Immediate administration of intravesical mitomycin C after tumour resection for superficial bladder cancer

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OBJECTIVE

To assess the feasibility and safety of administering intravesical mitomycin C in theatre immediately after transurethral resection of bladder tumour (TURBT).

PATIENTS AND METHODS

A protocol was developed to allow the safe administration of mitomycin C in theatre immediately after TURBT. Over a 32-month period all patients not excluded by the protocol were given mitomycin C in theatre after TURBT, and any adverse events reported.

RESULTS

In all, 177 instillations were carried out; there were two minor patient-related complications, and no staff-related adverse events.

CONCLUSION

The immediate administration of mitomycin C in theatre after TURBT is feasible and safe for patients and staff. It provides the earliest and surest prophylaxis against tumour cell re-implantation at TURBT.

KEYWORDS

bladder cancer, intravesical chemotherapy, mitomycin C

INTRODUCTION

The administration of one immediate instillation of intravesical chemotherapy after transurethral resection (TUR) for Ta and T1 single or multiple superficial bladder cancers decreases the risk of recurrence [1–4]. A recent meta-analysis [5] confirmed the magnitude of this effect. In 1476 patients studied in seven randomized control trials, TUR with immediate intravesical chemotherapy gave a 39% decrease in the risk of recurrence (odds ratio 0.61; $P < 0.001$) compared to TUR alone. Immediate instillation was considered to be one within 24 h of TUR.

Arguably, for maximum benefit and to prevent immediate tumour re-implantation, intravesical chemotherapy should be administered within 6 h of TUR [1]. Despite this evidence, this policy does not seem to have been universally adopted, partly because the co-ordination of timely administration can often be difficult.

The Mito-In™ delivery device (Kyowa Hakko UK Ltd, Slough, UK) is a closed, user-friendly, safe and rapid method of reconstituting and delivering intravesical mitomycin C [6]. We previously described the successful administration of intravesical mitomycin C in theatre using the Mito-In delivery system immediately after TUR of bladder tumour (TURBT) [7,8]. We present the results of immediate intravesical mitomycin C delivered via the Mito-In system in 177 consecutive cases.

PATIENTS AND METHODS

In all, 210 patients had TURBT over a 32-month period, of whom 177 received mitomycin C in theatre using the Mito-In delivery system (Fig. 1), according to the protocol outlined in Appendix 1; 33 patients were excluded based on the protocol exclusion criteria, and are summarized in Table 1.

RESULTS

In all, 177 mitomycin C instillations were administered in theatre immediately after TURBT. Adverse events occurred in two (1%) of these cases. In one patient the catheter balloon spontaneously deflated in the recovery ward, causing the catheter to fall out. This resulted in a minor leakage of mitomycin C onto the patient's skin that was washed with water and 8.4% sodium bicarbonate solution. The second patient complained of suprapubic pain after surgery, which was assumed to be due to extravasation of mitomycin C. This settled after immediate drainage of the mitomycin C from the bladder.

