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Efficacy of traditional Chinese herbal therapy in adult atopic dermatitis

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There has been considerable interest in traditional Chinese herbal therapy (TCHT) as a new treatment for atopic dermatitis. To establish the efficacy and safety of this treatment, a daily decoction of a formula containing ten herbs that has been found to be beneficial in open studies was tested in a double-blind placebo-controlled study.

40 adult patients with longstanding, refractory, widespread, atopic dermatitis were randomised into two groups to receive 2 months' treatment of either the active formulation of herbs (TCHT) or placebo herbs, followed by a crossover to the other treatment after a 4-week washout period. The main outcome measures were extent and severity of erythema and surface damage as judged by standardised body scores. The patients' own assessments of the overall response to treatment were also sought. The geometric mean score for erythema at the end of active treatment was 12·6 (95% confidence interval [CI] 5·9 to 22·0) and at the end of the placebo phase was 113 (65 to 180). The geometric mean score for surface damage was 11·3 (5·8 to 21·8) and 111·0 (68 to 182), respectively. The 95% CI for the mean geometric ratio for the two values with active treatment was 0·04 to 0·22 for erythema ($p<0·0005$) and 0·04 to 0·27 for surface damage ($p<0·0005$). Of the 31 patients who completed the study and expressed a preference, 20 preferred that phase of the trial in which they received TCHT whereas 4 patients preferred placebo ($p<0·02$). There was a subjective improvement in itching ($p<0·001$) and sleep ($p<0·078$) during the TCHT treatment phase. No side-effects were reported by the patients although many commented on the unpalatability of the decoction.

TCHT seems to benefit patients with atopic dermatitis. Palatability of the treatment needs to be improved and its safety assured.

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Introduction

Atopic dermatitis is a common, pruritic disorder that most often begins in early infancy and frequently occurs in patients with a personal or family history of atopic disease. Atopy is becoming more common—the cumulative incidence of atopic diseases from birth to age 11 years is now 32·5% and that for atopic dermatitis is 21·2%.[1] For those who do not have a remission of their dermatitis before puberty, this disease can become a severe handicap in adult life and has been shown to have a serious effect on quality of life.[2] Standard treatment includes general advice about the avoidance of irritants, regular use of emollients, and careful use of topical corticosteroids. For more severe cases, courses of ultraviolet light either in the form of ultraviolet B (UVB) or as oral psoralen photochemotherapy (PUVA)[3] may be advised, and if this fails, hospital admission or treatment with systemic corticosteroids or cyclosporin may be required.[4] Despite this range of therapies, many patients have refractory disease.

During the past 5 years several patients with resistant atopic dermatitis have attended a traditional Chinese medical practitioner in London who prescribed a mixture of dried plant materials from which a decoction is made by boiling them in water. This drink is freshly made and taken once daily. Many of the patients under our care, whose disease had not been adequately controlled by any of the orthodox treatments available, have been impressed by the improvements after this treatment.

A serious difficulty of assessing traditional Chinese herbal therapy (TCHT) scientifically is that normally each patient is prescribed an individualised prescription, based upon an evaluation of the nature of the pulse and appearance of the tongue as well as features of the disease itself. These features

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include the degree of pruritus and erythema, the amount of exudation, whether the skin is infected, and the constitutional disturbance due to the skin disease. It is common practice for about 10 herbs to be prescribed at any one time and these may be frequently changed during a course of treatment.

After consultation with the Chinese medical practitioner, a standard formula was written for patients having a particular type of atopic dermatitis so that this could be used in clinical trials. Encouraging results were observed with this formula in open studies[5] and to confirm these findings, two double-blind placebo-controlled studies were undertaken, one with children (which has already been reported[6]) and the present study with adults.

Patients and methods

Patient selection

40 consecutive adult patients with refractory atopic dermatitis, diagnosed according to clinical criteria,[7] who attended the dermatology outpatients department were selected. This study had received approval from The Royal Free Hospital ethics committee and all patients gave written informed consent to take part. Patients had extensive (>20% of the body surface area) lichenified or urticated papules or plaques of atopic dermatitis but no active exudation or infection. Only patients between the ages of 16 and 65 years were included and all patients were required to have normal full blood counts and renal and hepatic function tests before starting the study. Patients were excluded if they had any other serious concomitant illness, were pregnant or intending to become pregnant, or were breastfeeding. All women of childbearing age agreed to take appropriate contraceptive precautions. In addition, patients who had received systemic corticosteroids, antibiotics, PUVA, or other immunosuppressive treatment within the previous 2 months were excluded. Patients were asked to maintain their current diet and dermatological treatments (in particular, not to increase the potency or frequency of topical corticosteroid use) throughout the trial.

