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CONTINUOUS BLADDER IRRIGATION AFTER TRANSURETHRAL RESECTION OF NON-MUSCLE INVASIVE BLADDER CANCER FOR PREVENTION OF TUMOUR RECURRENCE – A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Non-muscle invasive bladder cancer (NMIBC) can recur despite transurethral resection of bladder tumour (TURBT) that clears macroscopic disease, partly from reimplantation of exfoliated cells. Immediate instillation of intravesical chemotherapy (IC) can reduce recurrence, is guideline-recommended but is under-utilised. Bladder irrigation (CBI) immediately post TURBT is postulated to prevent re-implantation, and may provide a simple, cheap and practical alternative. We undertook a systematic review to assess the effect of CBI on NMIBC recurrence.

Methods: Following PRISMA guidelines, relevant publications were identified by online search of databases including Ovid Medline and EMBASE (1980-2019). All published prospective randomized controlled trials (RCTs) comparing CBI post-TURBT to a control group were included. The primary endpoint was recurrence.

Results: Our search yielded 514 studies of which six met inclusion criteria. Two studies (935 participants), albeit without peer-reviewed publication, comparing CBI to no CBI both showed a reduction in recurrence at 2 years. Four publications from 3 trials (331 participants) compared CBI to IC, showing similar recurrence rates at 1 year (OR 1.29, 95% confidence interval 0.78 to 2.13) but a lower risk of adverse events (6 – 34% vs 27 – 48%).

Conclusion: CBI post TURBT appears to yield one-year recurrence rates of NMIBC comparable to immediate IC. However, existing studies are small and of heterogenous design, precluding definitive conclusions. Further trials are required to determine if CBI can be implemented routinely to reduce NMIBC recurrence, as well as the optimal irrigant, volume and duration.

INTRODUCTION

Bladder cancer is common, with almost 500,000 new diagnoses globally in 2018.[1] Most of these present as low-grade non-muscle-invasive tumours (NMIBC), which have a low risk of progression and are rarely lethal. Nonetheless, these tumours can be associated with a significant risk of recurrence, and hence require periodic invasive procedures for cystoscopic surveillance and appropriate treatment by transurethral resection of bladder tumours (TURBT).

The risk of recurrence varies, ranging between 15 and 60% at 12 months, and is definable on the basis of well-established risk factors.[2] Recurrence can result from a number of underlying pathogenetic mechanisms[3]: a precancerous “field change” affecting the entire urothelium,[4] incomplete resection of identified tumours as well as missed tumours too small or subtle in appearance and reimplantation of tumour cells exfoliated during TURBT.[5]

Intravesical instillation of cytotoxic chemotherapy (IC) immediately following TURBT can be effective against all three modes of recurrence. Two separate meta-analyses of multiple randomised controlled trials (RCTs) utilising various agents for IC have demonstrated a 35-38% reduction in recurrences,[6, 7] and hence, current guidelines for the management of NMIBC strongly recommend IC within 24h of TURBT.[2] However, the real-world use of IC remains far from universal, with surveys demonstrating IC use in only 171 of 1010 (17%) TURBTs in the USA[8] and 413 of 954 (43%) TURBTs in Europe.[9]

Various factors are thought to underlie these practice patterns. Firstly, notwithstanding the clinical trial data available, some clinicians question whether the benefits of IC are clinically meaningful, given that recurrences can be effectively managed surgically anyway.[10] Secondly, although the prospective studies document a low rate of adverse events, rare but catastrophic outcomes of chemotherapy extravasation can occur.[11, 12] For some urologists, that risk can outweigh the potential benefits. Finally, in many centres there are practical barriers to delivering IC, including the cost of drug and instillation, the difficulties in ensuring drug availability (particularly agents such as mitomycin that require compounding) and the lack of nursing expertise to manage cytotoxic agents within post-surgical settings.[8, 9]

Continuous bladder irrigation (CBI) has been proposed as a simple, cheap and safe alternative to IC. Haematuria, a common occurrence after TURBT, is typically managed with the placement of a catheter and CBI. The primary aim of CBI is to wash out blood and prevent it from clotting and occluding bladder drainage, but it may have a beneficial effect on recurrence by implantation, as it washes out exfoliated tumour cells from the bladder lumen. Published IC trials have inconsistently used CBI, but a non-randomised comparison within the 2016 individual-patient-data meta-analysis[7] demonstrated that CBI was associated with a 21% reduction in the relative risk of recurrence, even adjusting for IC use and EORTC recurrence risk score.

