Review Article

Applications of electromotive drug administration in urology

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Abstract

To review all published evidence regarding the use of Electromotive Drug Administration (EMDA) for the management of urological conditions, focusing on efficacy and safety, and highlighting areas that require further study. The PubMed and Medline databases were searched up to July 23, 2019. All studies reporting the use of EMDA to enhance the intravesical administration of therapeutic drugs for urological conditions were included. Two reviewers independently screened all articles, searched the reference lists of retrieved articles, and performed the data extraction. Thirty-two studies were included. The use of EMDA has been reported in the following urological conditions: (1) nonmuscle-invasive bladder cancer (NMIBC); (2) overactive bladder; (3) bladder pain syndrome; (4) radiation cystitis; (5) detrusor acontractility; and (6) for analgesia prior to transurethral procedures. Overall, most studies are nonrandomized trials with small numbers of patients. The use of EMDA is reported to be safe and effective in all these conditions, with the highest level of evidence in NMIBC in the neoadjuvant and adjuvant setting. However, the low overall quality of evidence limits the conclusions that can be reached. The use of EMDA to improve the efficacy of intravesical treatments is promising, but the low overall quality of the evidence base has limited its widespread use. Future studies should compare EMDA to passive diffusion and current standard of care in large, randomized, and long-term studies to determine the efficacy, safety, and cost-effectiveness of this modality.

Keywords: Bladder cancer, bladder pain syndrome, botulinum toxin, electromotive drug administration, interstitial cystitis, overactive bladder

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INTRODUCTION

Therapeutic drugs are most commonly administered either orally or by intravenous injection. Oral administration however is not always ideal, as first-pass metabolism means there may only be a low dose reaching the bladder, and there can be a number of unpleasant systemic side effects with parenteral administration.[1] Intravesical instillation is an alternative, offering a more site-specific delivery. With a greater quantity of the medication being delivered directly to the bladder and a lesser systemic side effect profile, intravesical administration is now used for a variety of urological conditions.[1,2] However, intravesical administration relies on passive diffusion of the medication across the relatively impermeable urothelium, which can be slow and unreliable. Furthermore, dilution of the drug with urine and expulsion on voiding reduce the concentration of the drug and the time that it remains in contact with the bladder. Several enhanced drug delivery techniques have, therefore, been described with the aim of improving the dwell time and penetration

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of the drug into the bladder. These include intravesical devices that provide a slow release of a therapeutic agent over a longer period, hydrogels, nanocarriers (such as liposomes), chemothyperthermia, and electromotive drug administration (EMDA).[3]

EMDA uses an electrical current of 0–30 mA DC at 0–55V between 2 electrodes to drive drug transportation across the urothelium,[2,4] based on the principles of iontophoresis, electro-osmosis and electroporation. It has been shown to result in a greater depth of penetration of molecules into the bladder compared to passive diffusion alone, but whether this improves clinical efficacy remains uncertain.[2,5,6]

METHODS

A literature search was performed using the PubMed and Medline databases up until July 23, 2019, using the search terms electromotive drug administration OR EMDA. The reference lists of included studies were also searched for relevant articles. All types of studies assessing the use of EMDA for the intravesical administration of therapeutic drugs for a urological condition in humans were eligible for inclusion. Only English language publications were considered and those that were not related to a urological condition were excluded. Conference abstracts and review articles were also excluded. Two reviewers (SH and SM) independently screened all abstracts and full-texts following the search.

RESULTS

A total of 136 studies were identified in the initial search, of which 32 were eligible for inclusion in this review. The baseline characteristics of all included studies are shown in Table 1. A total of 1630 patients were recruited across all indications. Studies using EMDA to enhance intravesical drug administration have been reported for the following conditions: nonmuscle-invasive bladder cancer (NMIBC), overactive bladder (OAB), bladder pain syndrome/interstitial cystitis (BPS/IC), radiation cystitis, detrusor acontractility, and for anesthesia prior to transurethral urological procedures.

Nonmuscle-invasive bladder cancer

A total of 9 trials (total 989 patients, 484 treated with EMDA) examining the effect of electromotive administration of mitomycin C (MMC) in the management of NMIBC were included [Table 2]. There were 3 randomized controlled trials, with 2 nonrandomized comparative studies and 4 prospective cohort studies. Five trials assessed EMDA MMC in the adjuvant setting after transurethral resection of bladder tumor (TURBT), whilst 3 studied its role in the neoadjuvant setting, and one evaluated its efficacy in treating bacille calmette-guerin (BCG)-refractory disease.

