Stress İnkontinansta Enjeksiyon Tedavisinin Etkinliği: 8 Yıllık Sonuçların Retrospektif İncelenmesi

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Özet

Anahtar Kelimeler
SÜI, Transüretral Enjeksiyon, VKİ, Geçirmiş Anti-İnkontinans Cerrahisi, Menopozal Durum

Abstract
Aim: To evaluate the long term affectivity of transurethral Calcium Hydroxylapatite (CaHA; Coaptite®) injection therapy and the predictive importance of Body Mass Index (BMI), menopausal status and previous anti-incontinence surgery in selected female patients with stress urinary incontinence (SUI). Material and Method: Forty-five female patients with SUI, and having high risks for general anesthesia, received transurethral injection therapy, were evaluated retrospectively. First month, 12th month, and 8th year of post-injection period were evaluated in terms of International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF), Quality of Life (Qol) score, and ped test. Results: While the pad test of 1st and 12th months’ showed statistically significance, the pad test of last visit was found insignificant, when compared with pre-injection term. Through the evaluations of questionnaire forms similar to the pad test, it was observed that the post- injection scores showed statistically significance. However, unlike to the pad test, for each of both questionnaires, statistically significant differences were detected at the last examination’s scores, as well. When we examined the success of the transurethral injection treatment according to menopausal status, BMI, and previous anti-incontinence surgery, it was observed that Qol and ICIQ-SF score %variation, and 24 hr pad test values did not show any statistically significant differences at long term control, compared with the pre-injection term. Discussion: Transurethral injection is a cheap, easily performed and effective method for selected patients with SUI and BMI, previous anti-incontinence surgery, and menopausal status do not affect transurethral injection results at long term.

Keywords
SUI, Transurethral Injection, BMI, Previous Anti-Incontinence Surgery, Menopausal Status
Introduction
Incontinence is a serious health problem which has social and economic effects on society. Stress urinary incontinence (SUI) is the most common type of urinary incontinence (%49) among women [1,2] and defined by International Continence Society (ICS) as complaint of involuntary leakage on effort or exertion, or on sneezing or coughing [3]. It is possible to say that since the first injection used in treatment of incontinence, there have been important developments. The first study about injection was published by Murless in 1938. By injecting sodium morrhuate, which is a sclerosant substance into anterior vaginal wall, Murless aimed to strengthen of bladder outlet, however serious complications were observed after the injection [4].

Short-termed efficiency of injection therapy prevented this procedure from being a standard treatment in SUI [5,6]. In most publications searching the efficiency of this procedure, it is emphasized that patient selection is important apart from material selection, and best candidates are women who have intrinsic sphincter deficiency with minimal urethral mobility and normal detrusor function [7,8]. Today, discussions on efficiency of transurethral injection treatment and to what kind of patients it should be used have been going on. Recent studies emphasize that transurethral injection should be taken into account on patients who still have stress incontinence despite the usage of anti-incontinence surgeries, patients with surgically high risks for general anesthesia, patients who need constant anticoagulant treatment, and those plan to have children in the future [9]. Transurethral injection treatment is easy to implement, and does not require general anesthesia. It is the minimal invasive method with least morbidity. Following failed operations such as pubovaginal sling (PVS), transobturator tape (TOT) or tension-free vaginal tape (TVT), it has a wide scope to be carried out in a wide patient population as a supplementary or primary treatment option. Today, many materials are used for injection therapy. By producing focal but firm expansion, the mechanism of action of these materials increases the transmission of pressure into proximal urethra [10].

In this study, we examined the long term efficiency of transurethral Coaptite® (BioForm Medical, San Mateo, California, USA) injection retrospectively in selected female patients having SUI. Apart from this, we also searched for the predictive importance of BMI, menopausal status and previous anti-incontinence surgery on the results of transurethral injection treatment.

Material and Method
In this study, 45 female patients with SUI, and received transurethral injection treatment between 2002-2010, were evaluated retrospectively. This study was approved by the local ethics committee and each patient’s consent for the use of their information was taken in writing.

Routine blood biochemistry and urine analysis examinations were carried out for all patients before the operation. In lithotomic position, with a detailed genital examination, Q type test was performed and patients were evaluated in terms of urethral hypermobility. When valsava maneuver was performed, formation of 30° or more angle in uretrovesical resultant was defined as urethral hypermobility, and injection treatment was not performed in patients who have certain urethral hypermobility. In the same way, injection treatment was not performed to patients with pelvic organ prolapsus higher than grade1 in genital examination. Observation of senile atrophic vaginal variations was considered to be an important criterion in deciding implementation of injection treatment. All patients have undergone urodynamic evaluations and patients having detrusor overactivity were not included in the study.

