

TITLE: The Use of the Electromotive Drug Administration System in Patients with Superficial Bladder Cancer: A Review of the Clinical Effectiveness, Safety, and Cost-Effectiveness

DATE: 17 September 2014

CONTEXT AND POLICY ISSUES

Non-muscle (superficial) invasive bladder cancer accounted for about 6% of all cancers in Canada in 2008.¹ To treat this condition, systemic drug delivery to the bladder is generally ineffective as the bladder's wall prevents therapeutic substances from diffusing through.² Intravesical therapy delivers drugs through a catheter directly into the bladder and is therefore more effective, but still faces limitations resulting in the need for a high frequency of instillations among other issues.² Furthermore, superficial bladder cancer has a high recurrence rate.¹ In 2006, the condition was reported to cost \$65,158 per patient on average in the U.S., largely as a result of complications and surveillance of recurrence.³

In the last two decades, the use of electromotive force has emerged as an option to increase diffusion of drugs into the bladder. Electromotive drug administration (EDMA) has shown some potential in treatment of various bladder conditions such as detrusor overactivity⁴ and bladder pain syndrome,⁵ conditions that face similar drug-delivery challenges to bladder cancer. However Canadian guidelines on treatment for bladder cancer issued in 2010 did not find enough evidence to provide recommendations on this therapy.¹ The aim of this review is to examine the evidence regarding the efficacy, safety, and cost-effectiveness of using EDMA to treat superficial bladder cancer.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of the electromotive drug administration system in patients with superficial bladder cancer?

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2. What is the cost-effectiveness of the electromotive drug administration system in patients with superficial bladder cancer?

KEY FINDINGS

There is little evidence on the efficacy and safety of EDMA to treat non-muscle invasive bladder cancer. However the one article included was considered high quality and suggested administering mitomycin via EDMA prior to transurethral tumour resection (TURBT) results in improved long term outcomes compared to TURBT alone, or passive diffusion of mitomycin post-TURBT. No evidence on the cost effectiveness of EDMA for bladder cancer was identified

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 8), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and August 15, 2014.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the studies retrieved in the search and assessed full-texts for inclusion according to selection criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Patients with superficial bladder cancer/non-muscle invasive bladder cancer
Intervention	Electromotive drug administration of any therapy for bladder cancer
Comparator	Standard drug administration or none
Outcomes	<p>Research question 1: Clinical benefit (survival, quality of life, patient outcomes) Clinical harm (adverse events)</p> <p>Research question 2: Cost effectiveness</p>
Study Designs	Systematic reviews/meta-analyses, health technology assessments, randomized controlled trials, observational studies, economic evaluations

Exclusion Criteria

Studies were excluded if they were published before January 1st, 2009, were non-English, reported on a therapy other than EDMA or used EDMA to treat a condition other than bladder cancer, or were conducted in animals.

Critical Appraisal of Individual Studies

Guidance by the Scottish Intercollegiate Guidelines Network was used to appraise the papers. The body has created lists for different study types. In this review, the randomized controlled trial methodology checklist was used (<http://www.sign.ac.uk/methodology/checklists.html>). This checklist classifies studies on a qualitative scale from low to high quality.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 46 citations. The full text for 10 studies was reviewed and one randomized controlled trial⁶ was included (Appendix 1). A further seven grey literature sources were identified, none of which were included. Additional references of potential interest (some of which pre-dated the inclusion criteria of 2009) are included in Appendix 2. No studies on cost-effectiveness were identified.

Summary of Study Characteristics

Setting

The parallel group randomized control trial was conducted at three centres in Italy.⁶

Patient population

Eligible patients were >18 years old with confirmed diagnosis of pTa or pT1 urothelial carcinoma of the bladder, without previous history of bladder cancer or history of intravesical chemo/immunotherapy. The participants were stratified based on unifocal versus multifocal tumours, and by cancer grade (1, 2 or 3) before randomization.

Intervention

117 patients were treated with 40 mg intravesical EDMA mitomycin dissolved in 100mL sterile water about 30 minutes before TURBT. The solution was retained in the bladder for 30 minutes with a simultaneous external pulsed electric current.

Comparators

The control groups in this study received either passive diffusion of mitomycin within 6 hours after TURBT (n=119) or TURBT alone (n=116). Passive diffusion patients received a mitomycin dose of 40 mg in 50mL of sterile water, retained in the bladder for 60 minutes with catheter clamping.

Outcomes

The primary outcomes were recurrence and disease-free interval. The secondary outcomes included time to disease progression (to muscle invasive disease), overall survival and disease-specific survival. The outcomes were assessed with abdominal ultrasonography, cystoscopy and urinary cytology.

