EMDA®

Electromotive Drug Administration

Executive Summary Electromotive Drug Administration (EMDA) Functional Urology

PHYSION®

SUMMARY

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ELECTROMOTIVE DRUG ADMINISTRATION (EMDA) AND HYDRODISTENSION OF THE BLADDER FOR THE TREATMENT OF INTERSTITIAL CYSTITIS AND BLADDER PAIN SYNDROME

1 - Electromotive Administration of intravesical lidocaine in patients with interstitial cystitis - Journal of Endurology October 1996; 10 (5): 443-447 - Gürpinar T, Wong H, Griffith PD- Department of Urology, Baylor College of Medicine, Houston, Texas, USA.

METHOD	PATIENTS	RESULTS
100 ml acqueous solution with lidocaine 1.5% and epinephrine 1:100,000. 15 mA for 40 min. Blood sample were drawn before, at the middle (20 mins) and at the end of treatment and assayed for lidocaine: serum concentration remained below (<0.1 µg/dL- 0.6 µg / dL) the typical therapeutic venous concentrations (1.5-5 µg /dL).	6 pts with long-standing IC (they have been treated from 3 to 20 years for IC but all remained significantly symptomatic).	Bladder volume increase in all patients. Quality of life (VSQL) score improved and voiding symptoms decreased as did soprapubic and perineal pain: in 4/6 pts (66%) these results have been durable (follow-up for 3 to 18 months). The procedure was well tolerated in all cases and the pts didn't experience pain or significant discomfort. No systemic side effects.

EMDA treatment and bladder dilatation are safe, weel tolerated and helpful.

2 - Intravesical Electromotive Drug Administration for the treatment of non-infectious chronic cystitis- International Urogynecology Journal 1997; 8: 134-137- Riedl CR, Knoll M, Plas E, Stephen RL, Department of Urology and Ludwig Boltzmann Istitute of Andrology, Municipal Hospital Lainz, Vienna, Austria, University of Salt Lake City, Utah, USA.

METHOD	PATIENTS	RESULTS
Drug solution: 150 ml lidocaine 2.6% with dexamethasone 20 mg and epinephrine 0.75 mg. 22 mA for 20 min. EMDA/cystodistension was performed on an out-patient basis in all patients, it lasts an average of 45 min and was easily performed by the medical staff. (*) CR group: 5/9 (55%) IC pts, 4/6 (66%) RD. Mean duration of complete remission was 5.4 months in IC group and 9.5 months in RC group.	17 pts with non-infectious chronic cystitis (NICC): IC (9), radiation cystitis (RD) (6), chemocystitis (1), lupoid cystitis (1). A total of 46 treatment (1-5 per pts) was performed: retreatments were performed at pts request whenever bladder symptoms recurred. For final evaluation, all pts compiled a questionnaire regards to their quality of life and their judgment as to the efficacy of the therapy.	Complete resolution of symptoms (*) for an average of 7,5 months was observed in 11 pts (65%), partial improvement in 4 (23.5%). Cystometric bladder capacity was increased by an average of 65%. No complications occurred. The treatment was excellently accepted: 16/17 (94%) stated that cystodistension with EMDA anesthesia is tolerable and they would undergo retreatment anytime. After a mean follow-up period of 10.8 months treatment was judged effective with a significant improvement of quality of life by 11/177 pts (65%).

Complete resolution of symptoms in two-third of NICC patients for an average 7.5 months. EMDA treatment is effective, feasible, without serious side effects and cost effective.

3 - Electromotive Drug Administration of lidocaine and dexamethasone followed by cystodistension in women with interstitial cystitis- International Urogynecology Journal 1997; 8 (3): 142-145-Rosamilia A, Dwyer PL, Gibson J- Department of Urogynecology, Royal Women's Hospital Carlton, Victoria and Westmead Hospital, Sydney, Australia.

METHOD	PATIENTS	RESULTS
Drug solution: 2% NaCl-free lidocaine hydrochloride, 1.5 mg adrenaline, 16 mg dexamethasone in 150 ml sterile water. 30 mA (*) for 20-30 min.	21 females with IC diagnosed. The time between initial diagnosis of IC and EMDA was 6 months to 14 years with a median of 3.5 years) Assessment was 2-day urinary diary and pain score (0-10 scale) performed before treatment and 2-and 6-monthly review. (*) Very high maximum output current: not recommended.	18/21 pts (85%) had a good response (reduction of frequency and in pain score by 3 or more and) at 2 weeks, with 14 (63%) still responding at 2 months. An excellent response (pain score of 0) was obtained in 4/16 pts (25%) at 6 month review (pretreatment score:4-10) No pts asked for treatment to be terminated. Cystodistension was well tolerated in all cases. Cystometric bladder capacity was increased from an average of 200 ml before to an average of 600 ml after EMDA.

There was a significant improvement in pain score at 2-month and 6-month review, with an improvement in urinary frequency at 2-month.

4 - Intravesical Electromotive Drug Administration technique: preliminary results and side effects - The Journal of Urology June 1998; 159 (6): 1851-1856 - Riedl CR, Knoll M, Plas E, Plüger H - Department of Urology and Ludwig Boltzmann Institute of Andrology, Municipal Hospital Lainz, Vienna, Austria.

METHOD	PATIENTS	RESULTS
Drug solution: 150 cc 2% lidocaine, 0.75 mg epinephrine, 20 mg dexamethasone for 20 min with maximum current of 22 mA. Following EMDA, hydrodistension of the bladder was performed to 150 to 200% of cystometric capacity, with a maximum pressure of 80 cm $H_2$0 nd was mantained for 5 min. Cystoscopy was performed after the first distension to confirm the diahnosis. All pts underwent cystometry and symptom evaluation before and 1 week after EMDA. Retreatment was performed when symptoms recurred and when requested by pts. A questionnaire was mailed to all pts for final evaluation.	25 pts (20 female, 5 male), mean age 63, 65 EMDA treatments (1-6/pts). IC (16pts), radiocystitis (6 pts), chemocystitis (3 pts), lupoid cystitis (1 pts).	15 of 25 pts (60%) was free of symptoms for a mean of 6.6 months. 3 (12%) had partial response and 7 (28%) no improvement. Cystometric bladder capacity was increased by an average of 73% from 244 cc before to 421 cc after EMDA with significantly reduced urinary frequency. The questionnaire was evalueted for the first 17 pts after a mean follow-up of 10.8 months: of the respondents 10 (59%) reported complete resolution of bladder symptoms and judged treatment effective with a significant improvement of quality of life and 16 (94%) stated that EMDA and cystodystension were tolerable and that they would undergo re-treatment at any time.

		Since all pts had cystitic symptoms at the time of treatment, 6/17 respondents (35%) reported moderate and 3/17 (18%) severe scomfort during the first minutes of EMDA before local anesthesia was effected but pain was tolerable and never led to terminate the treatments.

EMDA can safely and effectively be used for bladder hydrodistension, taking advantage of increased drug administration without systemic side effects: 60% complete and 12% partial remission rate for an average of 6.6 months were observed. Bladder capacity was increased to 173% which significantly reduced urinary frequency.

5 - Electromotive Drug Administration and hydrodistension for the treatment of interstistial cystitis - Journal of Endourology June 1998; 12 (3): 269-272 - Riedl CR, Knoll M, Plas E, Plüger H - Department of Urology and Ludwig Boltzmann Istitute of Andrology, Municipal Hospital Lainz, Vienna, Austria.

