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Original Article

Comparison of the Subcutaneous and Intramuscular Estradiol Regimens as Part of Gender-Affirming Hormone Therapy

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ABSTRACT

Objective: Gender-affirming hormone therapy guidelines describe the estradiol (E2) doses for intramuscular (IM), but not subcutaneous (SC), routes. The objective was to compare the SC and IM E2 doses and hormone levels in transgender and gender diverse individuals.
Methods: This is a retrospective cohort study at a single-site tertiary care referral center. Patients were transgender and gender diverse individuals who received injectable E2 with at least 2 E2 measurements. The main outcomes were the dose and serum hormone levels between the SC and IM routes.
Results: There were no statistically significant differences in age, body mass index, or antiandrogen use between patients on SC (n = 74) and those on IM (n = 56). The weekly doses of SC E2, 3.75 mg (IQR, 3-4 mg), were statistically significantly lower than those of IM E2, 4 mg (IQR, 3-5.15 mg) (P =.005); however, the E2 levels achieved were not significantly different (P =.69), and the testosterone levels were in the cisgender female range and not significantly different between routes (P =.92). Subgroup analysis demonstrated significantly higher doses in the IM group when the E2 and testosterone levels were >100 pg/mL and <50 ng/dL, respectively, with the presence of the gonads or use of antiandrogens. Multiple regression analysis demonstrated that the dose was significantly associated with the E2 levels after adjusting for injection route, body mass index, antiandrogen use, and gonadectomy status.
Conclusion: Both the SC and IM E2 achieve therapeutic E2 levels without a significant difference in the dose (3.75 vs 4 mg). SC may achieve therapeutic levels at lower doses than IM .

Introduction

Gender-affirming hormone therapy (GAHT) for transgender and gender diverse (TGD) individuals may consist of estradiol (E2) and antiandrogen therapy to align physical appearance with gender identity.[1] Current practice places emphasis on the use of 17-β- E2 in various preparations (parenteral, oral, and transdermal), moving away from the historical use of ethinyl E2 and conjugated estrogens because of concerns of an increased adverse risk profile.[1,2] Doses recommended to achieve premenopausal E2 levels that also suppress the pituitary/gonadal axis for GAHT may be higher and more frequent than the current Food and Drug Administration–approved indications for cisgender female estrogen deficiency.[1]

When used for GAHT, E2 formulation, dosing, and route may depend on multiple factors, including geographic variation and availability, insurance coverage and financial affordability, patient preference, and concern for route-specific adverse effects.[3,4] Prior studies have shown that parenteral E2 use varies greatly between practices, with some studies reporting minimal use in TGD individuals.[5,6] Parenteral E2 is available in various esters, most commonly as valerate and cypionate. Pharmacokinetics varies

Abbreviations: BMI, body mass index; E2, estradiol; GAHT, gender-affirming hormone therapy; IM, intramuscular; SC, subcutaneous; TGD, transgender and gender diverse.

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depending on the specific ester with the duration lasting between 4 and 14 days and the peak E2 level achieved 2 to 3 days after an injection.[7-10] Existing recommendations for GAHT suggest intramuscular (IM) doses of 2 to 10 mg every week or 5 to 30 mg every 2 weeks.[1,2] As opposed to data and guideline recommendations about subcutaneous (SC) testosterone for GAHT in TGD individuals, there are little data to support SC E2 recommendations to date.[1] In studies directly comparing IM testosterone and SC testosterone in transgender men, there was a clear patient preference for the SC route, with patients reporting increased tolerability and less injection site related pain.[11,12] When compared, most transgender men in these studies achieved cisgender male testosterone levels and menstrual cessation with no difference between those on SC testosterone and those on IM testosterone.[11-14]

In initial studies, SC E2 was reported to be well tolerated with fewer local side effects than IM E2 and without any difference in feminization.[15] The recommended dosing ranges specifically for the SC route of E2 are not widely available in current publications.[16,17] Based on few high-quality studies with limited sample sizes, the current recommended SC E2 doses equate to those of IM E2, although few studies directly compare these 2 parenteral routes. Studies in cisgender women show equivalent pharmacokinetic profiles between SC E2 and IM E2, although parenteral use is minimal in this population compared with that in TGD individuals.[7,18,19]

In this study, we aimed to directly compare the parenteral routes of E2 administration as part of GAHT. The primary aim was to compare the doses between the SC and IM routes and the serum E2 and testosterone levels in TGD individuals. The secondary goals included comparing the effect of antiandrogens, gonadectomy status, and the use of E2 cypionate vs valerate on doses between SC administration and IM administration.