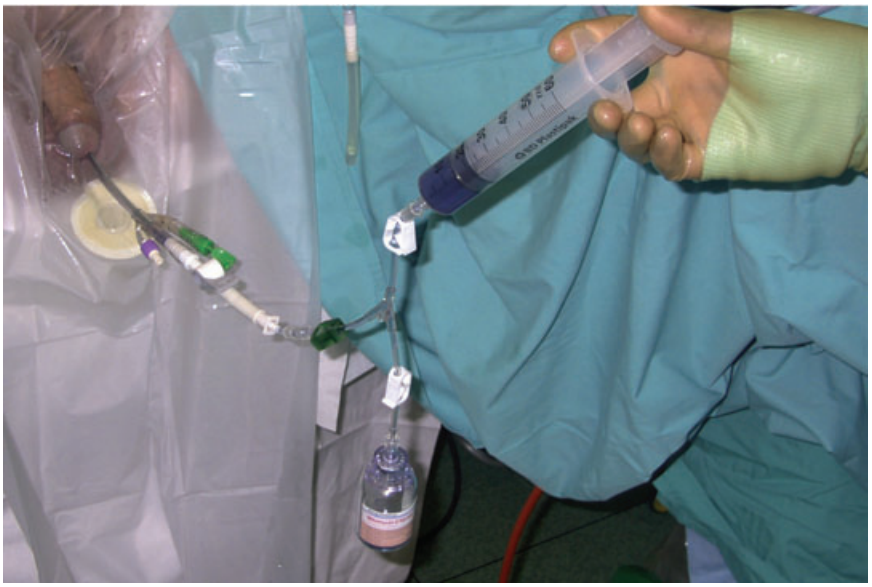
DISCUSSION

It is well recognized that early intravesical instillation of mitomycin C after TUR for superficial bladder tumours is associated with significantly lower recurrence rates, and several large randomized trials investigated and supported the efficacy of this strategy [1,3,5]. One important mechanism of tumour recurrence is tumour cell implantation after TUR, and there is clinical and laboratory evidence to show that early intravesical chemotherapy prevents this implantation process [1,9]. Solsona *et al.* [10] used intravesical instillation within 6 h after TURBT and Bouffioux *et al.* [3], reporting on two trials, concluded that early treatment within 24 h of resection was better than delayed treatment. Based on this evidence, we think that immediate instillation of mitomycin C in theatre after TURBT offers the earliest and most effective prophylaxis against tumour cell implantation.

The practice of providing intravesical chemotherapy later, when the patient returns to the ward, is fraught with problems of either obtaining the medication from pharmacy in

time, the need for specialized nursing, or complying with safety measures associated with biohazardous chemical agents on the ward. This often leads to an unsatisfactory delay, with the instillation being given much later in the day or the next day after TURBT. Immediate instillation of mitomycin C in theatre after TURBT overcomes all these problems. The mitomycin C is stored in theatre and does not have to be ordered from the pharmacy. The agent is instilled after TURBT and therefore entails no additional specialized nursing time and biohazard precautions on the ward to administer it. Both the surgeon administering the mitomycin C and the scrub nurse preparing it are already wearing protective clothing in case of accidental spillage. The equipment is simple to use and requires no formal training. Finally, after TURBT the patient is under close nursing supervision in the recovery area, and any problems following intravesical instillation can be promptly managed.

FIG. 1. The method for administering mitomycin C in theatre immediately after TURBT.



In the present series, there were only two minor complications after 177 instillations. In one case the catheter was dislodged due to a faulty balloon, resulting in spillage of mitomycin C, but this may occur after conventional instillation on the ward. In the second case the patient complained of suprapubic pain in recovery. Extravasation was suspected and the mitomycin C was released, with immediate relief of symptoms. As important, there were no staff-related adverse events (e.g. due to spillage) suggesting that using mitomycin C in a theatre and recovery setting is safe and feasible.

As mitomycin C must remain in the bladder for 1 h after instillation, continuous bladder irrigation is not possible with this technique. Therefore meticulous haemostasis is required during TURBT, and where there are doubts (as there were in four of the present patients) standard irrigation should be used. We also took the precaution of using a three-way catheter for instillation and spigotted the irrigation channel in case irrigation was required later. Despite these concerns, it is reassuring that although no irrigation was used after any of the 177 instillations, no patients required irrigation to be re-started later on the ward. The potential savings in cost and nursing time in eliminating bladder irrigation after TURBT are a further advantage of this technique over standard ward instillation.

Reason	N (%)
Suspected invasive tumour	13 (6)
Large resected area at TURBT	11 (5)
Significant bleeding at the end of the TURBT	4 (2)
Known or suspected bladder perforation	3 (1)
Diagnostic re-TURBT	2 (1)
Total	33 (16)

TABLE 1 Patients excluded from study by the protocol exclusion criteria

Finally, the technique is not suitable for all patients undergoing TURBT; 16% of the present patients undergoing TURBT during the study period were excluded. The commonest reason was suspected invasive tumour (6%) or a large resected area at TURBT (5%). Although both of these can only be assessed subjectively, we think that experienced urologists will intuitively know when it is safe to instil mitomycin C immediately after TURBT.

In conclusion, from 177 immediate instillations of mitomycin C in theatre after TURBT, there were only two adverse events. To our knowledge this has not been reported before. The immediate instillation of mitomycin C after TURBT is a feasible and safe method of administering intravesical chemotherapy, and may provide the earliest and most effective prophylaxis against tumour cell re-implantation at TURBT. The technique has additional practical and financial benefits by eliminating the need for ward-based chemotherapy instillation and bladder irrigation.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **TURBT**, transurethral resection of bladder tumour.