A number of other studies have specifically assessed the effect of CBI on NMIBC recurrence, which two recent systematic reviews have attempted to synthesise.[13, 14] However, these reviews both suffer from significant flaws, as a result of the inclusion of retrospective and non-randomised data as well as studies with CBI delivered in both treatment arms, which limit the level of evidence they can provide. Thus, we aimed to systematically review the available prospective evidence for CBI using saline or water as a viable intervention to reduce NMIBC recurrence.

METHODS

This systematic review was registered on the Prospero registry (CRD42020188593) and carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) standards. The databases searched included Embase, MEDLINE, Cochrane database of systematic review and Cochrane Central. Additional relevant studies were identified from citations within retrieved publications. The search period was from January 1980 to December 2019. Keywords used in the search included bladder neoplasms, non-muscle invasive bladder cancer, irrigation and their MeSH terms.

Pre-defined inclusion criteria were used to screen the returned search results by two investigators (ML and JT) for prospective RCTs in adults with NMIBC comparing CBI to a comparison arm (either no treatment or IC) and reporting end points relating to tumour recurrence: recurrence rate at a specified time point, recurrence-free survival or time to recurrence.

Non-muscle invasive bladder cancer was defined as Ta, T1 or Tis (CIS) bladder tumours. The tumour grade could be low or high grade, or G1-G3. All irrigant types (saline, glycine or water) were included, with studies stratified by irrigant. After the screening of titles and abstracts, publications that were considered relevant were imported into the Covidence online platform (a Cochrane platform, https://www.covidence.org) for full-text review by the same two investigators. Any discrepancy regarding study eligibility or inclusion were resolved in discussion with the senior investigator (SS) to reach a consensus.

Data from eligible studies were collected using a pre-defined extraction form by the same two investigators. Data collected included study design, patient demographics (age, gender), tumour characteristics (tumour stage/grade, first tumour, recurrence, risk factors), treatment groups (irrigation vs no irrigation, irrigation vs intravesical chemotherapy), end point (recurrence, progression) and toxicity.

Meta-analyses with pooling of odds ratios was performed using a DerSimonian-Laird random effects model. Heterogeneity was assessed with the Cochran's Q statistic and small study effects by Egger's test and funnel plots. Analyses were performed using Stata v13.0 SE (College Station, TX) with significance set at 0.05.

Risk of Bias was assessed using the Cochrane Collaboration’s tool as outlined in Cochrane Handbook for Systematic Reviews of Interventions (https://handbook-5-1.cochrane.org/front_page.htm). The assessment was conducted independently by two reviewers (ML & JT) with discrepancies resolved in discussion with the senior author (SS). The overall quality of selected studies was also assessed using the Oxford Quality Scoring System and GRADE framework (Grading of Recommendations, Assessment, Development and Evaluations).

RESULTS

A total of 514 studies were found in our search, of which 15 were deemed to be relevant after abstract screening (Figure 1). A total of 6 publications describing 5 trials were found to fulfil the inclusion criteria, while a further six retrospective studies (Supplementary Table 1) which also assessed the effect of CBI on NMIBC recurrence were excluded per protocol from our review.

Two trials compared CBI to no CBI, but neither have been published in peer-reviewed literature. Given the limited data available from these trials, meta-analysis was not possible, hence their results have been summarised narratively (Table 1). A large trial involving 866 participants was run across 18 centres by the UK Medical Research Council but the only data available is from an abstract for a presentation at the American Society of Clinical Oncology meeting. This study found an improvement in the time-to-recurrence with irrigation (HR 0.83, 95% CI 0.69 – 1.00, p=0.05), translating into 2 year recurrence-free rates of 51% vs 45%.[15] A smaller single centre trial from Israel, published as part of a book chapter, compared 31 participants receiving 12L of water over 24h post-TURBT to 38 participants receiving no CBI. The recurrence rate at 24mo was significantly lower in the irrigated group (25% vs 58%, p=0.007) but no difference was seen with longer follow-up to 10 years (37% vs 31%, p=0.61).[16]

Three trials have compared CBI to IC, with the results from one having been presented in two separate publications (Table 2). A single-centre RCT from Kurashaki Central Hospital in Japan compared 20h of CBI with saline to 20h of

Epirubicin instillation. The 1-year recurrence-free rate was 32% vs 56% overall (p=0.17) and 48% vs 88% for single tumours (p=0.06). On subgroup analysis, the only significant difference in recurrence rates between the two treatments was noted in participants with grade 3 tumours (p=0.01), but this was based on only 7 patients. Side effects were found to be comparable between the groups (34% vs 48%).