Treatment

Patients were entered into a 5-month, double-blind, placebo-controlled, crossover study. Each patient was randomly allocated to receive either the active treatment (TCHT, Zemaphyte, UK patent application 9104286.1) for 8 weeks and then, after a 4-week wash-out period, an identically packaged placebo for 8 weeks or the same treatments in the reverse order.

Active treatment consisted of a standardised formulation* of plant materials in widespread use in China, which have been provisionally identified by their botanical names as: *Ledebouriella seseloides, Potentilla chinensis, Clematis armandii, Rehmannia glutinosa, Paeonia lactiflora, Lophatherum gracile, Dictamnus dasycarpus, Tribulus terrestris, Glycyrrhiza glabra, Schizonepeta tenuifolia*. Every effort was made to standardise the treatment given by use of top-grade ingredients from a single supplier of medicinal herbs (OPTEC, Shanghai, China) or herbs of equivalent quality from UK suppliers. The herbs, grown in mainland China, were prepared by methods described in the Chinese Pharmacopoeia (CP 1988). All materials were checked before use for heavy metal content and for possible microbial contaminants. Thin-layer chromatography was used to "finger-print" each batch of every constituent, and batches were rejected (about 10%) if they differed substantially from the reference material. The herbs were then finely ground in a hammer mill until they passed through a 1 mm screen and were packaged as 10 g sealed porous sachets by Phytopharm Ltd (Brough, UK). *Schizonepeta tenuifolia* contains volatile oils and this herb was therefore packed in separate sachets. Treatment was freshly prepared as a decoction each day. Four large sachets containing the plant materials were boiled in 800 ml tap water and after 90 min of simmering, four small sachets (containing *Schizonepeta tenuifolia*) were added for a final 3 min. This decoction (about 200 ml) was drunk while it was still warm, and patients were requested not to eat during the next hour.

The same weight of placebo consisted of *Humulus lupulus, Hordeum distichon, Hordeum distichon ustum*, baker's bran (wheat), sucrose, *Salvia* spp, *Thymus vulgaris, Rosmarinus officianalis, Mentha piperita*, and *Oleum caryophylli*. This mixture has no known benefit in atopic dermatitis but had a similar smell and taste to the active treatment.

* Available from the authors for the purposes of research.

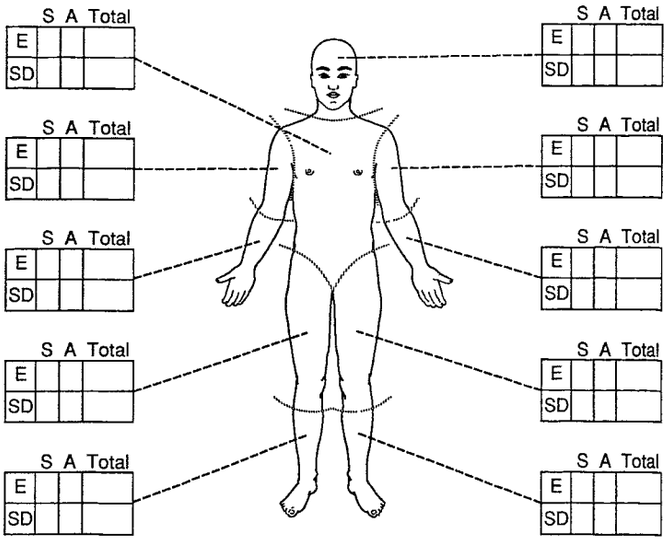

Fig 1—Standardised disease activity scoring system.

E = erythema, SD = surface damage, S = severity, A = area.

Assessments

Patients were assessed at 4-weekly intervals. Quantitative measurement of erythema and surface damage (ie, papulation, vesiculation, scaling, excoriation, and lichenification) was made with a standardised scoring system.[8] The body surface was divided into 20 roughly equal areas (fig 1), and within each area, a score of 0 (none) to 3 (severe) for the degree of erythema and surface damage was made. For each of these clinical features an estimate of the percentage area within each zone affected by that particular feature was measured; a score of 1 where the area affected was <33%, 2 where the area was between 34 and 66%, and 3 where the area was >67%. The sum of the severity scores multiplied by the area scores provided a total body score for each feature, the maximum being 180. The scores for each patient at the end of each 8-week study period were compared.

