A cluster randomised trial, cost-effectiveness analysis and psychosocial evaluation of insulin pump therapy compared with multiple injections during flexible intensive insulin therapy for type 1 diabetes: the REPOSE Trial

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Scientific summary

Comparison of insulin pump therapy with MDIs for T1DM: The REPOSE Trial

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Scientific summary

Background

People with type 1 diabetes mellitus (T1DM) require insulin therapy to sustain life. Insulin is generally administered using multiple daily injections (MDIs), but can also be delivered using an infusion pump (continuous subcutaneous insulin infusion). Pump therapy is a more costly option, but has potential benefits. The UK National Institute for Health and Care Excellence (NICE) has approved the use of pumps only for patients with the greatest need (such as inability to achieve reasonable control without hypoglycaemia). Far fewer UK adults use pumps than in comparable countries. Previous trials of pump therapy have been small and of short duration, and have failed to control for training in flexible insulin therapy.

Objectives

We aimed to assess the clinical effectiveness and cost-effectiveness of insulin pump therapy compared with MDIs for people with T1DM, when both have received high-quality structured education.

The specific objectives were to:

1. measure, over 2 years, (1) biomedical, (2) psychosocial (quantitative and qualitative) and (3) adverse event (AE) outcomes
2. undertake a cost-effectiveness analysis to determine whether or not the marginal benefits of pump therapy over optimised MDI (if demonstrated) are commensurate with the marginal costs, as reflected in a cost per quality-adjusted life-year (QALY) acceptable to NICE
3. conduct a mixed-methods psychosocial evaluation of pump therapy in order to identify factors that predict and/or help explain outcomes on pump therapy.

Methods

Design

We undertook a pragmatic, multicentre, open-label, parallel-group cluster randomised controlled trial, with embedded cost-effectiveness analysis and mixed-methods psychosocial evaluation. Participants were allocated a place on a 1 week-long DAFNE (Dose Adjustment For Normal Eating) course in flexible insulin therapy. The course groups were then randomly allocated in pairs to either pump or MDI treatment, with allocation concealed. Following the course, participants received the trial treatment for 2 years.

Setting and participants

Eight secondary care diabetes centres in the UK took part (five in England and three in Scotland). DAFNE courses (clusters) comprised between five and eight participants. Participants were adults with T1DM for at least 12 months, willing to undertake intensive insulin therapy, with self-monitoring of blood glucose levels, carbohydrate counting and insulin self-adjustment, who had no preference for either pump or MDI and had a need for structured education to optimise diabetes control. People were excluded if they had already completed a diabetes education course or used a pump within the past 3 years, or had strong clinical indications or a strong desire for pump therapy.

Interventions

Participants in the MDI arm attended a standard DAFNE structured education course. Courses were conducted over five consecutive days and were delivered to groups of five to eight adults in an outpatient

setting. Participants in the pump arm attended a modified DAFNE course, which had been tested in a pilot study. The 5-day structure of the course was maintained, while incorporating the additional skills and learning outcomes that were considered necessary to use pumps successfully. The need to introduce 'pump skills' required an additional pre-course group session, delivered 1–3 weeks before the 'proper' DAFNE course. All of the participants were invited to an additional DAFNE follow-up group session at 6 weeks post course. MDI participants used insulin analogues. Pump participants used a Medtronic Paradigm® Veo™ (Medtronic, Watford, UK) insulin pump, loaded with insulin aspart (NovoRapid, Novo Nordisk, Gatwick, UK). All of the participants had access to a bolus calculator to aid calculation of insulin doses.

Outcome measures

Clinical outcomes

The primary outcome was the change in glycated haemoglobin (HbA_{1c}) at 2 years in those participants whose baseline HbA_{1c} was $\geq 7.5\%$ (58 mmol/mol). The key secondary outcome was the proportion of all participants meeting the NICE target of HbA_{1c} of $\leq 7.5\%$ at 2 years. Other outcomes measured at 6, 12 and 24 months included moderate and severe hypoglycaemia, insulin dose, body weight, proteinuria and diabetic ketoacidosis.

All analyses were intention to treat (ITT) unless stated otherwise. A per-protocol analysis was also performed, excluding participants who had switched treatment.

Health economic outcomes

Two economic analyses were undertaken: the Economic Evaluation alongside the Clinical Trials (EEACT) and a model-based evaluation of lifetime outcomes. Both analyses took a UK NHS and Personal Social Services perspective. All costs and health benefits were discounted at a rate of 3.5%. The yearly cost of insulin pump therapy, including the cost of insulin pumps and consumables, was estimated using a survey of REPOSE Trial centres. The economic analysis alongside the trial took a 2-year time horizon, and the model-based evaluation took a lifetime time horizon. Both economic analyses measured outcomes in terms of an incremental cost-effectiveness ratio (ICER).

