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Extrusion of testosterone pellets: a randomized controlled clinical study

S. Kelleher, L. Turner, C. Howe, A. J. Conway and D. J. Handelsman

Andrology Unit, Royal Prince Alfred Hospital &, Department of Medicine, University of Sydney, Australia

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Summary

BACKGROUND It has previously been shown that testosterone implantation is an effective and well accepted form of androgen replacement therapy, but that pellet extrusion was the most frequent side-effect. The present study aimed to reduce the extrusion rate.

OBJECTIVE To determine whether the washing of testosterone pellets to remove potentially surface-adherent particles decreased the rate of extrusion of pellet implants.

DESIGN Prospective, randomized parallel group design in a single centre with consecutive procedures to be randomized (1 : 1) into a wash or control group.

PATIENTS The study included 251 testosterone implantation procedures in men with known androgen deficiency.

MEASUREMENTS The primary endpoint, extrusion rate per procedure, was evaluated prospectively by telephone contact at 1 week and then 3 and 6 month intervals. Secondary end-points included peri-procedure adverse events (bleeding, skin reaction, excessive discomfort) noted at the time of implant. Bruising, bleeding and infection were also evaluated as later adverse events by telephone and personal follow-up. Explanatory variables recorded as possible covariables included the number of implants used, production batch number of the implants, the operator, as well as other demographic and medical factors.

RESULTS In the wash group, the extrusion rate was 12% per procedure (19 pellets from 15 subjects) whereas in the control group, the extrusion rate was 11·1% per procedure (18 pellets from 14 subjects), indicating no evidence of any benefit of the wash procedure (OR = 1·09 [95% CI 0·47–2·6] per procedure). There was no evidence of benefit in secondary endpoints including total adverse events (7·1%, OR 1·28 [0·44–3·9], bleeding/bruising (8·8%, 1·23 [0·47–3·3]) and infection (4·0%, 1·54 [0·35–7·6]) per procedure. Among men reporting an infection requiring antibiotic treatment according to their own general practitioners, six/ten (60%) subsequently experienced an extrusion. There were no significant differences in extrusion rate between four different operators ($P = 0·24$) nor among 12 different batches of pellets used during the course of the study ($P = 0·77$).

CONCLUSIONS The pellet washing procedure used during implantation does not reduce the subsequent extrusion rate. The higher rate of both primary and secondary adverse events in this prospective study compared with the previous retrospective survey may reflect either more rigorous follow-up or a secular trend.

Since testosterone was first used clinically more that six decades ago (Deansley & Parkes, 1937; Hamilton, 1937), numerous modalities for testosterone replacement have been developed (Nieschlag & Behre, 1998). These are designed to overcome the pharmacological limitations of testosterone as a therapeutic drug, namely its very low oral bioavailability and short half-life in the bloodstream. These features led to the pharmaceutical development of oral androgens as well as parenteral, depot formulations. Over the last few decades, intramuscularly injectable testosterone esters in vegetable oil formulations have been the mainstay of androgen replacement therapy. The limitations of life-long testosterone replacement with injectable, oral and transdermal formulations, including excessively frequent administration or painful injections with wide fluctuations in circulating testosterone concentrations (Mackey *et al*., 1995), have prompted continued searching for better tolerated modalities of testosterone delivery. Novel developments include newer testosterone formulations such as testosterone buciclate (Behre & Nieschlag, 1992), testosterone microspheres (Bhasin *et al*., 1992), and sublingual testosterone cyclodextrin complex (Stuenkel *et al*., 1991). In addition, depot testosterone implants have undergone a resurgence of popularity within the last decade (Nieschlag, 1996). Testosterone implants are a well accepted modality of androgen replacement

Correspondence: Professor D. J. Handelsman, Department of Medicine (D02), University of Sydney, Sydney, NSW 2006, Australia. Fax: + 61 2 9351 4560; E-mail: djh@med.usyd.edu.au

therapy as indicated by high continuation rates during treatment (Handelsman *et al*., 1997). A retrospective review of nearly 1000 consecutive implantation procedures indicated very few adverse effects (minor infection 2·3%, bleeding 0·8%) apart from pellet extrusion (8·5%).

Extrusion occurs when a pellet is expelled usually by tracking back along the insertion track to exit via the original insertion site. Extrusions are wasteful, uncomfortable to the patient, may lead doctors to suspect an infection and compromise testosterone delivery so as to require earlier re-implantation. The pathophysiology of extrusion is unknown. Features of pellet extrusions include: (a) being characteristically delayed with an average latency of 2 months after implantation; (b) multiple extrusions are more frequent and single extrusion less frequent than expected by chance; and (c) increased habitual physical activity at work and at leisure were predictors of extrusion (Handelsman *et al.*, 1997). The non-independence of extrusions events and the fact that all patients appeared to be at similar risk suggest that extrusions were determined by factors inherent in the implantation procedure or the implants themselves. Testosterone implants are packaged in glass vials containing sterile cotton wool. Microscopic surveillance of unused implants suggested that fragments of the packaging materials might be adherent to the implants. As glass fragments or cotton-wool fibres can be irritating and could potentially establish a foreign body reaction, the present study was based on the premise that extrusion of implants may be related to surface-adherent particles causing a sterile inflammation like a foreign body reaction. It was hypothesized that the removal of these particles through a washing procedure may decrease the extrusion rate.

Materials and methods

Design

The study had a prospective, randomized parallel-group design. All androgen deficient men about to undergo an implantation were offered randomization into either the wash group or the non-wash group. Randomization in balanced blocks of eight with a 1 : 1 ratio was undertaken by codes sealed in envelopes opened at the time of randomization. Inclusion criteria for the study involved the willingness of the subjects to sign informed consent forms and to co-operate with regular telephone follow-up.

