Integrated sensor-augmented pump therapy systems [the MiniMed® Paradigm™ Veo system and the Vibe™ and G4® PLATINUM CGM (continuous glucose monitoring) system] for managing blood glucose levels in type 1 diabetes: a systematic review and economic evaluation

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Scientific summary

Pump therapy for managing blood glucose levels in type 1 diabetes

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Scientific summary

Background

Diabetes affects an estimated 3.75 million people in the UK. Approximately 250,000 of these 3.75 million people have type 1 diabetes mellitus (T1DM).

This assessment will focus on the use of integrated sensor-augmented pump therapy systems for people with T1DM.

The characteristic feature of diabetes is high blood glucose (BG) levels, also known as hyperglycaemia. T1DM is caused by the destruction of the pancreatic beta cells that produce insulin, and the mainstay of treatment is injection of insulin, which is necessary to sustain life. Intensive insulin treatment, aimed at tightly controlling BG levels, reduces the risk of the long-term complications of diabetes, such as retinopathy and renal disease. Intensive insulin treatment is a package of care consisting of either multiple daily insulin injections (MDIs) or continuous subcutaneous insulin infusion (CSII) with an insulin pump, frequent testing of BG, self-adjustment of insulin dosages in response to BG levels and lifestyle interventions, such as a restricted diet and undertaking required levels of physical activity.

In recent years, meters for the continuous monitoring of interstitial fluid glucose have been introduced to help people with T1DM to achieve better control of their disease. Increasingly sophisticated integrated methods of glucose monitoring and insulin delivery are designed to provide a closer approximation to the body's natural system and achieve acceptable glycaemic control while minimising the risk of hypoglycaemic episodes. Current continuous glucose monitoring (CGM) systems rely on the user taking action, and this may not occur, particularly at night. Hypoglycaemia that occurs at night is known as nocturnal hypoglycaemia. Alarms may wake people up, but those with nocturnal hypoglycaemic events often sleep through them and recurrent hypoglycaemic events can lead to hypoglycaemia unawareness.

A recent development in CGM/pump technology, available in the UK since 2009, is the MiniMed® Paradigm™ Veo system (Medtronic Inc., Northridge, CA, USA), wherein the CGM device can stop (suspend) the insulin infusion from the pump for up to 2 hours. After that, insulin infusion is restored at a basal rate.

The population considered for the current assessment comprised adults and children with T1DM. The interventions assessed (integrated CGM and insulin pump systems with or without a suspend function) aim to provide better monitoring and dose adjustment and hence achieve acceptable glycaemic control while minimising hypoglycaemic episodes.

Objective

The overall objective of this project was to summarise the evidence on the clinical effectiveness and cost-effectiveness of the MiniMed Paradigm Veo system and the Vibe™ (Animas® Corporation, West Chester, PA, USA) and G4® PLATINUM CGM system (Dexcom Inc., San Diego, CA, USA) for the management of T1DM in adults and children.

To address this objective, we assessed the clinical effectiveness and cost-effectiveness of integrated insulin pump systems compared with:

- CSII with self-monitoring of blood glucose (SMBG) by capillary blood testing (CSII + SMBG)
- MDIs with SMBG by capillary blood testing (MDI + SMBG)
- non-integrated, stand-alone CSII and CGM (CSII + CGM)
- MDIs with CGM (MDI + CGM).

Methods

Assessment of clinical effectiveness

The study populations eligible for inclusion were adults, including pregnant women, and children with T1DM, and the relevant setting was self-use supervised by primary or secondary care. The interventions are described above (see *Background*) and the main outcomes were glycated haemoglobin (HbA_{1c}) levels, the frequency of hyperglycaemic events and the frequency of hypoglycaemic events.

We searched 14 databases, three trial registries and two conference proceedings from inception up to September 2014. Data relating to study details, participants, intervention and comparator tests, and outcome measures were extracted, using a piloted, standard data extraction form. The assessment of the methodological quality of each included study was based on the Cochrane Collaboration quality assessment checklist.

