Efficacy and safety comparison of rapid-acting insulin aspart and regular human insulin in the treatment of type 1 and type 2 diabetes mellitus: a systematic review

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CRD summary
This well-conducted review found that rapid-acting insulin aspart resulted in moderately better metabolic control and treatment satisfaction than regular (short-acting) human insulin for patients with type 1 diabetes, and improvement in postprandial glucose for patients with type 2 diabetes. These conclusions are likely to be reliable.

Authors' objectives
To compare clinical outcomes of treatment with insulin aspart (rapid-acting insulin analogue) with those of regular human insulin in patients with type and type 2 diabetes.

Searching
MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and CRD databases (not specified) were searched up to July 2009. References of retrieved articles were searched.

Study selection
Randomised controlled trials (RCTs) that compared insulin aspart with regular human insulin, or biphasic insulin aspart with biphasic human insulin, in patients with type 1 or type 2 diabetes were eligible for inclusion. Eligible trials had to include at least four weeks follow-up. Trials of less than 10 patients or of patients with gestational or secondary diabetes were excluded. Outcomes assessed by the review included levels of fasting glucose, postprandial glucose and glycated haemoglobin levels. Data on weight gain, quality of life, and incidence of hypoglycaemia were also considered.

Included trials assessed adults and children with type 1 diabetes and adults with type 2 diabetes. Mean baseline glycated haemoglobin ranged from 6.9% to 9.8%. Mean baseline body mass index of patients with type 2 diabetes ranged from 28 to 32kg/m² and from 21.2 to 35kg/m² or more in patients with type 1 diabetes. Most trials administered insulin by multiple daily subcutaneous injections; three studies used biphasic daily insulin injections and two used a continuous subcutaneous insulin infusion. Most trials adjusted insulin doses using target values of fasting glucose, preprandial glucose, and postprandial glucose levels. Treatment duration ranged from two to 12 months.

Two reviewers independently selected studies for inclusion; disagreements were resolved through discussion or referral to a third reviewer.

Assessment of study quality
Trial quality was assessed using the Jadad scale for randomisation, blinding and withdrawals; summary quality scores were not calculated. Information on concealment of treatment allocation was also considered.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Two reviewers independently extracted data to calculate relative risks (RRs) for dichotomous data, and mean differences (MDs) and standardised mean differences (SMDs) for continuous data, with 95% confidence intervals (CIs). If data on means and standard deviations were not reported, attempts were made to extract values from aggregated data.

Methods of synthesis
Summary relative risks, weighted mean differences (WMD) and standardised mean differences were calculated using a fixed-effect model if data were homogeneous (p>0.10), otherwise a random-effects model was used. Heterogeneity was assessed using $I^2$ and $X^2$.

Results were stratified according to whether patients had type 1 or type 2 diabetes. Subgroup analysis was conducted to
investigate the influence of insulin regimen.

**Results of the review**

Twenty-eight RCTs (number of participants unclear) were included in the review. Eighteen trials were parallel group and 10 used a cross-over design. Only four trials were double blinded and only four had adequate concealment of treatment allocation.

**Type 1 diabetes (18 RCTs)**

Insulin aspart resulted in a significant decrease in glycated haemoglobin levels (WMD -0.11%, 95% CI -0.16 to -0.06; I²=17.5%; 13 RCTs) compared with regular human insulin. When the results were stratified according to insulin regimen, a significant difference remained for insulin aspart given as continuous subcutaneous insulin infusion (WMD -0.31%, 95% CI -0.55 to -0.08) and as a basal bolus (WMD -0.12%, 95% CI -0.17 to -0.06) but not between mixtures.

Insulin aspart was associated with improvements in post-breakfast glucose (WMD -1.43mmol/L, 95% CI -1.75, -1.11; five RCTs), post-lunch glucose (WMD -1.11mmol/L, -1.61 to -0.61; five RCTs) and post-dinner glucose (WMD -0.97mmol/L, -1.25 to -0.69; six RCTs), but there was no significant difference in fasting glucose levels compared with regular human insulin.

There was an increased risk of hypoglycaemic episode with insulin aspart (RR 1.06, 95% CI 1.01 to 1.10; six RCTs) but no difference in the risk of nocturnal or severe hypoglycaemic episodes.

Patients who received insulin aspart were significantly more satisfied with treatment based on Diabetes Treatment Satisfaction Questionnaire scores (SMD 0.30, 95% CI 0.20 to 0.40; three RCTs) and with treatment flexibility based on the same questionnaire (WMD 0.31, 95% CI 0.15 to 0.47; two RCTs).

**Type 2 diabetes (11 RCTs)**

There were no significant differences in glycated haemoglobin levels between insulin aspart and regular human insulin groups, although after exclusion of one trial (in which all participants used a continuous glucose monitoring system) a significant improvement was found with insulin aspart (WMD -0.10%, 95% CI -0.19 to -0.02; eight RCTs).

Insulin aspart was associated with improvements in daily mean postprandial glucose (WMD -1.18mmol/L, 95% CI -1.88, -0.47; three RCTs), post-breakfast glucose (WMD -0.83mmol/L, -1.45 to -0.21; 3 RCTs) and post-lunch glucose (WMD -1.32mmol/L, -2.16 to -0.49; one RCTs), but there was no significant difference in fasting glucose levels compared with regular human insulin.

There was no difference in the risk of any type of hypoglycaemic episode.

**Authors’ conclusions**

Treatment with insulin aspart in patients with type 1 diabetes resulted in moderately better metabolic control and treatment satisfaction than with regular human insulin. For patients with type 2 diabetes, insulin aspart improved postprandial glucose but not other outcomes.

**CRD commentary**

The review addressed a clear question and inclusion criteria were defined. The literature search was limited to three databases with no further attempts to locate additional published or unpublished data. It was unclear whether any language or publication restrictions were applied. Appropriate steps were taken to minimise bias and errors during the review.

Trial quality was assessed using appropriate criteria; the results of the assessment were reported. Appropriate methods were used to pool data including assessment of heterogeneity.

The authors’ conclusions were supported by the results of the review and are likely to be reliable.
Implications of the review for practice and research
The authors did not state any implications for practice or research.

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