Errors of insulin therapy: Real-life experiences from developing world

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ABSTRACT

A significant bulk of people living with diabetes is on insulin therapy aiming for satisfactory glycemic control and resultant reduction in vascular complications of diabetes. Insulin undoubtedly is the most potent antihyperglycemic agent. However, a significant proportion of insulin-treated diabetics fails to achieve the desired glycemic goal. Errors of insulin therapy remain an important and correctable factor in many of them. Such errors of insulin therapy can potentially arise at each and every step starting from the office of the clinicians while prescribing it for the first time up to the point of administration. Here, we share some of our clinical experiences on potential errors of insulin therapy and discuss preventive measures to overcome these simple barriers to achieve long-term glycemic control. We believe, these unfortunate but interesting scenarios, though rampant in the developing world may not be uncommon in the other parts of the world if carefully looked for. It is important for the clinicians to learn from these experiences with insulin therapy because it represents, for a majority of patients, the last option in our therapeutic armamentarium.

Keywords: Faulty injection technique, injection site abscess, insulin therapy, lipodystrophy, medication errors

Introduction

The prevalence of diabetes is rising exponentially across the globe and according to the 8th edition of IDF atlas, published in 2017, there are about 424.9 millions of people aged between 20-79 years living with diabetes in the world.¹ India is the home of about 72.9 millions of them. Diabetes, one of the four major noncommunicable diseases, accounts for about ⅓ million deaths in a year. Adequate glycemic control can significantly reduce the vascular complications and all-cause mortality in all forms of diabetes. Insulin is a “fact of life” in all patients with type 1 diabetes. Almost half of all adults with diabetes are in between the ages of 40 and 59 years and with growing prevalence of obesity and physical inactivity worldwide, type 2 diabetes is being increasingly recognized in young individuals. It has been shown beyond doubts that β-cell function declines relentlessly and progressively in type 2 diabetes regardless of interventions.² Hence, it is not surprising that a bulk of type 2 diabetes patients ultimately requires insulin therapy in the course of the disease for effective glycemic control. About 35% of people living with diabetes in India currently are on insulin.³ Insulin undoubtedly is the most potent antihyperglycemic agent. However, a significant proportion of insulin-treated patients fails to achieve the desired glycated hemoglobin (HbA1c) level. Errors of insulin therapy remain an important and correctable factor in many of them. Medication error is defined as “any preventable event that can cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health-care professional, patient, or consumer” and avoiding such errors in insulin-treated patients is critical to the therapeutic success. Such errors of insulin therapy can potentially arise at each and every step starting from the office of the clinicians while prescribing it for the first time up to the point of administration.

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Here, we share our clinical experiences on potential errors of insulin therapy and discuss preventive measures to overcome these simple barriers to achieve long-term glycemic control.

**Discussion**

**Prescriptions as a source of error**

Illegible prescription or inadequate explanation regarding injection technique/storage to the patients/accompanying party/health-care providers is an important cause of unacceptable outcome.

Illegible prescriptions are not uncommon in a busy diabetic clinic. We have seen patients admitted with major hypoglycemia after using 44 U of insulin instead of 4 U [Figure 1a] and 100 U instead of 10 U [Figure 1b] because of misinterpretation of the prescription. We strongly feel that clinicians should avoid the potentially dangerous use of the abbreviation “u” to indicate the number of units while prescribing insulin. It is also suggested to replace BD, a nonstandard abbreviation to mean before dinner as the former abbreviation may be interpreted as twice daily by nurses or community health-care providers.

**Improper storage**

Specific storage recommendations provided by the insulin manufacturer should be strictly followed. Insulin pens, unused cartridges and vials should preferably be refrigerated. If kept between 2°C and 8°C, stored insulin can be used till the expiration date provided by the manufacturer. It is emphasized that insulin should never be allowed to be frozen and if frozen, it should be discarded. We usually ask our patients to keep insulin in a place within the refrigerator which is distant from the deep freezer compartment. We had experienced insulin losing its bioavailability when vials were stored in the topmost part of the refrigerator door and getting exposed to the very low temperature of the deep freezer due to the malfunction and/or broken door of the deep freezer [Figure 2]. Pens should not be stored with needles on to avoid potential air-clogging and leak in thermoinsulation.[4]

A large number of individuals with diabetes in the developing world reside in rural areas or remote places without access to a refrigerator. It should be remembered that the shelf-life of insulin is about 4 weeks if stored at <30°C. In the absence of a refrigerator, insulin should be kept in a cool, airy, and dark place away from direct sunlight. It is advisable to put the unused vial in a clean plastic bag, secure it properly, and store it in an open wide-mouthed bottle or earthen pot filled with water. We also advise a miniature and modified version of the “Zeer pot” containing water or wet sands which utilizes the concept of evaporative cooling for storage of insulin in these patients [Figure 3].[5] It is needless to say that like all other medicines, insulin should also be kept out of reach of children.