The following investigations were completed at baseline and at the end of each treatment period: full blood count, serum bilirubin, aspartate aminotransferase, alkaline phosphatase, albumin, urea and electrolytes, creatinine, calcium and phosphate, glucose, creatine phosphokinase, and 24 h urinary creatinine clearance. At each monthly visit, blood pressure and weight were measured and side-effects monitored.

During the study, patients were asked to keep a daily diary to record their compliance with treatment and any side-effects. At the end of each treatment period, patients were asked to comment on whether they had itched less, slept better, or had fewer episodes or less severe asthma than usual during that phase of the trial; in addition, at the end of the study they were asked to state whether they preferred the first or second period of treatment.

The protocol specified that patients who showed persistently abnormal full blood counts, increases in serum total bilirubin or liver enzymes to above $1\frac{1}{2}$ times the normal range, a diastolic blood pressure that remained persistently above 95 mm Hg, or other complications believed to be due to treatment, should be withdrawn from the study. Furthermore, patients who failed to comply (a failure to take the treatment on more than 5 days in any 4-week period) or who were given systemic antibiotics or corticosteroids for whatever reason during the study were withdrawn.

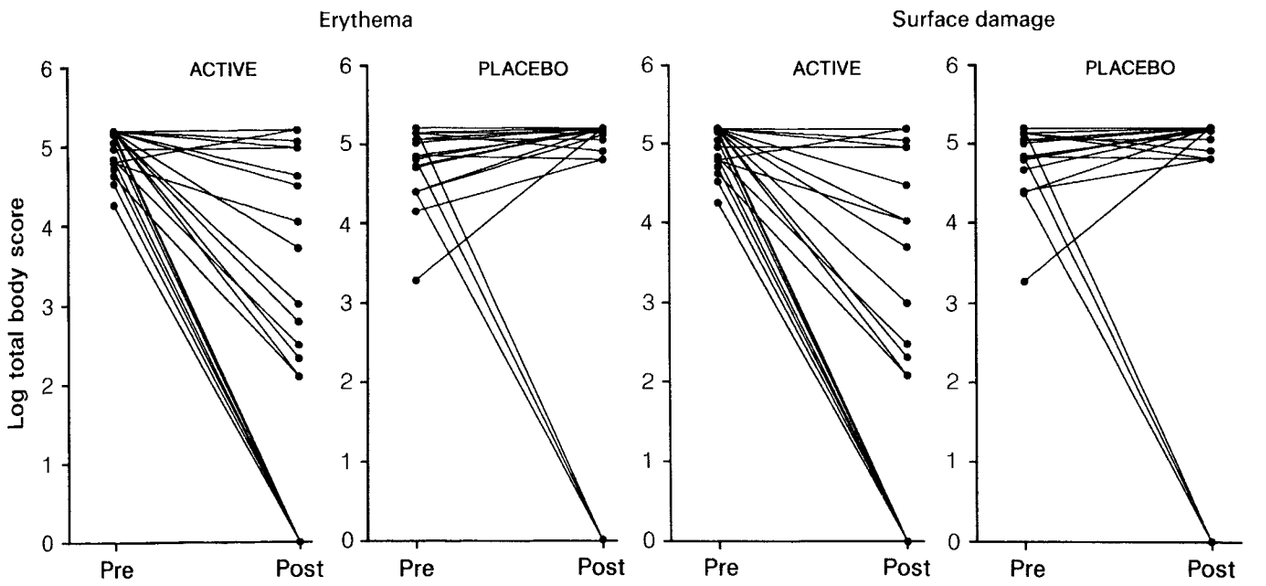

Fig 2—Changes in the log clinical score of erythema and surface damage for individual patients taking active treatment or placebo.

Statistics

The scores for each clinical feature (erythema and surface damage) were logarithmically transformed to allow standard parametric analysis. The transformed scores after 8 weeks of active and 8 weeks of placebo treatment were compared by means of a paired *t* test. The reduction in scores during the active phase was also expressed as a proportion of the score at the end of the placebo phase for each patient. The patients' subjective assessments of itch, sleep, asthma, and preference were evaluated with non-parametric confidence intervals for the difference between proportions (Wilcoxon-based method).[9,10]

Results

40 patients were entered in the study (17 male, 23 female; mean age 30·2 years, range 19–57). 20 were allocated to the TCHT-placebo sequence and 20 to the placebo-TCHT sequence. Of the patients selected, 35 were caucasian, 4 Afrocaribbean, and 1 was Chinese. All had longstanding atopic dermatitis (mean duration 29·1 years, range 3·5–40) that had failed to respond to intensive standard therapy. 17 patients had previously taken prolonged courses of systemic corticosteroids and 11 had had PUVA of whom 6 had had combined treatment with both oral corticosteroids and PUVA. 9 patients had received UVB phototherapy. Most patients had sought alternative forms of treatment, 18 having tried homoeopathy. 24 patients had concomitant asthma and 15 had allergic rhinitis. 16 patients (11 female, 5 male) had heights at or below the 3rd centile.

