

Will Long Acting Insulin Analogs Influence the Use of Insulin Pump Therapy in Type 1 Diabetes?

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Abstract: Insulin pump therapy enjoys a steadily growing number of users and is associated with an approximately 0.5% lower A1c as compared to flexible insulin injection therapy in type 1 diabetes patients. An important question is whether superiority of insulin pump therapy persists in the era of rapid acting analogs and will persist in the era of long acting analogs. Pooled data of three randomized clinical trials using rapid acting analogs in both arms shows a 0.35% lower A1c when on the pump. Treatment effect was shown to be larger in those with higher baseline A1c's. Results of three trials comparing insulin pump therapy with regimens consisting of both rapid acting and long acting analogs are inconsistent, probably indicating the advantage of pump therapy at group level is likely to have become relatively small. Therefore, the challenge for the treatment team is to identify those patients who benefit most from insulin pump treatment. Poor glycemic control merits a trial of insulin pump therapy in the motivated patient. Other indications for insulin pump therapy include the need for several basal rates, a life style characterized by unpredictable physical activity and patient preference.

Keywords: Insulin pump therapy, insulin injection therapy, diabetes mellitus, insulin dependent [MeSH].

INTRODUCTION

Originally developed as a research tool in 1978, insulin pump therapy is now used worldwide by an estimated 200,000 diabetes patients [1]. In 2002, a meta-analysis of randomized clinical trials, comparing insulin pump therapy to insulin injection therapy, estimated the advantage of insulin pump therapy in terms of A1c to be 0.51% [2]. Blood glucose values were shown to be less variable, and insulin dose while on pump therapy was lower. The A1c advantage of insulin pump therapy appeared to be remarkably consistent over decades, equally notable in the eras of conventional and intensive insulin therapy. This review explores the question whether superiority of insulin pump therapy persists and will persist in the new eras of rapid acting and long acting analogs, respectively.

Benefits of Insulin Pump Treatment - 1978 to 2002

Using insulin pump therapy, basal insulin supplementation rates can be adjusted if needed hourly to match insulin requirements during the 24 hours of the day. Thus, it is possible to effectively counteract the dawn phenomenon [3]. Shortly after its introduction in 1978, small – up to 50 patients - randomized clinical trials comparing insulin injection and insulin pump therapy were undertaken, and this type of trial continued to be carried out throughout the eighties and nineties. In 2002, Pickup, one of the inventors of insulin pump therapy, and co-authors published a meta-analysis of nearly all trials published between 1982 and 2000

[2,4]. This meta-analysis included twelve trials with 600 patients randomized to either pump or injection therapy and treated for 2.5 to 24 months. Insulins used mainly included unmodified human and Neutral Protamin Hagedorn (NPH)/Zinc insulins. The advantage of insulin pump therapy in terms of A1c was estimated to be 0.51%. Blood glucose values were shown to be 27% less variable, and daily insulin dose while on pump therapy was 14% lower. With respect to other important outcome measures when comparing insulin injection and insulin pump therapy, the authors of the meta-analysis argued that frequency of severe hypoglycemia and ketosis could not be assessed because of poor reporting and short duration of studies. Quality of life was not or insufficiently investigated in the early trials of insulin pump therapy.

All the above mentioned advantages of insulin pump therapy follow from the superiority of insulin pump therapy over NPH insulin in providing basal insulin supplementation. For decades, NPH insulin has been the mainstay of basal insulin supplementation using injection therapy. NPH insulin consists of regular insulin and protamin, extending its duration of action. The shortcomings of intermediate-acting NPH insulin include its peak action four to five hours after injection [5], its waning after this peak, and the large variation in intraindividual absorption, of up to 25% [6]. The waning coincidences with the late night / early morning rise of counterregulatory hormones, most notably growth hormone. This is named the dawn phenomenon [7].

What has the Impact of Rapid Acting Analogs been on Insulin Injection Therapy and Insulin Pump Therapy, Respectively?