Another Japanese single-centre study which originally randomised 250 participants to receive 18h of CBI with normal saline (n=124) or 30mg Mitomycin C (n=126). The first publication from this trial analysed 227 participants with G1-2 NMIBC, finding no differences in recurrence at 1, 3 or 5 years. Progression was rare (4.4% vs 6.2%) and comparable between the groups. However, the adverse event rate was lower for the saline irrigated group (6% vs 27% $p<0.05$), with haematuria, pain and frequency the main ones reported.[17]

A subsequent re-analysis of the data from this trial pertaining to participants with high-grade NMIBC (partially overlapping with the groups analysed in the original report) compared 75 participants receiving CBI to 71 participants receiving IC.[18] Again, no differences were found in recurrence at 1, 3 or 5 years. The progression rate was somewhat higher in this study, but still comparable between treatment groups (8.9% vs 8.2%). The adverse event rate was again noted to be lower for saline irrigation (7.7% vs 35.6%, $p<0.001$).

Finally, a small randomised trial from an Indian centre compared 19 participants undergoing 24h of sterile water CBI to 17 participants receiving 40mg of mitomycin

instilled within 6h of TURBT.[19] The 12mo RFS was comparable between the groups, being 53% and 47% respectively (p=0.9) as were the recurrence-free intervals of 9.8 (range: 8.4 – 11.2) vs 10.9 (range: 10.0 – 11.8). The AE rate was lower for CBI at 10% compared to 37% for IC (p=0.047), The main complications noted were minor irritative symptoms in the IC group and self-limiting hyperkalaemia in the CBI group.

The two partially overlapping analyses from the Onishi trial[17, 18] posed some challenges for meta-analysis of these studies, but this was overcome by using the overall outcome data from the trial as included in a previous systematic review.[14] The pooled odds-ratio (Figure 2) for recurrence at 1 year for CBI compared to IC was 1.29 (95% confidence interval 0.78 to 2.13). Given that only one study used water for CBI and 2 used saline, analysis stratified by irrigant type was not undertaken.

The risk of bias was found to be moderate, but assessment was limited by lack of detail in the studies (Table 3). There was no evidence for publication bias, but as seen in Figure 3, the assessment was limited by the small number and size of the studies. GRADE evaluation of the level of evidence was judged to be low based on these assessments as well as significant imprecision, notwithstanding the consistency of findings.

DISCUSSION

In this systematic review, we have found six publications on five prospective RCTs examining the effect of CBI on recurrence of NMIBC, two comparing CBI to no CBI and three comparing CBI to IC. Neither of the two trials comparing CBI to no CBI have been published in full but were included on the basis that sufficient published data were available from a conference abstract and book chapter respectively.[15, 16] Each trial demonstrated a lower risk of recurrence at 2 years with CBI. However, further follow-up up to 10 years in the smaller single centre trial demonstrated no difference in longer-term recurrence rates. The findings from these two RCTs are consistent with the analysis of the non-randomised comparison of CBI vs no CBI within RCTs of IC after TURBT, which showed that CBI reduced the risk of recurrence by about 21%, even after adjusting for IC use and EORTC risk score.[7]

The use of IC after TURBT in order to reduce recurrence of NMIBC is supported by level 1 evidence[6, 7] and recommended by international guidelines.[2, 20] Hence, this may be seen as a more appropriate control group to compare the effects of CBI. Of the three trials to have undertaken such a comparison, one utilised epirubicin[21] and other two mitomycin.[17-19] Our meta-analysis of these trials showed a pooled odd-ratio for recurrence at 1 year that favoured IC but with a wide confidence interval that included 1. However, the published studies individually and even collectively appear to have had insufficient power to establish whether CBI is non-inferior to IC in reducing recurrences, and we have assessed the level of evidence as being low.

Collectively, the data from prospective RCTs do provide suggestive evidence that CBI has some effect in reducing the recurrence of NMIBC compared to no CBI, but it remains unclear whether this may be as effective as IC (recommended as standard of care by guidelines). Interpreting the evidence comes with a number of caveats, most importantly that the observed similarity in recurrence rates may very well represent a Type 2 error, in that the 3 published trials cumulatively included only 331 participants. We estimate that to adequately power an assessment of non-inferiority of CBI compared to IC would need a sample size of around 1500 participants.