All studies included patients with intermediate or high-risk NMIBC, but there was heterogeneity in terms of EMDA protocol used, treatment schedule and comparator group [Table 2]. The following clinical scenarios have been studied:

Adjuvant induction treatment – Electromotive Drug Administration mitomycin C alone or versus passive mitomycin C

Riedl *et al*. evaluated the effect of weekly EMDA MMC for 4 weeks on the recurrence rate of NMIBC.[6] This cohort study included patients with low and high-grade disease (G1-3, pTa-T1, and pTis), but the majority had G2pTa tumors. 56.6% were free of recurrence at a mean follow-up time of 14.1 months. The treatment was well-tolerated but 1.1% developed a severe adverse event (bladder ulceration). A multicenter comparative study of 28 patients with low/intermediate-risk tumors (G1-G2, pTa-T1, <1.5 cm tumor) did not find any difference in complete response (defined as absence of visible or microscopic tumor and negative cytology) between an 8 week course of EMDA MMC compared to passive MMC in patients with intermediate risk NMIBC, but in those who responded to treatment a lower recurrence rate and longer disease-free interval were demonstrated with EMDA MMC.[7] However, a randomized trial of EMDA MMC (n = 36) versus passive MMC (n = 36) for high-risk NMIBC (CIS plus concurrent pT1 carcinoma) revealed a significantly higher response rate with EMDA MMC and a longer time to recurrence.[8] It should be noted that this study was found to have a high risk of bias in a recent Cochrane review.[9] The role of induction and maintenance (lasting 6 months) EMDA MMC has also been studied in 26 patients with BCG refractory disease (defined as persistent high-grade NMIBC after first or second induction BCG) in a prospective cohort study.[10] At 3-year follow-up 61.5% preserved their bladders, with disease-free rates highest for those without CIS. Although promising, these data require validation in randomized trials against other modalities of treatment for BCG refractory disease and most importantly, longer-term follow-up.

Adjuvant induction treatment – Electromotive Drug Administration mitomycin C versus BCG

A single randomized trial of 72 patients reported similar complete response and time to recurrence rates between EMDA MMC and BCG,[8] but high risks of bias limit the confidence in the conclusions reached from this study.

Table 1: Baseline characteristics of included studies

Study	Study design	Condition being treated	Total number of patients	Number of patients treated with EMDA	Length of follow-up (months)
Brausi 1998	Multicenter, nonrandomized comparative study	NMIBC	28	15	Mean 16.3 (6-24)
Colombo 2001	Single center, nonrandomized comparative study	NMIBC	80	15	7-10 days
Decaestecker 2018	Prospective cohort study	NMIBC	32	32	2-4 weeks
Di Stasi 2003	Prospective randomized comparative study	NMIBC	108	36	Median 45
Di Stasi 2006	Prospective randomized comparative study	NMIBC	212	107	Median 88
Di Stasi 2011	Multi center, randomized, parallel-group study	NMIBC	374	124	Median 86
Gan 2016	Prospective cohort study	NMIBC	107	107	24
Riedl 1998a	Prospective cohort study	NMIBC	22	22	Mean 14.1
Racioppi 2018	Prospective cohort study	NMIBC	26	26	Median 36
Bach 2009	Prospective cohort study	OAB	84	84	8 weeks
Di Stasi 2001	Prospective comparative study	OAB	10	10	N/A
Gauruder-Burmester 2008	Prospective cohort study	OAB	72	72	12 months
Kajbafzadeh 2011	Prospective cohort study	OAB	15	15	9
Ladi-Seyedian 2018	Prospective cohort study	OAB	24	24	72
Riedl 1998a	Prospective cohort study	OAB	14	14	1 week
Koh 2019	Prospective cohort study	OAB	12	12	4-6 weeks
Gurpinar 1996	Prospective cohort study	BPS/IC	6	6	
Gulpinar 2014	Prospective randomized comparative study	BPS/IC	31	16	24
Riedl 1997	Prospective cohort study	BPS/IC	17	17	Mean 10.8
Riedl 1998a	Prospective cohort study	BPS/IC	16	16	Mean 10.8
Riedl 1998b	Prospective cohort study	BPS/IC	13	13	Mean 10
Rosamilia 1997	Prospective cohort study	BPS/IC	21	21	6
Riedl 1998a	Prospective cohort study	Radiation cystitis	6	6	Mean 10.8
Riedl 1997	Prospective cohort study	Radiation cystitis	6	6	Mean 10.8
Riedl 1998a	Prospective cohort study	Detrusor acontractility	14	14	1
Riedl 2000	Prospective comparative study	Detrusor acontractility	45	45	6 weeks
Dasgupta 1998	Prospective cohort study	Anesthesia prior to transurethral procedures	8	8	Immediate assessment of pain following procedure
Fontanella 1997	Prospective cohort study	Anesthesia prior to transurethral procedures	91	91	Immediate assessment of pain following procedure
Jewett 1999	Multicenter comparative study	Anesthesia prior to transurethral procedures	94	76	Immediate assessment of pain following procedure
Riedl 1998a	Prospective cohort study	Anesthesia prior to transurethral procedures	11	11	Immediate assessment of pain following procedure
Rose 2005	Retrospective comparative study	Anesthesia prior to transurethral procedures	21	11	Immediate assessment of pain following procedure
Schurch 2004	Prospective comparative study	Anesthesia prior to transurethral procedures	38	28	Immediate assessment of pain following procedure