Patients were surveyed in detail by age,parity, menopausal status, BMI, previous incontinence surgery, pregnancy volition, diseases requiring constantly drug usage, and the results were recorded. At lithotomic position during pre-process, local anesthesia was provided through injection of 10 ml of 5% lidocain into urethral wall and bladder neck. Following this, with the accompany of cystoscope, by using a 23Gauge injection needle, submucosal Calcium Hydroxylapatite (CaHA) was injected into 0.5cm distal to the bladder neck at 4 and 8 o’clock positions transurethrally. The material was injected into bladder neck until coaptation was provided. When material extravasation observed or injection got very close to the surface, injection needle was relocated, and the process was repeated. At the post-injection process, patients’ bladders were filled with saline solution, and it was monitored via valsava maneuver that if urinary leakage occurs or not.

Before the procedure all subjects received quinolone antibiotics, and the treatment continued for 3 days post-operatively. During follow-up, patients were invited for controls at 1st and 12th months of the post-operative period. Then, in July 2010, available patients were invited for the last examination again. During the whole examination process, all patients filled out questionnaires of International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF) and Quality of Life (QoL), 24-hour pad test was performed. According to Stamey, patients were graded between 0 and 3 in terms of incontinence [11]. The results of the pre-operative Stamey grades were compared with the post-injection 12th month and last examination Stamey grades. Stamey grades; Grade 0: continence (dry), Grade 1: urine leakage which occurs with heavy physical activities such as heavy lifting and coughing, but not in bed, Grade 2: urine leakage which occurs with minimal activities such as walking or standing, Grade 3: is determined as constant urine leakage occurring with any kind of case independent from activity or position. According to these stages, patients who became totally continent (Stamey Grade 0) were accepted “cure”, patients who got better by at least 1 Stamey Grade were accepted “improvement”, and patients who did not change or got worse were accepted as “failure”. Patients who were “failure” in post injection were re-injected with CaHA.

Post operative 1st month’s and 12th month’s QoL and ICIQ-SF scores and the last examination’s QoL and ICIQ-SF scores were compared with the same scores of the pre-operative period, and the percentage changes between these scores were calculated. These parameters were defined as “QoL score %variation” and “ICIQ-SF score %variation”.

Statistical Analysis
Data analyses are progressed through Statistical Package for
Social Science (SPSS Inc, Chicago, Illinois, USA) 16.0 version programme. Continue data are given as mean ± standard deviation. Data are examined in terms of statistical significance through Wilcoxon Signed Rank and Mann-Whitney U non-parametric tests. Categorical data are emphasized by numerical value and percentage (%). P value below 0.05 is considered as statistically significant.

**Results**

The mean age of the patients was 60.07±10.2 (range 30-81) years. In terms of concomitant diseases, 12 of them had Diabetes Mellitus (DM), 17 of them had hypertension (HT), 9 of them had DM+HT, 3 of them had hypercholesterolemia, and 4 of them had congestive heart failure. As a result of such kind of comorbid cases, patients were receiving medical therapy.

Twenty of the patients involved in the study, had anti-incontinence surgery previously because of SUI (15 had PVS, 5 had TOT). Fourteen of the other patients having high risks of general anesthesia, 3 having future pregnancy volition, 5 having regular anticoagulant drug usage, and 3 refusing to have sling surgeries were decided to perform transurethral injection therapy.

Of the 45 patients, transurethral injection was performed to 6 patients twice and to 1 patient 3 times. During the first operation, total injected CaHA was 3.65±2.6 cc. The mean weight of substance injected to 7 re-injected patients was detected as 3.66±0.8 cc. Administration of the re-injection time was 8 months for the second injection, and 13 months for the third injection.

In 24 hour pad test performed at the pre-operative term, the mean pad weight of 45 patients was determined as 22.5±8.3 gr. This value was determined as 5.3±8.01 gr at 1st month of post-injection examination, and 8±1.17 gr. At 12th month of post injection examination. At the last examination, 24 hour pad weight of 32 available patients with a mean observation duration of 6.1±2.3 years (range 3-8 years) was determined as 16.2±2.02 gr. However, when the values of pad test during 1st and 12th month’s examinations were compared with the values of the pre-operative period, the differences were statistically significant; the pad test value of last examination at 2010 July was found statistically insignificant (Table 1).