Highlights

- Both subcutaneous estradiol (E2) and intramuscular E2 are effective as gender-affirming hormone therapy to achieve therapeutic E2 levels
- The median subcutaneous E2 doses of 3.75 mg vs the intramuscular doses of 4 mg achieved therapeutic E2 levels
- The initial and maintenance parenteral doses needed to achieve therapeutic E2 levels were lower than previously recommended

Clinical Relevance

Lower doses of parenteral estradiol (E2) than previously described achieved therapeutic E2 levels. Both subcutaneous and intramuscular E2 preparations as gender-affirming hormone therapy should be discussed to individualize treatment for each patient.

Methods

TGD patients under care at our tertiary referral institution were identified through an existing registry spanning January 2011 to May 2022. This retrospective study was approved by the institutional review board at Mayo Clinic. Adult TGD patients aged ≥18 years on GAHT were included if they had ≥2 serum E2 levels and were utilizing either IM or SC E2. We excluded participants with 1 serum E2 level because they may have included patients not followed longitudinally or without dose adjustment. Patients had their E2 dose adjusted by their medical providers according to the serum E2 levels, testosterone levels, and goal feminization. Timing of E2 blood draw in relation to injection was not protocolized.

Patient records were reviewed to extract age, body mass index (BMI), gonadectomy status, antiandrogen use, serum E2 levels, testosterone levels, and the use of GAHT (including doses and formulation of E2) at their most recent clinical visit. These data were compared with corresponding laboratory data within 2 months of the visit. The E2 doses were analyzed as a weekly dose equivalent because few patients utilized every 2-week dosing. The total numbers of E2 levels available were collected; however, only the most recent level was used for analysis. The most recent clinical note was utilized in collection of doses of E2 in lieu of the medication list if it had not been updated. The duration of therapy was defined as the duration of SC or IM therapy only because patients may have received prior oral or transdermal therapy. Antiandrogen was defined as the use of any agent to lower or inhibit endogenous androgen production including, but not limited to, spironolactone, gonadotropin-releasing hormone agonists, or 5-α-reductase inhibitors. Gonadectomy status was defined as the status of patients who underwent bilateral orchiectomy with or without vaginoplasty. E2 monotherapy was defined as the E2 therapy of patients with gonads present without the use of antiandrogens. An E2 level of >100 pg/mL (target E2 levels as defined by the 2017 Endocrine Society guidelines[1]) represented a categorical value. Testosterone suppression represented a categorical value defined as a serum testosterone level of <50 ng/dL (cisgender female range, as defined by the 2017 Endocrine Society guidelines[1]). Additionally, for individuals on SC E2, we also recorded prior E2 use and reasons for changing routes when these details were available.

Available E2 levels were measured using liquid chromatography-tandem mass spectrometry, with high accuracy (% bias, <4) and precision (% coefficient of variation, <7.5) at broad linear dynamic ranges (0.005-20 ng/mL).[20] No radioimmunoassay E2 levels were included for this study.

Patient Education for SC Administration

For all patients who were new to injections, education on self-administration and educational pamphlets were provided by nursing staff. Several patients chose to administer their first injection during this teaching. Prescriptions for 1-mL syringes (for optimal visualization and accurate dosing) and 2 sizes of needles, 18-gauge 1.5-inch needles for drawing hormone from vial and 25-gauge 5/8-inch needles, were provided. Patients were advised to administer the E2 into the SC tissue of the abdomen or thighs and allow a 5-second pause with plunger depressed before needle withdrawal.