**Storage of insulin during travel**

Another important issue is storage of insulin during tours (leisure/official) as many of our insulin-treated patients are frequent travelers. During travel insulin should preferably be stored in an insulated bag or cooled thermoflasks with ice if the ambient temperature is expected to be higher than 30°C. For the same reason, insulin should not be kept in the glove compartment of a car or in a locked car with closed windows.

While travelling by air, insulin should not be placed in the checked-in baggage to avoid exposure to extreme temperatures (mostly freezing).[6] One of our insulin-treated
patients, a frequent flyer, used to keep his insulin pens inside the checked-in luggage and experienced uncontrolled sugars immediately after air travel on a number of occasions. It took quite a long period to find the underlying etiology of unstable blood sugars and solve the issue effectively.

**Dosing errors**

In India, availability of both U-40 and U-100 insulin vials and syringes increases the probability of dosing error unless patients are informed and acquainted with both types of vials and syringes at the time of initiating insulin therapy. Patients should be informed that U-100 vials should be used with U-100 syringes (orange cover and black scale markings each denoting 2 units) and U-40 vials with U-40 insulin syringes (red cover and red scale marking each denoting 1 unit) only. In our country, U-40 vials and syringes are commonly used by the patients. One of our type 2 diabetes patients had been prescribed bedtime insulin glargine and daytime sulfonylurea therapy and had satisfactory glycemic control. However, due to financial constraints, he was shifted to neutral protamine Hagedorn (NPH) insulin from glargine after 6 months. We noticed grossly elevated blood sugars during subsequent visits. A detailed history revealed that he was using U-40 NPH vial and injecting with U-100 syringe resulting in 2.5 times less insulin than what had been prescribed [Figure 4]. We also feel the red-colored cap of U-40 syringe and orange-colored cap of the U-100 syringe are very similar in appearance and may be difficult to differentiate at times by the patients.

Insulin stored in the refrigerator should be kept at room temperature for at least 30 min before use which may reduce the frequency of injection site irritation and pain caused by cold insulin. Premixed insulins are the most commonly used insulin preparation in India, and perhaps, in many parts of the globe. Resuspension of premixed insulins and all other cloudy insulins is important not only to ensure proper dosing but also to maintain appropriate concentrations of insulin remaining in the container. Very often, we find it quite difficult to control blood sugars in patients with type 1 diabetes with two shots of premixed insulins and many times they are put on split-mix insulin regimens, by mixing appropriate rapid/short- and intermediate/long-acting insulin to maintain round the clock euglycemia. For a split-mix dose, the right sequence of mixing (clear insulin should be drawn first followed by cloudy insulin) should be strictly followed to avoid undesired changes in the chemical and pharmacodynamic properties of insulin components. A young type 1 diabetes patient of our clinic was put on split-mix insulin regimen (regular and NPH insulin) and had persistently elevated postmeal sugars with normal-low fasting values and frequent episodes of interprandial hypoglycemia despite repeated and appropriate increase in regular insulin and decrease in NPH dosage. The patient was then asked to bring all the insulin vials, and we found the soluble insulin losing its property due to the improper sequence of mixing [Figure 5]. The soluble insulin lost its crystal clear appearance and became cloudy due to contamination with the NPH insulin and lost its character.

**Issues related to injection site**

Except periods of hyperglycemic crisis and in some hospitalized patients in intensive care settings, insulin is administered by subcutaneous injection over anterior abdomen, anterior and outer mid-thighs, upper arms (lateral mid-third), and upper and outer quadrants of the buttocks. The presence of subcutaneous fat and very few nerves in these regions makes injections less painful and helps adequate absorption of injected insulin. However, we commonly encounter “innovative” patients or quacks injecting insulin over the ventral forearms and even calves [Figure 6].

**Cleansing**

The injection site should be properly and thoroughly cleaned with water-soaked cotton balls or alcohol swabs before each injection to prevent healthcare-associated local infections. Cleansing should be started in the middle of an area and moved outward in a circular motion away from the center. If alcohol is used, the skin should be allowed to dry up completely before injection to avoid stinging sensation. The top of the insulin vial

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**Figure 4:** Syringe-vial mismatch: Patient drawing insulin from U-40 NPH vial with U-100 syringe

**Figure 5:** Cloudy soluble insulin in the used vial (left) compared to its crystal clear appearance in the unused vial (right) due to improper mixing in split-mix regime
Improper care of the vials, injection sites, and poor hygiene leading to local infections are not uncommon in our patient populations [Figures 7 and 8]. These soft-tissue infections can potentially lead to surgical interventions, uncontrolled sugars, and significant cosmetic disfigurements [Figure 9], and ultimately end up in poor patient compliance. However, needles should not be cleaned with alcohol as alcohol removes the silicon coating of the needle and makes injections more painful.