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Through the evaluations of questionnaires, it was found that mean QoL score was 25.7±7.7, and mean ICIQ-SF score was 18.5±2.4 at the pre-injection period. QoL and ICIQ-SF score of 1st month’s examination were 4.1±9.2 and 2.3±5.3 respectively. At 12th month’s examination QoL score and ICIQ-SF score were 4.3±1.06 and 3.07±7.4 respectively, and for the 32 patients evaluated at the final examination were 13.5±1.8 and 8.3±1.1 respectively. Similar to the pad test, it was observed that these data were statistically significant when compared with the pre-operative period. However, unlike to the pad test, for each of both questionnaires, when compared to pre-operative period, statistically significant differences were detected at the last examination’s scores, as well (Table 1).

From 45 patients involved in the study, BMI of 24 patients was above 25, and BMI of 21 patients was 25 or below 25. The success of transurethral injection treatment was monitored in this both subgroups formed according to BMI. When we look through to the values of QoL score % variation, ICIQ-SF score % variation and 24 hour pad test at whole examination process for each subgroup in terms of the achievement, there were not statistically significant differences between these groups (Table 2).

Before the transurethral injection, 15 out of 45 patients had undergone to PVS, and 5 of them to TOT procedures without surgical success, thus transurethral injection was performed as a complementary procedure afterwards. Those 20 patients who have had anti-incontinence surgery previously as well as 25 patients who have not had surgery, were evaluated in two subgroups in order to search the affects of the previous anti-incontinence surgery on predicting the success of the transurethral injection therapy. During the controls in the 1st and 12th months, it was observed that percentage variation in QoL score, percentage variation in ICIQ-SF score, and the 24 hour pad test results have shown statistically significant differences compared to the pre-operative term. However, according to the results of the 32 patients who were re-evaluated at the last control, it was determined that there has not occurred any statistical significant difference compared to the pre-operative term (Table 3).

Twenty-two of the 45 patients were at the pre-menopausal pe-

<table>
<thead>
<tr>
<th>Table 1. The comparison of pre and post injection term QoL scores, ICIQ-SF scores and pad test (24 h/gr)</th>
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</thead>
<tbody>
<tr>
<td><strong>Pre-injection term</strong> (n=45)</td>
</tr>
<tr>
<td>QoL</td>
</tr>
<tr>
<td>ICIQ-SF</td>
</tr>
<tr>
<td>Pad test (24 h/gr)</td>
</tr>
</tbody>
</table>

*Wilcoxon nonparametric test.

P¹: The comparison of pre-injection term QoL score, ICIQ-SF score, and Pad test values with the 1st month's visit.

P²: The comparison of pre-injection term QoL score, ICIQ-SF score, and Pad test values with the 12th month's visit.

P³: The comparison of pre-injection term QoL score, ICIQ-SF score, and Pad test values with the last visit.

<table>
<thead>
<tr>
<th>Table 2. The predictive value of BMI on the success of transurethral injection</th>
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<tbody>
<tr>
<td><strong>1st month</strong> (n=45)</td>
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<tr>
<td>BMI &lt;25</td>
</tr>
<tr>
<td>QoL score % variation</td>
</tr>
<tr>
<td>ICIQ-SF score % variation</td>
</tr>
<tr>
<td>Pad test (24 h/gr)</td>
</tr>
</tbody>
</table>

Mann-Whitney U test

P¹: The comparison of QoL score % variation, ICIQ-SF score % variation and Pad test values between the patients BMI<25, and BMI≥25 at the 1st month's visit.

P²: The comparison of QoL score % variation, ICIQ-SF score % variation and Pad test values between the patients BMI<25, and BMI≥25 at the 12th month's visit.

P³: The comparison of QoL score % variation, ICIQ-SF score % variation and Pad test values between the patients BMI<25, and BMI≥25 at the last visit.
who had previously been at grade 3, 2 patients
(9.3%) were at grade 2, and 6 (18.7%) were at grade 3.