The primary endpoint of the study was the extrusion rate per procedure. This was evaluated prospectively by telephone contact with the subjects made at 1 week, then 3 and 6 months post implantation. The information sought at these times included whether the subject had experienced an extrusion, the date of the extrusion and whether there were any other associated problems. If the subject had had an extrusion they were asked to record the date and retain the extruded remnant for analysis. Data collected at the time of the implantation procedure included the number of pellets implanted, implant batch numbers, the operator, the number of previous implantations, the site of the implant, height and weight of the patient, and the cause of androgen deficiency. Other procedure-related problem including the secondary end-points (bruising, bleeding, infection) were recorded on the study sheet.

Procedure

Implants are placed subdermally in the lower abdominal wall lateral to the umbilicus under clean conditions for routine minor office surgery. The skin is cleaned with alcohol, the incision site draped and the intended tracks are infiltrated with 2% xylocaine. A 2-cm incision is made through anaesthetized skin and tracks are created subdermally by advancing the trochar to its hilt. The pellets are then delivered, via the wide-bore cannula, each to the end of one track. Following implantation, manual pressure is applied over the incision site until any bleeding ceases and the incision site is covered with sterile adhesive strips and a transparent waterproof dressing for 1 week.

The wash group had, in addition, a washing procedure prior to placement of the pellets. The washing procedure involved vigorously agitating the pellets, one at a time, in filtered sterile alcohol solution for 5–10 s, after which they were rinsed in normal saline solution for up to 15 min prior to implantation. Pellets for control (non-wash) implantations were untreated.

Results

During the study period, 262 procedures for androgen deficient men requiring testosterone pellet implantation were undertaken. Of these, men undergoing 251 (96·5%) implantations were eligible and agreed to be randomized. The study included 35 men having one, 51 men having two, 30 men having three, four men having four, and two men having five procedures. Eleven procedures were ineligible and therefore excluded because of involvement in other studies ($n = 3$) or inability to give informed consent ($n = 8$).

In the wash group, 15 men (12%) experienced extrusions (total of 19 pellets extruded) among 125 procedures whereas in the control group, 14 men (11·1%) experienced extrusions (total of 18 pellets extruded) among 126 procedures (OR = 1·09 [95% CI 0·47–2·6] per procedure). This gives an overall rate of extrusion of 29/251 (11·6%) per implantation procedure or 37/1004 (3·7%) per pellet implanted. Extrusions occurred at a median of 9 weeks (range 3–16 weeks). Infections were observed in both wash ($n = 6$) groups and control non-wash

($n = 4$) groups, and where an infection occurred, six/ten men subsequently experienced an extrusion within nine weeks. In contrast, bleeding, infection or other adverse peri-procedural events were unrelated to subsequent extrusions.

The total number of adverse events other than extrusion was 7·1% (OR 1·28 [0·52–2·2]) per procedure. Infection occurred after 4% (OR 1·54 [0·25–7·6]), and bleeding/bruising after 8·8% (OR 1·23 [0·47–3·3]) of procedures. There were no significant differences in extrusion rate between four different operators ($P = 0·24$) or among 12 different production batches of pellets used during the course of the study ($P = 0·77$).

Discussion

The present study demonstrates that the wash procedure developed for testosterone pellets prior to implantation, which aims to remove potentially surface-adherent particles, does not decrease the pellet extrusion rate. The two main alternative explanations are that either such particles are not involved in extrusion – they are not present or if present, not irritating – or the particles do determine subsequent extrusion but were not successfully removed by the wash procedure. It is difficult to fully exclude the latter possibility as, due to the cost of implants, systematic surveys were not undertaken to determine the rate of particle adherence to the implants or to assess how consistently the wash procedure removed the particles. Preliminary studies did demonstrate that the wash procedure effectively removed those particles observed under low power light microscopy (Howe, personal communication).

It remains unclear whether extrusion is primarily related to the procedure or to some property of the pellets. Extrusion was unrelated to any of the four experienced operators, although it is well known that extrusion is more frequent when implantation is performed by inexperienced operators. Overall, the evidence does not support any suggestion that extrusion is primarily determined by the pellet and/or procedure itself. On the contrary, the absence of any predilection among production batches argues against the possibility of factors related to pellet manufacture. Previously, the only predictors of extrusion identified in the retrospective survey were habitually increased physical activity at work and/or leisure (Handelsman *et al.*, 1997). The present study identifies that infection may predispose to subsequent early extrusion(s). Among the 10 men who had an infection requiring antibiotics following their implantation, six subsequently underwent one or more extrusions with a mean latency of 5·1 weeks (median 4 weeks). This time interval is significantly shorter than the latency to extrusion in men experiencing an extrusion without evidence of overt infection (median 9 weeks). The latter, larger group may, however, have a more indolent infective process due to organisms of low-grade pathogenicity.

Interestingly, the extrusion rate in this prospective study (11·6% overall) was higher than observed in the previous retrospective survey where the extrusion rate was 8·5% (Handelsman *et al.*, 1997) and the rates for infection and bleeding were significantly higher ($P < 0·001$). This discrepancy may be attributable to the more rigorous follow-up inherent in the prospective study, or to a secular trend in underlying extrusion rate. Further studies would be needed to evaluate these possibilities.

This study demonstrates that the pellet washing procedure does not reduce the pellet extrusion rate. In addition, adverse event rates were higher in this prospective study compared with the previous retrospective survey. At present, further studies are needed to identify other approaches to determine the cause and effective prevention measures of pellet extrusion. Despite extrusions, testosterone implants for androgen replacement therapy remain convenient, safe and well tolerated by recipients.

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