APPENDIX 1

Protocol for administering mitomycin C in theatre after TURBT

Storage

The following items for reconstitution will be stored in a secure container in theatre:

- Mitomycin C 40 mg vial.
- Mito-In™ delivery system (Kyowa Hakko UK Ltd, Slough, UK).
- Sterile Bag to hold Mitomycin Vial (Comes with Mito-In™ packaging).
- Catheter connector (Comes with Mito-In™ packaging).
- 50 mL sterile Luer-lock syringe.
- Sterile saline (0.9%).
- 21 G green needle (Luer lock compatible).
- Flip-Flo™ catheter valve (Bard Ltd, Crawley, UK).
- Catheter spigot.
- Cytotoxic mask.

Reconstitution

A trained, scrubbed nurse wearing suitable protection for cytotoxic handling, including protective eyewear should carry out the process of reconstitution. Any nurses supporting the process of reconstitution should also be wearing protective clothing and eyewear for the duration of this process. The reconstitution should be carried out in a well-lit and ventilated area.

Administration

Absolute exclusion criteria: known or suspected bladder perforation; heavy bleeding at the end of the procedure.

Relative exclusion criteria: suspected invasive tumour; large resected area.

The urologist should determine whether it is safe to proceed with instillation and then follow the steps outlined below.

Action/rationale

Before starting the TURBT procedure the scrub nurse and assistant should open all sterile items and place them on a sterile trolley for reconstitution. The assistant should remove mitomycin C from the box, remove the pink cap and place the vial with its top facing upwards in a sterile bag held by the scrub nurse. Detach the two mitomycin C labels from the box and preserve for later use

Dropping the mitomycin C vial into the sterile bag contained within the Mito-In packaging allows the vial to be used whilst maintaining sterility, and protects against spillage in case of vial breakage

Reconstitute the mitomycin C using the Mito-In system by following instructions on Mito-In packaging.

On completing TURBT, the urologist should insert a three-way urethral catheter in the standard manner. The Flip-Flo valve is inserted into the drainage channel ensuring that the valve is in the closed position, whilst the spigot is inserted into the irrigation channel.

A three-way catheter and spigot is used in case the patient requires irrigation postoperatively due to bleeding. The Flip-Flo valve is used to maintain a closed system during administration and drainage of mitomycin C.

Insert the Mito-In system into the Flip-Flo valve using the supplied catheter connector and ensure that the green clamp of the Mito-In system is closed. Open the Flip-Flo valve and green clamp of Mito-In system and slowly instil all 40 mL of mitomycin C into bladder. Close the Flip-Flo valve and green clamp on Mito-In system (*ensures mitomycin C is held within the bladder*)

Remove the Mito-In system and discard in its entirety as cytotoxic waste (*to protect against cytotoxic contamination*).

Attach drainage bag to the Flip-Flo valve (*to enable mitomycin C and residual urine to be drained after 1 h*).

Attach one mitomycin C label to the drainage bag, and the other to the patient's records (*to warn staff of cytotoxic status of drainage bag contents*).

Transfer the patient to the recovery area, on a bed protected by incontinence pads (*in case of potential leakage around catheter*).

If at any time the patient complains of pelvic or abdominal pain the urology team should be contacted to review the patient (*to exclude possible extravasation of mitomycin C or bladder perforation*).

If the patient bypasses mitomycin C or the catheter comes out accidentally then look for signs of mitomycin C spillage and follow separate cytotoxic spillage protocol (*see spillage protocol below*)

After at 1 h, open Flip-Flo valve and empty residual mitomycin C into patient's drainage bag (*safely collects and stores mitomycin C until it can be discarded*).

Detach patient's drainage bag and dispose of in its entirety as cytotoxic waste. Replace bag with new one to ensure drainage can continue (*ensures protection against cytotoxic contamination*)

Transfer the patient back to the urology ward.

Spillages

Full protective equipment (apron, double gloves, plastic sleeves, overshoes and eye protection) must be worn at all times when dealing with any spillage. If there is contact with skin, the area must be bathed immediately with sodium bicarbonate 8.4% and then washed with warm soapy water. If there is contact with the eyes, they should be washed immediately with copious amounts of eyewash.

Spillage onto the floor should first be covered with liquid Milton or a solution of Presept, then mopped up with disposable adsorbent towels, starting at the outside of the spill and working inwards. When the entire spill has been mopped up, the floor should then be washed and dried at least three times with copious amounts of soapy water.

All affected linen and waste (including protective clothing) must be placed in a yellow clinical waste bag with a group D clinical waste sticker, and some cytotoxic warning tape and a cytotoxic residue sheet.

Copies of this protocol are available from Kyowa Hakko UK Ltd, 258 Bath Road, Slough, Berks SL1 4DX, UK.

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