Further complicating the synthesis of the evidence is the possibility that the nature, volume and duration of CBI, which vary significantly across the studies, may have significant impact on its effectiveness on reducing recurrence. The most commonly utilised irrigant for CBI, both in clinical practice and the studies included in this review, is normal saline. This may help reduce recurrence by washing out exfoliated tumour cells, but sterile water used for CBI may have additional effectiveness by causing osmotic lysis not only of exfoliated cells, but possibly also on incompletely resected tumours. In vitro studies have shown water to have an osmolytic effect on bladder cancer cell lines that may be equivalent to or even greater than the cytotoxic effect of mitomycin,[22, 23] although the effect was only modest when exposure time was restricted to five minutes.[24] With only one small trial of water CBI vs no CBI and another even smaller trial vs IC, there was insufficient data available to compare the effects of different irrigants in this review.

The duration of CBI is also likely to be critically important for reducing NMIBC recurrence. As discussed above, the RCTs of CBI included in this review that have

shown a reduction in recurrence compared to no CBI or comparable outcomes to IC have typically utilised 18 to 24h of irrigation. Retrospective studies utilising a similar duration of CBI have also demonstrated similar findings.[25, 26] Conversely, at least two retrospective studies of CBI over 2 or 3 hours have shown no reduction in recurrence compared to no CBI[27, 28] and a significantly shorter recurrence-free survival compared to IC.[27]

Based on this, it may be hypothesised that CBI for a period of 18 to 24h after TURBT may be necessary in order to effectively reduce NMIBC recurrence. However, this duration of CBI may limit its cost-effectiveness and applicability, as many bladder tumours currently treated as day-case or outpatient procedures would end up requiring hospital admission.[27] Hence, it is important that further studies define whether a shorter duration of CBI that can be implemented after day-case TURBT is effective at reducing NMIBC recurrence.

Adverse event rates were reported from all 3 trials comparing CBI to IC, with one showing comparable rates[21] while the other two demonstrated significantly lower rates with CBI.[17-19] This, along with the relative ease of administration provides additional argument for wider implementation of CBI as an intervention to reduce NMIBC recurrence. Currently, although IC is recommended in guidelines, it remains limited in its application, with significant variability of practice internationally.[8, 9] As discussed before, potential factors underlying this practice variation include concerns regarding adverse events and difficulties with the practicalities of managing cytotoxic agents. Additionally, health systems with significant resource constraints may find it easier to implement CBI rather than IC as an intervention following TURBT.

There have been two previous systematic reviews[13, 14] that have examined this question, but with some methodological limitations. Both include retrospective non-randomised studies,[26, 29] in one case contrary to the stated inclusion criterion of RCTs only.[14] Therefore, the previous systematic reviews can at best be considered to only provide Level 2 evidence.[30] Additionally, both reviews also erroneously include studies that are actually RCTs of IC vs no IC, with CBI utilised in both treatment arms,[31, 32] which evidently cannot provide data to answer the study question. As a result, the pooled estimate of recurrence-free survival for CBI using water in one of the reviews includes 205 of 463 participants who actually received a peri-operative instillation of 50mL of water (as a placebo for IC) followed by 24 hours of CBI using saline.[13]

Despite these limitations, both these reviews reached conclusions very similar to ours, namely that CBI administered after TURBT appears to have a similar effect as IC on recurrence of NMIBC, but with fewer adverse events. Both reviews call for additional prospective studies, but neither really addressed the limited sample size of available studies and the resulting lack of power to detect differences between treatment groups. If CBI is to be implemented as an intervention to reduce NMIBC recurrence, the key prerequisites are to define a shorter duration that may be effective, so as to enable day-case TURBT, and evaluate this for non-inferiority to IC in an adequately powered RCT.