Statistical Analysis

Statistical analysis was conducted using BlueSky Statistics v7.40 (BlueSky Statistics LLC). Given that some variables were not normally distributed, the nonparametric Wilcoxon test (Mann-Whitney *U* test) was used for continuous variables. The χ^2 analysis and Fisher exact test were performed for categorical variables between groups and subgroups. To better examine E2 dosing differences between the SC and IM groups, the Kruskal-Wallis test was used to evaluate differences in the median doses by route (stratifying for subgroups achieving the target E2 level of >100 pg/mL), suppressed testosterone (<50 ng/dL) in patients without gonadectomy, gonadectomy status, and antiandrogen use. Multiple linear regression analysis was used to determine whether the association of E2 dose

and levels was affected by route and/or variables that were different between the SC and IM groups. Statistical significance was defined as a *P* value of <.05.

Results

Baseline Characteristics

A total of 306 adult TGD patients were initially identified on GAHT with ≥2 E2 levels. From this cohort, we identified 24.1% (n = 74) of patients utilizing SC E2 and 18.3% (n = 56) of patients utilizing IM E2. Table 1 shows the baseline characteristics of these 2 groups. Age, BMI, the duration of treatment, and antiandrogen use did not significantly differ between the groups. Most utilized weekly dosing, and there was no statistically significant difference between the numbers of patients utilizing every 2-week dosing (IM, 8.9% vs SC, 1.4%; *P* =.08). Of those 6 patients on every 2-week dosing, the median E2 dose was 8.5 mg every 2 weeks (range, 6-16 mg). The proportion of patients who underwent gonadectomy was higher in the IM E2 group than in the SC E2 group (53.6% vs 24.3%; *P* =.001). Although no difference was noted in the duration of injectable E2 use, there were statistically significantly fewer E2 levels drawn throughout the study period in the IM group (median, 4 [IQR], 2-7.3]) than in the SC group (median, 6 [IQR, 4-8]) (*P* =.005).

Hormone Levels

The median levels of the most recent E2 were determined not to be statistically significantly different between SC administration and IM administration (196 pg/mL [IQR, 125-298 pg/mL] vs 189.5 pg/mL [IQR, 122.5-257 pg/mL], *P* =.70) (Table 1 and Fig. *A*). The proportion of patients who had levels of >100 pg/mL was not different between patients on SC E2 (n = 61, 82.4%) and those on IM E2 (n = 44, 78.6%) (*P* =.58). Likewise, in patients with gonads present, there was no difference in the median testosterone level or in whether testosterone suppression was achieved between the groups (Table 1). Most testosterone levels were drawn at the same time as E2; however, in 23 patients (29.1%), the levels were from separate draws.

E2 monotherapy was utilized in 17 patients (20.7%) with gonads present: 4 (23.5%) in the IM group and 13 (76.5%) in the SC group. Therapeutic E2 levels were achieved in all patients, with a median E2 level of 220 pg/mL (IQR, 180-264 pg/mL) and median dose of 4 mg (IQR, 3-6 mg). Of those patients, most (15 patients, 88.2%) achieved testosterone levels of <50 pg/mL.

Table 1
Baseline Characteristics and Estradiol/Testosterone Levels Achieved by Intramuscular vs Subcutaneous Estradiol Route