EMDA: Electromotive drug administration, NMIBC: Nonmuscle-invasive bladder cancer, OAB: Overactive bladder, BPS: Bladder pain syndrome, IC: Interstitial cystitis

Adjuvant induction and maintenance treatment – Sequential Electromotive Drug Administration mitomycin C + BCG versus BCG alone

The role of sequential EMDA MMC and BCG over a 9-week induction regime followed by maintenance BCG has been compared in a randomized trial of 212 patients with high-risk NMIBC to induction BCG alone over a 6-week period followed by a maintenance regime.[11] A significant improvement in recurrence rate, progression rate and disease-free interval was demonstrated with sequential therapy at long-term follow-up (mean 88 months). A more recent cohort study using the same regime of sequential therapy reported complete response rates of 71% at 1 year and 63% at 2 years, but the conclusions from this study are limited by the lack of randomization against BCG alone.[12]

Neoadjuvant treatment-Electromotive Drug Administration mitomycin C versus passive mitomycin C versus hyperthermia mitomycin C

The use of EMDA MMC has been compared to passive MMC and hyperthermia MMC in the neoadjuvant setting prior to TURBT.[13] Patients with small, low/intermediate risk NMIBC were treated with a 4-week neoadjuvant course of intravesical therapy with significant complete response (defined as no macroscopic evidence of disease, negative

Table 2: Summary of studies evaluating the use of electromotive drug administration in nonmuscle-invasive bladder cancer

