Original paper

Injectable Bulking Agents in the Treatment of Female Stress Urinary Incontinence due to Intrinsic Sphincter Deficiency

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Abstract

Background and objectives: Stress urinary incontinence(SUI) has a significant impact on the quality of life for many women and it is caused by weakening of pelvic floor muscle that support the bladder and urethra. It affects (1 of 3 women) and it is often associated with childbearing and can be defined as a brief involuntary loss of urine due to increase abdominal pressure in the absence of detrusor activity.
Injectable agents have been used to manage SUI for more than a decade but their application has been limited by placement, durability, antigenicity and other compatibility issues. Therefore, there is a continuous development of techniques and materials for newer bulking agents. Our study was to evaluate the efficacy and safety of the urethral injectable agent DEXELL SUI in women with stress urinary incontinence after 12 months follow up.
Materials and Methods: A prospective, cohort study conducted in Iraq from January 2014 – January 2016 and data for the study was including 25 female patients (20 -52) years old with SUI due to intrinsic sphincter deficiency attending the department of Obstetrics and Gynecology, Urological department, out patients and privet clinic in Al-Diwaniya and AL-Najaf cities. All patients were treated with DEXELL SUI periurethral injection under local anesthesia. Patients were evaluated for efficacy and safety parameters at 6 weeks visit, 3 months and 12 months visit after injection.
Results: The mean stamey incontinence grade significantly decreased from 1.92 at baseline visit to 0.28 at 12 months visit($P<0.001$).None of the patients were dry at baseline,64% were dry at 6 week visit, 80% at 3 months visit and 72% at 12 months visit. There was significant reduction in number of pads used per 6 hours per day from 2.44 to 0.40 after 12 months visit($P<0.001$). Eight patients (32%)developed minor complications related to injection procedure and all were treated successfully.
Conclusion: DEXELL SUI is effective urethral bulking agents with moderate adverse effects used in the treatment of female SUI due to intrinsic sphincter deficiency with less invasive technique.
Key words: Stress urinary incontinence(SUI), Intrinsic sphincter deficiency, Urethral bulking agent.

Introduction

Urinary incontinence (UI) is defined as" the compliant of any involuntary leakage of urine". It is classified as stress urinary incontinence (SUI) when leakage occurs on efforts, exertion, sneezing and coughing; and urge urinary incontinence (UUI) when leakage is accompanied by or immediately preceded by urgency; or mixed urinary incontinence (MUI) when leakage is associated with urgency and also with efforts , exertion , sneezing and coughing [(1)].

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UI is common in women with negative impact on their life quality, and SUI was the most overall prevalent subtype of UI in these women [2].

Stress urinary incontinence (SUI) can be defined as a brief involuntary loss of urine associated with an increase of abdominal wall pressure and in the absence of detrusor activity, and the patients with SUI have been divided into 2 groups: those with urethral hypermobility and those with intrinsic sphincter deficiency (ISD) [3].

ISD a term defined in 1992 and is used to describe damage to the urethral sphincter mechanism regardless of the etiology, leading to weakening of the urethra and is characterized by the inability to stop the involuntary flow of urine in situations of increased intra-abdominal pressure, such as laughing, coughing, sneezing, or physical exercise(3). It is often diagnosed by urodynamic study with a valsalva leak point pressure (VLPP) of less than 90 mmHg[3].

The urethra might be damaged owing no fixation as in cases of spine bifida , prior surgery or denervation or muscle damage during childbirth and we now know that ISD and hypermobility can exist concomitantly as well as alone[3]. Urinary incontinence exacts a high price both financially and in terms of quality of life and has a substantial impact on individual patients, health care organization insurer and society as a whole[4].

Surgical approach could provide ultimate cure for the SUI as urethral sling operation, tension free vaginal tape (TVT), and trans-obturator vaginal tape.

However, a substantial number of women with SUI seek for less invasive procedures with lower risk of complications [5,6]. Patient with SUI may have co-morbidities that do not make them good candidates for surgical repair, such patients include the elderly who have weakened urethra and women who have had vaginal deliveries and still not completing her family[5,6].

