CLINICAL STUDY

Use of human GH in elderly patients with accidental hip fracture

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Abstract

Objective: To investigate whether early intervention with recombinant human growth hormone (hGH) after hip fracture improves functional recovery and long-term outcome.

Subjects and methods: Functional recovery after hip fracture is often incomplete. The catabolic situation that develops after the hip fracture accident, and a state of malnutrition either pre-existing or developing after surgery, are main contributing factors for the poor clinical outcome. hGH has been used to promote anabolism in a variety of clinical catabolic situations. The study design was randomized, double-blind and placebo-controlled. A total of 111 patients older than 60 years with an accidental hip fracture (mean age 78.5 ± 9.1 (s.d) years) were randomized to receive either hGH (20 μg/kg per day) or placebo for a period of 6 weeks, starting within 24 h after the hip fracture accident. Thereafter patients were followed up for an additional period of 18 weeks. Efficacy was assessed by comparing the changes in the Barthel Index score of activities of daily living and in a patient’s living situation between the hGH- and the placebo-treated subjects.

Results: Eighty-five (78.5%) patients completed the first 8 weeks of the study and 76 (68.5%) the entire study period of 24 weeks. When split according to age, a trend was found that for patients older than 75 years the changes in Barthel Index score from baseline were less in the hGH group than in the placebo group 218 ± 18 vs 228 ± 26† at 6 weeks after surgery  P, 0.075†. There was an overall trend to a higher rate of return to the pre-fracture independent living situation in the hGH group than in the placebo group. Analysis by age revealed a significantly higher proportion of hGH- than placebo-treated patients returning to the pre-fracture living situation for subjects older than 75 years (93.8 vs 75.0%,  P <= 0.034). hGH treatment increased IGF-I values to levels in the range of those of normal subjects of 50±60 years of age.

Conclusions: A 6 week treatment with hGH (20 μg/kg per day) of otherwise healthy patients after an accidental hip fracture may be of benefit if given to subjects older than 75 years of age. The rate of return to the pre-fracture living situation in subjects of this age treated with hGH was significantly increased when compared with the placebo-treated group. The treatment intervention was well tolerated and no safety issues were recorded.

Introduction

Hip fractures are a large and increasing health problem, with estimates that about 1.7 million occurred world-wide in 1990 (1, 2). Recent reports document an incidence of 96.1/100 000 (Europe) to 80/100 000 (United States) (3–6). Cooper and co-workers applied available incidence rates from various parts of the world to projected populations in 1990, 2025 and 2050 (7). They calculated that the number of hip fractures occurring in the world every year will rise from 1.66 million in 1990 to 6.26 millions by the year 2050.

Functional recovery after fracture is often incomplete and many patients cannot resume their previous living habits (8, 9). Rates of institutional care are high and remain higher than average as the individual grows older (10–12). Reasons for the poor outcome of hip fracture patients include their general catabolic state, loss of muscle tissue and a state of malnutrition either pre-existing or developing after surgery (12, 13). Nutritional support alone has been shown to have limited effect in controlling the rate of catabolism in acute and chronic illnesses (14, 15). Recombinant human growth hormone (hGH) has been shown to promote nitrogen retention and to preserve lean body mass in humans (16–19), and has been used as...
a pharmacological agent to promote anabolism in a variety of disorders associated with increased catabolism (20–22). Therefore it might be possible to keep hip fracture patients in an anabolic state by administration of hGH from the early phase after the fracture until recovery after operation, thus improving short-term remobilization and long-term clinical outcome. The present study was designed to investigate whether an early therapeutic intervention with hGH could improve functional recovery thus affecting also long-term outcome.

Patients and methods

Patients

Patients were male or female, older than 60 years of age, with an accidental hip fracture, defined as requiring surgery with open reduction and internal fixation (to exclude hemiarthroplasty, which was not considered desirable for the purpose of the study). Patients were required to have a pre-fracture Modified Barthel Index score ≥85 (see below). Patients with overt congestive heart failure, hypertension, hepatic or kidney insufficiency, active cancer disease, neuromuscular condition, rheumatoid arthritis or diabetes were excluded from the study.

Study design

The study used a double-blind, placebo-controlled design, conducted by 12 investigators in two countries (The Netherlands and Germany). The study was conducted in accordance with EC Good Clinical Practice Guidelines and in compliance with local institutional review board/ethics committee regulations. Informed consent was obtained before enrolment into the study. Subjects fulfilling the entry criteria were randomized to either hGH (Humatrope; Eli Lilly and Company, Indianapolis, USA) or placebo. Treatment was started within 24 h of hospital admission. Patients were treated for a period of 6 weeks, starting at a dose of 10 μg/kg per day and increasing to 20 μg/kg per day within the first 6 days. After 6 weeks the dosage was decreased during a period of 6 days, and therapy then stopped. To assess the long-term outcome, blinded follow-up of the patients was continued for an additional 18 weeks. Thus, the total study period was 24 weeks (6 months).