METHOD	PATIENTS	RESULTS
- Pts with low-capacity bladders (<250 ml): solution of 100 ml of lidocaine 2% with dexamethasone 16 mg and epinephrine 0.5 mg. Electric current set at 15 mA for 20 min. - Pts with bladder capacity (>250 ml): solution of 150 ml of lidocaine 2.6% with dexamethasone 20 mg and epinephrine 0.75 mg. Electric current set at 22 mA for 20 min.	13 pts with diagnosed CI. Total treatment: 42 As soon as bladder symptoms recurred, pts returned for retreatment. Retreatment 1 to 6 per pts. (*) Complete responders: complete resolution of urgency,bladder pain and urinary frequency for at least 1 week. (**) Partial responders: reduction of bladder symptoms for less than 1 week.	8/13 (62%) pts reported complete resolution(*) of bladder symptoms lasting an average of 4.5 months. 3 (22%) pts reported partial (**) improvement, while 2 (16%) aggravation of pain for several days (<4 days) after therapy. At 1 week post EMDA, cystometric bladder capacity was increased by an average of 66% and consequently urinary frequency was reduced as demostrated by 45% decrease of nocturia. Cystodistension after EMDA was uniformly painless. Retreatments were effective in all cases for a similar or even a longer period of time.

The combination of EMDA and hydrodistension shows some significant advantages: remission rates appear to be superior and there is no need for general anesthesia and hospital admission, which reduces therapeutic costs and treatment time (about 1 hour including cystoscopy after EMDA). Moreover EMDA is easy to perform and has high acceptance by patients: in this series, 93% pts judged EMDA and hydrodistension well tolerable and said they would undergo retreatment any time.

6 - The stability of lidocaine and epinephrine solutions exposed to the electrical current and comparative administration rates of the two drugs into pig bladder wall - Urological Research 2003; 31: 169-176- Di Stasi SM, Giannantoni A, Navarra P, Massoud R, Zavaglia D, Bertucci PF, Vespasiani G, Stephen RL- Department of Urology, University of Perugia, Perugia, Department of Urology, Tor Vergata University, Rome.

DRUG SOLUTION	METHOD	RESULTS
Drug solution was the same as that used in clinical application: 50 ml lidocaine HCl 4% (NaCl-free), 1 ml di epinephrine HCl 1/1000, 50 ml water.	To measure the duration of drugs stability (with mass spectrometry), the mixture was placed in open steel bowl and stored for up 7 days at room temperature in the lighting and in the dark and at 4°C in the dark. Transport rates with passive diffusion and with EMDA was determinated: the solution was placed in two chamber cell with the donor compartments (drugs) separeted from the receptor compartments (NaCl solution) by a viable pig bladder wall. This was subjected to the application of an electric current (20 mA and 30 mA) for 20, 30 and 45 min. The viability and structural features of tissue were assessed with trypan blue exclusion test and histological examination.	Lidocaine remained stable throughtout the 7 days under all conditions, epinephrine remained stable under all condition during day 1 only and for 7 days when stored at 4°C in the dark. With the application of an electric current (30 mA for 45 min), both drugs remained stable. In bladder tissue, all lidocaine levels following electromotive administration is significantly exceeded the corresponding levels following passive diffusion: the ratio of tissue lidocaine levels, EMDA/passive diffusion was 6:1. Same results for epinephrine and tissue levels ratio was 9:1. There was no trypan blue staining of epithelial, subepithelial or muscle cells indicating the viability of tissues. Histological examination of the bladder wall showed a normal structure.

The combination lidocaine and epinephrine remains stable for 1 days and when exposed to 30 mA for 45 min. Electric current accelerates the transport rate of lidocaine and epinephrine.
No tissue damage was detected histologically or by trypan blue test.

7 - Office bladder distension with Electromotive Drug Administration (EMDA) is equivalent to distension under general Anestesia (GA)- BMC Urology 2005; 5: 14 - Rose AE, Avezedo KJ, Paine CK - Department of Urology, Stanford University Medical School, Stanford, California, USA.

METHOD	PATIENTS	RESULTS
Two prospective protocols have been conducted to investigate the utility of EMDA anesthesia for office bladder: -the first examined the role of EMDA distention in the initial diagnosis of IC; -the second examined the efficacy of EMDA distension in pts who had previously responded to a distension in the operating room with GA (*). Median time elapsed between GA distension and EMDA distension was 10 months. (*) General Anestesia	11 pts participating in two protocols of EMDA bladder distension who also underwent bladder distension under GA either prior to or after the EMDA procedure. -First protocol: 2 pts who later went on to have a bladder distension under GA; -second protocol: 9 pts Most of the pts recruited for the study had already at least 3 previous IC therapies and many are considered “end stage” patients with ulcers and low bladder capacity.	The distension capacity achieved in the office was nearly identical to that in the operating room an the cystoscopic findings very similar. The median absolute difference in bladder capacity between GA and EMDA was only 25cc (5%). Cystometric bladder capacity was increased by an average of 135% Serum lidocaine levels were drawn from the 7 pts with bladder ulcers: all were less than 1.1 µ/ml.

This study represents the first comparison between distension with EMDA vs general anesthesia: EMDA provides an equivalent degree of distension to the standard procedure performed in the operating room as essentially the same bladder capacity is achieved. These results confirms the feasibility of performing bladder distension in an office setting without risk and cost of general anesthesia.

8 - Pilot study of the feasibility of in-office bladder capacity distension using Electromotive Drug Administration (EMDA)- Neurology and Urodynamics 2005; 24: 1-7- Rose AE, Paine CK , Avezedo KJ- Department of Urology, Stanford University Medical School, Stanford, California, USA.

METHOD	PATIENTS	RESULTS
- First group of 10 pts underwent bladder distension under local anesthesia with instillation of 5 mg/kg alkalized lidocaine 4% buffered by 5 cc 8.4% sodium bicarbonate; - Second group of 11 pts had lidocaine EMDA anesthesia prior to distension. Drug solution: 75 cc lidocaine 4%, 2 cc epinephrine 1:1,000, 70 cc sterile water, 40 mg dexamethasone. Peak current 30 mA, rise rate 50 for 25 min.	21 pts presenting with simptoms of urinary frequency , urgency and bladder pain were recruited.	In the alkalized lidocaine group, 6/10 distensions were aborted for intolerable pain after less than 5 min at only 40 cm H_2O. 4/10 completed the procedure. In the EMDA group, 7/11 distensions were completed using 60 H_2O for 7 min. Despite the lower pressure used in the alkalized lidocaine group, the median distension time was only 3 min compared to 7 min using EMDA and the cystometric bladder capacity was increased by an average of 75% compared of 135% with EMDA.

EMDA provides a sufficient anesthesia to complete an office bladder distension.

9 - Electromotive-Drug-Administration (EMDA)-Verfahren: Eine innovative minimal-invasive Therapieoption bei Interstitieller Cystitis- 2007, Dissertation Saarland: Medizinische Fakultät der Universität des Saarlandes-Dilk O.

METHOD	PATIENTS	RESULTS
First drug solution: dexamethasone (40 mg in 10 ml), lidocaine 4% (NaCl free) in 50 ml, epinephrine 1/1000 2 mg in 2 ml. 15-25 mA, positive polarity. After emptying the bladder, the second drug solution was instilled: pentosan polyphosphate 200 mg in 150 ml distilled water 20-25 mA, positive polarity. Time of treatment: 20-35 min.	78 pts with diagnosed IC were selected from 2004 to 2006 and treated with EMDA. All these pts had received other treatments in the past before EMDA. Urodynamic data were collected pre and post EMDA. For final evaluetion pts compiled a questionnaire regards quality of life (improvement of symptoms: urgency-frequency, pelvic pain) and their judgement as to the efficacy of EMDA.	63 of the 78 patients replied to the questionnaire. 84% of IC patients noticed an improvement of their symptoms: 48% of the effect was evident, 13% strong, 23% mild. 80% of pts showed effects for at least 1 month, 38% for 6 months or more. 49% had no post-therapeutic problems, 24% urinary tract infections, 11% hematuria. In 84% of EMDA treated patients the procedure was successful.

EMDA improves patients' quality of life with a success rate of 83%.

10 - Electromotive Drug Administration for treatment of therapy-refractory overactive bladder-International Brazilian Journal of Urology November/December 2008;34 (6): 758-764- Gauruder-Burmester A, Biskupskie A, Rosahl A, Tunn R - German Pelvic Floor Center, Urogynecology Section, St. Hedwig Hospital, Berlin, Germany.