Study	Inclusion criteria	Timing of EMDA	Treatment regime	Control group	Outcome
Brausi 1998	G1-G2, pTa-T1, <1.5 cm tumor	Adjuvant	EMDA MMC 15 mA (40 mg in 50 ml distilled water) retained in bladder for 20 min weekly for 8 weeks	40 mg MMC in 50 ml distilled water (retained in the bladder for 2 h), weekly for 8 weeks	CR 41% in EMDA group compared to 41.6% in control; RR 33% in EMDA group compared to 60% in control group; DFI 14.5 months in EMDA group compared to 10.5 months in control group
Colombo 2001	G1-G2, pTa-T1, <2 cm tumor	Pre-TURBT	EMDA MMC 20 mA (40 mg on 150 ml distilled water) retained in bladder for 20 min weekly for 4 weeks	40 mg MMC in 50 ml distilled water versus hyperthermia MMC 40 mg MMC in 50 ml distilled water (retained in the bladder for 1 h), weekly for 4 weeks	CR 40.0% in EMDA group compared to 27.7% in control group
Decaestecker 2018	Primary or recurrent, single or multiple, papillary tumors <2 cm	Pre-TURBT	EMDA MMC 25 mA (60 mg in 100 ml distilled water) retained in the bladder for 25 min	N/A	CR occurred in 25%
Di Stasi 2003	Multifocal carcinoma *in situ* (Tis) +/− concurrent pT1 tumor	Adjuvant	EMDA MMC 20 mA (40 mg in 100 ml water) retained in bladder for 30 min weekly for 6 weeks	40 mg MMC in 100 ml water (retained in bladder for 60 min) weekly for 6 weeks versus 81 mg BCG retained in bladder for 120 min weekly for 6 weeks	CR for EMDA MMC versus passive MMC versus BCG: 53% versus 28% versus 56% at 3 months, 58% versus 31% versus 64% at 6 months; median TTR 35 versus 19.5 versus 26 months
Di Stasi 2006	pT1 bladder cancer (G2 or 3 or pT1+CIS)	Adjuvant	81 mg BCG retained in bladder for 120 min weekly for 2 weeks followed by 40 mg EMDA MMC 20 mA for 30 min weekly as one cycle, for 3 cycles	81 mg BCG retained in bladder for 120 min weekly for 6 weeks	For sequential BCG and EMDA MMC group versus BCG alone: DFI 69 months versus 48 months; RR 41.9% versus 57.9%; PR 9·3% versus 21·9%
Di Stasi 2011	Primary pTa and pT1 tumor	Pre-TURBT	EMDA MMC 20 mA (40 mg in 100 ml sterile water) retained in bladder for 30 min	TURBT alone versus immediate post-TURBT intravesical passive MMC 40 mg in 50 ml sterile water within 6 h of TURBT (retained for 60 min)	RR 38% (EMDA group) versus 59% (passive MMC) versus 64% (TURBT alone); DFI 52 months (EMDA group) versus 16 months (passive MMC) versus 12 months (TURBT alone)
Gan 2016	High-risk NMIBC	Adjuvant	81 mg BCG retained in bladder for 120 min weekly for 2 weeks followed by 40 mg EMDA MMC 20 mA for 30 min weekly as one cycle, for 3 cycles	N/A	CR 71% at 1 year, 63% at 2 years
Riedl 1998a	High-risk NMIBC	Adjuvant	EMDA MMC 15 mA (40 mg in 100 ml water) retained in bladder for 20 min weekly for 4 weeks	N/A	CR 56.6% at mean 14.1 months
Racioppi 2018	BCG refractory (persistent high-grade NMIBC after first or second induction BCG)	After failed induction BCG	EMDA MMC 20 mA (40 mg in 100 ml of sterile water) retained in the bladder for 30 min, induction course of 6 weekly instillations followed by a maintenance course of 6 monthly instillations	N/A	61.5% preserved their native bladder. At 36 months follow-up, disease free rates 75% (TaG3), 71.4% (T1G3), 50% (Cis), 25% (TaT1G3 + Cis)

CR: Complete response, DFI: Disease-free interval, TTR: Time to recurrence, PR: Progression rate, RR: Recurrence rate, MMC: Mitomycin C, EMDA: Electromotive drug administration, NMIBC: Nonmuscle-invasive bladder cancer, TURBT: Transurethral resection of bladder tumor, N/A: Not available, BCG: Bacille calmette-guerin

cytology and no residual viable tumor cells in histology from TUR specimen after treatment). There were no serious adverse events, but the effect appeared to be greater for thermotherapy (66% complete response vs. 40% with EMDA). However, the heterogeneity between groups means that no conclusions can be drawn in comparative efficacy, and furthermore, the long-term effect of this treatment compared to the current standard of care remains to be determined.

Neoadjuvant treatment – Electromotive Drug Administration mitomycin C versus transurethral resection of bladder tumor alone v single postoperative dose of passive mitomycin C

The administration of a single dose of EMDA MMC 30 min prior to TURBT was shown in a randomized trial to be superior to TURBT alone and to single postoperative passive MMC in terms of recurrence rates and disease-free

rates at median 7-year follow-up, with no difference in adverse events.[14] These results have not been replicated in other centers, and the comparison against current standard of care requires further study to confirm efficacy, safety, and cost-effectiveness.

Overactive bladder syndrome

Studies on OAB are limited to small cohort studies [Table 3]. A total of 7 studies (231 patients) have evaluated EMDA with various agents for treating anticholinergic-refractory OAB, but significant limitations exist. Studies are heterogeneous in terms of indication (idiopathic vs. neuropathic), the agent used (oxybutynin, botulinum toxin A, combination of lignocaine, dexamethasone and epinephrine), the outcome measure studied, and the fact that studies are small and nonrandomized.

Two studies have investigated the effect of a cocktail of lignocaine, dexamethasone and epinephrine with varying regimes on OAB symptoms.[15,16] Although both studies reported improvements in urinary frequency and cystometric capacity, the durability and long-term efficacy is unknown and there is no comparison against passive instillation of these agents.

