

# Mitomycin-C in Endoscopic Dacryocystorhinostomy: a Randomised Controlled Trial

## **Authors**

<sup>1</sup>Peter J Wilson, PhD (corresponding author)

<sup>1</sup>Graeme Sharpe, MRCOphth

<sup>2</sup>Paul S White, FRACS

<sup>1</sup>Caroline J MacEwen, MD

## **Affiliations**

- 1 Department of Ophthalmology, Ninewells Hospital & Medical School, Dundee, DD1 9SY
- 2 Department of Otorhinolaryngology, Ninewells Hospital & Medical School, Dundee, DD1 9SY

## **Contact Details**

Address Department of Ophthalmology, Ninewells Hospital & Medical School, Dundee, DD1 9SY

E-mail [pj.wilson@nhs.net](mailto:pj.wilson@nhs.net)

Telephone +44 1382 632713

Fax +44 1382 632893

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## **Disclosure**

None of the authors have any conflict of interest regarding the material presented in this manuscript.

## ***Abstract***

### **Introduction**

As the technique of endoscopic DCR (EDCR) continues to evolve, and outcomes of surgery improve, the role of anti-metabolites such as Mitomycin C (MMC) in improving success is unknown. This study evaluates the effect of MMC in a placebo-controlled RCT of EDCR.

### **Methodology**

126 patients (141 eyes) underwent DCR, randomised to receive either MMC or placebo. Outcomes were documented at 1 and 3 months, and at final review, assessing symptoms and patency of the ostium.

### **Results**

There was no significant benefit in symptoms or ostium patency with the use of MMC.

### **Discussion**

This study adds to the existing literature in establishing that MMC does not have a role in routine EDCR surgery.

## **Introduction**

Obstruction of the nasolacrimal system is a common complaint, leading to symptoms of epiphora and discharge, and complications such as dacryocystitis.<sup>1</sup> The first descriptions of lacrimal outflow obstruction can be found in ancient documents, although modern surgical approaches have evolved from the techniques described by Caldwell and Toti.<sup>2,3</sup> For most of the 20<sup>th</sup> century, the external approach to dacryocystorhinostomy (DCR) prevailed, due to the difficulties in visualising the uncinata process and in the technical manipulation required to create the fistula. These difficulties were overcome with the introduction of high quality surgical nasendoscopes, allowing a cadaveric demonstration of the feasibility of endoscopic DCR (EDCR).<sup>4</sup> Thereafter, endoscopic DCR was pioneered by McDonogh and Meiring in 1989,<sup>5</sup> and since then has become the preferred approach in many centres, with benefits including better aesthetic outcome, preservation of the orbicularis oculi pumping mechanism, and quicker recovery time.<sup>6-9</sup>

Many studies have demonstrated that in experienced hands external and endoscopic approaches yield similar outcomes in terms of patency and reduction in symptoms, with 80-86% success, depending on the population and outcome measures applied. Factors that are associated with poor success rates include revision surgery, inflammatory disease (e.g. Wegener's granulomatosis), female gender.<sup>10</sup>

In attempts to improve outcomes in EDCR, supplementary techniques have been trialled including corticosteroids, laser, diathermy and antimetabolites (ref). Although many studies have been performed, these have often been

retrospective, non-randomized, or insufficiently powered to demonstrate any significant effect.<sup>11</sup>

This study presents a randomized, placebo-controlled trial of Mitomycin C as an adjunctive therapy in EDCR.

## ***Methodology***

Patients being listed for EDCR were invited to participate in the study, and – following informed consent – randomised to receive MMC or saline. EDCR was performed in the standard fashion: nasal preparation with Adrenaline 1:1000; mucosal incision to expose uncinata process, with thorough haemostasis; drilling of the Agger; probing of the nasolacrimal duct through the inferior punctum; lacrimal sac incision to create a mucosal flap which is tucked inferiorly; application of trial solution for 2 minutes; passage of O'Donoghue tubes which are tied in the nose. The study was conducted following approval from the local ethics committee and the Medicines and Healthcare Regulatory Authority (MHRA), and in accordance with CONSORT guidelines.

Patients were reviewed in clinic pre-operatively, and at 1 and 3 months post-operatively. The primary outcome measures were symptom score, fluorescein appearance / disappearance, and examination of the ostium (Table 1). In the case of missing data for visual analogue score (VAS), symptoms reported by the patient were interpreted as per Table 2.

A success was defined in subjective terms ( $\geq 75\%$  reduction in symptom score), objective terms (ostium patent and draining freely), both subjective and objective success, and whether revision was required.