To ensure adequate protein repletion after the hip fracture accident and the surgical intervention (15), nutritional intake was optimized as far as possible by giving patients at least three bottles of enriched protein beverage (each bottle containing 150 kcal, 6.5 g fat, 5 g protein and 17.9 g carbohydrates) when their food intake was less than 1500 kcal per day. Clinical assessments were performed on hospital admission (within 24 h) and then at 2, 4, 6, 8, 12 and 24 weeks after surgery.

Methods

Functional status after hGH or placebo and rates of return to pre-fracture living situation were the essential features to be assessed. To assess the functional status of the patient (e.g. bathing, toilet, dressing, transfers, climbing stairs) the Modified Barthel Index of activities of daily living (ADL) was chosen (23, 24). The index consists of ten individual items with the values assigned to each item based upon the amount of assistance required to perform the task. The total score ranges from 0 to 100, where 100 indicates the patient is fully independent in his ADLs and zero that the patient is totally dependent.

Housing and living situation was documented at admission (to determine pre-fracture living status) upon discharge from hospital, and at subsequent follow-up visits after discharge. Patients were classified into three groups as follows: 1. house/flat, old people’s flat, service flat; 2. sheltered accommodation, retirement home, nursing/convalescent home; 3. hospital. Group 1 was defined as in an independent and group 2 as in a dependent living situation. The separation between independent and dependent living situations was made at the level of sheltered accommodation as in the countries in which the study was performed (The Netherlands and Germany) adjustments which affect mobility items (e.g. handrail/grabrail in bathroom) are primarily introduced at this level of care.

Hormone assays

Serum insulin-like growth factor-I (IGF-I) and IGF-binding protein (IGFBP)-1 and -3 levels were measured by a central laboratory at each visit. Investigators ensured that appropriate medical care was maintained throughout the study and after the trial and were also responsible for monitoring the safety of patients and for reporting immediately any adverse event or any event that seemed unusual. Safety of hGH- and placebo-treated patients was assessed through laboratory data, vital signs, rates of discontinuation and treatment-emergent adverse events. Treatment-emergent adverse events were those which occurred for the first time during active therapy or events present at baseline and which became more severe during the active treatment phase.

Statistical analysis

Published data on the use of the Barthel Index to assess hip fractures outcome were used for sample size calculations (24). The study was powered to detect a 12 point difference in the Barthel Index between treatment groups after 8 weeks at a significance level of 0.05.

The null hypothesis that no difference existed in clinical recovery between the two treatment groups was analyzed in several ways using different techniques. The change in ADL score from baseline to endpoint was used to determine a patient’s quality of recovery toward their pre-fracture status. This was tested using ANOVA in SAS PROC GLM.
Analyses were performed on the original data and on the rank-transformed data derived using SAS PROC RANK. Analysis of effects of hGH treatment on GH-dependent parameters was done using methods identical to those given for the ADLs. Post-hoc exploratory analyses to look into the pattern of changes in living situation were performed using categorical repeated measures technique with weighted least squares in SAS PROC CATMOD (25). Analysis was performed firstly with a full model consisting of treatment, visit, and the treatment-by-visit interaction. If the interaction was not significant (P > 0.10) then it was removed from the model and the main effects model remained. Incidence rates for each adverse event were analyzed using a Pearson chi-square test with 1 degree of freedom.

### Results

**Patient characteristics**

The baseline characteristics of the patients are presented in Table 1. A total of 111 patients (55 hGH, 56 placebo) were assigned to receive double-blind therapy. There were no significant differences observed between the two treatment groups, except in the patient living situation at pre-fracture where more placebo-treated patients came from an independent living situation compared with hGH-treated patients (96.4 vs 76.4%, P = 0.011).

A total of 83 (74.7%) patients completed the first 8 weeks of the study and 76 (68.5%) completed the entire study period of 24 weeks. The primary reason for discontinuation during the study was patient decision (12.6%). Only four (3.6%) patients discontinued due to an adverse event (three hGH, one placebo), and for three of these the event was present at study completion (24 weeks).