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FIGURE LEGENDS

Figure 1: Prisma flow-chart outlining selection of included studies

Figure 2: Forest plot showing 1-year recurrence rates comparing CBI with IC

Figure 3: Funnel plot demonstrating no evidence of publication bias in included studies

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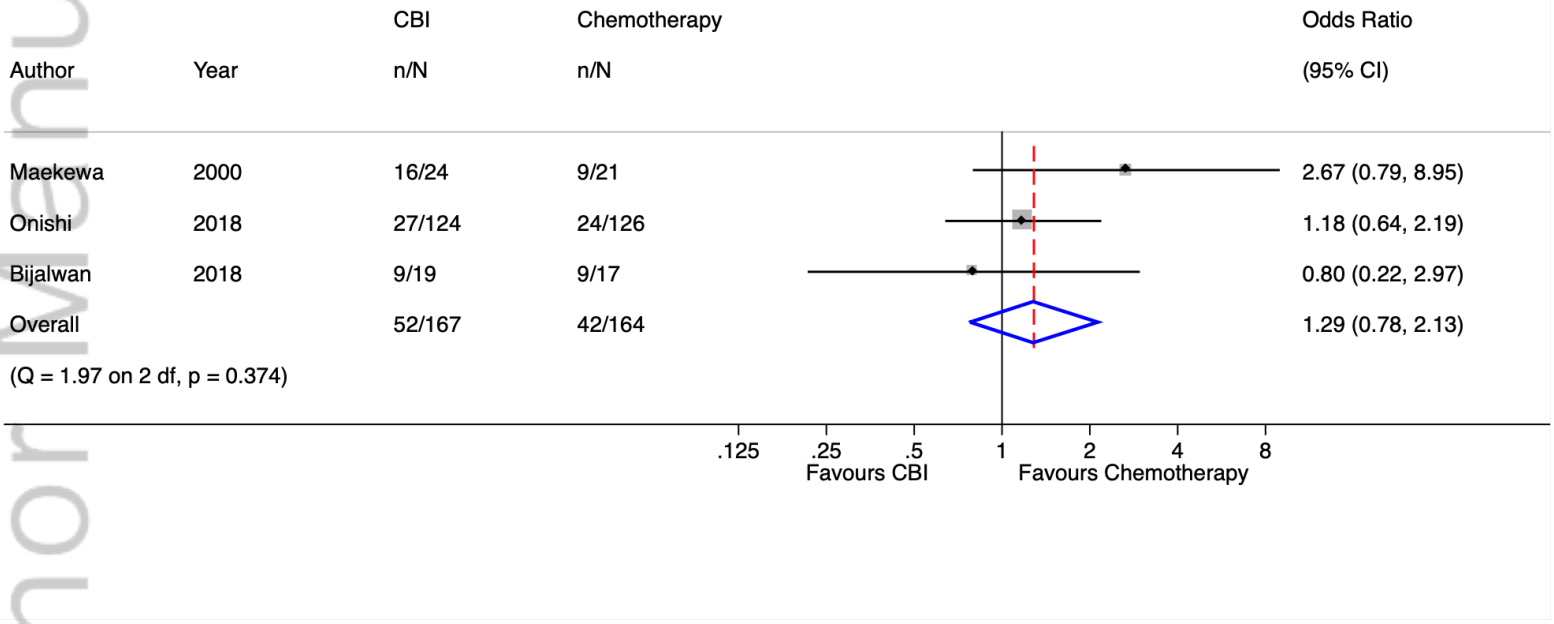