Following injection of human regular insulin, insulin levels start to rise after about 40 minutes, peak at about two

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hours and remain elevated for six to eight hours, approximately. The maximum glucose lowering effect occurs at about three hours. Therefore, insulin action starts slower, peaks later and lasts longer as compared to the physiological mealtime insulin secretion pattern. This obviates good postprandial glycemic control and increases the risk of late postprandial hypoglycemia. In response to these shortcomings, rapid acting analogs have been developed [8]. Following substitution of one or two amino acids at the terminal end of the B chain of the insulin molecule, subcutaneous hexamerization following injection of insulin is prevented. This results in a more rapid absorption and onset of action. Two rapid acting insulin analogs have been marketed. Following injection of the first, insulin lispro, insulin levels start to rise after 20 minutes, peak at about 50 minutes and remain elevated for four hours, approximately. This very well mimics the meal-related peaks in the physiological insulin profile. The maximum glucose lowering effect occurs at about two hours. This has repeatedly been shown to result in improved postprandial glycemic control [8]. In a meta-analysis, a reduction in severe hypoglycemic events has been reported [9].

The second rapid acting insulin analogue is insulin aspart. In large scale investigations, a lowering in A1c of 0.12% to 0.17% was seen with the use of insulin aspart, as compared to human regular insulin [10-13].

Four trials compared a rapid acting insulin analogue with human regular insulin in a cross-over design in insulin pump treated patients [14-17]. A 0.13% to 0.5% lower A1c was seen in these trials. The weighted mean reduction in A1c in these studies is 0.24%. Therefore, a rapid acting insulin analog seems to be the preferable pump insulin. The above mentioned trials were carried out using insulin lispro. Insulin aspart has been shown to be compatible for insulin pump use as well [18]. Therefore, rapid acting analogs can be regarded as the mealtime insulin of choice in both insulin injection therapy and insulin pump therapy for type 1 diabetes.

Recently, authors of the three published trials comparing insulin pump therapy with intensive injection therapy have pooled their data, using advanced statistical techniques [19]. Overall, a 0.35% advantage in A1c for insulin pump therapy just failed to reach statistical significance ($p=0.08$). No differences in hypoglycemia rate could be noted. Importantly, the interaction between baseline A1c and treatment modality emerged as an independent predictor of A1c response. The treatment effect could be predicted using a formula, $A1c\ response = 1.2158 - 0.1861 \times baseline\ A1c$. Thus, at a baseline A1c of 6.5%, no benefit in terms of A1c can be expected from pump therapy, whereas a patient starting at 10% can statistically look forward to a 0.65% decrease in A1c. Interestingly, this formula predicted the A1c advantage noted in the most recently reported trial comparing rapid acting analog based insulin injection therapy to insulin pump therapy (0.22% vs. 0.21% predicted) [20]. Two of the three published trials investigated quality of life as an endpoint. The trial by Tsui and co-workers found no differences between treatment groups in all subscales of the DQOL, the Diabetes Quality of Life instrument, developed by the DCCT investigators [21]. The trial by

DeVries and co-workers trial reported better quality of life on two subscales of the SF-36, the most widely used generic quality of life instrument, for patients on insulin pump therapy [22].

For many it goes against the grain that poor control emerges as a primary indication for insulin pump therapy. It is felt that patients do not qualify for insulin pump therapy if they cannot achieve reasonable A1c's with injection therapy. A recent review stated 'patients who are unable to control their diabetes because of psychosocial or other problems are rarely successful when switching to CSII' (continuous subcutaneous insulin infusion, insulin pump therapy) [23]. Passionate discussions may ensue, where blame for poor control when on injection therapy may be put on bad doctors and or bad patients. Where bad doctors, not knowledgeable on insulin pharmacodynamics, certainly exist, a bad patient is rarely or never encountered. When we are honest, we know very little about why patients are in persistent poor control [24]. Too much emphasis seems to have been given to patient-related factors, where many other factors are at work. A more useful model is taking into account both disease burden and coping capacity of each individual patient. Poor control can simply be seen as a result from a disbalance between one individual's diabetes burden and coping capacity. Insulin pump therapy can then be regarded as a way to ameliorate this disbalance in a poorly controlled patient, provided the patient is motivated for pump therapy and ready to change. In other words, some patients in poor control need better tools to improve their control, i.e. a pump.