31 patients completed the study (mean age 30·8 years, range 17–57). Of the patients randomised to the placebo-TCHT sequence, 1 did not complete the first period and 2 did not complete the second period. In the TCHT-placebo sequence, 3 did not complete the first period and 3 did not complete the second period. Thus, 9 patients were excluded from the analysis, 8 because of non-compliance due to the unpalatability of the decoctions and 1 because she had become pregnant.

Patients in both treatment sequences showed a rapid and continued improvement in both erythema and surface damage scores on TCHT (figs 2 and 3). The geometric mean for erythema at the end of active treatment was 12·6 (95% confidence interval [CI] for mean, 5·9 to 22·0) and at the end of the placebo phase 113 (65 to 180). Similarly, the geometric mean for surface damage scores at the end of the active phase was 11·3 (5·8 to 21·8) compared with 111 (68 to 182) at the end of the placebo phase. The 95% CI for the mean geometric ratio of the two values was 0·04 to 0·22 with active treatment for erythema ($p < 0·0005$) and 0·04 to 0·27 for surface damage ($p < 0·0005$). Based on logarithmic values, the mean proportional change between the end of the placebo phase and the end of the active phase for erythema was 46% (95% CI 25·2% to 67%). Similarly, the mean proportional change for surface damage between the end of

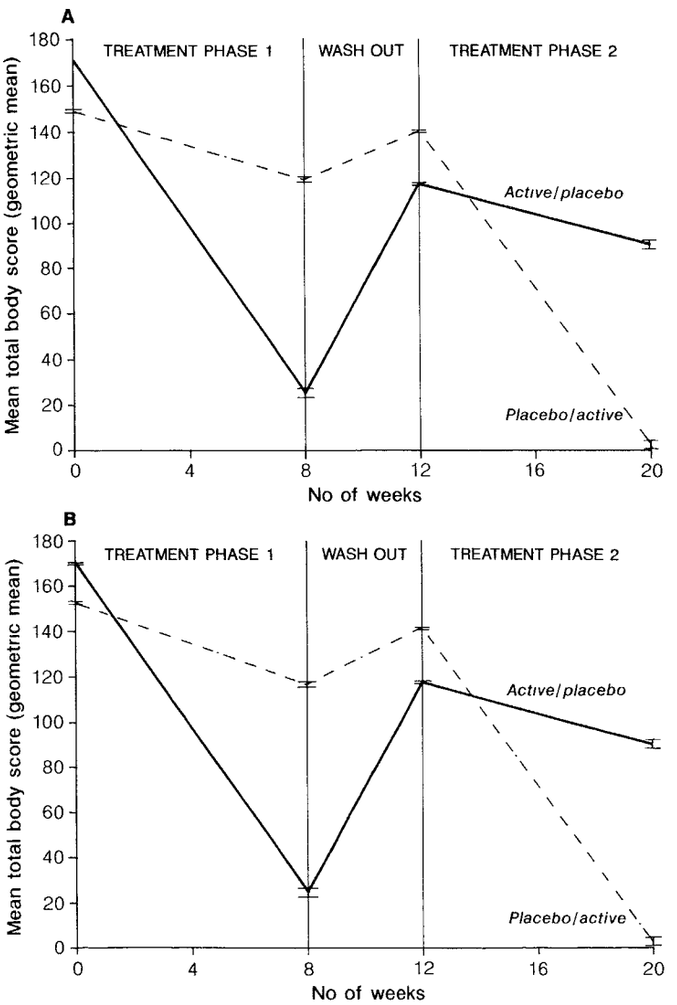

Fig 3—Sequential total body scores (geometric means) for (A) erythema and (B) surface damage.

the placebo phase and the end of the active phase was 49% (27% to 71%). There was no evidence of an order effect with either treatment for erythema or for surface damage. There was no evidence of a carry-over effect of treatment in that there was no significant difference in the scores for erythema and surface damage at the end of the washout period between patients who started on active treatment and those who started on placebo treatment (unpaired Student's *t* test).