Injection therapy with urethral bulking agents is a good example for a less invasive treatment of the SUI caused by intrinsic sphincter deficiency (ISD)[7]. Many urethral bulking materials have been used in clinical trials, but an ideal bulking agent should be biocompatible, non-immunogenic, causes no fibrosis after infiltration of the urethral tissue ,not antigenic and a cellular. Also it should retain its bulking characteristics for a prolonged interval and should not be biodegrade or migrate, and easy to prepare and implant[7]. Bulking agents have a long medical history in fields outside urology as they have been used for gastroesophygeal reflex, for scares and wrinkles as well as for patients with glottis insufficiency[8,9].

A variety of compounds have been used with varying degree of success and when the bulking agents are used in the urethra the goal is coaptation of the urethra during storage phase and maintenance of that coaptation during periods of increased abdominal pressure[7].

Although safety is a main advantage of bulking agents the most common complications are pain during injection and transient urinary retention and voiding dysfunction after implantation[7,10]. Since the human body absorbs any strictly biologic agents overtime, so reinjections are usually required to maintain long term benefits, and synthetic agents less likely require reinjection therefore improving long term efficacy[7,10]. There are a number of FDA-approved urethral bulking agents available for this incontinence treatment either biological (collagen, autologous fat) or synthetic materials as (silicon particles, carbon beads, calcium derivatives). Cross linked collagen (contigen) which is a biological urethral bulking agents found to be absorbed over time and symptoms

could recur and requiring additional injections [11].

Other biological urethral bulking agent was autologous fate which was difficult to harvest and absorbed from the injection site with high rate with risk of fat embolism and death [11].

Synthetic urethral bulking agents less likely require reinjections, therefore improving long term efficacy as Carbone-coated beads (Duraspher), ethylene vinyl alcohol copolymer implants (Uryx), particles of calcium hydroxyapatite in a gel carrier (Coaptite), and polydime-thylsilox ane (Silicone, Macroplastique) [12]. All demonstrate success to one degree or another[11,12].

The aim of the current study was to determine the efficacy and safety of synthetic urethral bulking agents (DEXELL SUI) in the treatment of women with stress urinary incontinence (SUI) due to intrinsic sphincter deficiency (ISD).

Materials and methods

This was a clinical prospective cohort study that included 25 women with SUI in Iraq- Al-Diwaniya maternity and pediatric teaching hospital, Obstetrics and Gynecological department, Al-Sadar teaching hospital in Al-Najaf, Urological department, outpatient clinic and privet clinic, from the period of January 2014 – January 2016. The study was approved by local Iraqi ethical committee and all patients signed an informed consent. Inclusion criteria: were women age (20-52) years with a stamey grade 1-3 on the stamey urinary incontinence scale." Grades on stamey scale were defined as follows: 0=dry; 1=urine leakage with vigorous activity; 2=urine leakage with minor activity; 3=urine leakage all the time regardless of the activity or position " [13]. All patients should had urodynamically proven SUI due to intrinsic sphincter deficiency (ISD) which was diagnosed by urodynamic study with valsalva leak point pressure(VLPP) of less than 90mmHg, and all of them had positive preoperative cough test and should not be on anticholinergic treatment and the bladder capacity should be 300ml or more and postvoide residual urine of less than 100ml, not diabetic, no evidence of malignancy no pelvic inflammatory disease, and all are with minimal caffeine diet. Exclusion criteria: were women with urodynamically diagnosed detrusor over activity or urge incontinence, uterine prolapse, suspicion of neurogenic bladder, long term indwelling catheter with local fibrotic urethral/bladder neck tissues, pregnancy, previous surgery for SUI and evidence of urinary tract infection.

Injectable implant: (DEXELL SUI, IstemMedikal, Turkish) which is made of cross linked hyaluronic acid gel 17mg with dextranomer microspheres (80-120 µm) in diameter . It is a large particle diameter, so decrease the likelihood of particle migration and there by lending itself to longer period with longer results for the patients. The injectable implants is presented in a special kit that includes: 4 pieces pre-filled syringes with DEXELL SUI injection each 1 ml, and 2 sterile application needles 19 gauge with 1 Foley catheter. The material can be administered under local anesthesia with cystoscopy control as an outpatient procedure. The patients were put in lithotomy position under local anesthesia with 1% lidocaine and an application device was introduced into the urethra, the device allows for periurethral administration of the bulking material.