METHOD	PATIENTS	RESULTS
Drug solution: 100 ml 4% lidocaine hydrochloride (NaCl-free), 40 mg dexamethasone sodium phosphate, 2 ml epinephrine, 100 ml distilled water. The regimen consisted of three treatment cycles each with 3 instillations at 2-week intervals. Current applied: 15-25 mA for 20-25 min Patients underwent follow-up 12 months after the last treatment. The combination of drugs was selected to control urge and pain as well as chronic inflammation of bladder tissue. EMDA allows a bladder distension for improving bladder capacity without the need for anesthesia.	72 pts with therapy-refractory chronic overactive bladder were treated with EMDA. 15 pts (21%) had a history of incontinence surgery and 19 (27%) had undergone prolapse surgery Symptoms were: frequency, nocturia and urge incontinence. The purpose was to evaluate the benefits of EMDA in terms of improvement of symptoms, quality of life and sexuality. All patients underwent urodynamic testing and cytoscopy before and after the EMDA treatment, kept a voiding diary and compiled a quality of life and sexual exploration questionnaire before and after treatment.	Bladder capacity improved significantly by 110 ml in 51 pts (71%). The number of micturitions/day decreased significantly to 7 times a day (pts had an average voiding frequency of 16 times a day). Nocturia showed a tendency to improve from 5 to 2. The first urge was premature in 41 (57%) pts before treatment versus 18 (25%) after treatment. Quality of life was improved in 54 pts (75%) and sexuality in 39 (54%). Signs of dysuria and hematuria were observed in 21 pts (29%). Urinary tract-infection occurred in 10 women (14%) and was treated with a 7-day regimen of 250 mg ciprofloxacina.

Overactive bladder (OAB) has a socioeconomic impact that is comparable to that of diabetes mellitus. As life expectancy is increasing this condition will become even more important in the future. Symptoms of overactive bladder tend to markedly improve using EMDA for treatment. EMDA can improve both quality of life and sexuality in pts with therapy-refractory chronic overactive bladder.

11 - Electromotive Drug Administration: a pilot study for minimal-invasive treatment of therapy-resistant idiopathic detrusor overactivity - Neurology and Urodynamics, 2009, 28 (3): 209-213 - Bach P, Wormland RT, Möhring C, Goepel M - Department of Urology, Klinikum Niederberg Velbert, Academic Hospital, University of Duisburg-Essen, Velbert, Germany.

METHOD	PATIENTS	RESULTS
Drug solutions: 2000 mg 4% lidocaine hydrochloride (50 ml), 2 mg epinephrine 1:1000 (2ml), 40 mg dexamethasone-21-dihydrogen phosphat (10 ml) in a total volume of 100 ml. EMDA was performed once in four weeks for a period of three months.	84 pts (72 female, 12 male) with urge syndrome and urodinamically-proven idiophatic detrusor overactivity (IDO) were treated with EMDA over a periods of 27 months. All patients underwent urodynamic testing before and after each EMDA session. Quality of life improvement was evaluated using a Kings Health Questionnaire (KHQ). Pts continued to document drinking and micturition data during this 3-month period.	Mean daytime frequency (DF) was 14.1 +/- 7.7 per day and nocturia (N) 5.1 +/- 5.1 per night before EMDA. After two EMDA sessions, DF decreased to 9.4 +/- 6.2 per day and N 2.5 +/- 2.4 per night. The use of pads could be lowered from 4.5 +/- 4.1 per 24 h to 1.8 +/- 2.4. Uninhibited detrusor contractions were seen in all patients before treatment and were reduced to 46.4% after two EMDA sessions. Maximal cystometric bladder capacity increased from 192.3 +/- 106.6 ml to 239.6 +/- 114.9 ml. 53.6% (45/84) of reported a completely withdrawal of symptoms and 28.6% (24/84) indicated a remarkable reduction.

EMDA significantly improves urodynamic parameters, quality of life and pad usages in patients with urge syndrome and therapy-resistant idiophatic detrusor overactivity (IDO).

12 - Instillation of hyaluronic acid via Electromotive Drug Administration can improve the efficacy of treatment in patients with interstitial cystitis/painful bladder syndrome: a randomized prospective study-Korean J Urology 2014; 55: 354-359-Gülpınar O, Haliloğlu AH, Gökce Mİ, Arıkan N- Department of Urology, Ankara University Faculty of Medicine, Ankara, Department of Urology, Ufuk University School of Medicine, Ankara, Turkey.

METHOD	PATIENTS	RESULTS
Randomized prospective study. Patients were randomly assigned to two group: -group A: pts received hyaluronic acid directly with a catheter (40 mg acid hyaluronic retained for at least 60 min); -group B: pts received hyaluronic acid with EMDA (40 mg acid hyaluronic in 40 ml saline solution, treatment time 25 min). The two group was similar in baseline parameters. In both groups instillation were performed weekly in the first month and then monthly after 2 months.	31 (6 males, 25 females) pts with IC/BPS diagnosed were randomized to two groups similar for baseline parameters: - group A: 15 pts; - group B: 16 pts. They were followed for 24 months and the two group were compared at certain intervals. Primary endpoint of the study were VAS score, GRA (Global Response Assessment) and micturition frequency in 24 hours. Secondary endpoint were mean voided volume, number of nocturia episodes, IC symptom and problem scores. Follow-up: 24 months.	There was a significant improvement in EMDA group at 6 and 12 months in term of micturition frequency, mean voided volume, number of nocturia episodes IC symptom and problem score, VAS score and GRA. The difference between the two groups was not significant at months 1 and 24. None of the patients experienced any serious adverse side effects and no patients refused treatment.

Instillation of hyaluronic acid via EMDA increase the tissue uptake and improve the efficacy of the treatment.

13 - Improvement in the effectiveness of bladder instillation therapies in the treatment of interstitial cystitis by means of EMDA (Electromotive Drug Administration): outcomes of a randomised, placebo-controlled, double blind trial. 2018; Münstermann N, Dilk O, Heinecke A, van Ophoven A- Mechernich, Homburg/Saar, Münster, Herne, Germany.

METHOD	PATIENTS	RESULTS
Randomized, controlled, double-blind trial. Drug solution: 40 mg dexamethasone, 20 mg butylscopolamine bromide, 100 ml 4% lidocaine, 2 ml adrenaline 1:1000, 100 ml water for injection. Patients were randomly assigned to two group: -Group A: 25 pts received an EMDA instillation (rise 30 µA/s, intensity of current 20 mA for 30 min) administered twice (interval of 4 weeks). Group B: 15 pts received the instillation alone without EMDA (same drug solution, identical duration of treatment but pulsed electric current was not applied. Physionizer was mute in both group at all times).	40 pts with confirmed IC were randomized to two groups. Group A: 25 pts. One pts was excluded, so become 24 pts. Group B: 15 pts. Total of 80 treatment: 50 with EMDA, 30 without EMDA. Primary outcomes: response rate to therapy. Pts who reported a marked improvement or freedom from symptoms in GRA(*) questionnaire were categorised as responders. Secondary outcomes: duration of relief from symptoms (duration of response) and change in: pain, urgency, micturition frequency and volume (bladder capacity). (*) General Response Assesment	The effectiveness of the treatment was assessed prior and at 2 and 6 weeks after the second EMDA instillation. Group A: 10/24 pts was responders 6 weeks after the second treatment. Group B: 2/15 pts was identified as responders. The EMDA treatment tended to lead to an improvement in terms of a reduction of urgency, micturition frequency and pain in comparison with instillation treatment alone. Serious adverse events did not occur with any of the total of 80 treatments.