### Efficacy

No significant differences in the changes in the Modified Barthel Index score between treatment groups were observed at any time point during the study (Table 2). However, when the change from baseline to end of the active treatment phase (8 weeks) for all patients was analyzed in relation to their age and irrespective of treatment, it was found that in subjects younger than 75 years little if any change in the Modified Barthel Index score was observed after the fracture and during the post-surgical period (Fig. 1), whereas for patients older than 75 years it showed a more variable recovery. Accordingly, changes in the Modified Barthel Index were analyzed in patients younger and older than 75 years of age separately. While no trend emerged in patients younger than 75 years, the changes from baseline in the older group were less in the hGH group than in the placebo group at any time point during the treatment phase, the difference being greatest after 6 weeks of therapy, with a change in score of −18.6 ± 18 in the hGH group vs −28.1 ± 26 in the placebo group (P < 0.075, data not shown).

At baseline, the distribution of independent/dependent living situations was different between treatment groups, being 76.4%/23.6% in the hGH group and 96.4%/3.6% in the placebo group (Table 1). Analysis by age groups showed that this was essentially caused by the fact that in the hGH group the proportion of subjects older than 75 years who were in a dependent living situation was larger than in the placebo group (40.7 vs 8.3%). Because of this uneven baseline distribution, further analysis of the changes in living situation was performed by comparing only those patients who were in an independent living situation at baseline.

The results of this analysis, summarized in Table 3, show that for all patients again no significant differences in the distribution of the living situation...
are apparent throughout the study, although from visit
two to six the rate of return to the pre-fracture
independent living situation is higher in the hGH
than in the placebo group. When patients are split
according to age, no differences between hGH and
placebo are seen for patients <75 years. After visit six
the percentage of patients in an independent living
situation in the treatment group dropped to 54.4% due
to re-hospitalization of two subjects. However, in
patients older than 75 years the proportion of patients
returning to the pre-fracture living situation over time
was statistically significantly different between treat-
ment groups (*P = 0.034). In the hGH treatment group
no patient was in hospital after visit four and at the end
of the 6 month follow-up period 93.8% were in an
independent and 6.2% in a dependent living situation.
This compares with 75.0 and 25.0% respectively in the
independent living situation in the placebo group.

Given the different trends emerging from the above
analysis, the changes in Barthel Index in relation to
living situation and age were investigated. For this
analysis, the changes in Barthel Index in relation to
placebo group.

<table>
<thead>
<tr>
<th>Visit (week)</th>
<th>hGH</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (2)</td>
<td>50</td>
<td>46</td>
</tr>
<tr>
<td>3 (4)</td>
<td>42</td>
<td>45</td>
</tr>
<tr>
<td>4 (6)</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>5 (8)</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>6 (12)</td>
<td>36</td>
<td>39</td>
</tr>
</tbody>
</table>

Table 2 Changes from baseline in the modified Barthel Index score
for ADL. *n = number of patients with a baseline and at least one
post-baseline measurement in that treatment group.*

<table>
<thead>
<tr>
<th>Visit (week)</th>
<th>hGH</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (2)</td>
<td>50</td>
<td>46</td>
</tr>
<tr>
<td>3 (4)</td>
<td>42</td>
<td>45</td>
</tr>
<tr>
<td>4 (6)</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>5 (8)</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>6 (12)</td>
<td>36</td>
<td>39</td>
</tr>
</tbody>
</table>

Safety

There were five deaths reported for patients participa-
ting in the study, three in the hGH group and two in the
placebo group. Of the three patients in the hGH group
two died after the end of the active treatment phase.
Only one patient discontinued due to a serious adverse
event during the active phase and this was caused by
ventricular fibrillation, which was not considered to be
related to hGH. The most frequently reported treat-
ment-emergent adverse events were edema (hGH
29.1%, placebo 30.4%), urinary tract infection (hGH
25.5%, placebo 14.3%), and constipation (hGH 16.4%,
placebo 17.9%). There were no statistically significant
differences between the groups for any of the adverse
events.

No statistically significant changes from baseline
were observed for body weight, supine systolic or
diastolic blood pressure and heart rate at any time
during the study. There were no patients discontinu-
ations due to clinical laboratory results and none of the
laboratory abnormalities noted were thought to be
clinically relevant or related to study drug treatment.
There were four patients who had elevated blood
sugar concentration during the study, but none of
these occasions were considered clinically relevant to
study drug treatment.

Discussion

In the present pilot study we developed a clinical model
to assess the effects of hGH treatment on the clinical
outcome of subjects with accidental hip fractures. Critical aspects in designing the study were patient selection criteria, outcome measures, hGH dosage and duration of treatment, and follow-up period.