The bulking material was injected through 19 gauge needle periurethrally at the following position 2, 6, and 10 o'clock position.

Postoperative coaptation of the urethra was noted under cystoscopy control, catheter 14 F inserted postoperative for 6-12hours. Pre and postoperative antibiotics cover for

all patients. Follow up of the patients with postoperative questionnaire of the symptoms and signs of irretative voiding symptoms as urgency, frequency, suprapubic pain and tenderness, obstructive symptoms as straining on voiding, urine retention, weak stream, and number of changing pads per 6 hours and positive subjective cough test.

The primary efficacy endpoint was to determine if the patients will show and maintain a decrease in stamey urinary incontinence scale of one or more grades at 6 weeks, 3 months, 12 months visits.

The secondary outcome was to determine the safety and adverse events related to injectable implants.

Results

Twenty five women with a mean age of 34 (20 – 52) years old were included in the study. Cough test performed after injection of DEXELL SUI was negative for all patients The mean stamey urinary incontinence grades showed a significant decrease from 1.92 at baseline visit to 0.36 at 6 weeks visit, 0.20 at 3 months visit and 0.28 at 12 months visit(P<0.001) (Table 1). The proportion of patients who were dry at baseline visit was 0%, increased to 64% at 6 weeks visit, 80% at 3 months visit, and 72% at 12 months visit with improvement of one continent grade or more (Table 2). The mean number of pads used per 6 hours per day showed a significant decrease from 2.44 at baseline to 0.4 at 12 months visit(P<0.001) (Table 3). Symptoms of SUI persist in (7 patient) 28% at 12 months visit with stamey incontinence grade 1.

Regarding safety outcome, there was no allergic reaction in all patients treated with DEXELL SUI bulking agents, 32 %(8 patients) developed complication related to injection procedure, 4 patients (16%) developed urgency, 1 patient (4%) developed urine retention, 1 patient (4%) developed dyspareunia, and 1 patient developed straining of voiding and all these complications treated successfully accordingly (Table 4). No trial for reinjection in our study.

Table 1. efficacy outcome of stamey incontinence grade(SIG) at baseline visit ,6 weeeks,3 months and 12 months visit.

Stamey scale grade	N	Mean	SD	% Mean reduction
SIG baseline visit	25	1.92	0.57	0.00
SIG 6weeks visit	25	0.36	0.49	81.25
SIG 3months visit	25	0.20	0.41	89.58
SIG 12months visit	25	0.28	0.46	85.42

P<0.001

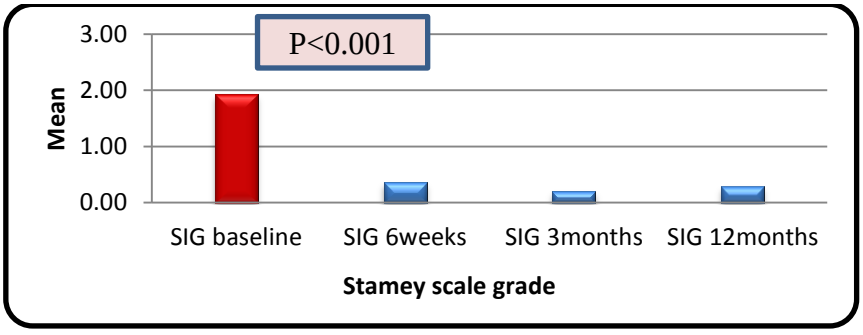

Figure 1. efficacy outcome of stamey incontinence grade(SIG) at baseline visit ,6 weeeks,3 months and 12 months visit after injection.

Table 2. efficacy outcome of number of changing pads per 6 hours per day at baseline visit , 6weeks , 3 months and 12 months visit after injection.

