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From Insulin Pumps to Artificial Pancreas: Indian Experience over 12 years

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ABSTRACT

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Insulin pumps are time tested gadgets in use for more than 50 years. The modern day models in addition to delivering insulin continuously subcutaneously, wirelessly receives signals from continuous glucose monitors and integrates sophisticated control algorithms for automatic delivery of insulin and suspension of insulin before the onset of hypoglycemia. Due to the variable basal rates and amenities for different types of bolus delivery, a near physiological delivery of insulin is made possible resulting in reduced glucose variability. These features contribute to multiple pleotropic benefits such as disappearance of peripheral neuropathic pain, improvement in sexual dysfunction, improvement in the pain of angina and overall improvement in quality of life. With advancements in technologies and with newer rapid acting insulins, the design and function of pumps are improving at a faster pace and the first generation artificial pancreas 640G is already available in the global market including India. In this review, we are also sharing our clinical experience and the Indian evidence using Insulin pumps in type 1 and type 2 diabetes over 12 years.

Keywords: Insulin Pump, Artificial Pancreas, CSII

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INTRODUCTION

Continuous Subcutaneous Insulin Infusion (CSII)or insulin pump therapy (IPT) is a sophisticated insulin delivery method which involves the use of a small programmable pump connected to the body via an infusion tube delivering a rapid acting analogue insulin via the sub cutaneous route continuously. The first insulin pump was introduced in the early 1960s by a Los Angeles doctor by the name of Arnold Kadish.[1] We started using pumps in our center since 2004. We shall be sharing our Indian experience too in this brief review.

Though insulin pumps have been in use for more than half a century, in the initial years, it was used only as a research tool. Though pumps gained popularity in the 1980s as a delivery device,it was wrought by several limitations including the bulkiness of the device, anecdotal reports detailing episodes of severe hypoglycaemia or diabetic ketoacidosis in some patients on insulin pumps. Interest in the Efficacy and utility of CSII rekindled soon after both the Diabetes Control and Complications Trial (DCCT)[2] and the U.K. Prospective Diabetes Study(UKPDS),[3] highlighted the importance of intensive therapy in achieving tight metabolic control and improving long-term health.

First generation insulin pumps lacked many of the features that are now standard in modern pumps such as alarms for malfunction, low-battery state, bolus dose adjustment and cannula occlusion. Integrated bolus calculators were included in the insulin pumps in 2002 and options for flexible basal rates were introduced later. Insulin pumps subsequently underwent tremendous technological innovation and bioengineering to closely approximate insulin delivery from a human pancreas. In 2006, Medtronic MiniMed (Northridge, CA), introduced real-time insulin pumps where the glucose sensor and the pump were combined. The introduction of real-time insulin pumps was a major breakthrough toward "closing the loop" of insulin delivery. These

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smart insulin pumps integrated and augmented with glucose biosensors to provide blood sugars in real-time were followed by features for early detection of hypoglycemia and prevention of occurrence of hypoglycemia. The dream of 'closing the loop' is near to reality with encouraging results from recent artificial pancreas trials using the modified control algorithms.[4]

TYPES OF INSULIN PUMPS

There are 2 types of insulin pumps- durable pumps and patch pumps. The durable Insulin pumps consist of a reservoir, a pump, and an infusion set. They are designed to last several years and the infusion set and reservoir need to be changed every 2–3 days.

The patch pumps are attached directly to the body (pod) with a small length of plastic tubing going directly from the base of the pump into the subcutaneous tissue. The pod houses the insulin reservoir and motor. It is controlled by a separate controller known as Personal Digital Assistant (PDA).[5]

Why insulin pump therapy?

Sophisticated pump technology and accumulating evidence base for the efficacy of pumps vs. multiple daily injections(MDI) and guidelines on the indications for using CSII from various organizations, based on clinical benefit and cost-effectivenesshave largely helped make insulin pumps popular. Insulin delivery via CSII is more consistent and precise in providing insulin requirements with low risk of severe hypoglycaemia. Evidence from several studies indicate that CSII provides equal or better glycaemic control, lower hypoglycaemic episodes, better quality of life, improved psychosocial functioning and more flexibility with lifestyle when compared to MDI therapy. Patients poorly controlled on MDI may benefit tremendously from CSII.