Outcomes		Evaluation
Primary	Response rate to therapy	GRA questionnaire
Secondary Change in:	Micturition frequency	Micturition diary
	Micturition volume	
	Symptoms and perception of symptoms	Symptom score based on O'Leary/Sant IC index
	Pain	Visual Analogue Scales (VAS)
	Urinary urgency	Visual Analogue Scales (VAS)
	Duration of response	Visual Analogue Scales (VAS)

EMDA is well tolerated and safe to administer, including with repeated treatments. EMDA achieves a clinically relevant prolongation and increase in the reduction of symptoms compared with simple instillation treatment.

14 - The care situation of patients with interstitil cystitis in Germany. Results of a survey of 270 patients - Urologe A May 2013; 52 (5): 691-702-Jocham D, Froehlich G, Sandig F, Ziegler A - Urologische Klinik und Poliklinik, Universität zu Lübeck, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Germany.

Using a comprehensive questionnaire the care situation of 270 pts (94% women, 6% men) with IC and bladder pain syndrome in Germany was recorded.

The average age of women was 53.5 years and that of men 67 years.
The diagnosis of IC was made most frequently (62.22%) by biopsy and histological examination followed by urodynamics, potassium test, hydrodistension and cystoscopy. The average duration of the diagnosis was 9 years, 46.67% of the patients consulted a doctor more than 20 times before the diagnosis was made.
51.84% had to pass water more than 14 times per day.
Frequency, nocturia and pain were the leading symptoms and 25% of the pts complained of urge incontinence.

In the self-assessment success 61,34 % considered EMDA the best intravesical procedure.

15 - German SK2 Guideline Diagnostic and therapy of Interstitial Cystitis (IC/BPS) - Responsable: German Society of Urology, Edition 1, version 1, September 30, 2018: 30-31 (period of validity: 5 years).

3.5. Transurethrale Verfahren

3.5.4. Electromotive Drug Administration (EMDA®)

In one study, six IC / BPS pts were treated with EMDA® lidocaine and epinephrine administered at maximum distended bladder. Through this treatment, a significant increase in bladder capacity, a reduction in pain and the micturition frequency could been achieved. 66% of the treated pts described the efficacy as persistent (3).

Treatment of 21 female IC / BPS patients with lidocaine and dexamethasone by EMDA® showed good efficacy (reduction of frequency and pain) in 85% of pts two weeks after treatment. In 63% of pts, this effect lasted for two months. Complete pain reduction was also observed in 25% of pts six months after treatment (6).

In another study using the same technique and in which 13 pts with diagnosed CI were treated, it was shown that 62% of those treated reported a complete resolution of bladder symptoms. In addition, bladder capacity was increased by an average of 66% (5).

A study on the care situation of IC / BPS patients in Germany showed that 180 out of 270 study participants had used the EMDA® procedure for the treatment of the symptoms. When assessing the success of invasive treatment, more than 60% of those treated reported successful treatment (12).

Thus, the EMDA® method is the most effective invasive therapy in this study (9)... Recommendation can be considered strong consensus (100%).

ELECTROMOTIVE DRUG ADMINISTRATION OF LIDOCAINE TO PRODUCE BLADDER LOCAL ANESTHESIA FOR THRANSURETHRAL SURGERY

16 - Bladder and urethral anaesthesia with Electromotive Drug Administration (EMDA): a technique for invasive endoscopic procedures - British Journal of Urology 1997; 79: 414-420 - Fontanella UA - Saronno Hospital, Italy.

METHOD	PATIENTS	RESULTS
Lidocaine 4% (150 ml, NaCl free) is mixed with 150 ml of water and 3 ml of adrenaline (1mg/ml) added so that the final solution is: 2% lidocaine and 0.01 mg/ml adrenaline in 300 ml. Anxious pts were prescribed a benzodiazepine the night before surgery. Local anaesthetic gel is instilled into the urethra. Electric current applied: 25 mA for 25 min. Upon cessation of current, the catheter is removed and the patient enters the operating theatre within the next 5 min; if not, the drug solution retained in the bladder assists in maintaining the anaesthesia induced by EMDA.	91 pts (68 men and 23 women). Total of 131 procedures. Pts were excluded if they had a history of reactions to local anaesthetic drugs, psycosis, alcoholism or active, inflammatory lower urinary tract infections. 82 pts that underwent one to several invasive procedure (122 invasive procedures in total *) were asked to score their experiences with a simple pain scale: 0= absent to minimal discomfort 1= discomfort to tolerable pain 2= intolerable pain 9 underwent miscellaneous interventions all using rigid instruments.	In 111/ 122 procedures the discomfort was minimal or absent. In 6/122 procedures pain was tolerable. In pain 5/122 was described as intolerable and the peration were abandoned. With the present method, the patient has a comfortable anaesthetic duration of 50-60 min. Serum lidocaine levels was innocuous.

Before positioning the pts on the operating table, the urologist administered intravenous lorazepam: 2 mg in 83 pts (they remained fully conscious throughout their procedures and 4 mg in 8 younger and overly anxious pts.	(*) Invasive procedures were: 27 bladder- mapping biopsies, 62 TURBT of bladder tumors, 21 transurethral incisions on the prostate or on bladder neck, 12 TURBT of the prostate	

EMDA with lidocaine provides safe, effective anaesthesia for most invasive endoscopic procedure in the lower urinary tract.

17 - Intravesical electromotive drug administration technique: preliminary results and side effects - The Journal of Urology June 1998; 159 (6): 1851-1856 - Riedl CR, Knoll M, Plas E, Plüger H - Department of Urology and Ludwig Boltzmann Institute of Andrology, Municipal Hospital Lainz, Vienna, Austria.

METHOD	PATIENTS	RESULTS
Intravesical Volume: 100 - 150 cc Lidocaine 1% (3 pts), 2% (4 pts) or 2.6% (4 pts) and epinephrine 0.75 mg. 15-23 mA for 15 min. Intravenous anxiolysis sedation with 2.5 mg midazolam was administered to 5 pts undergoing resection. All pts were interviewed on pain sensation after the procedure. Exclusion criteria for thransurethral procedures under EMDA local anesthesia are large prostates that interfere with instrumentation, a history of multiple resections (resulting in a nonsherical bladder configuration and inhomogenous anesthetic drug distribution) and large tumors that cannot be safely resected within 40 to 50 min, which is the time limit for EMDA local anesthesia.	EMDA for local anesthesia was performed in 11 pts preceding thransurethral procedures: 6 male, 5 female, mean age 74.7. 12 EMDA treatments. Performed 20 minutes EMDA treatment (5 pts) or 2 treatment cycles of 15 mins in case of more extensive transurethral procedures (6 pts). Complete bladder tumor resection was performed in 5 pts (up to 4 cm in diameter as well multifocal tumors), tumor coagulation in 3 and multiple forceps biopsy in 3.	Performance of transurethral procedures was painless in 10 of 12 cases (83%). 1 pts reported tolerable pain from a cold forceps biopsy and 1 required general anesthesia because of intolerable pain. 1 pts underwent transurethral resection under local anesthesia twice: for the second procedure he was asked to choose among general, spinal or local anesthesia (he had had prior experience with all 3 methods) and he request the latter. Erythema of the posterior bladder wall was observed in 2 pts.

EMDA can safely and effectively be used for local anesthesia for endoscopic bladder surgery, taking advantage of increased drug administration without systemic side effects. EMDA reduces the need for hospitalization as all therapies are performed on an outpatient basis and total costs of medical treatment for the individual pts.

18 - Electromotive Drug Administration of lidocaine to anesthetize the bladder before intravesical capsaicin -The Journal of Urology June 1998; 159: 1857-1861 - Dasgupta P, Fowler CJ, Stephen RL - Uro-Neurology Department, Istitute of Neurology, London, UK.