EMDA with BTX-A has been investigated in 3 small trials of children with neurogenic detrusor overactivity who were already performing clean-intermittent self-catheterization

Table 3: Summary of studies evaluating the use of electromotive drug administration in overactive bladder

Study	Inclusion criteria	Treatment regime	Outcome	Adverse events
Bach 2009	Refractory urge syndrome with/ without urge incontinence	EMDA 2000 mg lidocaine-HCl 4% (50 ml), 2 mg epinephrine 2 ml, 40 mg dexamethason-21 - dihydrogen phosphate 10 ml in total volume 100 ml, once every 4 weeks for 3 months	Improvement in frequency from 14.1 per day and 5.1 per night to 9.4 per day and 2.5 per night; FDV and SDV improved from 94 ml to 142.2 ml and 155.6 ml to 199.5 ml; Reduced uninhibited detrusor contractions; maximal cystometric bladder capacity increased from 192.3 ml to 239.6 ml; 53.6% reported complete resolution of symptoms, 28.6% improvement in symptoms	10.7% did not continue therapy after 2 sessions
Di Stasi 2001	Refractory detrusor hyperreflexia unresponsive to standard oral and intravesical oxybutynin regimens	EMDA oxybutynin 5 mA (5 mg in 100 ml) for 30 min versus Passive intravesical oxybutynin 5 mg in 100 ml for 60 min versus Oxybutynin 5 mg orally	Reduced number, duration and amplitude of uninhibited detrusor contractions after EMDA compared to no change with oral or passive intravesical oxybutynin	Systemic side effects seen in oral administration, but none with intravesical or EMDA All EMDA treatments resulted in transient erythema of skin underlying electrodes
Gauruder-Burmester 2008	Refractory overactive bladder	EMDA 15-25 mA 100 ml 4% lidocaine, 100 ml distilled water, 40 mg dexamethasone, 2 ml epinephrine retained in bladder for 20-25 min. 3 treatment cycles each with 3 treatments at 2 weeks intervals	Bladder capacity improved by mean 109 ml in 71% patients. Number of micturitions per day decreased from 19 to 7	7/72 reactive hypertension which returned to normal without intervention 21/72 dysuria and hematuria 10 had UTI 1 developed urinary retention
Kajbafzadeh 2011	Refractory neurogenic detrusor overactivity (children)	EMDA botulinum toxin type A 10 mA (10 IU/kg) for 15 min	Increased mean reflex volume and maximal bladder capacity from 99 ml to 216 and 121 ml to 262; Decreased mean maximal detrusor pressure and end-fill pressure from 75 cm H_2O to 39 cm H_2O, and 22 cm H_2O to 13 cm H_2O; Urinary incontinence improved in 80% patients	Skin erythema and burning in 6/12
Ladi-Seyedian 2018	Refractory neurogenic detrusor overactivity (children)	EMDA botulinum toxin type A 10-15 mA (10 IU/kg) for 20 min	After a single treatment: 87.5% completely dry between 2 consecutive CICs after 6 months, 75%, 45.5%, 37.5%, 33%, 29.1% dry between 2 CICs at 1, 2, 3, 5 and 6 years, respectively	No major adverse effects
Riedl 1998a	Refractory detrusor hyperreflexia and/or urge incontinence	EMDA oxybutynin hydrochloride 15 mA (15-50 mg in 100 ml 0.3% saline) for 20 min	Improvement >1 week in 27%, <1 week in 36.5%, no improvement in 36.5%	No local or systemic side effects observed in this cohort
Koh 2019	Refractory neurogenic detrusor overactivity (children)	EMDA Botox (Allergan) 10 mA (3.3 IU/kg) for 15 min (5 patients) EMDA Botox (Allergan) 15 mA (10 IU/Kg) for 25 min (5 patients) EMDA Botox (Dysport) 10 IU/Kg (4 patients)	EMDA with either Botox or Dysport did not significantly change maximal cystometric capacity, bladder compliance or pDetmax 3/10 reported transient symptomatic benefit with Botox lasting a few days 3/4 reported transient symptomatic benefit with Dysport lasting a few days	All patients reported temporary redness at the site of the abdominal wall electrodes which resolved within 2 h No other adverse effects were reported

CICs: Clean-intermittent catheterizations, EMDA: Electromotive drug administration, FDV: First desire to void, SDV: Strong desire to void

(CIC).[17-19] An improvement in urodynamic parameters were noted in 2 studies and 75% were reportedly dry between 2 successive CICs at 1 year after a single treatment. However, a more recent study of 12 children was unable to reproduce these findings, with no difference in urodynamic parameters or symptomatic outcomes in patients who were treated with EMDA BTX-A.[19] Furthermore, its efficacy in the adult idiopathic OAB population has not been studied.