(68.5%) patients were at grade 0; 1 (3.1%) was at grade 1, 3
were re-evaluated in terms of Stamey grading. Accordingly, 22
grade 2. At the latest control in July 2010, 32 available patients
(8.8%) were at Stamey grade 1, and 6 (13.3%) were at Stamey
(77.7%) patients became completely dry (Stamey grade 0), 4
grade 3. During the 12st month control, it was observed that 35
15(33.3%) at Stamey grade 2, and 13 (28.8%) were at Stamey

Table 3. The predictive value of previous anti-incontinence surgery on the success of transurethral injection

<table>
<thead>
<tr>
<th>1st month (n=45)</th>
<th>12th month (n=45)</th>
<th>Last visit (n=32) mean 6.1±2.3 (3-8) years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Previous anti-incontinence surgery (n=20)</td>
<td>Patients without any Previous anti-incontinence surgery (n=25)</td>
<td>P&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>QoL score % variation</td>
<td>13.05</td>
<td>21.83</td>
</tr>
<tr>
<td>ICIQ-SF score % variation</td>
<td>11.76</td>
<td>25.41</td>
</tr>
<tr>
<td>Pad test (24 h/ gr)</td>
<td>18.5±24.7</td>
<td>2.2±11.5</td>
</tr>
</tbody>
</table>

Mann-Whitney U test
*statistically significant
P<sup>1</sup>: The comparison of QoL score % variation, ICIQ-SF score % variation and Pad test values between the patients with and without previous anti-incontinence surgery at the 1st month's visit.
P<sup>2</sup>: The comparison of QoL score % variation, ICIQ-SF score % variation and Pad test values between the patients with and without previous anti-incontinence surgery at the 12th month's visit.
P<sup>3</sup>: The comparison of QoL score % variation, ICIQ-SF score % variation and Pad test values between the patients with and without previous anti-incontinence surgery at the last visit.

Table 4. The predictive value of menopausal status on the success of transurethral injection

<table>
<thead>
<tr>
<th>1st month (n=45)</th>
<th>12th month (n=45)</th>
<th>Last visit (n=32) mean 6.1±2.3 (3-8) years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-menopausal patients (n=22)</td>
<td>Post-Menopausal patients (n=23)</td>
<td>P&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>QoL score % variation</td>
<td>20.18</td>
<td>20.79</td>
</tr>
<tr>
<td>ICIQ-SF score % variation</td>
<td>21.58</td>
<td>19.52</td>
</tr>
<tr>
<td>Pad test (24 h/ gr)</td>
<td>6.8±9.6</td>
<td>3.9±6.04</td>
</tr>
</tbody>
</table>

Mann-Whitney U test
P<sup>1</sup>: The comparison of QoL score % variation, ICIQ-SF score % variation and Pad test values between the pre-menopausal and post-menopausal patients at the 1st month's visit.
P<sup>2</sup>: The comparison of QoL score % variation, ICIQ-SF score % variation and Pad test values between the pre-menopausal and post-menopausal patients at the 12th month's visit.
P<sup>3</sup>: The comparison of QoL score % variation, ICIQ-SF score % variation and Pad test values between the pre-menopausal and post-menopausal patients at the last visit.

Table 5. Stamey Grading

<table>
<thead>
<tr>
<th>Pre-operative (n=45)</th>
<th>Post-operative 12th month (n=45)</th>
<th>Last visit (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0 (n,%)</td>
<td>35 (77.7%)</td>
<td>22 (68.5%)</td>
</tr>
<tr>
<td>Grade 1 (n,%)</td>
<td>17 (37.7%) 4 (8.8%)</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Grade 2 (n,%)</td>
<td>15 (35.3%) 6 (13.3%)</td>
<td>3 (9.3%)</td>
</tr>
<tr>
<td>Grade 3 (n,%)</td>
<td>13 (28.8%) -</td>
<td>6 (18.7%)</td>
</tr>
</tbody>
</table>

