

A randomized study on the effects of intramuscular injections with urinary gonadotrophins (Humegon or Pergonal) on pain, local redness and fever in infertile women opting for in-vitro fertilization

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The objective of this open, multicentre, randomized controlled study in women opting for in-vitro fertilization was to compare the occurrence of pain and redness at the injection site and of post-injection fever after i.m. injection with Humegon ($n = 89$) or Pergonal ($n = 92$). Assessments were scoring of pain and redness at the injection site and of post-injection fever during the next 24 h using self-administered questionnaires. Injection site pain was reported in 48.9% of injections with Humegon and in 44.9% with Pergonal ($P = 0.45$). A trend was seen towards more redness after Pergonal injection (24.0 versus 15.5%; $P = 0.08$). Post-injection fever was reported in 1.4% with Humegon and in 1.1% with Pergonal ($P = 0.80$). It was concluded that there are no statistically significant differences between Humegon and Pergonal after i.m. injection with respect to the prevalence of pain and redness at the injection site and of post-injection fever.

Key words: gonadotrophin/injection/intramuscular/IVF/pain

Introduction

Intramuscular (i.m.) injections of human menopausal gonadotrophin (HMG) preparations sometimes cause pain, swelling and redness at the injection site (Li and Hindle, 1993; Dore *et al.*, 1994). Until recently, there have been no reasons to assume that the commercially available urinary HMG preparations, Humegon and Pergonal, differed in the extent to which such post-injection reactions occur. However, in 1993 an Australian survey suggested that the prevalence of pain 1–3 h after injection was higher with Humegon (59%) than with Pergonal (41%) (Gilder *et al.*, 1993). If such a difference is genuine, this could have clinical implications, and a prospective, randomized controlled study was performed to investigate whether there were differences between the preparations in this respect. The objective of this study was to compare the occurrence of pain and redness at the injection site and of

post-injection fever after i.m. injection with Humegon or Pergonal.

Materials and methods

In a multicentre, open, group-comparative study, infertile women opting for in-vitro fertilization (IVF) were recruited in 1993 and 1994 from the IVF units of the participating study centres (in Rotterdam and Arnhem) and randomized to either Humegon (NV Organon, Oss, the Netherlands) or Pergonal (Ares Serono, Geneva, Switzerland). In order to control for possible seasonal effects on the subjective experience of pain or differences in attributable characteristics, assignment of subjects to each group was done by restricted block (2×5 subjects) randomization performed separately in each study centre. The study protocol was approved by the local ethics committees of the participating study centres and written informed consent was obtained from all subjects before inclusion into the study. The study was conducted in full compliance with the Declaration of Helsinki as well as local rules and regulations.

Both Humegon and Pergonal consisted of freeze-dried HMG for i.m. administration, containing urine-derived follicle stimulating hormone (FSH) and luteinizing hormone (LH) in a ratio of ~1:1. The indicated dosage (75, 150 or 225 IU) was dissolved in 1 ml NaCl 0.9%. After swabbing with 1% chlorhexidine solution, HMG injections were given in the upper outer quadrant of the gluteus maximus muscle, using a standard gauge injection needle.

Study subjects were eligible for inclusion if they had a referral for IVF, were willing to give written informed consent and were able to fill in the questionnaires. Exclusion criteria were ovarian stimulation with gonadotrophins within 6 months prior to start of the study, contra-indications to the use of gonadotrophins and history of allergic reactions following injections of any kind.

The treatment period covered one IVF ovarian stimulation cycle and subjects were required to visit the hospital once before the start of treatment for instruction on how to fill in the questionnaires, and subsequently for each HMG injection given during the treatment cycle. The effects of the study medication on occurrence and onset of injection site pain (0–1 h, 1–3 h and 3–24 h), injection site redness and post-injection fever were assessed by the subjects after each injection by means of completing the questionnaires. In addition to the assessments performed to study the treatment effect of the study medication, at each visit the investigator asked whether the subjects had had any other adverse experiences while using the medication.