Summary of Critical Appraisal

The included study⁶ was deemed high quality. The treatment and comparison groups showed similar baseline characteristics, the study exceeded the sample size required to detect a 20% increase in time to recurrence (n=297 required as per power calculation versus n=352 included in analysis) and analysis was completed by intention to treat. The randomization method was described in detail and the authors did not report any censoring due to loss to follow up. Staff conducting outcome assessments and data analysis were blinded to treatment assignment, though patients and physicians were not (presumably because this would not have been possible for this intervention).

Summary of Findings

Tumour Recurrence

Patients receiving EDMA treatment had 60% (Hazard Ratio [HR] 0.40, 95% confidence interval [CI] 0.28 to 0.59) lower hazard of recurrence relative to those receiving only TURBT over median 86 months follow up. There was no significant difference between patients receiving passive diffusion mitomycin versus TURBT alone (HR 0.84; 95% CI 0.61 to 1.17).

Disease-free interval

Patients receiving EDMA treatment had median 52 months disease free interval (interquartile range [IQR] 32 to 184 months) versus 16 months (IQR 12 to 168) in patients receiving passive diffusion and 12 months (IQR 12 to 37) for those only receiving TURBT.

Secondary outcomes

There were no statistically significant differences in progression to muscle-invasive disease, overall survival, or disease-specific survival between the treatment groups.

Adverse effects

99% of patients receiving EDMA treatment completed the instillation compared to 76% in the passive diffusion group. In the passive diffusion group, the instillation was stopped in the remaining 24% of patients due to pain, bladder spasm and solution leakage.

After TURBT, 6% of EDMA patients, 8% of passive diffusion patients and 4% of TURBT-only patients experienced overt bladder perforation, while 16%, 31% and 21% reported irritative bladder symptoms in the EDMA, passive diffusion and TURBT-only groups, respectively. Irritative bladder symptoms were longest lasting in the passive diffusion group.

Limitations

This study was conducted at three centres in Italy so generalizability beyond this context is unclear. Further, the study did not stratify results by centre, which would have provided insight into whether the setting affects the outcome.

The study compared EDMA before TURBT to passive diffusion just after TURBT, so a comparison of both treatments post-TURBT, or a combination of before and after treatment may

yield different results. Furthermore, testing for statistical significance was conducted relative to the TURBT-only intervention rather than comparing EDMA versus passive diffusion directly. The statistical significance comparing the disease-free interval between these groups was also unclear.

No evidence on cost-effectiveness was identified.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The results of this review suggest EDMA mitomycin before TURBT is a promising alternative to passive diffusion mitomycin post-TURBT or TURBT alone, with little (or even fewer) adverse effects. However more trials in different contexts would likely be needed to evaluate effectiveness and safety before a policy recommendation. There was also no evidence on cost-effectiveness which would be required to better understand policy implications.