Salient Features of Insulin Pump

1. A variable basal rate with multiple basal rates helps avoid high and low glucose levels. 48 different basal profiles can be set in an insulin pump.
2. Pump can deliver miniscule amounts of insulin, as low 0.025 units or 0.05 unit increments.
3. Multiple basal rate patterns can be set in the pump to meet the varying insulin requirements.
4. Temporary basal rate can be programmed for high, low and moderate intensity activities and for sick days.
5. Bolus calculators make bolus doses more accurate, provide bolus recommendations to match the carb intake, correcting a high blood glucose and minimize insulin stacking.[6]
6. Insulin pump has varied bolus options to suit the time and type of food.[7]
7. The new 640G has SmartGuard Technologywhich automatically suspends insulin delivery when sensor glucose levels are predicted to approach a low limit and resume insulin delivery once sensor glucose levels recover.
8. 640G has a glucose meter which ensures that patients do not have a manual entry error
9. 640G is waterproof up to 12 feet of water for 24 hours at a time. **(Figure 1)**
10. Insulin delivery being more physiological, insulin pump minimises the glycemic variability thereby reducing oxidative stress thus preventing vascular complications.

Figure 1. **640G**

Evidence favouring Insulin pump therapy

The Sensor-Augmented Pump Therapy(SAPT) for A1c Reduction (STAR) 3 study which integrates real-time continuous glucose monitoring (RT-CGM) with CSII, comparing the efficacy of SAPT to that of MDI in subjects with type 1 diabetes demonstrated reduced glycemic variability and reduced the number and severity of glycemic excursions. Moreover, it was also associated with significant improvement in glycatedhemoglobin levels when compared to MDI.[8,9]

In one of the largest randomised controlled trial (OpT2mise) comparing the efficacy of pump treatment and multiple daily injections in T2D, mean glycatedhemoglobin decreased by 1·1% in the pump

treatment group and 0·4% in MDI group resulting in a between-group treatment difference of −0·7% (p<0·0001). The mean total daily insulin dose was 97 units (SD 56) with pump treatment versus 122 units (SD 68) for multiple daily injections (p<0·0001), with no significant difference in bodyweight change between the two groups (1·5 kg [SD 3·5] vs 1·1 kg [3·6], p=0·322) proving pumps in T2DM as a safe and valuable treatment option.[10]

Reznik et al, in a recent study, demonstrated the sustained efficacy of insulin pump therapy in 161 patients with type 2 diabetes with MDI failure.Over 9 years of follow-up, HbA_{1c}decrease was maintained (P < 0.05), daily insulin requirements did not change, and weight gain was stable over 7 years. The percentage of patients lost to follow-up and pump withdrawal was 3.7% and 16.8%, respectively.[11]

Consensus Guidelines for use of Insulin Pumps

As per AACE, "the ideal CSII candidate would be a patient with T1DM or absolutely insulin-deficient T2DM who currently performs 4 or more insulin injections and 4 or more self-monitored blood glucose (SMBG) measurements daily and is motivated to achieve tighter blood glucose control, and is willing and intellectually and physically able to undergo the rigors of insulin pump therapy initiation and maintenance". AACE recommends insulin pump therapy for effective maintenance of glycaemic control in patients with T2DM requiring large doses of insulin.[12] According to the International Diabetes Federation guidelines, pump therapy should be considered only at the comprehensive care level and in type 2 diabetes mellitus it should remain as a potential option in highly selected subjects.[13]

In India, our center from Kerala was foremost in framing the consensus guidelines for the use of insulin pumps both in type 1 and type 2 diabetes, incorporating key opinion leaders.[14] Later, consensus evidence-based guidelines for use of IPT was formulated. According to this guideline,[15] pump therapy should be considered in

a. any patient (age no bar) on insulin therapy who can afford and is seeking improved quality of life
b. patients requiring better exogenous insulin therapy, provided, they are finding it difficult to achieve age specific optimised glycated haemoglobin with MDI therapy
c. patients whose insulin requirement is high, to control insulin doses compared to MDI
d. patients with diabetes related complications
e. patients experiencing frequent episodes of severe hypoglycaemia
f. patients with unpredictable fluctuations in blood glucose levels
g. women with diabetes during pregnancy or pre-pregnancy

As per the suggested guidelines,[14] insulin pumps are strongly indicated in patients with

- CKD/dialysis/post renal transplant
- Low C-peptide level
- Hypoglycemia unawareness
- Recurrent DKA
- Glycemic variability
- Intractable neuropathic pain
- Erectile dysfunction
- Dawn phenomenon
- Gastroparesis
- And frequent travellers and those with untimely food habits