Of the 31 patients who completed the study, 14 said that they itched less during the TCHT phase compared with 1 who itched less during the placebo phase. 16 patients denied any improvement in either phase (95·2% CI for difference between proportions, 0·18 to 0·48; $p < 0·001$). 15 patients said that they slept better during the TCHT treatment period whereas 6 said they slept better during placebo (0·02 to 0·56, $p < 0·078$). There was no significant change in asthma symptoms during the study. When asked to express a preference, 20 indicated that phase of the trial in which they received TCHT compared with 4 patients who preferred placebo (95% CI for this proportion 0·45 to 0·81, $p < 0·02$). Topical corticosteroid use, in terms of potency and quantity required, was found to be lower while on active treatment than on placebo.

Adverse effects were mild. 2 patients reported mild abdominal distension and headaches while taking TCHT. 1 patient receiving placebo had three episodes of facial herpes simplex and another patient reported loss of taste while taking placebo. Apart from eosinophilia which was detected in 24 patients at the beginning and end of the study, haematological and biochemical profiles remained normal throughout the study, and there was no change in blood pressure or weight.

Discussion

We have shown that TCHT affords substantial clinical benefit in patients whose atopic dermatitis had been unresponsive to conventional therapy. The fundamental principles underlying this treatment were first described in the Huang-di Nei-jing or Inner Classic of the Yellow Emperor, compiled by unknown authors between 300 and 100 BC. In that treatise, six of the herbs used in the present prescription were recommended for dry scaly skin. Subsequently, a review of open studies with this treatment approach in China has supported its efficacy in patients with atopic dermatitis.[11]

Our study is part of an effort to adapt and evaluate this traditional Chinese approach to the management of atopic dermatitis in a western clinical setting. The basic principles of traditional Chinese medicine were not adopted in this study; rather we applied western methods of clinical diagnosis, and the Chinese medicinal plants were used as a conventional drug prescription. Furthermore, dietary manipulation, which would be a standard part of the treatment regimen in China was not instigated. These results corroborate those in which we gave TCHT to children with severe atopic dermatitis.[6] However, we would emphasise that the patients selected in both studies had a particular pattern of atopic dermatitis characterised by erythema, lichenification, and plaques of dermatitis in the absence of active exudation or obvious infection. It is not known whether the present formulation is suitable for other types of dermatitis, especially those in which recurrent infection is a prominent feature, and this is now under investigation.

An understanding of the pharmacological basis for the beneficial effect of TCHT in atopic dermatitis is limited. Some of the herbs have anti-inflammatory properties (*Ledebouriella seseloides, Rehmannia glutinosa, Glycyrrhiza glabrae, Paeonia lactiflora*), some have antimicrobial action against *Staphylococcus aureus* (*Ledebouriella seseloides, Potentilla chinensis*), some have sedative effects (*Ledebouriella seseloides*), and one at least has been shown to have immunosuppressive properties.[12-14] The extract from the root of *Glycyrrhiza glabra* (liquorice) has been most extensively studied; the active component, glycyrrhizic acid, and its hydrolytic metabolite, glycyrrhetinic acid, have mineralocorticoid activity by inhibiting the metabolism of cortisol to the inactive cortisone through inhibition of the enzyme 11β-hydroxysteroid dehydrogenase.[15-17] Glycyrrhetinic acid potentiates the cutaneous vasoconstrictor activity of topically applied corticosteroids and possibly also their anti-inflammatory effects.[18] However, whether glycyrrhetinic acid has an important role in producing clinical benefit with TCHT has to be questioned since this compound was a constituent of the placebo in the controlled trial in children and yet there was still a pronounced deterioration during this phase of the study.[6] Moreover, our group has shown that the present formula does not have significant glucocorticoid activity (unpublished) and there was no significant change in patients' weight or blood pressure during the study.

Herbal treatments are potentially toxic, and hepatotoxicity caused by herbal remedies is well recognised.[19-21] To our knowedge, there has been one published case of hepatitis in a child receiving TCHT for atopic dermatitis, although the formula given to the child differed from that studied here and no pre-treatment liver function tests were done.[23] Nevertheless, we strongly recommend that, before receiving this therapy, all patients should have hepatic and renal function testing, which should be repeated at least every 6 months throughout the course of treatment. Furthermore, all patients with a history of jaundice or alcohol misuse should be excluded. Women of childbearing age should have adequate contraception during treatment. To date, animal studies have revealed no evidence of short or medium term toxicity (unpublished) although the possibility of idiosyncratic reactions in individual patients cannot be ruled out.