Long Acting Analogs

In response to the shortcomings of NPH insulin outlined above, long acting analogues have been developed. The first, insulin glargine, has alterations in both the A and B chains of the insulin molecule, and this results in slow resorption with a peakless action profile. In one of the two key phase 3 large-scale clinical trials, this insulin has been shown to result in less night time hypoglycaemic events, while A1c was unaffected in both trials [25,26]. A second long acting analogue is insulin detemir, in which a long chain fatty acid has been coupled to the B chain of the insulin molecule. This results in a high binding affinity for albumin, thereby prolonging its time of action. A peak remains, about half in magnitude as compared to the peak seen with NPH insulin. Insulin detemir has also been shown to lower overall and night time hypoglycaemia event rate [27,28]. Two trials have compared the conventional combination of basal NPH insulin and mealtime regular insulin to regimens with both rapid acting and long acting analogues. The first, comparing aspart/detemir with regular/NPH insulin, found A1c to be 0.22% [95% CI: 0.34 to 0.10], $P < 0.001$ lower with the analog regimen [29]. The second, so far published as abstract only, and comparing aspart/glargine with regular/NPH insulin, found A1c to be 0.5% lower [95% CI: 0.7 to 0.3]; $P < 0.001$ [30]. Interestingly, this last difference in A1c is roughly similar to the A1c advantage noted for insulin pump therapy as compared to the combination regular insulin-NPH insulin in the meta-analysis by Pickup and co-workers.

Will There Remain Benefits of Insulin Pump Therapy in the Era of Rapid Acting and Long Acting Insulin Analogs Combined?