Pads/6hrs	N	Mean	SD
pads (Baseline)	25	2.44	0.71
pads/ 6hrs (6w)	25	0.28	0.54
pads/6hrs (3m)	25	0.32	0.48
pads/6hs (12m)	25	0.40	0.65

P<0.001

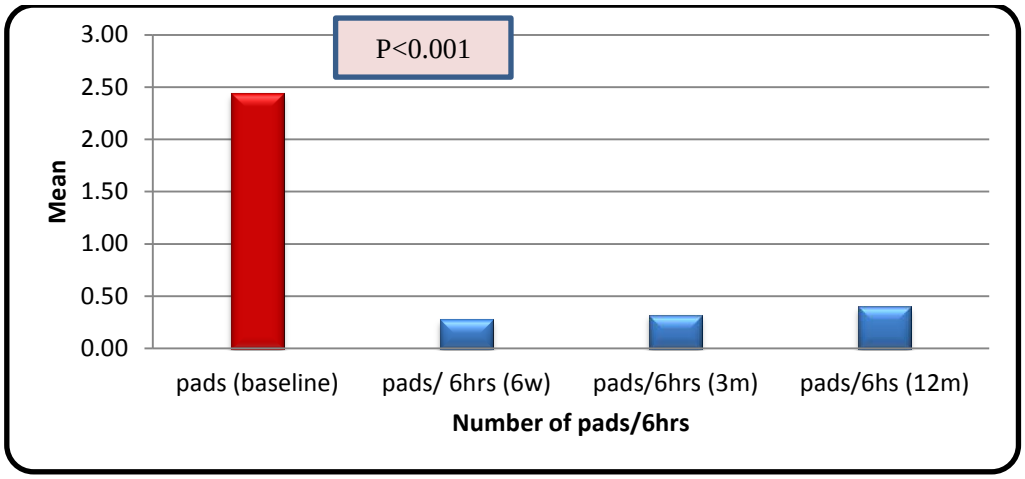

Figure 2. efficacy outcome of changing pads per 6 hours per day at baseline visit , 6 weeks , 3months and 12 months visit after injection.

Table 3. Proportion of female with improved stamey incontinence grade(SIG) after the procedure at baseline visit , 6 weeks , 3 months and 12 months visit.

	Baseline		6weeks		3months		12months	
SIG	N	%	N	%	N	%	N	%
0	0	0	16	64	20	80	18	72
1	5	20	9	36	5	20	7	28
2	17	68	0	0	0	0	0	0
3	3	12	0	0	0	0	0	0
Total	25	100	25	100	25	100	25	100
P-value	-----		<0.001		<0.001		<0.001	

Statistical analysis

Data were analyzed using SPSS version 20 and Microsoft Office Excel 2010. Data were presented as mean±SD (standard deviation), number and percentage. One proportion Z-test was used to study change in percent improvement. Freidman test was used to study changes in SIG score. P-value was considered significant when it was less than or equal to 0.05 and highly significant when it was less than or equal to 0.01.

Discussion

Stress urinary incontinence (SUI) has a significant impact on the quality of life for many women with an estimated prevalence for urinary incontinence of 30% in women aged 25 – 60 years with approximately half of the cases attributed to SUI (1 in 3 women) [14].