Variable	Intramuscular E2 n = 56	Subcutaneous E2 n = 74	*P* value
Age, y (median [IQR])	40.5 (29.75-55)	35 (28-51.75)	.34
Race/ethnicity			
White (n, %)	48 (85.7%)	65 (87.8%)	-
Black (n, %)	1 (1.8%)	1 (1.4%)	
Asian (n, %)	1 (1.8%)	2 (2.7%)	
Native American (n, %)	0 (0%)	0 (0%)	
Latinx (n, %)	0 (0%)	1 (1.4%)	
Other (n, %)	3 (5.4%)	2 (2.7%)	
Unknown/not reported (n, %)	3 (5.4%)	3 (4.0%)	
Duration of injectable E2 usage, mo (median [IQR])	36 (25.5-64)	36 (21.8-56)	.28
Injection frequency			
Weekly (n, %)	51 (91.1%)	73 (98.6%)	.08
Every 2 wk (n, %)	5 (8.9%)	1 (1.4%)	
E2 ester			
Valerate (n, %)	50 (89.3%)	64 (86.5%)	.63
Cypionate (n, %)	6 (10.7%)	10 (13.5%)	
Antiandrogen use			
Yes (n, %)	28 (50.0%)	43 (58.1%)	.36
Type of antiandrogen used (n, %)[a]			
Spironolactone	21 (37.5%)	38 (51.4%)	
Finasteride	11 (19.6%)	5 (6.8%)	
Other[b]	0 (0%)	3 (4.1%)	
No (n, %)	28 (50.0%)	31 (41.9%)	
BMI, kg/m^2 (median [IQR])	28.89 (25.73-32.99)	28.60 (23.10-33.44)	.56
History of gonadectomy			
Yes (n, %)	30 (53.6%)	18 (24.3%)	**.001**
No (n, %)	26 (46.4%)	56 (75.7%)	
Serum E2 level (pg/mL) (median [IQR])	189.5 (126.8-252.5)	196 (125.3-298.5)	.70
Serum T level (ng/dL), patients not having undergone gonadectomy (n = 79)[c]			
Median (IQR)	11 (0-19.8)	11 (0-20)	.92
Achieved T level of <50 ng/dL			
Yes (n, %)	22 (84.6%)	46 (86.6%)	.79
No (n, %)	4 (15.4%)	7 (13.2%)	
Median (range)	*174 (57-363)*	*72 (51-721)*	-

Abbreviations: BMI = body mass index; E2 = estradiol; T = testosterone.
[a] Four patients in both the subcutaneous and intramuscular estradiol cohorts utilized spironolactone and finasteride.
[b] Includes leuprolide (n = 2) and dutasteride (n = 1).
[c] Three patients in the subcutaneous estradiol group did not have available testosterone levels.

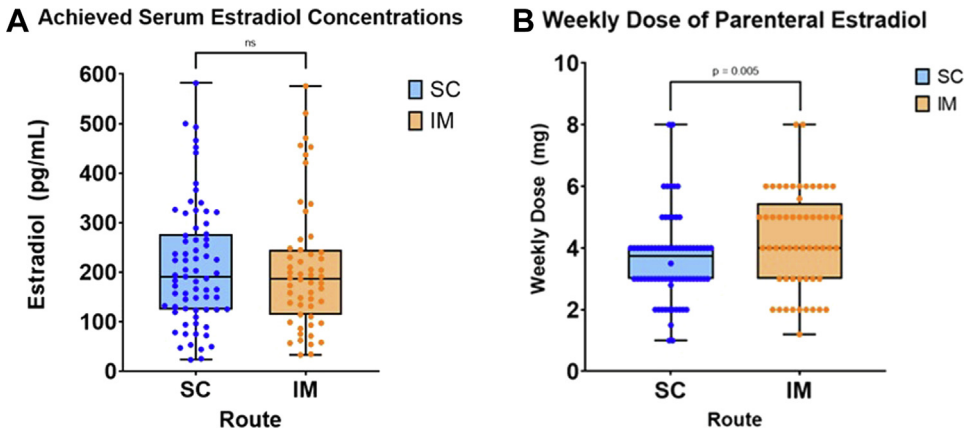

Fig. Comparison of the routes of administration by the achieved serum estradiol levels (pg/mL) (*A*) and weekly dose (mg) of estradiol (*B*). *IM* = intramuscular; *SC* = subcutaneous.

All patients with every 2-week dosing achieved E2 levels of >100 pg/mL and testosterone levels of <50 ng/dL.

SC vs IM Route

The difference in dosing by the SC/IM route is shown in Table 2 and Figure *B*. The median weekly dose for SC E2 was 3.75 mg (IQR, 3-4 mg) vs 4 mg (IQR, 3-5.15 mg) for IM E2, which was statistically significantly different (P =.005) (Table 2). On further stratification, patients treated with IM E2 had statistically significantly higher median weekly doses than those treated with SC E2 in the subgroups of patients achieving therapeutic E2 levels, patients achieving testosterone levels of <50 ng/dL, patients with gonads present, and patients on antiandrogens (Table 2). There was no statistically significant difference between the median weekly dosing when stratified by E2 levels of <100 pg/mL, patients who had undergone gonadectomy, and patients not using antiandrogens (Table 2).