Of course the question of superiority of either insulin pump therapy or intensive injection therapy deserves new clinical trials in the era of long acting analogs. Three such trials are completed, one published and two so far presented as abstract only. Doyle *et al.* performed a randomized clinical trial in 32 adolescents, age range 8-21 yrs, mean 12.5 ± 3.2 and 13 ± 2.8 in the insulin pump and injection group, respectively [31]. Insulin injection therapy consisted of insulin glargine as basal insulin and insulin aspart as mealtime insulin. While there was no significant A1c change in the glargine-aspart group (8.2% at baseline vs. 8.1% at 16 weeks), youth randomized to insulin pump therapy had a reduction in A1c levels, from 8.1 to 7.2% after 16 weeks of therapy ($P < 0.02$ vs. baseline and < 0.05 vs. glargine-aspart group). Total daily insulin dose was unchanged in the glargine-aspart group, but significantly dropped with insulin pump therapy (1.4 units/kg at baseline vs. 0.9 units/kg at 16 weeks, $P < 0.01$). Hypoglycemia rates were not reported. Bode *et al.* have presented work on 100 patients, all experienced pump users, who were randomized to a switch back to intensive insulin therapy using insulins glargine and aspart, using a cross-over design [32]. Mean serum fructosamine levels were significantly lower after pump therapy than injection therapy (343 ± 47 vs 355 ± 50 $\mu\text{mol/L}$, respectively, $P=0.0001$). The vast majority of subjects reported hypoglycemic episodes (pump: 92%, injection: 94%) and nocturnal (midnight to 8 am) hypoglycemic episodes (pump: 73%, injection: 72%). Duration of each mode of therapy was five weeks only. The mean A1c values for subjects at the end of the 10-week study were similar between treatment sequences (pump to injection, $7.3 \pm 0.7\%$ vs. injection to pump, $7.1 \pm 0.7\%$, $p > 0.05$, baseline value $7.5 \pm 0.8\%$), so subjects maintained overall glycemic control in both treatment sequences. Therefore, the main conclusion from this data is that experienced pump users can temporarily switch back to injection therapy, without experiencing large deteriorations in glycemic control. Bolli *et al.* presented data on people with type 1 diabetes (A1c $< 9.0\%$) naïve to pump and glargine who were randomized for 6 months to insulin pump therapy ($N=28$) or injection therapy with glargine as basal insulin and lispro as mealtime insulin ($N=29$) [33]. A1c decreased from 7.7 ± 0.7 (SD) to $7.0 \pm 0.8\%$ with insulin pump therapy, and from 7.8 ± 0.6 to $7.2 \pm 0.7\%$ with injection therapy, the baseline and center adjusted difference being -0.1% (95% CI $-0.5, 0.3$, NS). Mean daily blood glucose (BG) level decreased from 164 ± 41 to 146 ± 32 mg/dl and from 160 ± 30 to 144 ± 20 mg/dl respectively (difference 1 (-14, 15) mg/dl (NS)). The Mean Average Glycemic Excursion (MAGE, defined as the arithmetic mean of all glycemic excursions larger than 1 SD of the mean BG during one day of frequent or continuous blood glucose measuring) decreased from 144 ± 43 to 115 ± 40 mg/dl (insulin pump) and from 137 ± 31 to 115 ± 38 mg/dl (injection) (difference NS). Coefficient of variation of eight-point BG profiles decreased from 53 ± 10 to $46 \pm 8\%$ and from 52 ± 12 to $47 \pm 11\%$, respectively (NS). Confirmed hypoglycemic events per patient (BG < 72 mg/dl) over the 6 months were not statistically different (41 ± 8 (SE) vs. 35 ± 7 events).

Average cost per treatment was four times higher with pump. In summary, one trial in adolescents, who differ from adults in many ways, showed superiority of insulin pump therapy over injection therapy in A1c and insulin requirement, a second trial, in experienced pump users, showed equivalence in nearly all endpoints, fructosamin levels being slightly lower in the pump group, and finally a third trial showed overall equivalence.

CONCLUSION

Insulin pump therapy has been superior in lowering A1c in the era of regular and NPH insulin, both when using conventional and intensive insulin therapy. The advantage in A1c for the insulin pump appears to have become a little bit smaller in the era of rapid acting analogs. When seen at group level, it may well be that with the advent of long acting analogs, differences between insulin pump therapy and injection therapy have become even smaller. Of course selected individual patients may experience improvements in A1c when starting pump therapy, but given the fact that benefits to be derived from pump therapy nowadays are likely to be small, from a statistical point of view there must also be patients who experience no change or even a deterioration in A1c following initiation of pump therapy. The challenge for the treatment team is to identify those patients who benefit from insulin pump therapy, if necessary by offering those with non-satisfactory control a trial period. Taking pharmacokinetics of insulin into account, it may well be that insulin glargine with rapid acting analogs is a good substitute for insulin pump therapy using one basal rate, and twice daily insulin detemir with rapid acting analogs might be equivalent to insulin pump therapy using two basal rates. Patients requiring more than two basal rates are likely to benefit from their insulin pump even when compared to the most up to date insulin injection therapy. Also, those with a lifestyle characterized by unpredictable changes in physical activity can achieve an acute decrease in basal insulin supply to accommodate decreased insulin needs during and following physical activity far more easily by pump therapy than by injection therapy. Whether patients in poor control may experience lower A1c values when on pump therapy than on injection therapy with rapid and long acting analogs remains to be established. All this of course leaves a very important indication for insulin pump therapy unaffected, i.e. patient preference. In the light of the burden of disease associated with type 1 diabetes, the importance of this indication can hardly be overestimated.

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