Faulty injection technique

To deliver insulin in the subcutaneous adipose tissue, patients are advised to make a lifted skin fold and insert the needle into the skin at 90° angle, particularly in lean patients when the anticipated distance from the skin surface to the underlying muscle is expected to be less than the needle length. Injections can also be angled at 45° instead of using a skin-fold. Recently, available shorter needles (4, 5, and 6 mm in length) alleviate the risk of intramuscular administration and at the same time avoid intradermal delivery. Considering the fact that mean skin thickness is about 2.2 mm by ultrasound measurement, and there is no clinically significant variation in different population, a needle length of 4–6 mm is good enough for both children and adults. If skin folds are not used while using shorter needles, they should be injected at a 90° angle to the skin surface. Intradermal injection due to faulty technique is not uncommon in practice. Intradermal injections are more painful and result in cosmetically unaccepted hyperpigmented spots [Figure 10] and perhaps increased likelihood of insulin allergy.

Systematic rotation of the injection site is undoubtedly the most important issue to maintain healthy injection site, reduce risk of lipodystrophy, and ensure adequate insulin absorption. Lipohypertrophy, manifested by a focal swelling with soft, rubbery consistency is usually caused by repeated insulin injection in a particular site. The anabolic effect of insulin is thought to play the underlying pathophysiologic role. In our clinic, we frequently notice lipohypertrophy in patients with unstable glycemic control [Figure 11a]. Injection within the lipohypertrophic sites reduces the pain sensation but is associated with unpredictable and delayed insulin absorption. Patients are usually advised to divide the injection site into quadrants (abdomen) or halves (thighs, buttocks, and arms), and a single quadrant or half should be used per week. Injections within a particular quadrant or half should also be spaced at least 1–2 cm apart to avoid repeated trauma over a particular site. Unlike lipohypertrophy, lipoatrophy of the injection site is said to be rarely encountered. A common

![Figure 6: Wrong injection site: Hyperpigmented spots following insulin injection over ventral forearm (a) and calf (b and c)](image)

![Figure 7: Improper and unhygienic storage leading to accumulation of dust over the rubber cap of the insulin vials](image)

![Figure 8: Infection at injection sites due to poor hygiene and improper cleansing of injection sites (a,b,c)](image)

![Figure 9: Postinflammatory hyperpigmentation following infection over injection sites: thighs (a) and abdomen (b,c)](image)
occurrence in the prehuman insulin era, lipoatrophy seems to be an outcome of allergic reaction to insulin or any component of the solution. However, we do come across patients with lipoatrophy of injection sites not infrequently [Figure 11b].\[11\] It should be emphasized that before injection, the site has to be inspected (and palpated) for lipodystrophy, infections, and bruises and in the presence of any abnormality, a different site has to be chosen.

**Special precautions in pen-users**

All the precautions needed during vial and syringe use should also be taken in pen-users. Insulin pen should ideally be primed with two units of insulin before injection. This small amount then has to be discarded and the actual prescribed dose should be dialed in to remove blockage and avoid injecting air into the subcutaneous space. It is also advised to remove the needle from pen immediately after injection to prevent air entry into the cartridge as well as leakage of insulin. Omission of this simple step may result in unacceptable outcomes at times. We came across one such scenario when failure to follow the above instruction resulted in injection of air rather than insulin and significant glycemic variability [Figure 12].

**Conclusion**

Identification of potential errors and subsequent correction can effectively remove the barriers to insulin therapy and is a vital step toward successful management of diabetes. Patient’s compliance and long-term adherence to insulin therapy are often negatively affected by pain following an injection, which is an infrequent event if administered in a proper way. Correct injection technique can minimize or avoid injection-associated pain and improve compliance,\[12\] particularly when patients are put on multiple injections a day. There are evidences to show that adoption of proper injection technique and regular assessment of injection site can lead to HbA1c reduction of about 0.6% in 3 months which is equivalent to antihyperglycemic potency of many oral agents.\[13\]

We feel that establishment of a well-structured and fully equipped diabetes clinic in the resource-restricted remote areas of the developing countries is still a distant dream. A little more time spent by the physicians or nurses in a planned way while initiating therapy can help these patients to learn and execute appropriate insulin therapy. We also suggest that prescribing physician should indulge into a thorough discussion with patients regarding storage and administration of insulin and should inspect and palpate the insulin injection site ideally at every visit or at least every 6 months, particularly in the presence of suboptimal or erratic glycemic control. Providing the patients with injection grids or illustrative leaflets on proper injection technique may also be of help. Periodic patient education programs by health-care providers, clinicians and different patient groups/organizations are of utmost importance to maintain proper injection technique in insulin-treated diabetes patients.

Although the above observations essentially point toward our failures to provide appropriate diabetes education and care to these patients, they helped us a lot to rectify ourselves. We believe, such incidents are not uncommon in other parts of the world, and these interesting but sad clinical scenarios will definitely help health-care providers to recognize similar instances in their practice at the earliest opportunity and enable them to serve the insulin-treated diabetes patients in a better way.
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Conflicts of interest
There are no conflicts of interest.

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