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Research letter

Short-term effect of severe hypoglycaemia on glycaemic control in the Diabetes Control and Complications Trial

1. Introduction

In type 1 diabetes (T1D), intensive glucose control is the cornerstone of the prevention of chronic complications. However, a major pitfall is the risk of severe hypoglycaemia (SH), which increases when glucose targets are more stringent with significant negative impacts on health and quality of life [1–3]. Indeed, experiencing SH can lead to anxiety due to fear of recurrence and, thus, to the patient adopting maladaptive behaviours. Despite educational strategies, patients who have experienced SH may react by relaxing their glucose targets to prevent its recurrence. However, few data are available on the impact of SH on glycaemic control.

The aim of our present study was to describe the change in HbA_{1c} following an SH episode and the next assessment of HbA_{1c} in patients with T1D in the Diabetes Complications and Control Trial (DCCT).

2. Material and methods

The design, methods and outcomes of the DCCT have been reported previously [1]. Briefly, 1441 patients with T1D and aged 13–39 years were recruited at 29 centres from 1983 to 1989 and randomized to either conventional ($n = 730$) or intensive ($n = 711$) diabetes therapy. In 1993, after an average follow-up of 6.5 years, the DCCT was terminated early because of the clearly beneficial effects of intensive treatment on microvascular outcomes [1].

2.1. DCCT data access

Data access was granted by the US National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK NTIS Order No. PB96-501985). All definitions used here were taken from the DCCT Manual of Operations (NTIS Invoice No. PB96157367). Detailed descriptions of the eligibility criteria and randomization procedures for subjects entering the DCCT have been published elsewhere [4].

2.2. Definition of severe hypoglycaemia (SH)

SH was defined as an episode with symptoms consistent with hypoglycaemia in which the patient required the assistance of another person, or where prompt recovery was after oral carbohydrate or glucagon intake, or intravenous glucose [1,5].

2.3. Participants

From the DCCT database, our study included participants with at least one SH during the 6.5-year follow-up. In cases of recurrent SH episodes, the first was taken as the index event. The documented HbA_{1c} was measured immediately before the index SH and also 3 months later. Also documented were the insulin doses taken immediately before and 3 months after the index SH episode. As a control, 500 patients were randomly selected from the DCCT, and the mean change in HbA_{1c} between a randomly selected visit and the following one was calculated.

2.4. Statistical methods

The primary outcome was the change in HbA_{1c} between the index SH and 3 months later according to randomization group. The secondary outcome was the change in insulin dose after an SH episode.

Results are expressed as means ± SD for quantitative variables and as proportions for categorical variables. A log transformation was applied to several variables. Statistical testing was performed using the chi-square test or Mann–Whitney U test for categorical or non-normally distributed data, and Student's independent two-tailed *t*-test for continuous data. Differences were considered significant at the 5% probability level ($P < 0.05$) after adjusting for multiple testing. All calculations were performed using Statistical Analysis System 9.4 software (SAS Institute Inc., Cary, NC, USA).

3. Results

During the 6.5-year follow-up, a total of 664 subjects experienced at least one episode of SH. These patients had a significantly longer duration of diabetes (69.8 ± 49.7 vs. 75.1 ± 50.52 months; $P < 0.05$) and were slightly younger (26.2 ± 7.2 vs. 26.8 ± 7.1 years; $P = 0.05$). As expected, nearly

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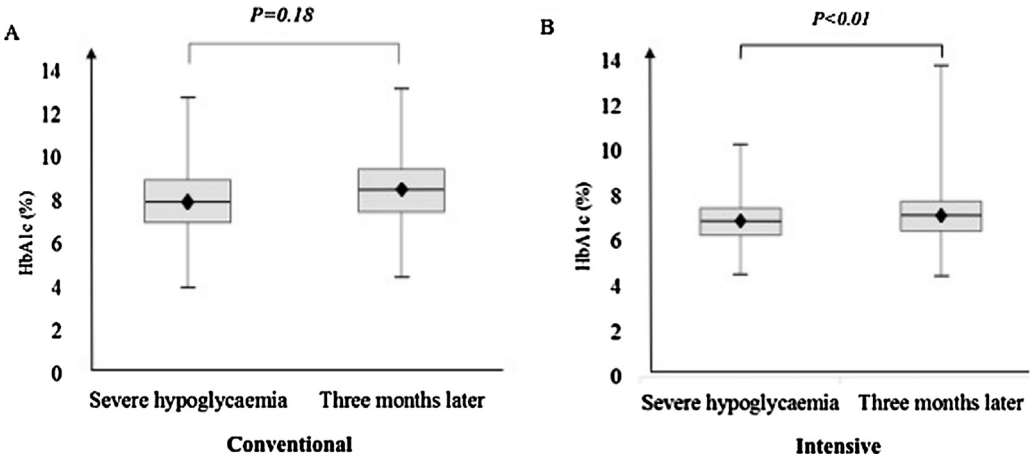

Fig. 1. HbA_{1c} levels before and 3 months after an episode of severe hypoglycaemia with conventional (A) and intensive (B) type 1 diabetes treatment.

twice as many patients in the intensive treatment randomization group had an SH compared with the conventional-treatment group (64.9% vs. 35.1%, respectively; $P<0.001$). No other difference was found in the baseline characteristics between patients with and without SH during follow-up.