The clinical impact of the hip fracture event per se had to be measurable in order to detect a treatment effect. Published data indicate that up to 50% of hip fracture patients do not return to their previous independent life and living situation (9, 11, 26–28). Accordingly, only patients living independently at the time of fracture, as characterized by ADLs and housing situation were enrolled into the study. Also, other existing disease entities had to be ruled out both for safety reasons and to avoid confounding treatment effects. To assess clinical outcome and possible treatment effects, ADLs and living situation were taken as measures which best describe the functional and health status after the hip fracture event. This is supported by the large amount of data in the literature, which demonstrate the close relationship that exists in hip fracture patients between these measures and early as well as late morbidity and mortality rates. A 6 week duration of treatment was chosen because the period of catabolism and of associated functional impairment after the surgical intervention may be present for several weeks. However, published data indicate that the overall clinical outcome 6 months after hip fracture does not change any further (8, 29, 30), and therefore a follow-up period of up to 6 months after the primary accident was considered appropriate for final evaluation.

No overall therapy effect in treatment vs placebo could be detected by the Barthel Index. However, in patients younger than 75 years of age there was only little overall change in the Barthel score, and therefore clinically relevant treatment effects could not be detected in this age group. Efficacy analysis by age

Table 3 Distribution in living situation* throughout the study of the patients who had an independent living situation pre-fracture; values are given as percentages.

<table>
<thead>
<tr>
<th>Situation</th>
<th>Baseline</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>hGH (n = 27)</td>
<td>Independent</td>
<td>100.0</td>
<td>22.2</td>
<td>51.9</td>
<td>55.6</td>
<td>66.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dependent</td>
<td>0</td>
<td>0</td>
<td>22.2</td>
<td>33.3</td>
<td>29.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hospital</td>
<td>0</td>
<td>77.8</td>
<td>25.9</td>
<td>11.1</td>
<td>3.7</td>
</tr>
<tr>
<td>Placebo (n = 43)</td>
<td>Independent</td>
<td>100.0</td>
<td>25.6</td>
<td>39.5</td>
<td>46.5</td>
<td>62.8</td>
<td>79.1</td>
</tr>
<tr>
<td></td>
<td>Dependent</td>
<td>0</td>
<td>11.6</td>
<td>32.6</td>
<td>34.9</td>
<td>32.6</td>
<td>18.6</td>
</tr>
<tr>
<td></td>
<td>Hospital</td>
<td>0</td>
<td>62.8</td>
<td>27.9</td>
<td>18.6</td>
<td>4.6</td>
<td>2.3</td>
</tr>
<tr>
<td>&lt;75 years</td>
<td>hGH (n = 11)</td>
<td>Independent</td>
<td>100.0</td>
<td>27.3</td>
<td>72.7</td>
<td>72.7</td>
<td>72.7</td>
</tr>
<tr>
<td></td>
<td>Dependent</td>
<td>0</td>
<td>0</td>
<td>18.2</td>
<td>18.2</td>
<td>18.2</td>
<td>27.3</td>
</tr>
<tr>
<td></td>
<td>Hospital</td>
<td>0</td>
<td>72.7</td>
<td>9.1</td>
<td>9.1</td>
<td>9.1</td>
<td>0</td>
</tr>
<tr>
<td>Placebo (n = 19)</td>
<td>Independent</td>
<td>100.0</td>
<td>42.1</td>
<td>57.9</td>
<td>63.2</td>
<td>84.2</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Dependent</td>
<td>0</td>
<td>5.3</td>
<td>31.6</td>
<td>31.6</td>
<td>15.8</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hospital</td>
<td>0</td>
<td>52.6</td>
<td>10.5</td>
<td>5.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥75 years</td>
<td>hGH (n = 16)</td>
<td>Independent</td>
<td>100.0</td>
<td>18.8</td>
<td>37.5</td>
<td>43.8</td>
<td>62.5</td>
</tr>
<tr>
<td></td>
<td>Dependent</td>
<td>0</td>
<td>0</td>
<td>25.0</td>
<td>43.8</td>
<td>37.5</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>Hospital</td>
<td>0</td>
<td>81.3</td>
<td>37.5</td>
<td>12.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Placebo (n = 24)</td>
<td>Independent</td>
<td>100.0</td>
<td>12.5</td>
<td>25.0</td>
<td>33.3</td>
<td>45.8</td>
<td>62.5</td>
</tr>
<tr>
<td></td>
<td>Dependent</td>
<td>0</td>
<td>16.7</td>
<td>33.3</td>
<td>37.5</td>
<td>45.8</td>
<td>33.3</td>
</tr>
<tr>
<td></td>
<td>Hospital</td>
<td>0</td>
<td>70.8</td>
<td>41.6</td>
<td>29.2</td>
<td>8.4</td>
<td>4.2</td>
</tr>
</tbody>
</table>

* Only includes patients who completed the study through 24 weeks (visit 7). P = 0.034 for the proportion of hGH- vs placebo-treated patients >75 years returning to the independent pre-fracture living situation over time.

