Safety and efficacy of glargine compared with NPH insulin for the treatment of type 2 diabetes: a meta-analysis of randomized controlled trials

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CRD summary
This review compared the efficacy of glargine and neutral protamine Hagedorn (NPH) in adults with type 2 diabetes. The authors concluded that there was no statistical difference in terms of glycaemic control, but glargine was associated with lower rates of hypoglycaemia and NPH with slightly less weight gain. This conclusion reflects the evidence presented and is likely to be reliable.

Authors' objectives
To examine the safety and efficacy of glargine and neutral protamine Hagedorn (NPH) insulin in adults with type 2 diabetes.

Searching
MEDLINE (1966 to 2007), EMBASE (1974 to 2007), Cochrane Central Register of Controlled Trials (CENTRAL) and American Diabetes Association abstract database were searched without language restriction. Search terms were reported. Reference lists from retrieved studies and relevant review articles were handsearched and experts were contacted to locate further material.

Study selection
Randomised controlled trials (RCTs) of at least four weeks duration that involved adults with type 2 diabetes treated with NPH insulin or glargine were eligible for inclusion in the review. Outcomes of interest included changes in insulin dose, fasting plasma glucose (FPG), glycated haemoglobin (HbA1c) and body weight from baseline to the end of the trial, and the corresponding variances (or sufficient data to estimate these) according to type of insulin. Approximately half the included participants were male. Mean age was 58.3 years (range 55.5 to 61.5 years). Mean body mass index was 28.4kg/m² (range 24.3kg/m² to 32.3kg/m²). Most studies included participants who were not using insulin. Diabetic treatment history, intervention regimens and treatment durations (mean 27.8 weeks; range four to 52 weeks) varied between the included trials. Definitions of hypoglycaemia varied. The chosen definition for the analysis was the percentage of participants who experienced symptomatic, asymptomatic, nocturnal and severe episodes.

Two reviewers independently selected studies for inclusion in the review. Discrepancies were resolved with the involvement of a third reviewer.

Assessment of study quality
Study quality was assessed in relation to treatment allocation procedures and blinding. Two reviewers independently performed the validity assessment. Disagreements were resolved by discussion.

Data extraction
Mean values for insulin dose, FPG, HbA1c, body weight and hypoglycaemic events were extracted on an intention-to-treat basis. Values were converted to mmol/Ln, percentage or kg in order to calculate the mean net change and 95% confidence interval (CI). Authors were contacted for missing data, where necessary.

Data extraction was performed by two independent reviewers. Disagreements were resolved by discussion.

Methods of synthesis
Mean net changes and 95% CIs were pooled in fixed-effect and random-effects (DerSimonian and Laird) meta-analysis weighted by the reciprocal of the variance. Heterogeneity was assessed using the X² test and explored in subgroup analysis based on HbA1c at baseline, trial size and duration, gender and age distribution, body mass index at baseline and titration regimen. Sensitivity analyses were conducted for each outcome based on trial design and methods.
Publication bias was assessed with a funnel plot.

**Results of the review**

Twelve parallel open label trials were included (n=4,385); two trials were included only in the subgroup analysis. Mean sample size was 366 (range 24 to 756) participants. There was no evidence of publication bias. No statistical heterogeneity was detected in any of the analyses.

There were no statistically significant differences between NPH and glargine in terms of changes in insulin dose, FPG, and HbA1c. The result for body weight favoured NPH and this was statistically significant (-0.33 kg, 95% CI -0.61 to -0.06; five trials).

Patient-reported symptomatic and nocturnal hypoglycaemia was reported to be lower following glargine (p<0.0001), but there was no statistically significant difference in pooled rates between the groups. Subgroup analysis revealed that the mean net change in FPG was significantly lower following treatment with glargine in trials with a duration greater than or equal to 24 weeks (0.261, 95% CI 0.041 to 0.481; eight trials) and in trials that contained a higher proportion of men (0.415, 95% CI 0.175 to 0.655; five trials).

Less weight gain was reported following NPH treatment in trials with sample sizes greater than 422 (-0.599, 95% CI -1.099 to -0.099; two trials) and those with a higher proportion of men (-0.410, 95% CI -0.742 to -0.77; three trials).

In sensitivity analysis, glargine was superior in terms of net change in FPG when two trials were excluded and in terms of lowered HbA1c when another trial was excluded.

**Authors’ conclusions**

There was no difference in glycaemic control between treatments with glargine and NPH insulin in participants with type 2 diabetes. Glargine was associated with lower rates of hypoglycaemia. NPH resulted in slightly less weight gain.

**CRD commentary**

This review addressed a clear question that was supported by potentially reproducible inclusion criteria. The search strategy contained some relevant sources and attempts were made to minimise language bias. It was unclear to what extent unpublished material was sought, but publication bias was explored and found not to be a threat to the review findings. A limited quality assessment was carried out. All aspects of the review process were conducted with sufficient attempts to minimise error and bias. Study details were adequately presented, statistical heterogeneity was assessed and explored and the method of synthesis appeared to be appropriate. The authors' conclusion reflects the evidence presented and is likely to be reliable.

**Implications of the review for practice and research**

**Practice**: The authors did not state any implications for practice.

**Research**: The authors did not state any implications for research.

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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.