Using multiple linear regression analysis, the E2 dose was significantly associated with the E2 level even after adjusting for E2 route, BMI, antiandrogen use, or gonadectomy status (Table 3).

Cypionate vs Valerate

When comparing different E2 esters, 86.5% (n = 64) of patients in the SC group and 89.3% (n = 50) of patients in the IM group were on E2 valerate. The remaining participants utilized E2 cypionate. There was no statistically significant difference in the utilization of E2 valerate and that of cypionate between the SC and IM groups (Table 1). In the IM group, there was no statistically significant difference between the median weekly doses of E2 cypionate (4 mg [IQR, 2.25-5 mg]) and E2 valerate (4 mg [IQR, 3-5.45 mg]) (P =.51). However, the median weekly E2 cypionate doses were statistically significantly lower than those of E2 valerate in the SC group (3 mg [IQR, 2-3 mg] vs 4 mg [IQR, 3-4 mg], respectively; P =.025).

Administration Route Changes

Thirty-six (48.6%) patients on SC E2 were previously on other routes of administration of E2 (oral and/or transdermal). The most common available reasons included nonefficacy (including suboptimal feminization or target levels of E2 not achieved), financial reasons (eg, lack of insurance coverage of other preparations), and patient preference (most commonly after awareness from the experience of other TGD patients on SC E2).

Adverse Events

No local site injection reactions with SC or IM injections were reported. No cardiovascular or venous thromboembolism events were reported during the study period.

Discussion

In this study, we compared the SC vs IM routes of injection as a part of GAHT in TGD individuals. There were no significant differences in demographic or baseline characteristics between the cohorts except for a statistically significant difference in the number of patients who underwent gonadectomy in the IM group. Statistically significantly lower median weekly doses of SC E2 were observed while achieving target E2 levels (SC E2, 3.75 mg [IQR, 3-4 mg], vs IM E2, 4 mg [IQR, 3-5.15 mg]). In Figure *B*, more individuals using the IM route clustered into a higher range of doses than the SC group. Subgroup analysis showed that the groups who achieved therapeutic E2 levels, testosterone levels of <50 ng/dL, patients with gonads present, and patients on antiandrogens had statistically significantly higher median IM E2 doses; however, patients with E2 levels of <100 pg/mL, those who had undergone gonadectomy, and those not using antiandrogen did not. To our knowledge, this is the first study to directly compare these 2 routes, and more importantly, it provides further direction on the doses of parenteral E2 for our TGD individuals.

In transgender men, the SC testosterone doses with autoinjector preparations have been reported to be lower than the IM testosterone doses, although doses are not different when using similar injection-related supplies.[11-14] This suggests patient-specific reasons, such as injection-related techniques, for decreased SC dosing ranges needed to achieve similar E2 levels in our patient cohort. It is also possible that patient comfort and compliance improved with SC injections compared with those with IM injections, which may explain the higher doses prescribed in the IM cohort than in the SC cohort. A dose-dependent increase in the E2 levels was observed in the IM or SC cohort based on the statistically significant difference on regression analysis, suggesting the need to start at lower doses with close E2 and testosterone level monitoring, because this is different than a previous study where this was not noted in IM and transdermal E2.[21]

From a pharmacokinetic standpoint, we could not ascertain a clear mechanism to suggest increased bioavailability in SC administration of E2 vs IM administration.[7-10,18,19] It is interesting that the significantly higher doses with IM injections were specifically observed in subgroups with gonads present or with those who

Table 2
Weekly Estradiol Doses by Route and Stratified by Therapeutic Effect, Gonadectomy Status, and Antiandrogen Use