A urodynamic study of EMDA with oxybutynin reported improvements in number, duration and amplitude of uninhibited detrusor contractions after EMDA compared to oral or passive intravesical oxybutynin, but clinical outcomes in a single small study appear poor.[6,20]

Bladder pain syndrome/interstitial cystitis and radiation cystitis

Six studies (89 patients) with a follow-up ranging from 6 to 24 months have evaluated the role of EMDA for BPS/IC, and 2 have included patients with radiation cystitis (6 patients), although the results are not separately presented [Supplementary Table 1]. Three studies are from the same author at the same time-period and so it is likely that there is overlap in the patient data presented.[6,21,22] Intravesical medications studied were a combination of lignocaine and/or epinephrine and/or dexamethasone, or hyaluronic acid.[6,21-25] Only one study was a randomized trial comparing EMDA hyaluronic acid versus passive hyaluronic acid weekly for 4 weeks and then monthly.[23] Significantly better improvements in pain scores were reported in the EMDA group at 12 months' follow-up, but this was not sustained at 24 months. In all other studies patients underwent bladder hydrodistension following intravesical instillation, and so the efficacy of EMDA itself is unknown. However, the instillation did enable hydrodistension to be performed without general anesthesia and was well-tolerated. Although promising results have been reported in other studies, the small, short-term, nonrandomized nature of these studies limits the applicability of the conclusions reached.

Bladder anesthesia prior to transurethral surgery

Six studies (243 patients) have investigated the efficacy of EMDA-assisted lignocaine for bladder anesthesia prior to transurethral surgery [Supplementary Table 2]. Differences between studies in terms of dosage and dwell-time of instillation, the complexity and length of the procedure performed, and lack of comparator group in most cases limit the validity of the findings. All studies found that EMDA-assisted instillation of local anesthetic was well tolerated and led to painless transurethral surgery in most cases, based on immediate postoperative pain scores. However, without a randomized trial against passive diffusion of local anesthetic, it is not possible to determine whether this effect is significantly enhanced by EMDA.

Detrusor acontractility

Two small studies from the same author evaluated EMDA with intravesical bethanechol in patients with urodynamically-proven detrusor acontractility [Supplementary Table 3]. Simultaneous cystometry demonstrated increased intravesical pressure and detrusor contraction during treatment, and this was only seen with EMDA treatment.[6] The authors concluded that the use of EMDA-assisted bethanechol may identify those patients with residual detrusor function who may benefit from longer-term management with oral bethanechol.[26]

Adverse events

Adverse events were inconsistently reported between studies. Commonest reported complications included local symptoms of transient urinary frequency, cystitis, and erythema and the site of the skin electrodes. In the largest trials of EMDA MMC for NMIBC, adverse events were not significantly different between passive BCG, passive MMC, and EMDA MMC.[8] In the neoadjuvant setting, persistent bladder symptoms were reported in 21% of the EMDA group, with a bladder perforation rate of 6%.[14] The most significant complication was a reported burn on the posterior bladder wall due to contact with the electrode catheter, reported in 2 studies.[6,27] In the vast majority of patients in all studies, however, the treatments were reported to be well-tolerated with no systemic side-effects reported.

Comment

Generally, to move across membranes molecules will take one of two pathways: transcellular movement through cells), or paracellular (movement through tight junctions and intercellular spaces). The urothelium, however, is one of the most impermeable mammalian membranes, composed of tightly-knit epithelial cells. This property prevents toxic urinary metabolites from contacting the underlying submucosa, and this is thought to be protective against a variety of chronic inflammatory bladder conditions.[28] However, the passive diffusion of drugs into the bladder is therefore also slow and uncontrollable, meaning that doses and clinical efficacy are variable.

