insulin among the 3 groups MN, ID, SC.

- Mean (SD) of C_{max} observed : MN is 212.7 (± 111.45 SD) µU/ml, ID is 278.06 (± 220.93) µU/ml, SC is 429.81 (± 335.92 SD) µU/ml
- Mean (SD) of T_{max} observed : MN is 46.5 (±22.85 SD) min, ID is 45 (±20 SD) min, SC is 31.5 (±11.06 SD) min
- Mean (SD) of $T_{1/2}$ observed : MN is 0.61 (± 0.57 SD) hr, ID is 0.47 (± 0.38 SD) hr, SC is 0.78 (± 1.17 min)

Conclusion

Data confirm microneedle intradermal injection's safety and efficacy, paving the way for human clinical studies.

Reference

[1] Liu D, Yu B, Jiang G, Yu W, Zhang Y, Xu B. Fabrication of composite microneedles integrated with insulin-loaded CaCO3 microparticles and PVP for transdermal delivery in diabetic rats. Materials Science and Engineering: C. 2018 Sep 1;90:180-8.

[2] Wang Y, Wang H, Zhu XX, Guan Y, Zhang Y. Smart microneedle patches for rapid, and painless transdermal insulin delivery. Journal of Materials Chemistry B. 2020;8(40):9335-42.