## ***Results***

Of the 147 patients that were invited to participate, 130 consented to the study. Of these patients, 124 patients (141 eyes) underwent surgery, of which 27 were revision procedures. EDCR was not performed in 8 cases, due to previous surgery with patent ostium, presence of tumour, or removal of a punctual plug. The mean age of patients undergoing EDCR was 63 (range 19-91), of whom 63 (57%) were female. The progress of patients through enrolment, intervention and follow-up is outlined in Figure 1.

There was no significant difference either in pre-operative variables or post-operative outcomes between the two groups. In particular, both the objective measures (fluorescein appearance) and subjective (symptom score) were comparable between those patients receiving MMC and placebo.

## ***Discussion***

Antimetabolites have an established role as an adjunct in many types of surgery, particularly if patency of a surgical ostium is to be maintained.<sup>12</sup>

However, the use of antimetabolites in DCR surgery has been variable, and dependent upon many factors such as revision surgery, patient age and surgeon preference. Previous studies have demonstrated negative or equivocal benefit of routine addition of MMC to DCR surgery.<sup>13 14</sup>

This study demonstrates no benefit of the routine use of Mitomycin-C as an adjuvant treatment in EDCR. Although no benefit was found for revision surgery, the study was not designed or powered to test the utility of MMC in this subgroup, and caution should be taken in extrapolating the data to those patients undergoing revision surgery.

A recent systematic review of MMC in EDCR found that the use of MMC was associated with improved success and larger ostium.<sup>13</sup> However, this difference was not significant once non-randomised trials had been excluded.

Furthermore, the difference in size of ostium was not significant after 6 months.

Interestingly, a systematic review of MMC in open DCR indicates that MMC is of significant benefit, yielding an OR of success of 2.11 (range 1.19-3.74,  $p=0.01$ ) over standard procedures.<sup>14</sup> The relative advantage of MMC in open vs endoscopic surgery may lie in the fact that the external approach involves incising more tissue, and therefore inciting a greater inflammatory response, which MMC is able to control. However, with a trend towards an endoscopic approach, the benefit of MMC in DCR will be marginalised.

This study differs from previous publications in covering an older population (average age 63 vs. 30-57). As healing is often slower in old age,<sup>15</sup> with lower

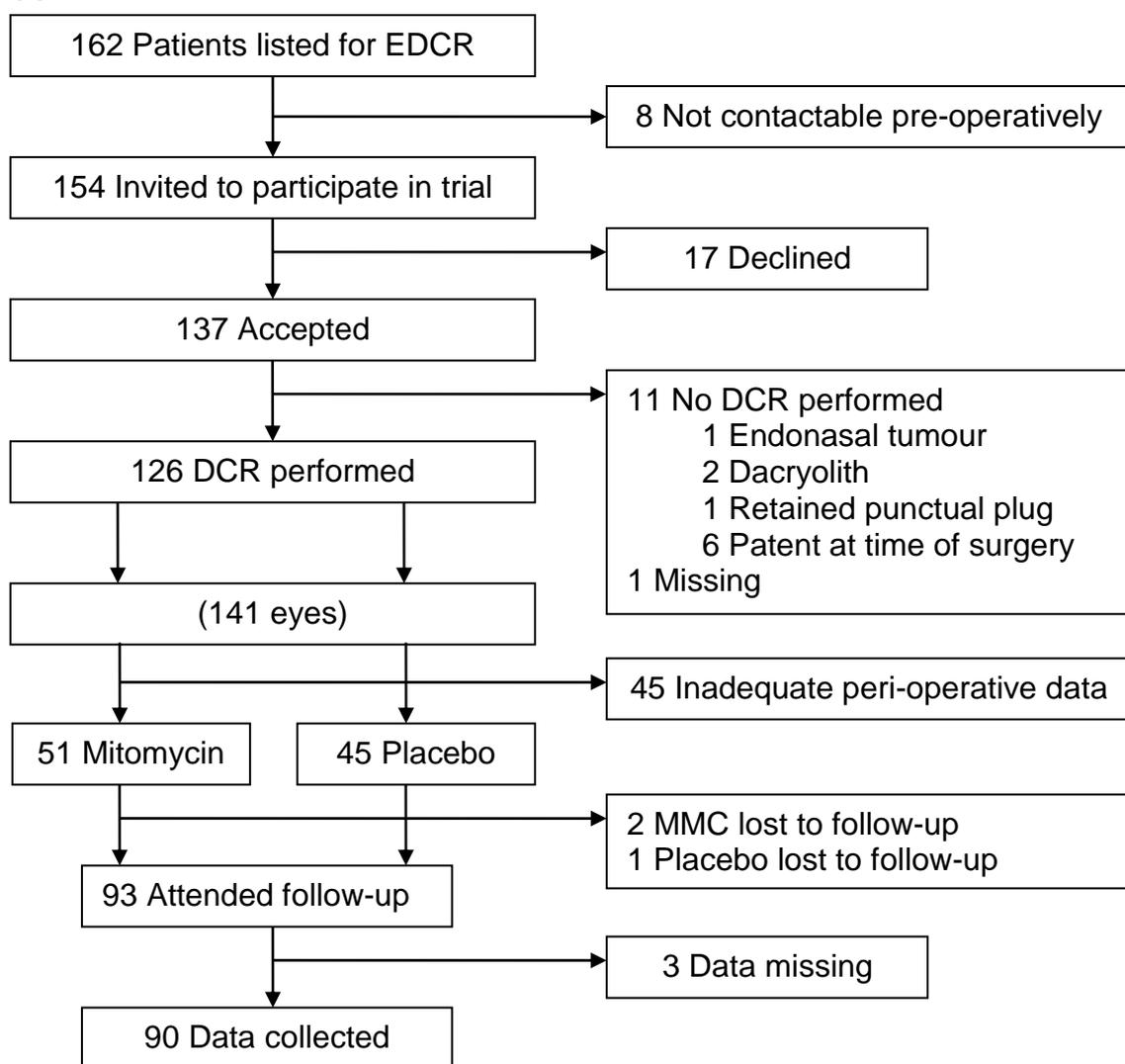
rates of scarring, this might account for the lack of benefit in this older age group. Indeed, the potential benefit of MMC will be determined by the underlying success rate of unaugmented surgery. As skills and techniques improve, and EDCR becomes more successful, the gain from addition of MMC will become progressively marginal. This observation is supported by the fact that MMC is more likely to be of benefit in revision surgery or if silicone tubes are omitted, i.e. in situations where scarring is likely to cause failure.