In the absence of randomised controlled trials directly comparing the MiniMed Paradigm Veo System or an integrated CSII + CGM system, such as the Vibe and G4 PLATINUM CGM system, with comparator interventions, indirect treatment comparisons were performed, if possible. Where meta-analysis was considered unsuitable for some or all of the data identified, we employed a narrative synthesis.

Assessment of cost-effectiveness

The IMS Centre for Outcomes Research and Effectiveness diabetes model (IMS CDM) version 8.5 (IMS Health, Danbury, CT, USA) was used for this assessment. This is an internet-based, interactive simulation model that predicts the long-term health outcomes and costs associated with the management of T1DM and type 2 diabetes mellitus. The model consists of 15 submodels designed to simulate diabetes-related complications, non-specific mortality and costs over time. As the model simulates individual patients over time, it updates risk factors and complications to account for disease progression.

Given the degree of validation of the model, and in order to be in line with the updated T1DM National Institute for Health and Care Excellence (NICE) guideline NG17 [National Institute for Health and Care Excellence. *Type 1 Diabetes in Adults: Diagnosis and Management. NICE Guideline (NG17)*. London: NICE; 2015. URL: www.nice.org.uk/guidance/indevelopment/gid-cgwaver122/documents (accessed 15 January 2015)] it was considered important not to use an alternative model or develop a de novo cost-effectiveness model for this evaluation. When possible, we estimated input parameters based on the studies identified in the systematic review. This was done to properly reflect our base-case population (i.e. those with T1DM eligible for an insulin pump). We used the results of indirect comparisons of change in HbA_{1c} levels and the rate ratios of severe hypoglycaemic events to model the treatment effects.

As the IMS CDM is not suitable for modelling long-term outcomes for children and pregnant women (because the background risk adjustment/risk factor progression equations are all based on adults), we had to limit the population for assessment to adults only.

The impact of the uncertainty about a number of input parameters and model assumptions on the model outcomes was explored through probabilistic sensitivity analyses and scenario analyses.

Results

Fifty-four publications resulting from 19 studies were included in the review. Two studies compared the MiniMed Paradigm Veo system with an integrated CSII + CGM system or with CSII + SMBG, respectively. Seven other studies compared an integrated CSII + CGM system with CSII + SMBG (three studies) or with MDI + SMBG (four studies). The remaining studies compared CSII + SMBG with MDI + SMBG (10 studies). None of the studies included a treatment arm with CSII + CGM or MDI + CGM as comparators. Although several studies included the integrated CSII + CGM system as a treatment arm, it is important to note that

none of these studies looked at the Vibe and G4 PLATINUM CGM system; in the included studies, the integrated CSII + CGM system was always a MiniMed Paradigm pump with an integrated CGM system.

Twelve studies reported data for adults, five studies reported data for children and five studies reported data for mixed populations (adults and children). Two of these studies reported data for all three groups. One study included pregnant women.

Most studies (11 out of 19) were rated as having a high risk of bias, four studies were rated with an unclear risk of bias and another four studies were rated as having a low risk of bias.

Twelve studies were included in the analyses for adults. The main conclusion from these trials is that the MiniMed Paradigm Veo system reduces hypoglycaemic events in adults more than the integrated CSII + CGM system does, without any differences in other outcomes, including changes in HbA_{1c} levels. Nocturnal hypoglycaemic events occurred 31.8% less frequently in the MiniMed Veo group than in the integrated CSII + CGM group {1.5 events per patient per week [standard deviation (SD) 1.0 event per patient per week] vs. 2.2 events per patient per week (SD 1.3 events per patient per week); $p < 0.001$}. Similarly, the MiniMed Veo group had significantly lower rates of combined daytime and night-time events than the integrated CSII + CGM group [3.3 events per patient per week (SD 2.0 events per patient per week) vs. 4.7 events per patient per week (SD 2.7 events per patient per week); $p < 0.001$]. Indirect evidence suggests that that there are no significant differences between the MiniMed Paradigm Veo system, CSII + SMBG and MDI + SMBG with regard to change in HbA_{1c} levels at 3-month follow-up. However, if all studies are combined (i.e. combining different follow-up times and including mixed populations), the MiniMed Paradigm Veo system is significantly better than MDI + SMBG, with regard to HbA_{1c} levels [weighted mean difference (WMD) –0.66%; 95% confidence interval (CI) –1.05% to –0.27%].

