Prandial premixed insulin analogue regimens versus basal insulin analogue regimens in the management of type 2 diabetes: an evidence-based comparison
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CRD summary
This review investigated the efficacy and safety of prandial premixed insulin analogue regimens compared with basal insulin analogue regimens in the management of type 2 diabetes. The authors concluded that the results indicated better glycaemic control with premixed insulin regimens than with basal insulin regimens. In view of the methodological limitations of the review, this conclusion should be interpreted with caution.

Authors' objectives
To investigate the efficacy and safety of prandial premixed insulin analogue regimens compared with basal insulin analogue regimens (with or without a prandial insulin analogue) in the management of type 2 diabetes.

Searching
MEDLINE and EMBASE were searched between 1995 and 2007 for reports in the English language; the search strategy was reported. The authors also searched the reference lists of the articles, and abstracts from the 2005 and 2006 meetings of the American Diabetes Association and the European Association for the Study of Diabetes, for relevant publications.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review. Both parallel and crossover designs were included.

Specific interventions included in the review
Studies that compared prandial premixed insulin analogue regimens (which provide both basal and prandial insulin coverage) with basal insulin analogue regimens (with or without an additional prandial insulin analogue) were eligible for inclusion. Premixed insulin could be administered 1 to 3 times daily while basal insulin could be given once or twice daily. The minimum treatment duration for inclusion was 12 weeks. Studies which employed concomitant additional oral antihyperglycaemic medication were eligible for inclusion, as were those which did not. In the included studies, 2- or 3-times-daily premixed insulin analogue regimens were compared with once-daily basal insulin analogue regimens (with and without additional prandial insulin analogue). Premixed insulin analogues that contained 75%/25%, 70%/30% and 50%/50% of basal and prandial insulin were investigated. Treatment duration in the included studies ranged from 24 to 32 weeks. The majority of included studies used additional oral antihyperglycaemic medication, including metformin and pioglitazone.

Participants included in the review
Studies of patients with type 2 diabetes, diagnosed using valid criteria, were eligible for inclusion. Participant characteristics varied among the included studies, e.g., in terms of baseline glycosylated haemoglobin (HbA1c) level, insulin naivety and concomitant medication.

Outcomes assessed in the review
Studies that used ‘well-accepted’ outcomes such as HbA1c, hypoglycaemia, and pre- and post-prandial blood glucose were eligible for inclusion. The outcomes assessed were HbA1c level, patients achieving HbA1c target, post-prandial blood glucose, fasting blood glucose, rate of hypoglycaemia, total daily insulin dose and change in body weight.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.
Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
The studies were grouped according to the interventions and presented in a narrative accompanied by tables. Due to clinical heterogeneity in the included studies, a meta-analysis could not be performed.

How were differences between studies investigated?
Differences between the studies were discussed in the text and were further apparent from the evidence tables.

Results of the review
Seven RCTs (n=1,687) were included in the review.

Twice-daily premixed insulin analogue regimens versus once-daily basal insulin analogue regimens (3 RCTs).
With regard to glycaemic control, the change in HbA1c levels ranged from -1.00 (standard deviation, SD, 0.85) to -2.79 (SD=0.11) percentage points for premixed insulin and from -0.42 (SD=0.92) to -2.36 (SD=0.11) percentage points for basal insulin; the results in each study were statistically significant (p<0.01).

Hypoglycaemia rates, adjusted per 1 year, ranged from 3.4 (SD=6.6) to 8.2 (SD=16.8) for premixed insulin and from 0.7 (SD=2.0) to 5.4 (SD=13.0) for basal insulin; the results in each study were statistically significant (p<0.05).

The total daily insulin dose ranged from 0.42 (SD=0.2) to 0.82 (SD=0.4) U/kg for premixed insulin and from 0.36 (SD=0.18) to 0.57 (SD=0.37) U/kg for basal insulin; the results in each study were statistically significant (p<0.05).