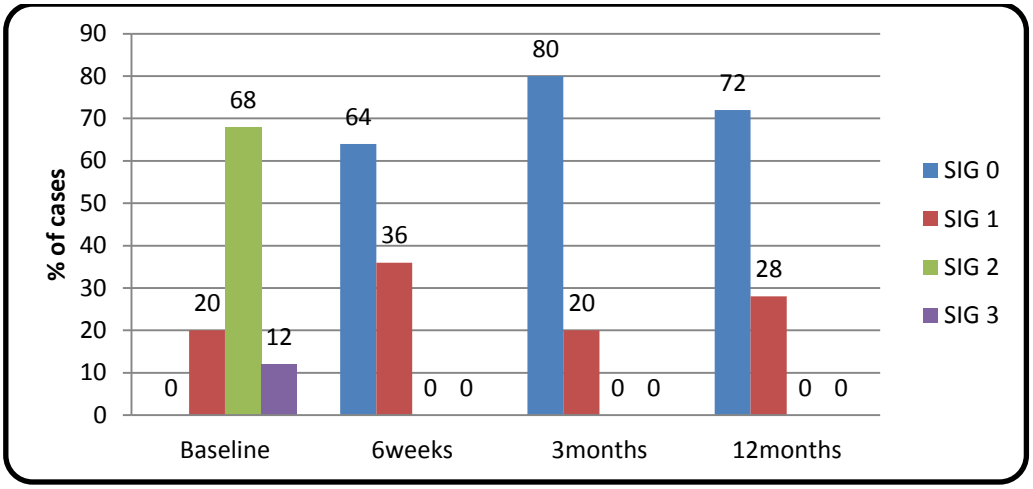

Figure3. Proportion of female with improved stamey incontinence grade(SIG) after the procedure at baseline visit , 6 weeks visit ,3 months and 12 months visit.

Table 4. safety outcome and the complications rate of the patient after the procedure.

Complications	N	%
Dysuria	4	16.00
Dyspareunia	1	4.00
Straining	1	4.00
Urgency	1	4.00
Retention	1	4.00
Total	25	100.00

Many women elect to have a surgical procedure for management of their SUI symptoms each year as surgical correction can provide a finite cure to most of these conditions. However these procedures are invasive and are associated with risk of failure , redo , and morbidities. Therefore many women seek for less invasive therapies with lower rate of complications [(6)]. Injectable therapy using bulking agents is a minimally invasive outpatient procedures and are extremely useful for treating women with SUI who wish to avoid invasive surgical procedures or in women with childbearing age who wish to have more children , or in any patients who are unwilling or not suitable to undergo surgery [(15)].

Our study presents the outcome of 12 months follow up after initial treatment of 25 women with SUI due to ISD using DEXELL SUI and the result show a successful treatment outcome in terms of efficacy and safety of this new bulking urethral implant as the mean stamey incontinence grade was significantly reduced from 1.92 at baseline visit to 0.28 at 12 months visit and the proportion of improved stamey grade was 0% at the baseline visit to 64% at 6 weeks visit , 80% at 3 month visit and 72% at 12 months visit with improvement of continent grade of one degree or more after the injection . The most common non-surgical treatment for SUI remained absorbent products such as pads and adult diapers and the market products are projected to grow at a rate of 25% per year indicating the severity of this medical condition especially with continuing and accelerating geriatric population growth rate [(14)]. In our study there was a significant decrease in the number of

changing pads pre 6 hours per day after urethral bulking agent injection from mean of 2.44 at baseline to 0.4 at 12 months follow up which was both socially and financially accepted for the patients . DEXELL SUI is not degraded but encapsulated by scare tissue and maintain its volume and its effect for long time and it will not migrate.

This result is similar to or even better than the 12 months outcome of other studies which applied Macroplastique bulking agents , as the Meulen et al study (2009) , reported 10 out of 18 (55%) patients who became dry (stamey grade 0) after 12 months of initial Macroplastique urethral injection therapy [(16)]. Ghoniem et al (2009) compared the cure rates of transurethral injection of Macroplastique or Contigen on 247 women with ISD, they reported 61.5% of patients have improvement after 12 months of initial therapy with Macroplastique versus 48% in patients received Contigen injections [(15)]. Moreover the 12 months follow up showed a greater cure rate of 36.9% in Macroplastique injection versus 24.8% injection with Contigen injection [(15)]. J.T. Tamanini et al (2006) , reported 73% of their patients to have (stamey grade 0) after 12 months of initial therapy with Macroplastique injections [(17)]. Martan et al study(2014), using (Bulkamid) injection which is polyacrylamide hydrogel in patients with SUI over 22 months follow up, it show 45.1% of patients showed improvements and 15.7% of patients were completely dry (stamey grade 0) [(18)].

The study of Anderson (2002) ,showed improvement of patients injected with (Durasphere) which is a carbon – coated beads over the course of 4 years showed that 80% of these patients sustained an improvement of 1 continant grade or more and 40% of these patients were dry [(19)]. Nevertheless, Chrouser et al(2004) , conducted a similar study over the course of over 4 years and found that only 33% of (Durasphere) patients remained effective 2 years after initial injection and merely 21% of patients showed continant improvement at 3 years follow up [(20)]. The efficacy of (Coaptite) which is caliciun hydroxylapatite had been tested by Mayer R.D et al (2007), at 12 months follow up of 231 patients showed 63.4% had sustained improvement ,and 39% remained cured and dry[(21)].