The EEACT used EuroQol-5 Dimensions (EQ-5D) data collected in REPOSE to construct a QALY for each trial participant and estimate their use of NHS resources. In the base case, differences in cost and QALYs between the two trial arms were estimated in the ITT population. Uncertainty in the economic analysis alongside the trial was explored using deterministic sensitivity analyses. In the deterministic sensitivity analyses, the effects of the cost of insulin pumps and consumables, imputing missing data and estimating the effects in the per-protocol population were explored.

The Sheffield Type 1 Diabetes Policy Model version 1.3, henceforth 'the model', was used to estimate the lifetime costs and QALYs associated with both trial arms. The model is an individual-level simulation that includes tracking of risk factors over time, including HbA_{1c}, and the subsequent occurrence of clinical events, including all microvascular, macrovascular and AEs associated with T1DM. Uncertainty in the long-term modelling was explored using probabilistic and deterministic sensitivity analyses. In the deterministic sensitivity analyses, the effects of the cost of insulin pumps and consumables, the use of different estimates of clinical effectiveness and the effects in different participant subgroups were explored.

Psychosocial outcomes

We used both quantitative (questionnaires) and qualitative (interviews) methods. Quantitative psychosocial outcomes were collected using participant self-report questionnaires at 6, 12 and 24 months. We measured diabetes-specific quality of life (QoL) [Diabetes Quality of Life (DSQOL) scale], generic QoL [World Health Organization Quality of Life Abbreviated Questionnaire (WHOQOL-BREF), Short Form questionnaire-12 items (SF-12) and EQ-5D], fear of hypoglycaemia (Hypoglycaemia Fear Survey), diabetes treatment satisfaction [Diabetes Treatment Satisfaction Questionnaire (DTSQ)], and anxiety and depression (Hospital Anxiety and Depression Scale). We undertook in-depth qualitative interviews with participants and staff at 2 weeks post course and again with participants at 6 months post course.

Results

Between November 2011 and April 2013, we randomised 46 courses comprising 317 participants, aged 18–77 years, of whom 267 attended a DAFNE course (132 pump and 135 MDI). A total of 260 participants was included in the ITT analysis set, of which 235 (119 pump and 116 MDI) had baseline HbA_{1c} of ≥ 7.5%. Among these, the mean HbA_{1c} change at 2 years in the pump group was a decrease of 0.85% (9.3 mmol/mol), whereas the mean decrease in the MDI group was 0.42% (4.5 mmol/mol). After adjusting for centre, DAFNE course and baseline HbA_{1c}, and accounting for missing data, the mean difference (MD) in HbA_{1c} change at 2 years in favour of the pump group was –0.24% [95% confidence interval (CI) –0.53% to 0.05%] or –2.7 mmol/mol (95% CI –5.8 to 0.5 mmol/mol; $p = 0.098$). The treatment difference was larger for the per-protocol analysis; MD in change of –0.36% (95% CI –0.64% to –0.07%) or –3.9 mmol/mol (95% CI –7.0 to –0.8 mmol/mol) in favour of the pump ($p = 0.015$). The proportion of participants with HbA_{1c} of ≤ 7.5% (58 mmol/mol) at 2 years was similar across the groups: 29 (22.7%) in pump and 25 (20.8%) in MDI, translating to an odds ratio of 1.26 (95% CI 0.62 to 2.58; $p = 0.523$). The number of severe hypoglycaemia episodes/participant episodes per year was 25/0.10 in the pump group and 24/0.10 in the MDI group. After adjusting for centre, DAFNE course, baseline HbA_{1c} and presence of at least one severe hypoglycaemic episode in the 12 months before baseline, there were no statistically significant differences between the treatment groups [incidence rate ratio (IRR) 1.13, 95% CI 0.51 to 2.51; $p = 0.766$]. Across both treatment groups, the IRR for the number of severe hypoglycaemic episodes in the 24-month follow-up, compared with the year before baseline, was 0.46 (95% CI 0.24 to 0.89; $p = 0.021$).

The annual cost of an insulin pump and insulin pump consumables was estimated to be £2060. In the EEACT base case, insulin pump therapy generated fewer QALYs (–0.004) at a higher cost (£2959) than MDI. This meant that in the base case the insulin pump therapy was dominated by MDI. In the long-term modelling base case, insulin pump therapy, compared with MDI, generated more discounted lifetime QALYs (0.1447) at a higher discounted lifetime cost (£20,448). The ICER was £141,312 per QALY gained. The most favourable ICER was in the sensitivity analysis, for which the cost of insulin pumps and insulin pump consumables was reduced by 50% in the long-term model. In this sensitivity analysis, the ICER was £46,578 per QALY gained. This ICER is above the usual cost-effectiveness threshold range of £20,000–30,000 per QALY gained used by NICE.

