Applications of electromotive drug administration in urology

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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.[2,3] 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.
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), chemotheryperthermia, and electromotive drug administration (EMDA).\[^{[1]}\]

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.\[^{[2,3,4]}\]

**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        | NMIBC                   | 28                       | 15                                   | Mean 16.3 (6-24)             |
| Colombo 2001           | Single center, nonrandomized      | NMIBC                   | 80                       | 15                                   | 7-10 days                   |
| Decaestecker 2018      | Prospective cohort study          | NMIBC                   | 32                       | 32                                   | 2-4 weeks                   |
| Di Stasi 2003          | Prospective randomized            | NMIBC                   | 108                      | 36                                   | Median 45                   |
| Di Stasi 2006          | Prospective randomized            | 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                   |
| Racioppii 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-Burmeister 2008 | Prospective cohort study        | OAB                     | 72                       | 72                                   | 12 months                   |
| Kajbafzadeh 2011       | Prospective cohort study          | OAB                     | 15                       | 15                                   | 9                           |
| Ladi-Sedayian 2018     | Prospective cohort study          | OAB                     | 24                       | 24                                   | 72                          |
| Koh 2019               | Prospective cohort study          | OAB                     | 14                       | 14                                   | 1 week                      |
| Gurpinar 1996          | Prospective cohort study          | BPS/IC                  | 6                        | 6                                    | 4-6 weeks                   |
| Gulpinar 1994          | Prospective randomized            | 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 |
| Schuch 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 regimen 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 regimen. 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.\textsuperscript{[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.\textsuperscript{[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 CR 40.0% in EMDA group compared to 27.7% 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 | N/A                                                                      |
| 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 | Adjunt       | 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 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% 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) |
| Di Stasi 2006  | pT1 bladder cancer (G2 or 3 or pT1+CIS)   | Adjunt       | 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 | N/A                                                                      |
| 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) | N/A                                                                      |
| Gan 2016       | High-risk NMIBC                           | Adjunt       | 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                           | Adjunt       | 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% (Gis), 25% (TaT1G3 + Gis) |

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 vs 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. 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. 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 40 mg dexamethasone-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 |
| Gauruder-Burmester 2008 | Refractory overactive bladder | EMDA 15-25 ml 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 | No other adverse effects |
| 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 H₂O to 39 cm H₂O, and 22 cm H₂O to 13 cm H₂O; Urinary incontinence improved in 80% patients 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 Improvement >1 week in 27%, <1 week in 36.5%, no improvement in 36.5% | 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 | No major adverse effects | No local or systemic side effects observed in this cohort |
| 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 | EMDA with either Botox or Dysport did not significantly change maximal cystometric capacity, bladder compliance or pDetmax | All patients reported temporary redness at the site of the abdominal wall electrodes which resolved within 2 h |
| 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) | 3/10 reported transient symptomatic benefit with Botox lasting a few days 3/4 reported transient symptomatic benefit with Dysport lasting a few days | No other adverse effects were reported |

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

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. Intravesical medications studied were a combination of lignocaine and/or epinephrine and/or dexamethasone, or hyaluronic acid. Only one study was a randomized trial comparing EMDA hyaluronic acid versus passive hyaluronic acid weekly for 4 weeks and then monthly. 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. 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.

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. In the neoadjuvant setting, persistent bladder symptoms were reported in 21% of the EMDA group, with a bladder perforation rate of 6%. The most significant complication was a reported burn on the posterior bladder wall due to contact with the electrode catheter, reported in 2 studies. 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. 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.[24] 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.[25] 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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There are no conflicts of interest.

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