Three-times-daily premixed insulin analogue regimens versus once-daily basal insulin analogue regimens (3 RCTs).
With regard to glycaemic control, the change in HbA1c levels ranged from -0.72 (SD=0.89) to -1.2 (SD=1.1) percentage points for premixed insulin and from -0.3 (SD=1.1) to -0.75 (SD=0.1) percentage points for basal insulin; the results in each study were statistically significant (p<0.01).

Hypoglycaemia rates (2 RCTs) ranged from 0.7 (SD=1.7) to 4.7 (SD=6.35) for premixed insulin and from 0.3 (SD=0.8) to 2.31 (SD=3.24) for basal insulin; the results were statistically significant for both studies (p<0.05).

The total daily insulin dose ranged from 0.35 (SD=0.26) to 0.7 (SD=0.3) U/kg for premixed insulin and from 0.28 (SD=0.21) to 0.6 (SD=0.3) U/kg for basal insulin; the results were statistically significant (p<0.01) (2 RCTs).

Twice-daily premixed insulin analogue regimens versus intensive basal bolus insulin therapy (1 RCT).
With regard to glycaemic control, the change in HbA1c levels was -1.56 (SD not reported) percentage points for premixed insulin and -1.23 percentage points for intensive basal bolus insulin; the results were statistically significant (p<0.01).

Minor hypoglycaemia was noted in about 30% of the patients in both treatment arms, but severe cases were noted in only 5% of the patients receiving intensive basal bolus insulin.

The total daily insulin dose was 0.86 U/kg for premixed insulin and 0.63 U/kg for intensive basal bolus insulin.
Other results (percentage of patients achieving HbA1c target, fasting blood glucose and change in body weight) were reported. Confidence intervals of the results were not reported.

Cost information
The authors reported that a cost-effectiveness analysis, based on the data of one of the included studies, had found long-term improvements in life expectancy and reduced incidence of retinopathy and nephropathy complications associated with a premixed insulin analogue compared with a basal insulin analogue. They also reported an incremental cost-effectiveness ratio of £6,951 per quality-adjusted life-year gained with premixed insulin analogue regimens.

Authors' conclusions
The results suggest that prandial premixed insulin analogue regimens yield better overall, pre- and post-prandial glycaemic control in patients with type 2 diabetes when compared with basal insulin analogue regimens.

CRD commentary
The review addressed a clear question and the inclusion criteria appear appropriate. Relevant sources were searched and search terms were stated. However, no attempt was made to locate unpublished studies, thus raising the possibility of publication bias and the omission of relevant data. The restriction to English language studies might also have resulted in the loss of some relevant data. The authors did not report an assessment of study validity. The methods used to select the studies and extract the data were not described, so it is not known whether efforts were made to reduce reviewer error and bias. The reliability of data derived from the included studies cannot therefore be fully assessed. Details of each included study were given but data on the baseline characteristics (e.g. demographics of the participants, gender or age) were limited. It may thus be difficult to generalise the review findings. Given the small number of studies and the clinical heterogeneity, a narrative synthesis with studies grouped by intervention was appropriate. In view of the above limitations, the conclusion should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors stated that prandial premixed insulin analogues are an effective option for initiating and intensifying insulin therapy in patients with type 2 diabetes.

Research: The authors stated that there is a need to explore how 2- or 3-times-daily premixed insulin analogue therapies compare with a basal insulin analogue when combined with other medications that lower post-prandial glucose levels.

Bibliographic details

Indexing Status
Subject indexing assigned by CRD

MeSH
Administration, Oral; Blood Glucose /drug effects; Diabetes Mellitus, Type 2 /blood /drug therapy; Drug Therapy, Combination; Hemoglobin A, Glycosylated /analysis; Hypoglycemic Agents /administration & dosage /adverse effects; Insulin /administration & dosage /adverse effects /analog & derivatives

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.