The mechanism of EMDA is based on three principles: iontophoresis, electro-osmosis and electroporation. Iontophoresis is the phenomenon of ionized molecules being actively transported across a membrane due to the application of an electrical current. Nonionized molecules are also transported due to electro-osmosis, which is the

movement of water due to the concentration gradient of ionized molecules also carrying the nonionized molecules. Electroporation is the increase in permeability of a membrane following the application of an electrical current.[2] The use of EMDA to improve the depth of penetration of certain drugs into the urothelium was originally documented in animal models. A study of EMDA instillation of methylene blue in dogs revealed that the dye had penetrated the entire thickness of the bladder wall including the mucosal and submucosal layers.[29] This review has summarized all subsequent clinical studies for the use of EMDA to enhance the penetration of different drugs across the urothelium for various urological diseases.

EMDA has been used to aid the intravesical treatment of NMIBC, OAB, BPS/IC, radiation cystitis, detrusor acontractility, and for anesthesia prior to transurethral urological procedures. Three randomized trials have shown significant benefit with EMDA MMC in the neoadjuvant and adjuvant setting compared to the current standard of care, but these trials were felt to have high risk of bias in a recent Cochrane review and the findings have not been reproduced in other randomized trials to date.[9] Large cohort studies have demonstrated good outcomes in patients with high-risk NMIBC and BCG-refractory disease, but these were limited by small numbers of patients and nonrandomized, noncomparative methodology. Future trials should also aim to assess whether the positive outcomes seen with EMDA are more or less effective than alternative enhanced drug-delivery techniques (such as hyperthermia), and whether an alternative agent (such as gemcitabine) would have any advantage over MMC.

The use of EMDA to treat OAB has been studied with oxybutynin, lignocaine, and botulinum toxin A with mixed results. Although urodynamic studies following instillation have reported improvements in those treated with EMDA, significant clinical efficacy has not been demonstrated. Furthermore, the durability of treatment has not been studied and comparative studies against oral anticholinergics or β-3 agonists, and injection of BTX-A or sacral neuromodulation, are required to assess its place in the treatment pathway of OAB. Although 2 studies in children with NDO reported considerable improvements with EMDA and BTX-A (Dysport) this was not reproduced in a recent UK series. This may be related to the high molecular weight of onabotulinumtoxin A (900 kDa) or abobotulinumtoxin A (300-900 kDa) which may limit the ability of this molecule to penetrate the urothelium. An immunohistochemical study of rabbit bladders following EMDA-assisted BTX-A instillation demonstrated uniform staining in urothelial, interstitial and muscular layers suggesting deep penetration of BTX-A.[30] However, future studies should prove the presence of cleaved Synaptosomal-Associated Protein-25 (SNAP-25) in the bladder following administration of BTX-A to more accurately determine whether there is any effect of instillation, in the first instance. Subsequent studies should compare EMDA-BTX-A to intravesical injections and to newer methods of drug delivery (such as with liposomes).[31]

The use of EMDA for reducing bladder sensation (in BPS/IC and prior to transurethral surgery) appears promising and warrants further study. The current literature is again limited by the low overall quality of the evidence, being based on small, noncomparative, and nonrandomized trials, with short-term follow-up. The role of EMDA in enhancing the penetration of antibiotics to treat chronic or recurrent urinary tract infection (UTI) (thought to be due to intracellular bacterial communities) has not been studied but may be a promising treatment modality for this difficult-to-treat patient group in future studies.

A limitation of this review is the inability to pool the data and perform a meta-analysis due to the considerable heterogeneity in the included studies. Indications, drug doses and regimes, treatment duration and outcome measures analyzed all varied between trials. Furthermore, safety data was not adequately and systematically reported in most studies, although EMDA was reportedly well tolerated and safe in the majority of patients with very low rates of serious adverse events. Overall the quality of evidence is very low, predominantly from small, nonrandomized, comparative studies. The only randomized trials have been for EMDA MMC in NMIBC and EMDA hyaluronic acid for BPS/IC. However, these studies were determined to have a high risk of bias, and the findings have not been replicated in other well-designed randomized trials.[9]

CONCLUSIONS

The use of EMDA to enhance the delivery of medications across the urothelium has been investigated for NMIBC, OAB, BPS/IC, radiation cystitis, detrusor acontractility, and for anesthesia prior to transurethral urological procedures. The most extensively investigated is the use of EMDA to enhance the penetration of intravesical MMC for NMIBC, both in the neoadjuvant and adjuvant settings. Although promising results have been reported for all indications, the evidence is limited by the low quality of evidence. Large randomized trials comparing EMDA to passive instillation or standard of care, with long-term follow-up, are warranted to determine the role of this technology in

the treatment of urological diseases, and to validate the preliminary findings presented in this review.

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