Despite the number of studies that have examined the efficacy, durability and complications of different urethral bulking agents, each one had a success rate for one degree or another. Currently there has been increased interest in autologous skeletal muscle derived stem cell injections for the treatment of SUI specifically due to ISD. The therapy involves obtaining a biopsy of the patients skeletal muscle which is then processed ex vivo to ensure a large quantity of myogenic cells in the product which is then injected into the urethral sphincter periutethrally or transurethrally which showed a decreased stress leak as early as within 1 month of treatment which is maintained for long period as their effect is improve sphincter function rather than coaptation from a bulking effect [(22)].

The complications rate in our study seemed to be moderate 32% (8 patients) , and all adverse events were of mild to moderate severity that could easily be treated, as 4 patients had dysuria and one patient had urgency that were treated with proper antibiotics and hydration. One patient had dyspareunia that was treated by removing the implant at 6 o'clock by small incision and the wound closed with few stiches. One patient had retention and one patient had straining on voiding that were resolved by insertion of urethral catheter for 3 days after which the patients voided spontaneously. Adverse events commonly seen with various types of urethral bulking agents as the development of urinary tract infection, temporary urine retention, urgency and transient hematuria [(15,17,21)]. J.T. Tamanini study (2006), showed the development of urgency in 24% of patients

and acute urinary retention in 17% of patients after Macroplastique injection[17]. Ghoniem et al study (2009) showed the occurrence of post-injection urine retention of 43.4% with Macroplastique injection compared to 24.0% with Contigen injection[15]. Three cases of urethral erosion were observed, two in Macroplastique group and one in the contigen group[15]. Abdelwahab H.A, Ghoniem G.M study(2007) . showed 15% of patients who were injected with Zuidex which consist of dextranomer/hyaluronic acid coplymer experienced pseudoabcess formation at site of injection[23]. So many of these injectable agents were withdrawn from the market due to safety issues [23]. Recurrent incontinence may occur making it necessary for the patients to be counseled for the repetitive need for reinjection of the urethral bulking agents. In order for a bulking agents to be considered safe for use there should be no indication of sever adverse effects such as the appearance of granulomas, abscesses or erosion of the urethral tissue and there should be no migration of the bolus bulking agents injected which were not complicating our study patients. Therefore a decision to be made on selecting a bulking agents to treat SUI would be made on the availability, safety, ease of use and surgeon preference. A limitation of the study is the small sample size and a large study group will justify the statistical and clinical outcome of our small series. Another limitation could be the difficulty to do shame procedures in most of the clinical studies.

Conclusion and Recommendation

DEXELL SUI is an effective urethral bulking agents in the treatment of female SUI with good and lasting efficacy for one year . It is fairly safe and show mild to moderate adverse events most of which were related to the injection procedure and could be treated with ease.

The search for the ideal injectable agents is continuous and tampered by the high rate of introduction of the new urethral bulking agents and the subsequent withdrawal of many bulking agents. So, strict criteria for introduction of newer agents should be implemented. However, recent researches on the injection of stem cells showed promise with regard to the efficacy and durability and required to be tested with improved facility.