Variable	Intramuscular E2 n = 56	Subcutaneous E2 n = 74	*P* value
Median doses (mg/wk) (IQR)	4 (3-5.15)	3.75 (3-4)	**.005**
Serum E2 level of >100 pg/mL (mg/wk) (IQR)			
Yes	4 (3-5)	3 (3-4)	**.028**
No	4.5 (3.75-6)	4 (3-4)	.12
Serum T level of <50 ng/dL (mg/wk) (IQR), patients not having undergone gonadectomy[a]	5 (4-6)	3 (3-4)	**<.001**
History of gonadectomy (mg/wk) (IQR)			
Yes	4 (3-5)	4 (2.5-4)	.26
No	5 (4-6)	3.5 (3-4)	**.002**
Antiandrogen use (mg/wk) (IQR)			
Yes	4 (4-5.25)	3 (3-4)	**.001**
No	4.5 (2.75-5.15)	4 (3-5)	.45

Abbreviations: E2 = estradiol; IQR = interquartile range; T = testosterone.
[a] Three patients in the subcutaneous estradiol group did not have available testosterone levels.

Table 3
Multiple Regression Model of the Effect of the Weekly Dose on Estradiol Levels

Variable	Estimate ± SE	*P* value
Weekly estradiol dose (mg)	57.42 ± 10.46	**<.001**
Estradiol route (SC and IM)	8.38 ± 45.09	.85
BMI (kg/m^2)	−2.62 ± 2.52	.30
Antiandrogen use	−74.42 ± 53.96	.17
History of gonadectomy	−51.32 ± 57.87	.38

Abbreviations: BMI = body mass index; IM = intramuscular; SC = subcutaneous.

were using antiandrogens. Although it may be expected that patients with gonads present may need higher E2 doses for testosterone suppression, this difference was not observed in the SC group. It is also difficult to explain the significantly higher doses with antiandrogens only in the IM group than in the SC group. Few patients utilized every 2-week dosing; these were analyzed in a weekly dose equivalent but may have had a slight impact on IM dosing considering that the median weekly dose equivalent utilized was slightly higher. Because testosterone suppression was achieved equally in both groups, IM use was not necessarily less effective at achieving hormonal effect. Instead, it is possible that gonadectomy status and antiandrogen use are surrogate markers for patients who opted for higher or earlier feminizing effects with higher-dose E2 via the IM route and androgen blockade.

Most patients on E2 monotherapy with gonads present were able to suppress testosterone appropriately without the use of antiandrogen. The median E2 level was higher at 220 pg/mL than in the group overall (SC, 196 pg/mL vs IM, 189.5 pg/mL). Although the median dose of 4 mg was similar to the SC and IM groups, the IQR for patients on E2 monotherapy was larger at 3 to 6 mg. This suggests that higher doses of injectable E2 and/or higher E2 levels are needed to suppress testosterone without the use of antiandrogens.

Prior studies used for the development of guidelines for parenteral doses are suboptimal given their small sample sizes or prespecified GAHT protocols with no adjustment of E2 doses or no information on hormone levels achieved. Deutsch et al[22] found that of 16 transfeminine patients, only 1 was administered parenteral E2 valerate at a dose of 20 mg IM every 2 weeks and that this patient achieved supratherapeutic E2 levels (defined as >1000 pg/dL). Mueller et al[23] used a protocol of IM E2 valerate (10 mg every 10 days) along with 3.8 mg of goserelin acetate every 4 weeks. The main outcome noted here was related to body composition and bone mineral density. The median nadir E2 levels for 84 patients were 93 pg/mL at 12 months and 191 pg/mL at 24 months,[23] which is higher than the goal because the E2 levels are ideally tested midway through the injection cycle, with the pharmacokinetics of the peak parenteral E2 level at day 4 after injection.[7]

Other studies not used for guideline development describe different protocols for parenteral E2. Yun et al[24], whose main purpose was to investigate changes in body composition, bone mineral density, and muscle strength, described that 1 of 11 patients used IM E2 valerate either 5 or 10 mg every 2 weeks; the specific E2 dose for this patient was not mentioned, although the dose was increased per protocol if the E2 levels were not significantly elevated at 6 months. Randolph[25] has provided recommendations for lower doses of 2 to 10 mg weekly, stating that these dose ranges are extrapolated from cisgender women utilizing other formulation of E2. Prescribing patterns in Australia show that oral E2 is preferred, and of those who responded to the study, 0% preferred parenteral E2 as their first-line therapy.[6] This low preference appears to be different than that in the TGD population in our practice.