The quantitative psychosocial questionnaires had high completion rates at 2 years (90%). In total, 45 participants (25 pump and 20 MDI) and 18 educators took part in qualitative interviews post course. Three participants could not be contacted for the follow-up interview. The quantitative measures showed improvement across most outcomes and time points for both treatment groups. The generic quality-of-life and health status instruments (SF-12, WHOQOL-BREF and EQ-5D) and the HADS score for depression and anxiety showed no between-group differences. The overall DSQOL score (on a 100-point scale) was improved by mean (standard deviation) of 8.2 (13.1) points in the pump group and 4.2 (13.2) points in the MDI group, translating to a MD in improvement of 3.8 points (95% CI 1.1 to 6.5 points; $p = 0.006$). The improvement in DSQOL diet restrictions was larger for the pump group than the MDI group at both 12 and 24 months (12-month adjusted MD in change from baseline –4.1, 95% CI –7.2 to –1.0; $p = 0.010$; 24-month adjusted MD in change from baseline –5.1, 95% CI –8.6 to –1.6; $p = 0.004$; lower scores represent better outcomes). A slightly smaller difference was observed at 6 months, which was just outside the 5% significance threshold (MD –3.3, 95% CI –6.9 to 0.2; $p = 0.061$). The pump group also had a better improvement in DSQOL daily hassle or functions at both 12 and 24 months; at 24 months the score had decreased by 10 points in the pump group compared with 4 points in the MDI group (adjusted MD –6.3, 95% CI –10.9 to –1.8; $p = 0.006$). Participants in the pump group had better improvement in treatment satisfaction at all time points. The difference was statistically significant at 12 and 24 months only ($p = 0.067$ at 6 months; $p < 0.001$ at both 12 and 24 months). These observations were supported by findings from the qualitative interviews. A recurrent theme was that after doing the DAFNE course, patients in both arms felt more in control and more confident in self-management. However, those on

pump therapy reported some additional benefits from the pump, including increased flexibility of lifestyles, avoidance of the frequent injections with MDI, more effective self-management around sporting activities and dietary variations, and the ability to administer very small doses of insulin, with different basal rates, at different times of day and night.

Conclusions

Insulin pump therapy did not provide additional significant improvement in glycaemic control compared with MDI, when both groups had received structured education in flexible insulin therapy. Our study suggests that extending the availability of pumps to adults with T1DM in suboptimal glycaemic control, and no firm desire to use this form of insulin delivery, is unlikely to result either in lower levels of glycaemia, as measured by HbA_{1c}, or lower rates of hypoglycaemia, and is unlikely to be cost-effective.

Implications for health care

1. Extending the availability of pumps to adults with T1DM with suboptimal glycaemic control, and no firm desire to use them, is unlikely to result either in lower levels of glycaemia, as measured by HbA_{1c}, or lower rates of hypoglycaemia or be cost-effective.
2. It is important that REPOSE is not considered to be a 'negative trial' of pumps. The failure to show a significant benefit of pump over MDI was because both groups improved following DAFNE training.
3. The current clinical pathway, as proposed by NICE, seems appropriate, in which people desiring improved diabetes control should initially undertake structured training in flexible insulin therapy with MDI alone.
4. The NICE guideline on the importance of providing structured training programmes is reinforced. Most individuals with T1DM are still not being offered evidence-based structured education despite considerable evidence for its effectiveness.
5. The evidence from REPOSE suggests that far more people with T1DM should participate in high-quality, structured self-management training. They may recognise the limitations of insulin delivery by MDI only once they are attempting to maintain flexible intensive insulin therapy following training. Those individuals could then be offered pump therapy to help them reach the stringent glucose target, as recommended by NICE, which is necessary to achieve an optimal HbA_{1c} or overcome problematic hypoglycaemia.

Recommendations for future research

1. It is important to understand why so few patients achieve the target for glycaemic control of HbA_{1c} of $< 7.5\%$, particularly as there is evidence that levels of glycaemic control are worse in the UK than in other European countries.
2. There is an urgent need to explore the barriers to successful self-management in adults with TD1M in the UK and understand why accessing appropriate training is left so long and rates of participation are so low.
3. Further research is needed to explain why some people do so well after training, whereas others do not.

Trial registration

This trial is registered as ISRCTN61215213.

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