METHOD	PATIENTS	RESULTS
Drug solution: 75 ml lidocaine hydrochloride 4% (NaCl-free) with 75 ml steril water, 1,5 ml 1:1,000 epinephrine giving a final solution of 150 ml lidocaine 2% with epinephrine 1:100,000. 20 mA, rise rate 30 µA for 15 min. Then bladder was drained and flushed and the capsacine solution was instilled for 30 mns under urodynamic monitoring: 100 ml capsaicin 2 mmol/l in 30% alcohol in saline Pts with positive urine cultures were treated with antibiotics before entering the study. Capsaicin instillation precede by EMDA were repeated once in 2 pts and twice in 1 pts when the effect of the previous dose diminished.	8 pts (4 men and 4 women) with detrusor hyperreflexia due to spinal cord disease. Previous treatment of incontinence using a combination of oral anticholinergics and clean intermittent catheterization had failed. The discomfort caused by intravesical instillation of capsaicin restricted its use, the purpose of this study was studied the efficacy of using EMDA to anesthetize the bladder before capsaicin. Each pts score suprapubic pain with a 10-point scale at 5 mns after starting the capsaicin instillation and at the end of procedure (30 min.): 0: no pain at all.	The pain scores during capsaicin instillations after EMDA of lidocaine were much lower than those during capsaicin instillations after lidocaine alone. EMDA eliminated the hyperreflexic contractions of bladder occurring during capsaicin instillations, thus reducing the risk of urethral leakage. For 5 pts who had received previous capsaicin instillation after lidocaine alone the pain scores during capsaicin instillations after EMDA were 0.6 ± 0.4 at 5 mns and 0.4 ± 0.5 at the end.

	10: worst pain imaginable Of the 8 pts 5 had previous capsaicin treatments and the scores were compared to previous scores when intravesical lidocaine without EMDA had been used as local anesthesia before capsaicin.	The pain score of 3 pts who received capsaicin after EMDA as initial treatment were 0, 1, 2 at 5 min. and 0, 3, 0 at 30 min. Of the 8 pts, 6 (75%) responded to the treatment: 5 became completely continent and 1 had decreased episodes of urge incontinence during the day. The duration of benefit was 3 months in 3 pts, 6 months in 2 pts and 8 months in 1pts.

Electromotive Drug Administration of lidocaine is a simple, safe and effective method of anesthetizing the bladder and reducing pain during subsequent intravesical capsaicin instillations.

19 - Electromotive Drug Administration of lidocaine as an alternative anesthesia for transurethral surgery- The Journal of Urology 1999; 161: 482-485 - Jewett Michael AS, Valiquette L, Sampson HA, Katz J, Fradet Y, Redelmeier DA - Divisions of Urology, Departments of Surgery, Universities of Toronto, Montreal and Laval, Montreal and Laval, Quebec, Departments of Psychology and Medicine, University of Toronto, Division of Clinical Epidemiology, Sunnybrook Health Science Centre and Toronto Hospital, Toronto, Ontario, Canada.

METHOD	PATIENTS	RESULTS
Multicenter study: 3 centers and 3 groups of pts participated to the study. Drug solution: 100 ml Lidocaine 4% (NaCl free), 100 ml sterile water and 2 ml epinephrine (1mg/ml) for a final concentration of 1:100,000. Current applied: 25 mA for 20-25 min. 1 to 2 mg sublingual lorazepam were administered as an anxiolytic to 50% of the biopsy and 90% of the transurethral bladder tumor resection/ fulguration pts. Anaesthetic gel was instilled into the urethra.	94 pts enrolled. Outcomes: to assess safety, efficacy and cost-effectiveness of EMDA/ lidocaine. Group 1 also included 6 pts with concurrent bladder tumor and interstitial cystitis who required bladder biopsy and hydrodistension, respectively. Group 1: 45 pts who required cold cup bladder biopsy with (27) or without (18) electromotive intravesical lidocaine (comparison trial of EMDA/lidocaine vs no anesthesia) Group 2: 43 pts undergoing transurethral resection/ fulguration who were offered EMDA/lidocaine as an alternative to general or regional anesthesia with EMDA/lidocaine.	For group 1 pain levels were significantly less intense for EMDA group than the control group during insertion of the cystoscope, biopsy and coagulation. For the group 2 median pain scores for the entire procedure were 0 (except for mild pain during cutting, 1.4). EMDA/ lidocaine for bladder biopsy and thransurethral bladder tumor resection/ fulguration was associated with higher patient satisfaction compared to previous treatments. 86% pts stated that they would be willing to repeat procedure. Group 3: 3 experienced more discomfort than those undergoing bladder procedures. The remaining 3 pts had remarkably pain-free procedures.

A numeric pain score was measured before during and after the procedures (biopsy, fulguration and resection) using an 11-point numeric rating scale with end points labeled 0 (no pain) and 10 (worst possible pain).	Group 3: 6 pts with benign prostatic hyperplasia (BPH)/carcinoma of prostate undergoing transurethral resection who agreed to be treated with EMDA/lidocaine.	The cost per pts was less with EMDA/lidocaine than with conventional general and spinal anesthesia.

The anesthetic technique with EMDA/lidocaine offers advantages in terms of effective, safety and cost while providing near equal levels of anesthesia for patients requiring transurethral bladder biopsy, resection or fulguration.

20 - The stability of lidocaine and epinephrine solutions exposed to the electrical current and comparative administration rates of the two drugs into pig bladder wall- Urological Research 2003; 31:169-176- Di Stasi SM, Giannantoni A, Navarra P, Massoud R, Zavaglia D, Bertucci PF, Vespasiani G, Stephen RL- Department of Urology, University of Perugia, Perugia, Department of Urology, Tor Vergata University, Rome.

The combination lidocaine and epinephrine remains stable for 1 days and when exposed to 30 mA for 45 min. Electric current accelerates the transport rate of lidocaine and epinephrine.
No tissue damage was detected histologically or by trypan blue test.

See pag 9

21 - Electromotive Drug Administration of lidocaine to anesthetize the bladder before botulinum-A toxin injections into the detrusor- Spinal Cord 2004; 42: 338-341. Schurch B, Reitz A, Tenti G - Swiss Paraplegic Center, Balgrist University Hospital Zurich, Department of Urology, University Hospital Zurich, Switzerland.

METHOD	PATIENTS	RESULTS
Drug solution for EMDA: 75 ml lidocaine hydrochloride 4% (NaCl-Free) with 75 ml sterile water and 1.5 ml 1/100000 epinephrine giving a final solution of 150 ml lidocaine 2% with epinephrine 1/100000 epinephrine. Urethra was lubrificated with 20 ml lidocaine 2% gel. Current applied: 25 mA for 20-25 min. 300 u of botulinum-A toxin (Botox®) was injected at 30 sites sparing the trigone.	28 pts (17 males, 11 females) with neurogenic detrusor overactivity but preserved bladder sensibility. Group of 10 pts: received conventional lidocaine instillation to anesthetize the bladder prior to the injection of Botox®. Group of 28 pts: received received EMDA enhanced lidocaine instillation prior to the Botox® injection. Pts scored the injection pain on a 10-point rating scale. Cost of the EMDA procedure were compared to general and spinal anesthesia.	For pts who underwent the injection of Botox® after conventional lidocaine instillation the mean pain score was 4.0. For pts who underwent EMDA enhanced lidocaine instillation the mean pain score after Botox® injection was 0.5. The Botox® injection after EMDA caused a slight pain in 12 pts and 16 pts reported no pain; no side effects and mucosa lesions were observed. Pts who had already undergone Botox® injection after conventional lidocaine instillation reported a remarkable reduction or even the absence of pain and would prefer the EMDA-enhanced lidocaine instillation in the future. Local anesthesia using EMDA saved around 15% of the costs.

EMDA enhanced instillation of lidocaine provides a sufficient anesthesia of the bladder wall that ensures a painless botulinum-A toxin injection into the detrusor muscle. This method may avoid general or spinal anesthesia with considerable cost reduction and avoidance of anesthesia-related risk and complications.

EMDA a simple and safe procedure.

ELECTROMOTIVE DRUG ADMINISTRATION OF OXYBUTYNIN FOR THE TREATMENT OF DETRUSOR HYPERREFLEXIA

22 - Electromotive Drug Administration of oxybutynin into the bladder human wall- The Journal of Urology July 1997; 158: 228-233- Di Stasi SM, Giannantoni A, Massoud R, Cortese C, Vespasiani G, Micali F - Tor Vergata University of Rome School of Medicine and the S. Lucia IRCCS Rehabilitation Hospital, Rome, Italy.