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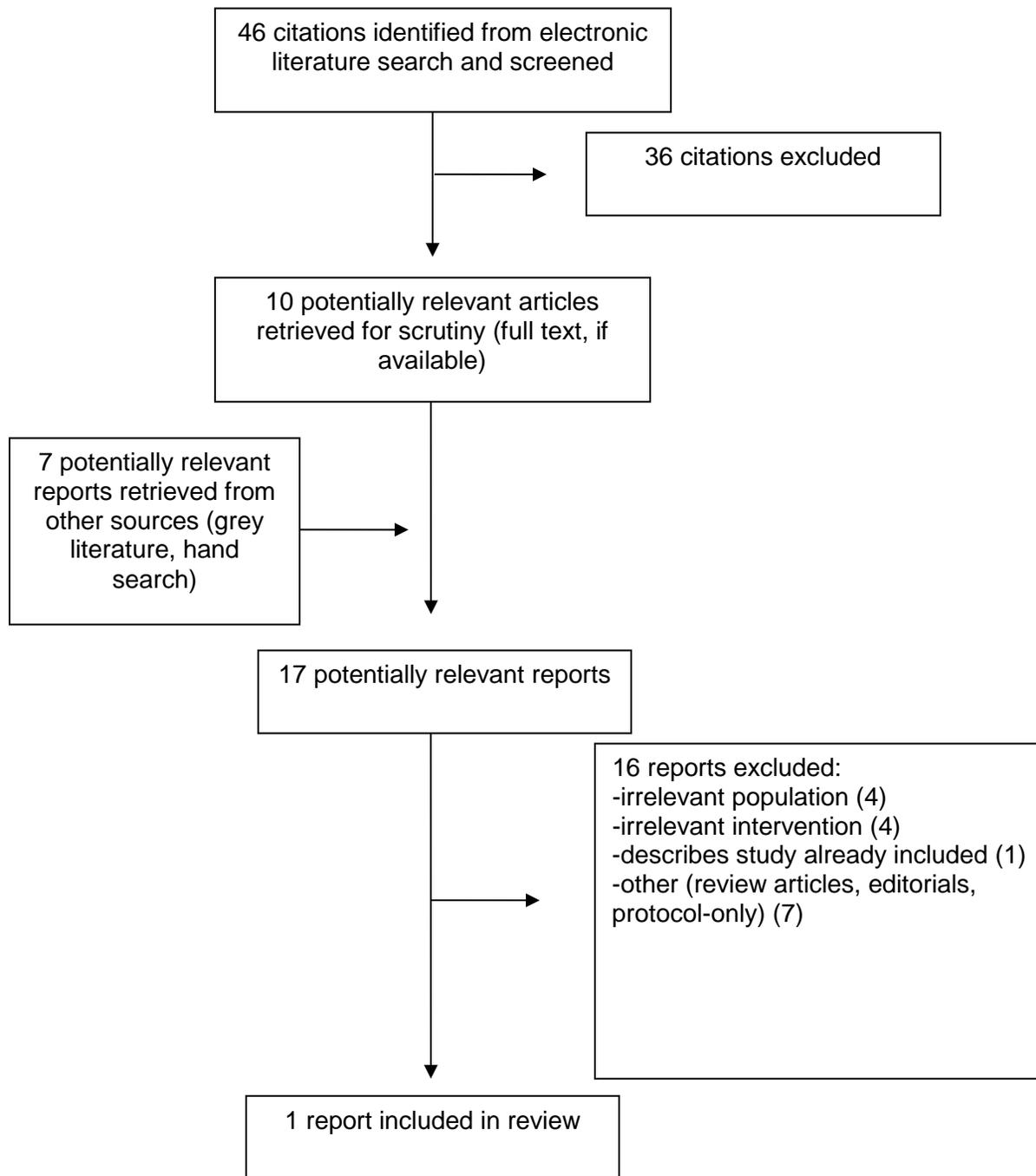
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REFERENCES

1. Kassouf W, Kamat AM, Zlotta A, Bochner BH, Moore R, So A, et al. Canadian guidelines for treatment of non-muscle invasive bladder cancer: a focus on intravesical therapy. *Can Urol Assoc J* [Internet]. 2010 Jun [cited 2014 Sep 16];4(3):168-73. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2874590>
2. GuhaSarkar S, Banerjee R. Intravesical drug delivery: challenges, current status, opportunities and novel strategies. *J Control Release*. 2010 Dec 1;148(2):147-59.
3. Avritscher EB, Cooksley CD, Grossman HB, Sabichi AL, Hamblin L, Dinney CP, et al. Clinical model of lifetime cost of treating bladder cancer and associated complications. *Urology*. 2006 Sep;68(3):549-53.
4. Bach P, Wormland RT, Mohring C, Goepel M. Electromotive drug-administration: a pilot study for minimal-invasive treatment of therapy-resistant idiopathic detrusor overactivity. *Neurourol Urodyn*. 2009;28(3):209-13.
5. Gülpinar O, Haliloglu AH, Gökce MI, Arıkan N. 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 Urol* [Internet]. 2014 May [cited 2014 Aug 27];55(5):354-9. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4026663>
6. Di Stasi SM, Valenti M, Verri C, Liberati E, Giurioli A, Leprini G, et al. Electromotive instillation of mitomycin immediately before transurethral resection for patients with primary urothelial non-muscle invasive bladder cancer: a randomised controlled trial. *Lancet Oncol*. 2011 Sep;12(9):871-9.

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Other References of Potential Interest (Did not meet inclusion criteria)

Di Stasi SM, Riedl C. Updates in intravesical electromotive drug administration of mitomycin-C for non-muscle invasive bladder cancer. *World J Urol.* 2009 Jun;27(3):325-30.

Electrically-stimulated intravesical chemotherapy for superficial bladder cancer [Internet]. London, UK: National Institute for Health and Clinical Excellence; 2008. (NICE interventional procedure guidance 277). [cited 2014 Sep 16]. Available from: www.nice.org.uk/guidance/ipg277/resources/guidance-electricallystimulated-intravesical-chemotherapy-for-superficial-bladder-cancer-pdf

Di Stasi SM, Giannantoni A, Stephen RL, Capelli G, Navarra P, Massoud R, et al. Intravesical electromotive mitomycin C versus passive transport mitomycin C for high risk superficial bladder cancer: a prospective randomized study. *J Urol.* 2003 Sep;170(3):777-82.

Di Stasi SM, Giannantoni A, Giurioli A, Valenti M, Zampa G, Storti L, et al. Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial. *Lancet Oncol.* 2006 Jan;7(1):43-51.