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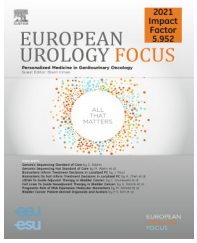

Clinical Studies Update

Comparing Rates of Polycythemia in Hypogonadal Men Using Nasal Testosterone Gel Versus Intramuscular Testosterone: Update of a Randomized Clinical Trial

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1. Introduction

In men who require testosterone therapy (TT), multiple potential side effects must be considered before prescribing treatment, including polycythemia, gynecomastia, and infertility. Polycythemia may be one of the more common side effects, occurring in up to 13% of men receiving TT [1]. Recent evidence has shown that the modality for TT delivery may affect the risk of polycythemia, among other side effects [2,3].We are conducting a randomized clinical trial to determine if short-acting nasal testosterone (NT) has a different risk of adverse events in comparison to more traditional, long-acting testosterone. We hypothesized that short-acting NT gel has less impact on hematocrit (HCT) and the risk of polycythemia in comparison to longer-acting intramuscular testosterone cypionate (TC) (Fig. 1).

2. Study details

This is an open-label, randomized clinical trial comparing the risk of polycythemia among patients undergoing TT with intramuscular TC versus NT gel.

2.1. Population

Only those who meet criteria for both testosterone deficiency (TD) diagnosis and treatment are enrolled [4]. Participants are required to be aged ≥18 yr with documented symptoms of TD and two testosterone levels <300 ng/dl in serum drawn in the morning. Full inclusion and exclusion criteria can be found on ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT04439799).

2.2. Intervention and comparison

Intramuscular TC is the most common treatment regimen for those experiencing TD in the USA, but is associated with polycythemia prevalence as high as 11.2% [5,6]. The rate of polycythemia with short-acting NT is reported as 1.3% [7]. There has been no head-to-head comparison of these formulations, leading to uncertainty about the differences in risk of polycythemia. Polycythemia is thus the primary endpoint of our study.

2.3. Outcomes

The primary outcome is the change in HCT after 4 mo of TT with either TC or NT. Secondary outcomes are changes in serum testosterone, estradiol, prostate-specific antigen

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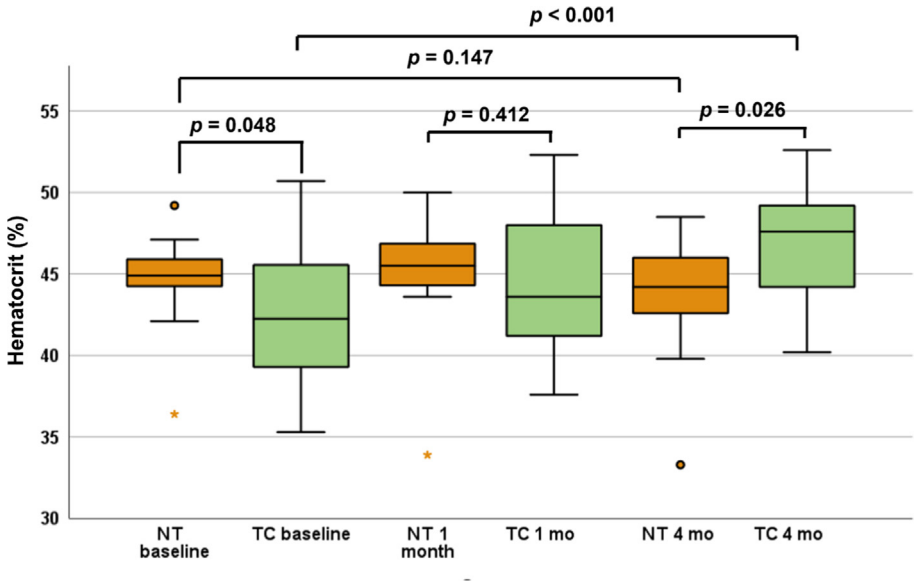

Fig. 1 – Box plot of the hematocrit change over time in the intranasal testosterone (NT) and testosterone cypionate (TC) groups.

(PSA), and 17-hydroxyprogesterone (17-OHP). Polycythemia is defined as HCT >52%.

2.4. Statistical considerations

Data analysis is performed using SPSS v28. Differences in obstructive sleep apnea (OSA) prevalence among groups is analyzed using a χ^2 test. Changes in testosterone, HCT, PSA, and estradiol over time within groups is evaluated using the Wilcoxon test. A p value <0.05 is considered statistically significant. Assuming an increase in HCT by 4–5%, a sample size of 25 subjects in each arm is required to achieve 90% power. To account for dropouts, we aimed to recruit 80 individuals to the study.

2.5. Duration of study participation

The total study duration is 4 mo and subjects are provided with enough testosterone to last until their next visit. Subjects receive NT 11 mg three times a day or TC 200 mg intramuscularly once every 2 wk. Participants attend three visits, at baseline, 1 mo, and 4 mo.

3. Results and progress

A total of 39 men with TD have been randomized to receive NT (n = 15) or TC (n = 24). The median participant age is 46 yr, with median baseline serum testosterone of 237 ng/dl and median baseline HCT of 43%. The OSA prevalence as measured using the STOP-BANG questionnaire is 67% for the NT group and 71% for the TC group. After 4 mo of treatment, TC users experienced a significant increase in HCT (p < 0.001) whereas NT users did not. The prevalence of polycythemia (HCT >52%) after 4 mo was 0% in the NT group and 4.2% in the TC group. In comparison to baseline, both treatment regimens significantly increased serum testosterone to eugonadal levels in 71% of men who received TC and 80% of men who received NT (p < 0.001). Among men who received TC, we observed an increase in serum estradiol (p = 0.003) and a decrease in serum 17-OHP (p < 0.001) at follow-up, whereas there were no significant changes for men who received NT. Reassuringly, neither regimen significantly impacted PSA at follow-up. At the time of writing, we are still recruiting patients for enrollment.

4. Discussion

This is the first randomized trial to conduct a head-to-head comparison of NT gel and intramuscular TC. Among the short-acting testosterone modalities, NT is dosed the most frequently and has the shortest half-life. This theoretically has the ability to more closely mimic physiological release of testosterone and thus lead to fewer adverse events [2]. It has been shown that NT preserves spermatogenesis and gonadotropins [2], and the evidence now suggests that it also appears to avoid secondary erythrocytosis. This is particularly important for comorbid men on testosterone, as polycythemia while on testosterone can increase the rates of major adverse cardiovascular events [8]. Having options to treat TD is essential for both providers and patients [9–11].

Conflicts of interest: Ranjith Ramasamy is a consultant for Acerus Pharmaceuticals, Boston Scientific, Endo Pharmaceuticals, and Coloplast; has received grants from Acerus Pharmaceuticals, Boston Scientific, Endo Pharmaceuticals, Coloplast, Empower Pharmacy, and Olympus; is an advisory board member for Hims, Inc.; and has received National Institutes of Health funding (1R01DK130991-01). Jesse Ory is a consultant for and has received grants from Acerus Pharmaceuticals. The remaining authors have nothing to disclose.

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