The primary study end-points were the injection-based rates of each of the symptoms (i.e. the percentage of all given injections at which a symptom occurred within 24 h after injection), whereas the secondary end-points were the patient-based rates (i.e. the percentage of patients for whom the symptom occurred within 24 h after at least one of the given injections). A power calculation indicated that in order to detect a real between-group difference of 20% [which was indicated from the Australian survey; Gilder *et al.* (1993)] with a probability of 80%, each group should consist of 107 subjects. The study end-points were statistically analysed using a randomization

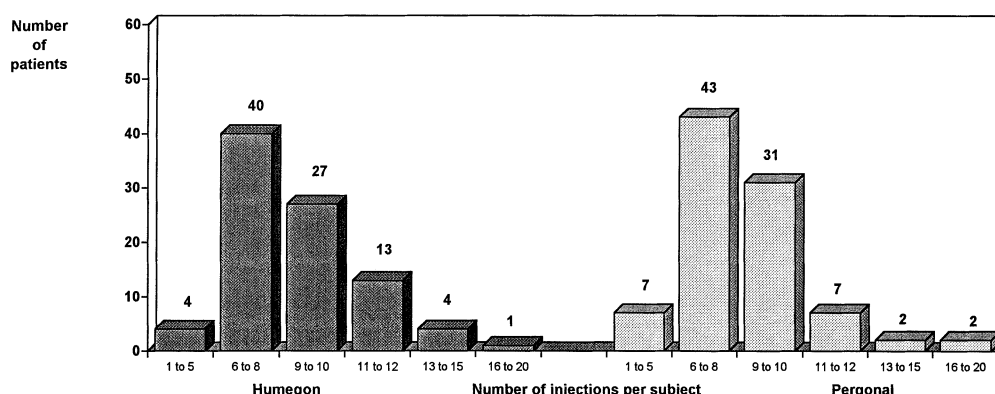


Figure 1. Distribution of the number of injections per patient according to the study preparation.

Table I. Baseline characteristics of the study groups (mean \pm SD)

| Characteristic | Humegon | Pergonal |
|---------------------------------|------------------|------------------|
| Age (years) | 32.0 \pm 4.5 | 32.6 \pm 4.5 |
| Systolic blood pressure (mmHg) | 113.4 \pm 11.4 | 115.0 \pm 10.3 |
| Diastolic blood pressure (mmHg) | 72.7 \pm 8.7 | 74.0 \pm 8.6 |
| Heart rate (beats per min) | 74.1 \pm 10.8 | 72.3 \pm 9.7 |
| Body height (cm) | 168.9 \pm 6.7 | 167.4 \pm 11.9 |
| Body weight (kg) | 67.6 \pm 14.4 | 66.2 \pm 11.1 |

test (primary end-points) or χ^2 -analysis (secondary end-points) with $\alpha = 0.05$. A two-sided *P*-value for the actual difference in percentage between the groups of <0.05 was considered statistically significant.

Results

In total, 250 subjects were randomized (125 to Humegon and 125 to Pergonal), of whom 181 were included in analyses (89 with Humegon and 92 with Pergonal). A total of 69 enrolled subjects were not included in the analysis: 34 for administrative reasons (20 subjects did not start an IVF cycle within the study period and for 14 subjects the questionnaire was missing), 24 due to protocol violations regarding inclusion criteria (e.g. gonadotrophin injections within 6 months prior to the study), and 11 due to protocol violations during treatment (e.g. incorrect injection site). The lower than anticipated number of evaluable subjects (107 in each group) resulted in a reduction of the power from 80 to 77%.

The study centre in Rotterdam recruited 95 evaluable subjects (43 on Humegon and 52 on Pergonal), whereas the centre in Arnhem recruited 86 evaluable subjects (46 on Humegon and 40 on Pergonal). There were no remarkable differences between the groups with respect to baseline characteristics (Table I).

The 181 evaluable patients recorded a total of 1547 injections with the study drugs. The mean number of injections in both groups was 8.8 ± 2.5 with Humegon and 8.3 ± 2.5 with Pergonal. The distribution of the number of injections per patient over the study preparations did not indicate relevant between-group differences (Figure 1).

Injection site pain was reported in 48.9% of injections with Humegon and in 44.9% with Pergonal, which was not statistically different between groups ($P = 0.45$). Redness was reported in 15.5% of injections with Humegon and in 24.0%

Table II. Occurrence and severity of injection site pain, injection site redness and post-injection fever

| Symptom and severity | Humegon (<i>n</i> = 783) | | Pergonal (<i>n</i> = 764) | |
|-------------------------------|---------------------------|------|----------------------------|------|
| | <i>n</i> | % | <i>n</i> | % |
| Injection site pain | | | | |
| None | 400 | 51.1 | 421 | 55.1 |
| Mild | 246 | 31.4 | 229 | 30.0 |
| Moderate | 112 | 14.3 | 100 | 13.1 |
| Severe | 25 | 3.2 | 14 | 1.8 |
| Injection site redness | | | | |
| No | 631 | 84.5 | 575 | 76.0 |
| Yes | 116 | 15.5 | 182 | 24.0 |
| Missing | 36 | – | 7 | – |
| Post-injection fever | | | | |
| No | 708 | 98.6 | 747 | 98.9 |
| Raised temperature | 0 | 0.0 | 4 | 0.5 |
| Fever ($>38^\circ\text{C}$) | 10 | 1.4 | 4 | 0.5 |