METHOD	PATIENTS	RESULTS
Tissue sections of human bladder were inserted into a diffusion cell with urothelium exposed to the donor compartment containing oxybutynin (4.5 mg in 100 ml NaCl 0.45%). Serosa was exposed to receptor compartments that were filled with 100 ml NaCl solution 0.9%. In the EMDA experiments an anode was placed in the donor compartment and a cathode in the receptor compartment; the electrodes were connected to the current generator and experiments were performed with pulsed electric current of 5 mA for 15 min. No electric current was applied in PD control experiments.	Oral oxybutynin and the clean intermittent catheterization (CIC) is the most common treatment of detrusor hyperreflexia. However there is a subset of pts who do not respond to oral anthicholinergic drugs or who experience intolerable systemic side effects. Intravesical instillations exposes the bladder wall tissues to much higher concentrations of drug those achieved systemically and may cause fewer systemic side effects: oxybutynin is well tolerated. Purpose of the study was to compare concentrations of oxybutynin in the human bladder wall after either passive delivery (PD) or EMDA.	Mean oxybutynin tissue concentrations were 3.84 µg/gm in samples exposed to EMDA and 0.87 µg/gm in samples exposed to PD. The mean quantities of oxybutynin transported into bladder wall samples by EMDA significantly exceeded the respective amounts administered by PD: 8.69 µg/gm vs 2.02 µg/gm. The mean coeficients of variation were 57.85% in EMDA experiments and 89.78% in PD experiments. Tissues were viable (trypan blue test demonstrated viability of tissue throughout the time of experiments) and undamaged histologically and no oxybutynin structural modification was observed.

12 paired experiments current /no current were performed using 24 bladder wall tissue samples from 12 different pts (underwent to radical cystectomy). Oxybutynin tissue contents were measured. Urothelium bladder integrity, tissue viability, morphology, pH and oxybutynin stability were assessed.		No significant differences were observed between post PD-pH and post EMDA-pH of tissue.

EMDA enhances oxybutynin administration into viable human bladder wall and reduces the variability in drug delivery rate. No histologic changes and structural modifications of oxybutynin were observed.

23 - Intravesical electromotive drug administration technique: preliminary results and side effects - The Journal of Urology June 1998;159 (6):1851-1856 - Riedl CR, Knoll M, Plas E, Plüger H - Department of Urology and Ludwig Boltzmann Institute of Andrology, Municipal Hospital Lainz, Vienna, Austria.

METHOD	PATIENTS	RESULTS
Drug solution: 15-50 mg oxybutynin hydrochloride in 100 cc saline 0.3%. Since instillations of 100 cc often cause detrusor contractions and leakage, they initially instilled 50 cc and let the current rise to 8 mA. Current was reset to zero and restarted until pts were able to tolerate 8 mA and the it was raised to 15 mA for 20 min with volume increased to 100 cc. Best dosage: 30 mg oxybutynin and increased the dosage at 10 mg increments if no response is observed.	14 pts with detrusor hyperreflexia and or urge incontinence who did not tolerate or improve on oral anticholinergics were treated with EMDA: 4 male, 10 female, mean age 67.3. 29 EMDA treatments. Pts was monitored for systemic anticholinergic side effects (blood pressure, heart rate, symptoms) during and immediately after EMDA. Bladder symptoms were controlled after 1 day and 1 week.	In 11 pts (78,5%) EMDA of oxybutynin reduced detrusor hyperreflexia. Due to contraction and leakage,treatment was terminated in 3 pts. 3/11 (27%) pts showed long term (> 1 week) improvement of bladder symptoms, 4/11 (36.5%) pts less than 1 week. No local or systemic side effects were observed.

EMDA can safely and effectively be used for the treatment of detrusor hyperreflexia and/or urge incontinence, taking advantage of increased drug administration without systemic side effects. EMDA of oxybutynin reduced or ablated bladder hyperreflexia up to several weeks. Improvements were also documented urodynamically. These data suggest that single EMDA treatment with oxybutynin may be superior to passive instillation and oral therapy that must be administered several times a day.

24 - Intravesical Electromotive Administration of oxybutynin in patients with detrusor hyperreflexia unresponsive to standard anthicolinergic regimens- The Journal of Urology February 2001; 165: 491-498- Di Stasi SM, Giannantoni A, Vespasiani G, Navarra P, Capelli G, Massoud R, Stephen RL - Department of Urology and Clinical Biochemistry, Tor Vergata University, Rome, Institutes of Pharmacology and Hygiene, Catholic University, Rome, Department of Urology, University of Perugia, Perugia, Italy.

METHOD	PATIENTS	RESULTS
Pts were treated at weekly intervals with: -5 mg oxybutynin orally or identical placebo tablet (control); - 5 mg oxybutynin in 100 ml sodium chloride 0.45% administered intravesically for 60 min with passive diffusion (PD) or 100 ml sodium chloride 0.9% administered with PD (control); - 5 mg oxybutynin in 100 ml sodium chloride 0.45% administered intravesically with EMDA for 30 min with 5 mA electric current or 100 ml sodium chloride 0.9% administered with EMDA (control).	10 pts (6 men, 4 women) with detrusor hyperreflexia unresponsive to standard oral anticholinergic and intravesical oxybutynin were treated. About 15% to 20% of the pts with detrusor hyperreflexia do not benefit from oral oxybutynin regimens, frequently because of side effects: this study was designed to determinate whether 1) accelerated intravesical administration of oxybutynin provided objective benefits in these previously unresponsive patients.	There was no significant objective improvement with oral or intravesical PD oxybutynin. Conversely there was significant improvement in 5 of 6 urodynamic measurements with electromotive drug administration (EMDA) of oxybutynin. Plasma profiles were a single peak and decay following oral oxybutynin and 2 distinct peaks with intravesical PD and EMDA oxybutynin. Area under the curve for intravesical PD were 709 ng per 8 hours vs oral 1.485 vs intravesical EMDA 2.781. Bladder content samples confirmed oxybutynin absorption.

Each treatment (plus oral placebo and two intravesical controls) was associated with an 8-hour full urodynamic monitoring session and periodic blood and bladder content sampling.	2) the results could be correlated with plasma levels and intravesical uptake of oxybutynin and 3) the presumptive benefits could be achieved without intolerable side effects.	Oral oxybutynin caused anticholinergic side effects in 7 of 10 pts,included dry mouth (4), nausea (3), headache (3) and blurred vision (2).There were no side effects with PD or EMDA.

Electromotive Drug administration of oxybutynin increases bioavailability and objective benefits without side effects compared with oral and intravesical passive diffusion oxybutynin administration.

25 - Intravesical oxybutynin: mode of action assesses by passive diffusion and Electromotive Administration with pharmacokinetics of oxybutynin and N-desethyl oxybutynin- The Journal of Urology December 2001; 166: 2232-2236 - Di Stasi SM, Giannantoni A, Navarra P, Capelli G, Storti L, Porena M, Stephen RL - Department of Urology, Tor Vergata University, Rome, Institutes of Pharmacology and Hygiene, Catholic University, Rome, Department of Urology, University of Perugia, Perugia, Italy.

