Hematocrit Response and Risk Factors for Significant Hematocrit Elevation in Testosterone Replacement with Implantable Pellets

Russell P. Hayden, Nelson E. Bennett and Cigdem Tanrikut*

From the Department of Urology, Massachusetts General Hospital, Boston, Massachusetts (RPH, CT), and Department of Urology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (NEB)

Purpose: We studied the incidence and risk factors for the development of erythrocytosis with implantable testosterone pellets.

Materials and Methods: A multi-institutional retrospective database analysis was used to evaluate men treated with testosterone pellets between 2009 and 2014. Inclusion criteria consisted of adult, hypogonadal males who had a full complement of pretreatment and posttreatment surveillance studies. Pretreatment and posttreatment values were compared with Wilcoxon signed rank tests. Multiple linear regression was used to identify potential risk factors for significant hematocrit elevation.

Results: A total of 97 patients were included in the study. The average age of the cohort was 52 years (range 24 to 80). Mean hematocrit before and after pellet implantation was 43.9% and 46.1%, respectively, corresponding to an increase of 2.2% (CI 1.4−2.9, p <0.001). The average increase in testosterone was 145.3 ng/dl from an initial mean of 278.9 ng/dl (CI 105.7−184.9, p <0.001). Multiple linear regression demonstrated that pretreatment hematocrit was inversely related to the expected change in hematocrit. Pretreatment comorbidity status (ie the presence of hypertension, hyperlipidemia, obesity or diabetes) was not associated with a significant increase in posttreatment hematocrit.

Conclusions: Although the data demonstrate a statistically significant increase in hematocrit, an increment of 2.2% is unlikely to translate into clinical relevance. Thus, for this cohort of patients implantable testosterone pellets appear safe in terms of the risk of polycythemia. Pretreatment hematocrit may serve as a predictor of a significant hematocrit increase after the initiation of therapy.

Key Words: hypogonadism, testosterone, polycythemia, hematocrit

Abbreviation and Acronym

BMI = body mass index

Accepted for publication June 1, 2016.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

* Correspondence: MGH Fertility Center, 55 Fruit St., YAW 10A, Boston, Massachusetts 02114 (telephone: 617-643-0044; e-mail: ctanrikut@mgh.harvard.edu).

The diagnosis and treatment of male hypogonadism have become increasingly popular in Western society as demonstrated by a threefold increase in testosterone prescriptions from 2001 to 2011.[1] The pharmaceutical industry has responded to the dramatic increase in demand, offering a multitude of formulations and drug vehicles.[2,3] Patients may now choose to supplement via topical gels, transdermal patches, transbuccal lozenges, intramuscular injections or subcutaneous implants. Subcutaneous testosterone pellets offer a unique advantage in that they require far less frequent dosing schedules than alternative treatment modalities.[4] Although a minor office procedure is required, many patients report high

0022-5347/16/1966-0001/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2016.05.110
Vol. 196, 1-6, December 2016
Printed in U.S.A.

satisfaction with this mode of therapy.[3,5,6] Compliance has even been shown to improve in challenging populations, as evidenced by previous work in adolescent patients with the Klinefelter syndrome.[7]

Subcutaneous testosterone pellets were initially approved by the Food and Drug Administration (FDA) in 1972, when regulations were less rigorous in terms of establishing safety and efficacy.[3] As a result, the testosterone pellets currently available in the United States have not undergone the same safety evaluation as more recently approved drugs. Although the subcutaneous pellet formulation was approved by the FDA more than 40 years ago, before 2008 no pellets were marketed in the United States despite their heavy use abroad. Much of the published experience is drawn from a product developed by Organon Laboratories (Cambridge, United Kingdom).[3,8] The testosterone pellets currently available in the United States, branded as Testopel®, are produced and marketed by Endo Pharmaceuticals (Malvern, Pennsylvania). This product is manufactured differently than the Organon product and, therefore, may provide distinct pharmacokinetics, efficacy and rates of adverse reactions.[3]

As with other forms of testosterone replacement, the principle dose limiting effect of implantable pellets is erythrocytosis due to increased erythropoiesis.[9–12] Marked increases in hematocrit represent a thromboembolic risk given the resulting change in blood viscosity.[10,13,14] Previous studies have shown variable risk profiles for polycythemia dependent on testosterone dose and form of administration, with intramuscular injections resulting in an increased risk.[15,16] With respect to testosterone pellets, prior experience with the Organon product has demonstrated safety with regard to hematocrit elevation.[8] Several studies in the United States using Testopel have also shown similar results with small increases in hematocrit.[4,6,17,18] Unfortunately most of these investigations represent small single institution series with short treatment times. Additionally, hematocrit response was a secondary outcome measure in all of these cohorts. The literature is lacking long-term studies of the Testopel product in which erythrocytosis represents the primary end point.

MATERIALS AND METHODS

A retrospective chart review was conducted at 2 tertiary referral centers in the greater Boston area. All adult males treated with implantable testosterone pellets for the management of hypogonadism between 2009 and 2014 were included in the analysis. We defined hypogonadism as a total testosterone level below 300 ng/dl with concomitant symptoms (eg erectile dysfunction, sarcopenia, mood disturbances). Patients who were naive to testosterone replacement, as well as those who received prior testosterone formulations and transitioned to testosterone pellets were included in the study.

The pellet implantation procedure at both institutions was completed according to manufacturer guidelines, as previously described.[17] Overall 8 to 12 pellets were used at each placement depending on BMI and dose response to prior implantations.[4,6] The procedure was typically repeated between 3 and 6 months after prior placement, depending on the testosterone trough and recurrence of symptoms.

All patients had at least 1 pre-pellet treatment testosterone and hematocrit available in the medical record. Posttreatment values represented the routine laboratory monitoring after treatment inception. All patients had a repeat hematocrit and serum total testosterone drawn between 3 and 6 months after initial placement, before any subsequent implantation procedure. Any patient who did not have documentation of the requisite monitoring laboratory values was excluded from the study. Only morning blood draws were considered when interpreting pretreatment testosterone. An expanded hormonal panel, including free testosterone, dihydrotestosterone and estradiol, was not included in the standard evaluation.

Demographic data collected included age at the start of treatment, race and the identity of the treating provider. Patients were stratified based on the absence or presence of diabetes (type I and type II), hypertension, hyperlipidemia and/or obesity (BMI greater than 30 kg/m^2). Before statistical analysis the pretreatment and posttreatment values of total testosterone and hematocrit were averaged when multiple data points were available.

Statistical analysis was conducted with JMP® Pro 11. Pretreatment and posttreatment hematocrit and testosterone were compared with Wilcoxon signed rank tests. Multiple linear regression was used to construct a model to predict change in hematocrit based on pretreatment variables (age, comorbidity status, pretreatment hematocrit, pretreatment total testosterone). All stated p values represent 2-tailed calculations. The study was approved by the institutional review boards at both institutions.

RESULTS

A total of 119 patients who had received pellet therapy were identified at the 2 sites. Of these patients 22 had incomplete data sets, leaving 97 patients to serve as the study population. Excluded patients most commonly had incomplete followup after pellet implantation (14 of 22), and so hematocrit and testosterone values after implantation were not available. Race distribution and comorbidity prevalence are listed in the table. Mean age of the cohort was 52 years (range 24 to 80). The majority of the study population was white, 64% of whom had at least 1 of the comorbidities investigated (obesity, diabetes, hypertension or hyperlipidemia). The average treatment period on pellets was 15.7 months (range 3 to 58). Nearly all patients (93%)