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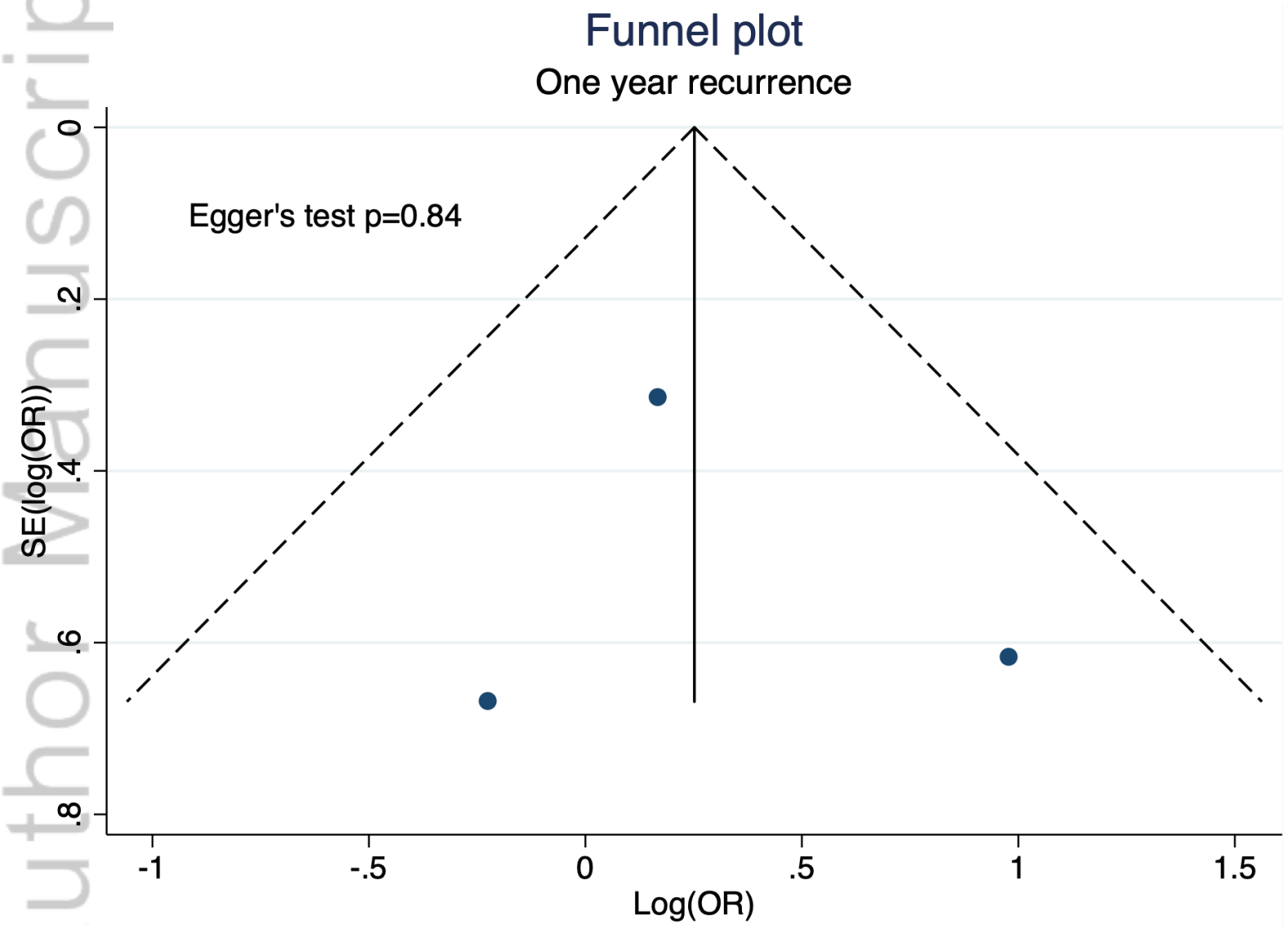