In view of the recommendations from existing guidelines, a set of generalised recommendations for use of insulin pump therapy for clinical practice specific to Indian population were framed.[15]

- Patient selection is most important. Well-motivated patients keen to achieve good glycaemic control and interested in SMBG could benefit from insulin pump therapy, provided they can afford
- Insulin pump therapy can be initiated in patients visiting out-patient department provided they have the mental and physical capacity to do so
- Patient should be adequately educated on pump use, including aspects such as infusion set insertion technique and basic insulin dose adjustments at the beginning of the insulin pump therapy
- Cannula of insulin pump should not be used beyond 72 hours and patients should be advised to change if they experience pain, irritation and/or inflammation
- Once patient is comfortable with insulin pump therapy, advanced pump therapy education including different bolus types, carbohydrate counting and use of advanced pump menu should be discussed
- Importance of SMBG should be emphasised to the pump users at every visit
- Patients undergoing pump therapy, should have their HbA1c monitored every 3 months and should be regularly followed up

- If HbA1c levels go beyond age specified targets, insulin dose should be adjusted until desired glycaemic targets are achieved
- Individual/group training sessions should emphasize to keep the patient in follow up and monitor the progress in management of diabetes

In type 2 diabetes, oral agents with multiple mechanisms of action offering complimentary benefits may be used along with IPT as in the case of MDI.

Ideal candidates for Insulin Pump

Ideal candidates for insulin pump therapy are listed in **table 1**.[16]

Table 1. Ideal candidates for insulin pump therapy

	Ideal candidates for insulin pump are:
1	Educated and affordable
2	Willing to learn and follow instructions
1	Demonstrates ability to perform Self Monitoring of Blood Glucose
2	Keep comprehensive records
3	Accurately count carbohydrates
4	Demonstrates compliance andmotivation
5	Appropriate family/social situation/responsible caregiver
6	Psychologically stable
7	Comfortable with gadgets and devices
8	Patients with Realistic expectations

Contraindications of insulin pump therapy

The absolute contraindications to insulin pump therapy are as follows.[16] **(table 2)**

Table 2. Contraindications of insulin pump therapy

1	Technical Inability - pump operation orset insertion
2	Reluctant to test blood glucose reliably
3	Unlikely to respond appropriately to hyperglycaemia / ketosis
4	Active psychiatric issues/depression
5	Inability to do basic arithmetic

Advantages & Disadvantages using insulin pump therapy

Advantages and disadvantages using insulin pump therapy are enumerated below:[14] **(table 3)**

Indian Experience using Insulin pumps

Modern day insulin pumps were first introduced in India in 2004and unlike in the West, majority of insulin pump users are patients with type 2 diabetes. Insulin pumps are still not covered under medical insurance which precludes its wider use. The cost of pump and the recurring cost of consumables and the necessity

Table 3. The advantages and disadvantages using insulin pump therapy

Advantages	Disadvantages
Precise and miniscule amounts of insulin delivery possible	Cost of pumps and consumables areexorbitantly high
Improvement in HbA1c	Risk of infection if the cannula is not changed once in every 3 days.
Reduction in blood glucose variability	Overeating and frequent bolusing could result in weight gain and misuse of an insulin pump
Reduction in major and minor hypoglycemic episodes, combat 'dawn' phenomenon	Improper use of insulin pump boluses can lead to insulin stacking and low sugars
Improvement in neuropathic pain and sexual function	Discomfort of having a gadget attached to the body
Reduction in total daily dose of insulin	Risk of missed boluses and hyperglycemia

to upgrade to newer versions of the pump hampers the popularity of the device despite the flexibility it offers. Now India has more than 5000 insulin pumpers 60% of which are type 2 diabetes patients. In 2004, we started using smart insulin pumps at our center. Weinitiated Real time pumps in 2007, Veo insulin pump with a Low Glucose Suspend(LGS) mechanism in 2012 and 640G with predictive low glucose suspend in 2015. This was the first step towards completely closing the loop – Artificial Pancreas.