Overall, the studies used to support the current dosing recommendation guidelines for parenteral E2 dosing are limited and incomplete with regard to hormone levels achieved and do not provide SC as an available option. The doses of E2 used in this study (with either the SC or IM approach) were successful in achieving serum E2 levels at the cisgender female range. Most importantly, compared with the current available guidelines and consensus statements,[1,2] these doses of E2 valerate are less than half of what is recommended for both the initial dosing and maintenance dosing and achieved suppression of testosterone.

In our study, the median E2 cypionate dose was statistically significantly lower than the E2 valerate dose in the SC group but not in the IM group. A study in 1980 evaluated the plasma levels of E2 in 9 to 10 subjects before and during 3 weeks after IM administration of a single dose of E2 cypionate, valerate, or benzoate.[7] Administration of E2 cypionate resulted in significantly lower peak levels of E2 than that of valerate but a significantly longer duration of elevated E2 levels.[7] The guidelines from Deutsch 2016[2] suggest lower doses of cypionate compared with those of valerate with references related to pharmacokinetics. The pharmacokinetic difference in the esters likely explains the difference observed. Whether the doses of cypionate (median weekly dose, 3 mg) and valerate (median weekly dose, 4 mg) are clinically relevant in terms of formulation selection when utilized SC remains not clear. Further studies with larger sample sizes are needed to examine the risks and benefits of specific parenteral E2 doses and formulations.

Strengths and Limitations

To date, this study includes the largest number of patients on parenteral E2 compared with those of previous studies. The

inclusion criteria, such as >1 documented E2 level and multiple clinical visits, suggest that hormone dosing details are more reflective of adequate maintenance dosing and expected feminization. Additionally, only liquid chromatography mass spectrometry–derived E2 levels were analyzed in this study, which had a higher accuracy and precision than those levels derived from a radioimmunoassay method.

The limitations of this study include the retrospective nature of this study and individualized approach to the use of parenteral E2 by the prescribing providers. In our practice, although E2 levels were generally checked midway through the injection cycle, we were unable to document with certainty the timing of the E2 laboratory testing, which may have influenced the results and/or the outliers. Testosterone levels did not always coincide, in terms of timing of blood draw, with E2 levels; however, this was infrequent, involving only 23 patients. The most recent E2 and testosterone levels were collected, and some results may have been influenced by earlier GAHT users. For local injection site reactions, documentation is typically performed if there is a patient-reported concern; however, milder or unreported symptoms (if not bothersome) may not have been captured. Finally, there are electronic medical record–related limitations when collecting data—all patients may not have been captured and abstracted data were contingent on appropriate and accurate clinical documentation. For example, doses from clinical notes may not match the electronic prescription details.

Conclusion

In conclusion, the use of SC or IM E2 for TGD individuals is an effective route for GAHT. Although the median SC dose was statistically significantly lower than the IM dose, the doses were not significantly different in terms of guiding initial dose selection. Lower doses of parenteral injections than previously described in the clinical practice guidelines achieved therapeutic E2 levels. Our data can serve as a dosing guide for the initial and maintenance use of parenteral E2, which is different than what has been previously described. Therefore, initiation of E2 GAHT in TGD individuals or considerations of different routes after initiation should include discussion of both SC and IM parenteral preparations to individualize treatments for each patient. Further studies are needed to analyze clinical outcomes and achievement of feminization in comparison with other preparations of E2, as well as additional risks vs benefits.

Disclosure

The authors have no multiplicity of interest to disclose.

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Author Contributions

C.J.D.-P. and A.Y.C. contributed equally to this work. J.S.H., A.K.M., S.J.C., T.B.N., C.J.D.P., and A.Y.C. designed the research; J.S.H., and A.K.M. collected the data; J.S.H., C.J.D.P., and A.Y.C. analyzed the data; J.S.H., A.K.M., T.B.N., C.J.D.P., and A.Y.C. drafted the manuscript; and J.S.H. revised the manuscript. All authors reviewed and approved the final manuscript.

Data Availability

Some or all data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

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