References

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck P, Victor A, Wein A. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. American journal of obstetrics and gynecology. 2002;1:116-26.
2. Hunskaar S, Lose G, Sykes D, Voss S. The prevalence of urinary incontinence in women in four European countries. BJU international. 2004 Feb 1;93:324-30.
3. Agency for health care policy and researches . Urinary incontinence in adults: clinical practice guideline .1996.
4. Agency for health care policy and researches .clinical practice guideline no.2.Urinary incontinence in adults: Acute and Chronic managements.1996.
5. Robinson D, Anders K, Cardozo L, Bidmead J, Dixon A, Balmforth J, Rufford J. What do women want?: interpretation of the concept of cure. Female Pelvic Medicine & Reconstructive Surgery. 2003 Nov 1;9:273-7.
6. Lucas MG, Bosch RJ, Burkhard FC, Cruz F, Madden TB, Nambiar AK, Neisius A, de Ridder DJ, Tubaro A, Turner WH, Pickard RS. EAU guidelines on surgical treatment of urinary incontinence. European urology. 2012 Dec 31;62:1118-29.
7. N.F.Davis, F. Kheradmand and T. Creagh. Injectable biomaterials for the treatment of stress urinary incontinence: Their potential and pitfalls as urethral bulking agents. International Urogynecology Journal, vol.24, no.6, 913-919, 2013.
8. O'Connor K.W, Lehman G.A. Endoscopic placement of collagen at the lower esophageal sphincter to inhibit gastroesophygeal reflux . GastrointestEndosc.1988;34:106-112.
9. Ford C.N., Bless D.M. Collagen implantation: Clinical applications and lesion selection. JDermatolSurgOncol. 1988;14:21-26.

10. Chapple CR, Wein AJ, Brubaker L, Dmochowski R, Pons ME, Haab F, Hill S. Stress incontinence injection therapy: what is best for our patients?. European urology. 2005 Oct 31;48:552-65.
11. Haab F. , Zimmern P.E ,Leach G.E. Urinary stress incontinence due to intrinsic sphincter deficiency: experience with fat and collagen periurethral injections.JUrol.1997;157:1283-1286.
12. Henly DR, Barrett DM, Weiland TL, O'connor MK, Malizia AA, Wein AJ. Particulate silicone for use in periurethral injections: local tissue effects and search for migration. The Journal of urology. 1995 Jun 30;153:2039-43.
13. T.A Stamey ."Endoscopic suspension of the vesicle neck for urinary incontinence ". Surgery Gynecology and Obstetrics,vol.136 , no.4 ,547-554 , 1973.
14. Hampel C, Wienhold D, Benken N, Eggersmann C, Thüroff JW. Definition of overactive bladder and epidemiology of urinary incontinence. Urology. 1997 Dec 1;50:4-14.
15. Ghoniem G. , Corcose J. , Comiter C. , et al . Cross-linked polydimethyl silicon injection for SUI :results of multicenter randomized controlled single blind study. J Urol. 2009; 181:204-210.
16. Ter Meulen PH, Berghmans LC, Nieman FH, Van Kerrebroeck PE. Effects of Macroplastique® Implantation System for stress urinary incontinence and urethral hypermobility in women. International Urogynecology Journal. 2009 Feb 1;20:177-83.
17. J.T. Tamanin 9, C.A. D'Ancona, et al. Macroplastique implantation system for female stress urinary incontinence. Jornal of Endocrinology .2006;vol.20,1082-1086.
18. Martan A, Masata J, Svabík K, Krhut J. Transurethral injection of polyacrylamide hydrogel (Bulkamid®) for the treatment of female stress or mixed urinary incontinence. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2014 Jul 31;178:199-202.
19. Andersen R.C. Long-term follow up comparison of Duraspher and Contigen in the treatment of SUI. JLow Genit Tract Dis.2002;6:239-243.
20. Chrouser KL, Fick F, Goel A, Itano NB, Sweat SD, Lightner DJ. Carbon coated zirconium beads in β-glucan gel and bovine glutaraldehyde cross-linked collagen injections for intrinsic sphincter deficiency: continence and satisfaction after extended follow-up. The Journal of urology. 2004 Mar 31;171:1152-5.
21. Mayer R.D. Multicenter prospective randomized 52-week trial of calcium hydroxyl apatite versus bovine dermal collagen for treatment of SUI.Urology. 2007;69:876-880.
22. Peters KM, Dmochowski RR, Carr LK, Robert M, Kaufman MR, Sirls LT, Herschorn S, Birch C, Kultgen PL, Chancellor MB. Autologous muscle derived cells for treatment of stress urinary incontinence in women. The Journal of urology. 2014 Aug 31;192:469-76.
23. Abdelwahab H.A, Ghoniem G.A. Obstructive sub urethral mass after transurethral injection of dextran hyaluronic acid copolymer. Int Urogynecol J Pelvic Floor Dysfunction. 2007; 18:1379-1380.