The benefit shown in this controlled trial with a standardised prescription of traditional Chinese medicinal plant materials in a selected group of adult patients with refractory atopic dermatitis offers a new treatment for this disease. For its future success the palatability of the treatment will have to be improved and its safety assured.

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SHORT REPORT

Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte

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Intracytoplasmic sperm injection (ICSI) is a promising assisted-fertilisation technique that may benefit women who have not become pregnant by in-vitro fertilisation (IVF) or subzonal insemination (SUZI) of oocytes. We have used ICSI to treat couples with infertility because of severely impaired sperm characteristics, and in whom IVF and SUZI had failed. Direct injection of a single spermatozoon into the ooplasm was done in 47 metaphase-II oocytes: 38 oocytes remained intact after injection, 31 became fertilised, and 15 embryos were replaced in utero. Four pregnancies occurred after eight treatment cycles—two singleton and one twin pregnancy, and a preclinical abortion. Two healthy boys have been delivered from the singleton pregnancies and a healthy boy and girl from the twin pregnancy.

Lancet 1992; **340**: 17–18.

Assisted-fertilisation methods—eg, partial zona dissection (PZD)[1] and subzonal insemination (SUZI)[2]—have been successful in some couples with severe male-factor infertility who could not be helped by in-vitro fertilisation (IVF). Pregnancies and births have been reported, but despite use of these methods some women still do not conceive. Intracytoplasmic sperm injection (ICSI) is a promising assisted-fertilisation technique. In rabbits and cattle, embryos obtained by such injections have been transferred to recipient mothers and live offspring have resulted.[3] In three recent reports,[4–6] two-pronuclear zygotes were seen in 30 oocytes after ICSI of 143 oocytes; placement of 4 zygotes in 2 women and of 11 embryos in 7 women did not result in pregnancy. We describe successful intracytoplasmic injection into metaphase-II oocytes of single spermatozoa from men with severely impaired spermatozoa characteristics after IVF and SUZI had failed.

The four couples (A, B, C, and D aged [female/male] 37/36, 31/32, 29/31, and 34/34, respectively) treated by assisted fertilisation had had primary infertility for between 3 and 13 years due to oligoasthenoteratospermia (couples A, B, and C) or asthenoteratospermia (couple D). Couples A, B, and D had undergone a total of 8 IVF treatment cycles, during which only 1 of 103 inseminated preovulatory oocytes had become fertilised. This lack of fertilisation persisted even after increasing the numbers of motile spermatozoa added to each oocyte. Couple C was not accepted for IVF because the spermatozoa count of the male partner was too low. During our study, couples were treated by both ICSI and SUZI.

Before treatment, women were superovulated by gonadotropin-releasing-hormone agonist then stimulated with human menopausal gonadotropins and chorionic gonadotropin (HCG). Oocytes were retrieved and cultured as described previously.[7] Men were asked to produce a semen sample 1 day before and on the day of oocyte retrieval. A combination of sperm-preparation techniques was used to retain as many spermatozoa as possible. The percentage of acrosome-reacted spermatozoa in the sperm suspension was increased by incubating the spermatozoa for 24 h in T6 medium and then exposing them to an electrical field of 1250 V/cm for 2·5 ms, followed by washing and incubation in T6 medium supplemented with 3·5 mmol/l pentoxifylline.[7,8]

Shortly after oocyte retrieval, cumulus cells and corona radiata were removed by transferring oocytes into M2 medium with 1 mg/ml hyaluronidase for up to 1 min. Only intact oocytes that had extruded the first polar body were microinjected. The holding and injection pipettes were made by drawing glass capillary tubes with a pipette puller. The injection pipette was opened and sharpened by

TABLE I—SEMEN CHARACTERISTICS BEFORE AND AFTER SPERM SELECTION

Average semen characteristics	Couple			
	A	B	C	D
Initial				
Volume (ml)	5·8	1·5	2·3	4·1
Concentration (× 10^6/ml)	2·2	0·7	0·1	57
Percent progressive motility	20	13	ND	7
Percent normal morphology	20	8	ND	13
After selection				
Volume (ml)	0·2	0·2	0·2	0·2
Concentration (× 10^6/ml)	2·95	0·27	ND	3·8
Percent total motility	46	88	ND	100
Percent normal morphology	37	ND	ND	50

ND = not done—ie, too few spermatozoa to allow assessment