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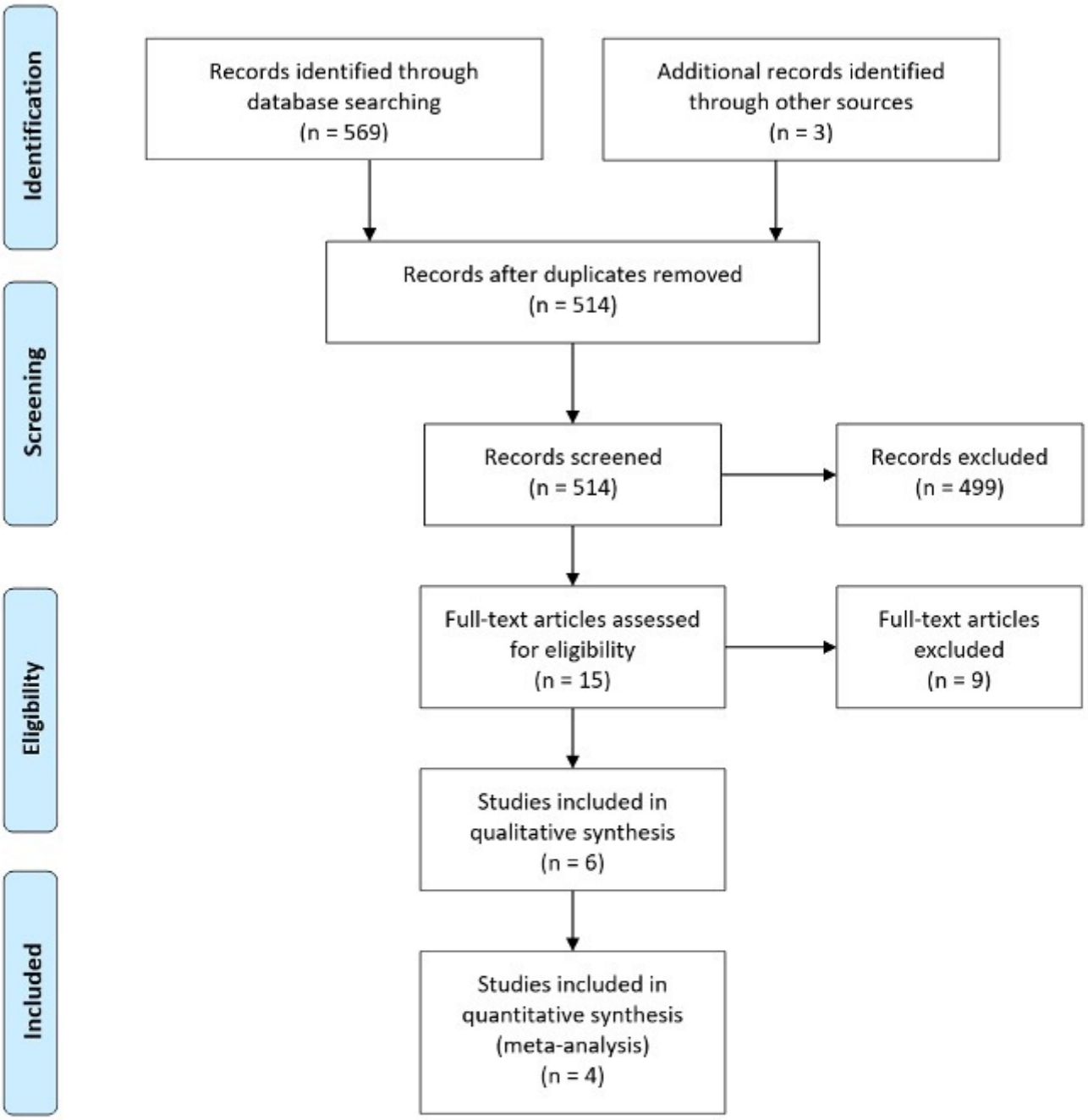

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Table 1: Randomised controlled trials comparing CBI to no CBI					
Study	**Setting**	**N**	**Intervention**	**Comparator**	**Outcomes**
Whelan 2001[14]	UK Multicentre (MRC)	866	Saline or glycine ≥18h N=427	No CBI N=439	RFR at 24mo: 51% vs 45%
Amos 2012[15]	Israeli single centre	69	Water 2L/4h x 24h N=31	No CBI N=38	Recurrence rate at 24mo: 8 (25%) vs 22 (58%), p=0.007

Table 2: Randomised controlled trials comparing CBI to IC					
Study	**Setting**	**N**	**Intervention**	**Comparator**	**Outcomes**
Maekawa 2000[16]	Japanese single centre	45	Saline 20h N=24	Epirubicin 20mg pre-op then 20μg/mL x 20h, N=21	1 yr RFR: 32% vs 56% (p=0.17) overall,
Onishi 2017[17] & 2018[18]	Japanese single centre	227 G1-2 NMIBC/250 randomised participants	Saline 11.5L over 18h, n=114	Mitomycin C 30mg/30mL x 1h, N=113	5y RFR: 62.6% (95% CI 0.49–0.73) and 70.4% (95% CI 0.59–0.78),
		147 HG NMIBC/ 250 randomised participants (re-analysis of above)	Saline 11.5L over 18h, n=75	Mitomycin C 30mg/30mL x 1h, N=72	5y RFR: 60.5% (95% confidence interval [CI]: 0.48-0.70) and 67.2% (95% CI: 0.54-0.77)

Bijalwan 2017[19]	Indian single centre	36	Water 8.5 – 9.5L over 18h, N=20	Mitomycin C 40mg/20mL x 1h	1yr RFR: 52.6% vs 47.1% (p=0.9)

Table 3: Risk of Bias assessment

	Random sequence generation selection bias	Allocation concealment selection bias	Personnel bias	Detection bias	Attrition bias	Selective reporting bias		Oxford Quality Scoring System
Bijalwan 2017	U	U	H	H	L	L		Low score
Onishi 2017/2018	L	U	U	L	L	L		Low score
Maekawa 2000	U	U	H	H	L	L		Low score
H/red=High risk; U/yellow=Unknown; L/Green: Low risk.								