The pleotropic benefits of being on CSII were first reported from our centre. In 2007, we presented at American Diabetes Association, the case of a 58-year-old subject with T2DM of 20 years' who reported disappearance of the intractable pain of neuropathy within 10 days of being on CSII.[17] In another study in 46 type 2 diabetes patients from this centre who were switched over to CSII from MDI, 83% of subjects noted an improvement in sexual function as opposed to when they were using MDI in 6 months. With respect to peripheral neuropathic pain, 87% of subjects reported significant reduction in pain after initiation of CSII.Mean HbA1c was reduced by 0.5% after 6 months. This outcome was statistically significant ($P < 0.0063$; 95% confidence interval, 0.161-0.921%). There was no statistically significant change in body weight or total insulin daily dose. Subjects reported high satisfaction with CSII and low interference with daily activities.[18] The disappearance of neuropathic pain and improvement in sexual function was further proved in an exploratory trial from the centre.[19]

In a study by Mohan V et al. 33 patients (type 1 = 17 and type 2 = 16) with recalcitrant diabetes on CSII therapy were followed up for a mean duration of 3.4 years. The study demonstrated statistically significant reduction in HbA1c after initiating CSII. The study

also stressed the importance of regular follow up of insulin pump patients after being on CSII since the greatest reduction in HbA1c levels occurred in the first 6 months and a slight deterioration thereafter possibly because some patients "relaxed" the control after the initial success with pumps.[20]

In another study which assessed the attitude and behaviour of type 2 diabetes patients, improvement in quality of life after being on pump was appreciated by 92% The level of satisfaction was rated as 'fully satisfied' by 52% of respondents while 26% found being on pump, 'satisfactory'. Ninety percent thought that the pump met their expectations.[21]

The rare case report of a patient with Wolfram syndrome (DIDMOAD) on insulin pump was also published from this centre. This was the sixth report of successful pregnancy in a patient with Wolfram Syndrome and the first from India. The positive impact of CSII in prolonging the life span and retarding neuronal damage in Wolfram syndrome need to be better studied with the patient still surviving, probably the oldest in the world, with Wolfram syndrome.[22]

The impression of probable pleotropic action of insulin pumps over and above that of reducing glycemicburden is rapidly gaining momentum. Evidence supports use of insulin pumps in alleviating neuropathic pain in diabetes, probably by virtue of its action in minimizingmean amplitude of glycemic excursions not possible with conventional insulin shots.Due to its ability to control insulin delivery and eliminate hypoglycemia, the new generation insulin pumps are also considered the best delivery systems for insulin during the holy month of Ramadan, despite the prerequisites for its optimal output and cost concerns.[23]

On account of the experience gathered over the years of using insulin pumps, the centre took the initiative of publishing the possible indications, contraindications and candidates for insulin pump therapy. According to this guideline, an affordable patient may not always be an ideal candidate for an insulin pump if he lacks the motivation and time to attend periodic pump training sessions.

Fully integrated systems with sophisticated control algorithms are continuously evolving. MiniMed 670G which got FDA approval employs 'SmartGuard HCL" algorithm that enables greater glucose control with reduced user input. It delivers continuously variable rates of insulin according to personalized needs, and take actions to minimize both high and low glucose levels. Users only need to enter mealtime carbohydrates, accept bolus correction recommendations, and periodically calibrate the sensor.[24] Artificail Pancreas (AP) systems will not only monitor glucose levels but also automatically adjusts insulin delivery to reduce glycemic excursions with little or no input from the patient.[25] "Bionic pancreas" is a dual-hormone (insulin and glucagon) configuration of AP and this platform was taken over by 'Beta Bionics' to develop 'iLet'. iLet has a built-in algorithm that can automatically analyse the information obtained fom the glucose sensor (Dexcom CGM) and automatically dictate insulin/ glucagon delivery as and when required. It requires minimal patient input and can be initiated simply with the data on the patient's body weight.[26] iLet in its single chamber mode (insulin-only) is expected to come into the market in 2018 and its bihormonal version in 2019.[27]

CONCLUSION

Insulin pump deployment is only a minor procedure, and is the first step towards achieving a major goal. The patients often have a wrong notion that this expensive equipment when adopted will ultimately be a cure for their illness, whereas the fact is that insulin pump usage will incur more responsibilities, more learning, more teaching, and more frequent blood glucose estimations until the blood sugars get stabilized.Advances in biotechnology, insulin delivery, control algorithms and new rapid acting insulins such as faster acting aspart are soon expected to change the future of diabetes technologies.

END NOTE

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Editor's Remarks: This article traces the origin of Insulin therapy in Diabetes mellitus. The advantages of the various options are discussed along with its disadvantages. The Indian experience is also outlined. Several important original studies regarding the management of diabetes mellitus have been published from this centre.

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