METHOD	PATIENTS	RESULTS
Pts were treated at weekly intervals with 6 modes of drugs and placebo: - 5 mg oxybutynin chloride and placebo orally in tablet form (control); - 15 mg oxybutynin in 100 ml sodium chloride 0.45% administered intravesically with passive diffusion (PD) for 60 min or 100 ml sodium chloride 0.9% administered with PD (control); - 15 mg oxybutynin in 100 ml sodium chloride 0.45% administered intravesically with EMDA for 30 min with 15 mA electric current or 100 ml sodium chloride 0.9% administered with EMDA (control). was associated with an Each administration mode per pts was associated an 8-hour urodynamic monitoring session during which oxybutynin and	The same 10 pts with detrusor hyperreflexia enrolled in the previous study (21) plus an additional 2 with the same characteristics (unresponsive to oral and intravesical passive diffusion of 5 mg oxybutynin) are enrolled. Total: 12 pts (7 men, 5 women) with spinal cord injury and neurogenic bladder dysfunction due to upper motor neuron lesions. An oral dose of oxybutynin of up to 15 mg daily had resulted in unacettable detrusor activity suppression and/or intolerable side effects. Intravesical administration of 5 and 10 mg oxybutynin by PD in 9 and 3 pts respectively had resulted in neither benefits nor side effects.	A dose of 5 mg oxybutynin orally induced no urodynamic improvement. PD oxybutynin resulted in 12 mg oxybutynin intravesical uptake and significant improvement in 3 of 8 urodynamic measurements. EMDA of oxybutynin resulted in almost complete intravesical uptake of the 15 mg dose, significant improvement in all 8 urodynamic measurements and an increases oxybutynin level vs oral and PD. EMDA oxybutynin caused significantly greater intravesical post-void residual urine volume and significantly fewer episodes of urinary leakage. The oral dose of 5 mg oxybutynin caused anticholinergic side effects in 8 of the 12 pts.

N-desethyl oxybutynin plasma levels, and intravesical oxybutynin uptake were measured. Administration was done in random and double blind-fashion with respect to identify of oral placebo or oxybutynin tablets and intravesical control and oxybutynin solution.		Neither intravesical PD nor EMDA caused side effects with an uptake of 12 and 15 mg, respectively and each resulted in a much lower mean area under the curve of plasma oxybutynin plus N-desethyl oxybutynin (2.123 for PD and 4.574 ng/8 hours for EMDA) than oral oxybutynin (16.297 ng/8 hours).

The clinical benefits of intravesical oxybutynin instillation is the result of localized direct action within the bladder wall: a large proportion of intravesical oxybutynin is sequestered, probably in the urothelium. Applying intravesical electric current (EMDA) enhances this effect.

ELECTROMOTIVE DRUG ADMINISTRATION OF BETHANECHOL FOR THE TREATMENT OF ACONTRACTILE DETRUSOR

26 - Intravesical electromotive drug administration technique: preliminary results and side effects - The Journal of Urology June 1998;159 (6):1851-1856 - Riedl CR, Knoll M, Plas E, Plüger H - Department of Urology and Ludwig Boltzmann Institute of Andrology, Municipal Hospital Lainz, Vienna, Austria.

METHOD	PATIENTS	RESULTS
Drug solution:10-30 mg bethanecol hydrochloride in 150 cc saline 0.3%. 15-23 for 20 min. Initially used 15 mg bethanecol and increased the dosage at 5 mg increments if no response is observed. Simultaneous cystometry during EMDA recorded pressure changes. Pts were monitored for cholinergic side effects during and immediately after EMDA and 1 day, 1 week and 1 month after EMDA.	14 pts with cystometric evidence of acontractile detrusors: 5 male, 9 female, mean age 67.5. 20 EMDA treatments. EMDA with saline and bethanecol instillations without current were performed for control.	In 10/14 (71.4%) pts urodynamic examination showed detrusor contraction during EMDA of bethanechol. Simultaneous cystometry during EMDA recorded intravesical pressure increase, starting about 5 minutes after the initiation of the procedure. When current was turned off, maximal intravesical pressure was maintained for another 5 min and the nit decreased to zero. Only the combination of intravesical bethanecol and current, and neither alone, increased intravesical pressure. During 20 treatments only once a pts experienced painful bladder contraction which stopped when current was turn off. No side effects were observed.

EMDA of bethanechol can safely and effectively be used for stimulating the acontractile detrusor muscle, taking advantage of increased drug administration without systemic side effects.
Restoration of bladder function was observed after EMDA.

27 - Electromotive Drug Administration of intravesical bethanechol and the clinical impact on acontractile detrusor management: introduction of a new test - The Journal of Urology December 2000; 164: 2108-2111- Riedl CR, Lukas LK, Knoll M, Plas E, Pflüger H - Department of Urology and Ludwig Boltzmann Istitute of Andrology, Municipal Hospital Lainz, Vienna, Austria.

METHOD	PATIENTS	RESULTS
Phase 1: 5 pts with detrusor areflexia were tested as controls with an intravesical instillation of 20 mg bethanechol in 150 cc of sodium chloride 0.3% with and without 20 mA of pulsed current applied. Cystometry simultaneously recorded intravesical pressure changes. Phase 2: 45 pts with detrusor areflexia were tested with EMDA of intravesical bethanechol. Phase 3: 25 mg bethanechol given orally once daily were prescribed for 15 pts and voiding control was assessed after 6 weeks of therapy.	A total of 45 pts (25 women and 20 men) with urinary retention and cistometrically verified detrusor areflexia were enrolled and stratified into subgroups with: chronic bladder dilatation greater than 4 weeks in duration, acute postoperative bladder over dilatation, neurological and idiopathic disease. It's often difficult to determinate the functional status of the detrusor muscle in pts with detrusor areflexia: the purpose of this clinical study was to establish a test defining residual detrusor capacity in such patients.	Neither bethanechol without current nor current through saline only led to increased intravesical pressure. However, we noted a mean pressure increase of 34 cm. water during the EMDA of bethanechol in 24 of 26 pts with areflexia and neurological disease compared to only 3 cm. water in 3 of 11 with a history of chronic bladder dilatation. Oral bethanechol restored spontaneous voiding in 9 of 11 pts who had had a positive response to the EMDA of bethanechol, whereas all 4 without a pressure increase during the EMDA of bethanechol did not void spontaneously.

Electromotive administration of intravesical bethanechol identifies pts with an atonic bladder and adequate residual detrusor muscle function who are candidates for restorative measures, such as oral bethanechol and intravesical electrostimulaton. Those who do not respond to EMDA of bethanechol do not benefit from oral bethanechol and are candidates for catheterization.

ELECTROMOTIVE DRUG ADMINISTRATION OF BOTULINUM TOXIN FOR THE TREATMENT OF OVERACTIVE BLADDER

28 - Intravesical Electromotive Botulinum Toxin Type A Administration - Part I-Experimental Study - Urology June 2011; 77 (6): 1460-1464- Kajbafzadeh AM, Montaser-Kouhsari L, Ahmadi H, Sotoudeh M -Pediatric Urology Research Center, Department of Pediatric Urology, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran.

METHOD	PATIENTS	RESULTS
15 rabbits were divided into groups: - 5 rabbits into BTX-A cytoscopic intravesical injection (a total dose of 10 IU/kg was injected into 10 sites of detrusor muscle); - 10 rabbits into BTX-A/ EMDA group. Animals into BTX-A/EMDA group were then allocated into 2 groups: - in the first group the bladder was filled with distilled water, containing 10 IU/kg BTX-A, to its maximal capacity. The device was set to deliver a maximum of 2-2.4 mA for 15 min; - in the second (electromotive saline administration group) the bladder was filled with a saline solution and the generator delivered electrical current with the same characteristics.	The objective of this experimental study is to evaluate the depth of penetration and distribution pattern of botulinum toxin type A (BTX-A) distribution throughout the rabbit bladder wall by intravesical EMDA and cytoscopic intravesical injection. 15 male healthy New Zealand white rabbits (weighing between 2 and 3 kg) were allocated in 3 groups of BTX-A injection into the bladder wall.	All study animals remained healthy and alive after the procedure. Immunohistochemical staining of specimens from BTX-A/EMDA group revealed a homogenous BTX-A distribution through the urothelium, interstitial layer and muscle layer. In electromotive saline administration group there was no detectable staining in specimens: urothelium, interstitial layer and muscle layer were intact. Pattern of immunohistochemical staining in bladder specimens from BTX-A injection group was weak and heterogeneous in urothelium, interstitium and muscle layer.