In primary EDCR with tubes a more highly-powered study might demonstrate statistical benefit. However, if statistical significance is found only with a large study population, then clinical significance may be doubtful.

This study encountered difficulties and limitations in recruiting and retaining patients, largely due to problems with clarity of documentation at and around the time of the procedure, in part due to shared care between the departments of ENT & ophthalmology. Nonetheless, sufficient numbers of patients completed participation in the trial to allow useful comparison between the two groups, and to contribute to the existing literature on the role of MMC in EDCR.

It is clear from this and previous studies that MMC does not significantly affect outcomes in routine EDCR. Nonetheless, its potential role in the higher risk population (young age group, inflammatory pathology, revision surgery, etc.) is still being defined by specifically focused RCT's.<sup>16</sup>

**Figures**



**Figure 1** – Flow diagram of patient recruitment and follow-up

## Tables

	Subjective	Objective
Pre-operative	VAS	Fluorescein dye disappearance test Lacrimal sac washout +/- Lacrimal scintigraphy
1 month post-operative	VAS	Ostium appearance Fluorescein appearance test
3 months post-operative	VAS	Ostium appearance Fluorescein appearance test

**Table 1** – Primary outcome measures

Symptoms	Multiplier
"No symptoms" "No watering" "Complete resolution" "100% better"	0.00
"Significant improvement" "Some watering, but satisfied" "Marked improvement" "Watering much improved"	0.25
"Not as bad" "Some improvement"	0.50
"Slight improvement" "Marginal improvement"	0.75
"No improvement" "Unchanged" "Just as bad"	1.00
"Epiphora worse"	1.50

**Table 2** – Symptoms converted to reduction in VAS

	MMC	Placebo	p
<b>Type of Block</b>			<b>0.896</b>
Partial	11	5	
Full	48	43	
Functional	2	2	
Post-operative (previous DCR)	2	5	
<b>Level of Block</b>			<b>0.749</b>
Distal	32	36	
Proximal	24	19	
Mixed	0	1	
Functional	1	1	
<b>Success</b>			
FAT free flow	42	41	0.468
FAT partial flow	3	0	
FAT no flow	5	5	
Symptoms improved	43	33	0.770
Symptoms no better	8	7	
Revision not needed	46	40	0.394
Revision needed	3	1	

**Table 3** – Type of nasolacrimal obstruction and outcomes of surgery.

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