For the integrated CSII + CGM system versus other treatments, head-to-head results showed significant effects, with regard to HbA_{1c} levels, in favour of the integrated CSII + CGM system compared with MDI + SMBG (WMD –1.1%; 95% CI –1.46% to –0.74%), but not if compared with CSII + SMBG (WMD –0.05%; 95% CI –0.31% to 0.21%); and significant results, with regard to quality of life, in favour of the integrated CSII + CGM system compared with MDI + SMBG (WMD 8.60; 95% CI 6.28 to 10.92) or with CSII + SMBG (WMD 5.90; 95% CI 2.22 to 9.58) were also found.

When comparing CSII versus MDI, only one of six trials showed a significant difference between CSII + SMBG and MDI + SMBG in terms of a change in HbA_{1c} levels: after 16 weeks of the trial, mean HbA_{1c} levels were 0.84% lower (mean = –0.84%, 95% CI –1.31% to –0.36%) lower in the CSII + SMBG group than in the MDI + SMBG group. No differences in the number of severe hypoglycaemic events were found in any trial.

Six studies were included in the analyses for children. None of the studies directly compared the MiniMed Paradigm Veo system with the integrated CSII + CGM system. An indirect comparison was possible using data obtained from 6-month follow-up from two of these studies, but only for HbA_{1c} levels, which showed no significant difference between groups.

One study compared the MiniMed Paradigm Veo system with CSII + SMBG. The only significant difference between treatment groups was the rate of moderate and severe hypoglycaemic events, which favoured the MiniMed Paradigm Veo system.

One study compared the integrated CSII + CGM system with CSII + SMBG. This trial found no significant difference in HbA_{1c} levels between groups [mean difference (MD) after 6 months of 0.4894% (standard error 0.2899%); $p = 0.10$]. One study compared the integrated CSII + CGM system with MDI + SMBG. This trial showed a significant difference in HbA_{1c} levels in favour of the integrated CSII + CGM system (MD after 12 months –0.5%; 95% CI –0.8% to –0.2%), but no significant difference in the number of children achieving HbA1c levels of $\leq 7\%$ (10 out of 78 vs. 4 out of 78; $p = 0.15$). Hyperglycaemia (as determined by BG levels of > 250 mg/dl) was significantly less common in the integrated CSII + CGM

group than in the MDI + SMBG group [area under the curve (AUC) 9.2 (SD 8.08) vs. 17.64 (SD 14.62); $p < 0.001$], but there was no significant difference in the occurrence of hypoglycaemia (as determined by BG levels of < 70 mg/dl) in these groups [AUC 0.23 (SD 0.41) vs. 0.25 (SD 0.41); $p = 0.79$]. There were no significant differences between groups for other outcomes.

For pregnant women, we found only one trial comparing CSII + SMBG with MDI + SMBG, which is not relevant to the decision problem.

The comparator MDI + CGM was not included in the cost-effectiveness analyses, since no evidence was found. In the absence of data comparing the clinical effectiveness of integrated CSII + CGM systems with stand-alone CSII + CGM systems, we assumed, in our cost-effectiveness analyses, that both technologies would be equally effective. The immediate consequence of this assumption is that stand-alone CSII + CGM systems always dominate the integrated CSII + CGM systems since stand-alone systems are cheaper, according to our estimated cost, but equally effective.