In socioeconomically developed societies, the number of the elders is rapidly increasing parallel to the prolongation in average human lifetime. This increase necessitates the less invasive methods in order to solve the problems of elder population. Being the least invasive method, transurethral injection should not be avoided in SUI therapy, which ensures significant patient satisfaction with acceptable long-term effectiveness [12]. The current primary therapies in SUI are the surgical procedures with long term success rates such as PVS, TOT and TVT. In many publications, in ten-year exceeding follow-up of the patients who received these surgeries, it is informed that the dryness rates of these patients were over 90% [13]. In a retrospective study which compares TVT, PVS and TOT surgeries in patients with SUI, it is indicated that the efficiency rate of these treatments was 87% in the first year, and the success of the surgeries declined to 55% in a re-evaluation performed 7 years later [14]. Similarly, in another study assessing the long term efficacy of in situ vaginal wall sling in 203 women with type 2 SUI, it was observed that 72.9% of patients were completely dry after 5 years.
was demonstrated that the cure, improvement and failure rates were found to be 80.9, 2.9 and 16.2% after 3 years follow-up, 65.7, 10.9 and 23.4% after 4 years follow-up and 60.8, 8.7 and 30.4% after 5 years follow-up [15]. Even though TOT and TVT are still considered the most affective treatment methods in female urinary incontinence [16], transurethral injection is still a promising method for a significant patient population-elders for whom these surgeries can not be performed, and patients with co-morbid diseases [7;17]. In a systematic review paper in Cochrane Database, it is indicated that injection treatment provides an option, which may be useful for short term symptomatic recovery in selected female patients with high co-morbidity [18]. There are many publications searching the efficiency of the injection therapy, however there does not exist any publication indicating the long term efficiency in a selected patient population. With this respect, even though it consists of few patients, our study declares that injection therapy is a convenient method in selected patients with successful results in long term follow-up as well as in short term.

The factors such as age, parity and obesity are proved risk factors that play role in SUI development [19;20]. Nevertheless, we do not have any information about the significance of previous anti-incontinence surgery, BMI and menopausal status in predicting the success of the treatment. In a study by Recherber et al., they searched whether or not BMI, menopausal status and age affect the result of sling operations for SUI. During the research, retropubic and transobturator sling procedures were applied to 537 female patients with SUI. After an 18 month follow-up, 398 patients were evaluated, and it was demonstrated that BMI did not have any affect on the surgery result, while menopausal status and age were found to be independent risk factors decreasing the success of the sling procedures [21]. In a study with 184 female patients where collagen was used as the periurethral injection material [22], similar to our study, it is reported that the previous anti-incontinence treatment is an important factor contributing to the success of the treatment in the patients who had been reported ‘cure’ for more than one year after the injection. In this study, analyzing the affects of obesity, menopausal status, hormonal treatment and the type of the incontinence on the results, it was ascertained that they did not make a significant difference [22]. Even though the affects of obesity and post-menopausal status on the development of SUI in females is very well known, and their significance in the prediction of the success of the surgeries was researched in many studies, the affects of these factors in the results of transurethral injection treatment are not known very well. In this study, while we analyzed the long-term efficiency of transurethral injection therapy, we also analyzed weather these factors have any affect on the results of the treatment. Although the number of the patients in the study that could be analyzed during long-term follow-up was few, we determined that transurethral injection was an effective method in selected patients with a mean follow-up of 6.1±2.3 (range 3-8 years) years, and that BMI and post-menopausal status do not have any affect on the success of the transurethral injection in the patients with SUI.

An ideal injection material should be biocompatible, non-anticigenic, non-carcinogenic, non-migrating, non-infectious, and cost affective. Nevertheless, the procedure should be able to be easily performed with local anesthesia [9]. The material should be able to be effective for a long time where it has been injected in. There still does not exist such a material with all these qualifications, but usage of new materials in injection therapy, and publication of positive results may be regarded as promising steps in terms of determination of the ideal injection material. Especially collagen, polyacrylamide hydrogel, hyaluronik acid and CaHA are the prominent injection materials in these days. Coapitise consists of spherical CaHA particles in a carboxymethylcellosolve gel carrier. The gel carrier withholds the CaHA particles in order to augment the bulking effect of the material. After a few months, the gel carrier degrades and enables ingrowth of a new tissue around the CaHA particles. The particles, surrounding the new tissue formation, compose the long term bulking effect [23]. The high dryness rates of the patients in the late follow-up may be contributed to the new structural composition of the CaHA particles in the soft tissue.

Recent studies state that we do not have yet enough information about the independent risk factors those could affect the result of the transurethral injection therapy. Although the information about selection of the ideal bulking agent and the best candidates for injection therapy still does not exist. Nevertheless, prospective studies with higher number of patients will contribute to better explanation of these subjects.

In conclusion transurethral injection is a cheap, easily performed and affective method for selected patient group in SUI. As the number of the studies giving positive opinion about the long-term effectiveness of that is gradually increasing, it is able to provide a comfortable living choice to the elderly patients having SUI and co-morbid diseases. Even though we think that the BMI, previous anti-incontinence surgery, and menopausal status do not affect the results of the transurethral injection treatment, prospective studies with larger patient series are needed which analyze the long term efficiency of the method as well as the affects of these risk factors on the results of the procedure.

References