Figure 2 Mean score for Modified Barthel Index of ADL for patients in independent or dependent living situations. The number of patients within each group varied at each time point since patients could change from being dependent to independent during the study.

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significantly reduced the number of patients in each age group. Also, when living situation was added, the uneven baseline distribution in independent vs dependent situations in subjects older than 75 further reduced the power of the analysis. However, the differences between hGH and placebo observed for patients older than 75 in rates of return to the previous independent living situation, as well as the higher Barthel Index scores observed in the hGH-treated group not returning to an independent living situation indicate that the clinical model described in the present paper has the potential to detect a treatment effect in favor of hGH in patients older than 75 years of age.

Although not within the anabolic range used in previous studies (20, 21), the hGH dose of 20 µg/kg per day was considered appropriate for a pilot study in an aged patient population. This dose was sufficient to increase the baseline serum IGF-I concentrations to values comparable with those of normal subjects of 50±60 years of age. The question, however, remains whether the IGF-I increase obtained with the hGH dose used was sufficient to elicit the desired clinical effect. Low IGF-I values have been reported in hip fracture subjects (31, 32) and also in our study baseline IGF-I values were low. These findings suggest that resistance to GH action, described for catabolic and surgical trauma patients (33), may also be a feature of patients with hip fracture. In patients after severe abdominal surgery it has been demonstrated that a minimal dose of 60 µg/kg per day is required to prevent a negative nitrogen balance (34, 35). We therefore speculate that a higher hGH dose than used in the present study may produce better clinical efficacy in the study model used.

Noteworthy, there was little change in serum IGFBP-1 concentrations and no difference between hGH and placebo, which is indirect evidence of intact substrate availability to the hGH action in the studied patient population, which as a matter of fact represents an otherwise relatively healthy patient population. By careful study monitoring, no significant safety issue emerged in this study. This is important as Takala and co-workers (36) recently reported the results of two studies on the effect of high doses of GH on the outcome in critically ill adults who were hospitalized for long periods. These two placebo-controlled trials in parallel involved 247 Finnish patients and 285 patients in other European countries who had been in an intensive care unit for 5 to 7 days and who were expected to require intensive care for at least 10 days. These patients received either GH (0.10 ± 0.02 mg/kg per day) or placebo until discharge from intensive care or for a maximum of 21 days. These investigators found that the relative risk of death for patients receiving GH was 1.9 in the Finnish study and 2.4 in the multinational study (36). At the time of enrolment, patients in our study were more or less healthy, except for the accidental hip fracture, which is possibly the explanation for the fact that no safety issues did emerge. Subjects with accompanying diseases excluded from the study would a priori not have benefitted from an

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**Figure 3** Baseline serum IGF-I concentrations in patients with acute accidental hip fracture. (○) females, (●) males. The normal range is given by the 5th, 50th and 95th percentile.

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**Table 4** Changes from baseline in serum IGF-I and IGFBP-1 concentrations (µg/l). *n* = number of patients with a baseline and at least one post-baseline measurement in that treatment group.

<table>
<thead>
<tr>
<th></th>
<th>hGH</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean</td>
</tr>
<tr>
<td>IGF-I baseline level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change at week</td>
<td>53</td>
<td>79.9</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>53.9</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>102.0</td>
</tr>
<tr>
<td>8</td>
<td>40</td>
<td>18.4</td>
</tr>
<tr>
<td>Endpoint (0–8)</td>
<td>47</td>
<td>26.4</td>
</tr>
<tr>
<td>IGFBP-1 baseline level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change at week</td>
<td>53</td>
<td>46.5</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
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<td>4</td>
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<td>−19.0</td>
</tr>
<tr>
<td>Endpoint (0–8)</td>
<td>44</td>
<td>−19.7</td>
</tr>
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</table>

* Two-way ANOVA performed on rank-transformed data.
hGH therapy or met contraindications already valid for GH deficiency replacement therapy.

In summary, hGH treatment with a dose of 20 μg/kg per day, started pre- (peri-)operatively and given for a period of 6 weeks to patients with an accidental hip fracture results in a significant increase in serum IGF-I and IGFBP-3 to levels comparable with mean concentrations in healthy subject of 50–60 years of age. Furthermore while no differences in treatment vs placebo were observed in ADL scores, in subjects older than 75 years a significant increase in the rate of return to the pre-fracture living situation was observed compared with placebo.

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