Overall, the cost-effectiveness results suggest that technologies which use SMBG (either with CSII or MDIs) are more likely to be cost-effective than the technologies which use CGM, since the higher quality of life and/or life expectancy provided by the latter do not compensate for the difference in costs. The MiniMed Paradigm Veo is extendedly dominated by stand-alone CSII + CGM. This means that CSII + CGM is more effective than MiniMed Paradigm Veo, but also better value, that is that the increase in cost compared with the next most effective choice, which is CSII + SMBG, is less for CSII + CGM than for the MiniMed Paradigm Veo system. We estimated that the incremental cost-effectiveness ratio (ICER) of stand-alone CSII + CGM compared with the next most effective choice, CSII + SMBG, is £660,376 and the ICER of CSII + SMBG compared with the least effective choice, MDI + SMBG, is £52,381. Thus, assuming a common threshold of £30,000 per quality-adjusted life-year (QALY) gained, MDI + SMBG, while being the least clinically effective option, would be considered the optimal choice; when uncertainty is taken into account, at that threshold, MDI + SMBG would have a 98% probability of being the optimal choice.

The finding that CSII + CGM is more effective than the MiniMed Paradigm Veo system might appear to contradict the clinical effectiveness conclusions, but this is explained by the fact that effectiveness is affected by both the difference in hypoglycaemic event rate and HbA_{1c} levels. Although the evidence shows that MiniMed Paradigm Veo is probably better in terms of reducing the hypoglycaemic event rate, it does show a small, albeit not statistically significant, disadvantage in terms of HbA_{1c} levels. Even this small difference seems to be sufficient, as a result of the consequences of hyperglycaemia, to outweigh the difference in hypoglycaemia, which is relatively rare and generally has less severe consequences. However, all of these results should be interpreted with caution as some studies on which effect estimates were based included all T1DM patients, whereas others included patients who had been on a pump for at least 6 months already and others included patients without experience of using a pump but with poor glycaemic control at baseline.

These results remained largely unchanged in scenario analyses, used to assess the potential impact of various input parameters on the model outcomes. Even when a large array of scenarios is considered, MDI + SMBG would be considered the optimal choice in all instances, assuming a threshold of £30,000 per QALY gained.

Conclusions

Overall, the evidence seems to suggest that the MiniMed Paradigm Veo system reduces hypoglycaemic events more than other treatments, without any differences in other outcomes, including changes in HbA_{1c} levels. In addition, we found significant results in favour of the integrated CSII + CGM system over MDI + SMBG with regard to HbA_{1c} levels and quality of life. However, the evidence base was poor. The quality of the included studies was generally low, often with only one study comparing treatments in a

specific population at a specific follow-up time. In particular, the evidence for the two interventions of interest was limited, with only one study comparing the MiniMed Paradigm Veo system with an integrated CSII + CGM system and only one study comparing the MiniMed Paradigm Veo system with CSII + SMBG in a mixed population.

Cost-effectiveness analyses indicated that MDI + SMBG is the option most likely to be cost-effective, given the current threshold of £30,000 per QALY gained, whereas integrated CSII + CGM systems and MiniMed Paradigm Veo are dominated and extendedly dominated, respectively, by stand-alone CSII + CGM. Scenario analyses, used to assess the potential impact of changing various input parameters, did not alter these conclusions. No cost-effectiveness modelling was conducted for children or pregnant women.

Suggested research priorities

In adults, a trial comparing the MiniMed Paradigm Veo system with CSII + SMBG is warranted. Similarly, a trial comparing the Vibe and G4 PLATINUM CGM system, or any integrated CSII + CGM system, with CSII + SMBG is warranted. In children, a trial comparing the MiniMed Paradigm Veo system with the Vibe and G4 PLATINUM CGM system, or any integrated CSII + CGM system, is warranted, as is a trial comparing an integrated CSII + CGM system with CSII + SMBG. For pregnant women, trials comparing the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system, or any integrated CSII + CGM system, with other interventions are warranted.

Future trials should include longer-term follow-ups and ratings on the European Quality of Life-5 Dimensions scale at various time points with a view to informing improved cost-effectiveness modelling.

Study registration

This study is registered as PROSPERO CRD42014013764.

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