Three different specimens from the bladder dome, posterior and anterior bladder walls were obtained and submitted for pathologic evaluation.		

This study showed that BTX-A/EMDA resulted in deeper and more homogeneous distribution of BTX-A into the rabbit wall when compared with cytoscopic intravesical BTX-A injection.

29 - Intravesical Electromotive Botulinum Toxin Type A Administration - Part II-Clinical Application - Urology February 2011; 77 (2): 439-445- Kajbafzadeh AM, Ahmadi H, Montaser-Kouhsari L, Sharifi-Rad L, Nejat F - Pediatric Urology Research Center, Department of Pediatric Urology, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran.

METHOD	PATIENTS	RESULTS
Catheterization was performed with a 10F indwelling catheter containing a silver spiral electrode, after providing a local transurethral anesthesia with 2% lidocaine gel. The bladder was filled with sterile water to its maximal capacity. A dose of 10 IU/kg was added to the intravesical solution. The device was set to deliver a maximum of 10 mA for 15 min. The urodynamic parameters, including reflex volume, maximal bladder capacity, maximal detrusor pressure and end-fill pressure, the urinary/fecal incontinence status and VUR grade were evaluated before and at 1, 4, and 9 months after treatment.	The objective of this study was to assess the effect of electromotive botulinum toxin type A administration on urodynamic variables, urinary/fecal incontinence and vesicoureteral reflux (VUR) due to refractory neurogenic detrusor overactivity in children with myelomeningocele. A total of 15 children (11 girls, 4 boys, mean age 7.8 years) were included. Eligible patients were those who had urinary/ fecal incontinence and had shown no response to clean intermittent catheterization and the maximal dose of oral anticholinergics or had had serious detrimental side effects from these treatments.	The mean reflex volume and maximal bladder capacity had increased considerably (99±35 mL versus 216±35 mL and 121±39 mL versus 262 ±41 mL, respectively; P<.001). In contrast, the mean maximal detrusor pressure and end-fill pressure had significantly decreased (75±16 cm H2O versus 39 ±10 cm H2O and 22 ±7 cm H2O versus 13±2 cm H2O) after treatment. The difference was statistically significant (P<.001). Urinary incontinence improved in 12 patients (80%). The VUR grade substantially decreased in 7 of the 12 children (mean VUR grade 2.25±1.3 versus 1.37 ±0.7; P=.001), and none of the children required surgical intervention. Fecal incontinence was alleviated in 10 (83.3%) of the 12 children; of the 10 patients, 6 (50%) had complete

During the monthly follow-up visits, the children were evaluated regarding possible side effects, including generalized muscle weakness, weakness in adjoining muscles in the pelvis, diplopia, dysphagia, blurred vision, and hematuria.	Children with coagulopathies and those receiving gentamycin were excluded from the present study.	improvement and 4 (33.3%) reported moderate improvement. Skin erythema and burning sensation were observed in 6 children.

The results of our study have shown that electromotive botulinum toxin type A administration is a feasible and safe method with no need for anesthesia. This novel delivery system resulted in considerable improvement in the urodynamic parameters, urinary/fecal incontinence, and VUR in patients with refractory neurogenic detrusor overactivity.

30 - Intravesical Electromotive Botulinum Toxin in women with overactive bladder- a pilot study- ARC Journal of Gynecology and Obstetrics 2017; 2 (2): 4-10, Schiotz HA, Ha T Mai, Zabielska R - Department of Obstetrics & Gynecology, Vestfold Hospital Trust, Tønsberg, Norway.

METHOD	PATIENTS	RESULTS
Pts underwent a single outpatient treatment session with botulinum toxin A (Botox®). The bladder was emptied and 60 ml of of onabotulinumtoxin A (Botox®) were instilled into the bladder. The device was set to deliver a maximum of 20 mA for 30 min. The participants were seen in the clinic after 2 weeks bringing a 24 hour voiding chart. At the visit urine flow rate and postvoid residual were measured and a treatment satisfaction VAS were recorded. After 4 weeks and 3 months the participants reported by letter with a 24 hour voiding chart, UDI-6, IIQ-7, ICIQ-OAB SF and a treatment satisfaction VAS, and after 6 months they were again seen in the clinic with the same procedure as the 2 week visit.	14 women with treatment resistant overactive bladder (OAB) were enrolled. The primary efficacy end-point was change in number of leakage episodes per 24 hours. Secondary endpoints were: change in grams leakage, number of voids and mean voided volume on a 24 hour voiding chart, change in score on the validated instruments UDI-6 (Urogenital Distress Inventory 6), IIQ-7 (Incontinence Impact Questionnaire 7), ICIQ-OAB SF (International Consultation on Incontinence Overactive Bladder Short Form) and a treatment satisfaction VAS, and change in flow rate and postvoid residual urine. Adverse events such as UTI and need for catheterization were recorded.	At both one and three months there was statistically significant reduction in leakage episodes and grams leakage per 24 hours as well as in UDI6 score. Statistically significant improvement was seen for IIQ7 and ICIQ-OAB SF scores and number of voids per 24 hours at one month, but not at three months. The response rate was 43% (6/14) at one month, 36% (5/14) at three months and 21% (3/14) at six months with continence achieved in 43%, 21% and 7%, respectively. At six months, all the three responders scored 8 on the treatment satisfaction VAS. There were no adverse events except three episodes of acute cystitis (14%) in two patients who both have a history of recurrent urinary tract infections:

		two episodes occurred within a week of treatment and the third eight weeks later. There was no change in postvoid residuals and no cases of urinary retention (no one required catheterization).

Electromotive botulinum toxin administration is a feasible, simple and safe non-invasive outpatient method with no need for anesthesia or cystoscopy. It can be administered by a nurse. A statistically significant improvement in overactive bladder problems was found after a single treatment session. Treatment response was 43% at one month, 36% at three months and 21% at six months.

31 - Intravesical Electromotive Botulinum Toxin Type "A" Administration for Management of Urinary Incontinence Secondary to Neuropathic Detrusor Overactivity in Children: Long-term Follow-up - April 2018; 114: 167-174 - Ladi-Seyedian SS, Sharifi-Rad L, Kajbafzadeh AM - Pediatric Urology and Regenerative Medicine Research Center, Children's Hospital Medical Center, Pediatric Center of Excellence, Tehran University of Medical Sciences, Tehran, Iran.

METHOD	PATIENTS	RESULTS
A total of 24 patients were assigned to receive 10 IU/kg of Dysport (BoNTA) with electromotive drug administration (EMDA) without anesthesia on outpatient basis. The device was set to deliver 10 mA for 20 min. The preliminary assessments were voiding diary, urodynamic study, kidney and bladder ultrasounds which were also performed annually. Follow-up for 6 years.	24 patients with myelomeningocele (mean age: 9 ± 3.6 years,) were included in the study and and followed up for 6 years. The objective was to investigate the long-term efficacy and success rate of intravesical electromotive botulinum toxin type A (BoNTA) "Dysport" administration in patients with myelomeningocele who had urinary incontinence due to neuropathic detrusor overactivity (NDO).	Prior to the treatment, all patients had NDO and urinary incontinence. During the follow-up, 18 of 24 (75%), 11 of 24 (45.5%), 9 of 24 (37.5%), 8 of 24 (33%), and 7 of 24 (29.1%) of the patients were completely dry between 2 consecutive clean intermittent catheterizations after once BoNTA-EMDA treatment at 1, 2, 3, 5, and 6 years of follow-up, respectively. The mean maximum detrusor pressure significantly decreased and mean maximal cystometric capacity significantly increased at follow-up ($P < 0.05$).

The results of the present study have shown that BoNTA-EMDA is a feasible, safe, reproducible, cost-effective, long-lasting, and pain free method on an outpatient basis, with long-term duration of effects without anesthesia or cystoscopy procedure. This novel delivery system resulted in considerable improvement in urinary incontinence and urodynamic study parameters in patients with refractory NDO.

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Rev. 1 2020/05/06