Of the 625 patients with available HbA_{1c} values before and 3 months after an SH, the mean change in HbA_{1c} was 0.20 ± 1.26 ($P<0.01$; Fig. 1). A significant interaction was observed between change in HbA_{1c} and randomization group ($P=0.01$). The mean change in HbA_{1c} was 0.21 ± 0.92 ($P<0.01$) in the intensive group and 0.19 ± 1.51 ($P=0.19$) in the conventional group.

Among the 500 randomly selected patients, the mean change in HbA_{1c} after a randomly selected visit was -0.01 ± 0.74% for the whole control group (0.03 ± 0.75% for patients in the conventional group and -0.04 ± 0.72% for those in the intensive group). Variations in HbA_{1c} levels were significantly greater in patients who experienced an SH compared with the randomly selected control group for the whole population (0.20 ± 1.26 vs. -0.01 ± 0.74; $P<0.01$) and for each treatment arm separately (0.21 ± 0.92 vs. -0.04 ± 0.72 in intensive group, 0.19 ± 1.51 vs. 0.03 ± 0.75 in conventional group; $P<0.01$ for both). An increase of 1 percentage point or more in HbA_{1c} was observed in 10% of patients with an SH, whereas a decrease of 1 percentage point or more was observed in only 5% of the participants ($P<0.01$).

Of the 406 (64.96%) patients who experienced a second SH episode, the change in HbA_{1c} between the time of the event and 3 months later was similar on both occasions (0.20 ± 0.83% and 0.18 ± 0.82% at the first and second occurrence, respectively; $P=0.62$).

A mean decrease of 0.02 ± 0.13 IU/kg/day ($P=0.05$) in insulin dose was observed for the whole population. The decrease was significant in the intensive group (0.04 ± 0.15 IU/kg/day; $P<0.01$), but not in the conventional group ($0.01 \pm .0.10$ IU/kg/day; $P=0.56$). A significant interaction was observed between change in insulin dose and randomization group ($P<0.01$). Also studied was the distribution of changes in insulin dose after an SH episode. An increase of ≥ 0.10 IU/kg/day was observed in 6% of participants and a decrease of ≥ 0.10 IU/kg/day in 22% ($P<0.01$).

4. Discussion

In the DCCT study, the occurrence of SH was followed by a significant and modest increase in HbA_{1c} 3 months later in all participants. This increase was significant only in the intensive treatment group, and was also associated with a modest but significant decrease in insulin dose. These findings suggest that the occurrence of SH can discourage patients with T1D from achieving glycaemic targets that are ambitious.

SH in people with diabetes is a subject of increasing concern. Hypoglycaemia is a frequent side effect of intensive therapy. Recent studies have reported a high rate of hypoglycaemia, including severe episodes, in patients with T1D [6–8]. As a consequence, the financial burden associated with hypoglycaemia is also important [9]. In addition, SH has been associated with psychological and health consequences, and loss of quality of life [2,3,10,11]. These factors may contribute to an aversion to hypoglycaemia and may be expected to compromise glycaemic control. However, so far, only very limited information is available regarding this issue.

It is possible that, due to an aversion to hypoglycaemia, people with prior SH may become poorly controlled because high mean glucose values are likely to limit the risk of extremely low values. Several studies have observed a strong link between lower HbA_{1c} levels and higher rates of SH [1,12,13]. However, there are few data on the direct impact of SH on glycaemic control. To the best of our knowledge, only a single study has directly assessed the change in HbA_{1c} after SH [14]. In that study, a small group of 20 young patients with T1D were followed after an SH episode; their mean HbA_{1c} rose significantly from 8.1 ± 1.3% to 9.1 ± 1.1% 6 to 12 months later, while their insulin doses gradually decreased from 0.82 ± 0.25 IU/kg/day to 0.69 ± 0.27 IU/kg/day. Similarly, Potter et al. [15] reported a decrease in insulin dose from 1.2 IU/kg/day to 0.8 IU/kg/day 1 year after an SH event requiring admission to the emergency department in insulin-treated patients. Such changes were much