Table III. Onset of injection site pain, injection site redness and post-injection fever

| Symptom onset (h) | Humegon | | Pergonal | |
|--|----------|------|----------|------|
| | <i>n</i> | % | <i>n</i> | % |
| Injection site pain onset (Humegon <i>n</i> = 783; Pergonal <i>n</i> = 764) | | | | |
| 0–1 | 240 | 30.7 | 137 | 17.9 |
| 1–3 | 76 | 9.7 | 103 | 13.5 |
| 3–24 | 67 | 8.6 | 103 | 13.5 |
| Injection site redness onset (Humegon <i>n</i> = 747; Pergonal <i>n</i> = 757) | | | | |
| 0–1 | 38 | 5.1 | 35 | 4.6 |
| 1–3 | 46 | 6.2 | 52 | 6.9 |
| 3–24 | 32 | 4.3 | 95 | 12.6 |
| Post-injection fever onset (Humegon <i>n</i> = 718; Pergonal <i>n</i> = 755) | | | | |
| 0–1 | 5 | 0.7 | 3 | 0.4 |
| 1–3 | 1 | 0.1 | 3 | 0.4 |
| 3–24 | 4 | 0.6 | 2 | 0.3 |

with Pergonal (not significant). Post-injection fever was reported in 1.4% of injections with Humegon and in 1.1% with Pergonal ($P = 0.80$) (Table II). Also, when percentages were based on the number of patients, there were no statistically significant differences between Humegon and Pergonal with respect to injection site pain (83.1 versus 81.5%; $P = 0.93$), injection site redness (29.2 versus 43.5%; $P = 0.07$) or post-injection fever (4.6 versus 5.5%; $P = 0.94$).

Of the 48.9% of injections with Humegon in which injection

site pain was reported, onset started usually within 1 h. In the Pergonal group, onset seemed somewhat delayed as compared to the Humegon group. The onset of injection site redness and post-injection fever was more equally distributed over the 24 h time-frame which was defined for each injection (Table III).

Discussion

From this randomized comparative study it can be concluded that there are no marked differences between Humegon and Pergonal after i.m. injection with respect to injection site pain, injection site redness and post-injection fever in patients undergoing IVF. The between-group difference regarding injection site redness (Pergonal 24.0 versus Humegon 15.5%; $P = 0.08$) may indicate a trend, but was not statistically significant.

All analysed injections were given in the buttock, whereas in clinical practice HMG injections may also be given in the upper thigh. However, this is not thought to have compromised the validity of the study results, since there are no indications that different skin reactions can be expected between i.m. injections in the buttock and upper thigh.

Unlike the results of the Australian survey (Gilder *et al.*, 1993), our study did not show significant differences in injection site pain between Humegon and Pergonal. Well-controlled studies have not previously been performed with respect to local reactions after i.m. administration, but these preparations have recently been compared in a double-blind randomized study (Odink *et al.*, 1995) with respect to local side-effects after s.c. injection. In that study, local pain was not observed with either preparation, but it should be emphasized here that the injected volume was only 0.1 ml. Pergonal-treated subjects showed significantly more induration at the injection site and greater erythema surfaces than Humegon-treated subjects, but the authors could not provide an explanation for the between-group differences (Odink *et al.*, 1995).

Both Humegon and Pergonal are comparable with respect to the amount and concentration of the active ingredient (Stokman *et al.*, 1993). Urinary HMG preparations contain a high amount of non-active proteins (~98% of the total protein amount) (Editorial, 1992; Biffoni *et al.*, 1994), which can give rise to local side-effects after injection. In addition, allergic skin reactions have been reported after HMG treatment which resolved after changing to more purified gonadotrophin preparations (Harika *et al.*, 1994; Redfearn *et al.*, 1995). Among the proteins that have been identified in urinary HMG preparations are tumour necrosis factor (TNF)-binding protein-I, transferrin and immunoglobulins (Giudice *et al.*, 1994). In a recent study with a recombinant FSH preparation (follitropin beta; Puregon; NV Organon, Oss, The Netherlands) which contains no protein contamination (<0.1%), local side-effects were recorded in a similar manner as in this study. The incidence of post-injection pain after i.m. injection of Puregon was 31.2%, which seems to be lower than the 45–49% recorded in the current study (Out *et al.*, 1997).

In conclusion, as far as the occurrence of local side-effects after i.m. injection is concerned, there is no reason to prefer one urinary HMG preparation over the other.

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