Bladder irrigation after transurethral resection of superficial bladder cancer: a systematic review of the literature

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Introduction: *The vast majority of bladder cancer is non-muscle invasive with transurethral resection (TURBT) as the gold standard for surgical treatment. There is a high recurrence of bladder cancer post surgery, which adds to the frustration in current urologic practice. Current standard of care to further reduce bladder cancer recurrence is instillation of intravesical chemotherapy (ICT), a practice that is not routinely followed. Several studies point to similar effects with normal saline or water irrigation alone. Our objective is to review the current available literature and provide practicing urologist with an alternative to ICT.*

Materials and methods: *A systematic search was performed through December 2017. Peer reviewed studies, which evaluated recurrence free survival (RFS) after bladder irrigation with saline or sterile water (SW) post-TURBT were included. Outcomes were analyzed in three groups: ICT, saline and sterile water.*

Results: *Six studies out of 981, including 1515 patients, were eligible. There was no significant difference between ICT, saline and SW groups regarding to the median RFS at 1 year [ICT: 81%, IQR (77.70, -81.00), SW: 74%, IQR (63.3-74.9), saline: 76.7% IQR (76.0, 77.7), p = 0.21]. While saline irrigation showed the highest median RFS among the groups, there was no statistically significant difference between the three groups [ICT: 70%, IQR (66.25, 73.75), SW: 64.1%, IQR (63.05, 65.15), saline: 73%, IQR (66.85, 74.50), p = 0.49]. Adverse events were more frequent amongst patients in the ICT group in comparison to the saline or water groups.*

Conclusion: *Saline and sterile water irrigation provide an alternative to ICT with equivalent recurrence rate and lower incidence of adverse events.*

Key Words: bladder irrigation, superficial cancer, transurethral

Introduction

Bladder cancer is found to be non-muscle invasive in 75%-85% of all cases. Management of non-muscle invasive bladder cancer (NMIBC) is challenging due to high recurrence rate despite aggressive transurethral resection. The high recurrence rate after TURBT (40%-80%) is widely suspected to be a result of implantation of floating cancer cells after the operation into the injured areas. It is also associated with about 25%-30% progression rate to muscle invasive disease.[1,2]

While TURBT remains the 'gold standard' of therapy for NMIBC, the American Urological Association (AUA) guidelines recommend single instillation of chemotherapy (CT) after TURBT to decrease the risk of recurrence in patients with NMIBC.[2] Controversy

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over the optimal postoperative intravesical agent has led to studies utilizing single dose intravesical CT (i.e. doxorubicin, epirubicin, mitomycin C (MMC), and gemcitabine (GEM)), or continuous bladder irrigation (i.e. saline and sterile water). A meta-analysis comparing post-TURBT intravesical chemotherapy (ICT) to TUBRT alone has demonstrated superiority of ICT in preventing recurrence, but not progression of disease.[3] In large part, ICT is well tolerated, but it is not devoid of complications. Several case reports have presented severe complications after early intravesical instillation including hemorrhagic cystitis, profound anemia, and death.[4] National trends in utilization of ICT show significant disparities in both USA and Europe based on geographic location.[5] With the limited utilization and the side effect profile associated with intravesical instillation, there is increasing interest in less toxic irrigants, such as water and saline, which show equivalent recurrence free survival.

In this systematic, we compared the recurrence free survival of postoperative ICT versus continuous irrigation with saline or sterile water. Furthermore, we examined the adverse events encountered during therapy as well.

Materials and methods

This review was generated in accordance to the MOOSE Guidelines for meta-analyses and systematic reviews.[6]

Literature search

Utilizing various databases (MEDLINE, EMBASE, Cochrane [with online Ovid interface], and Web of Science), an expert librarian conducted a search for studies utilizing different methods of bladder irrigation after TURBT. The search was limited to the English language between 1946 and December 2017. Search key words included MeSH and EMBASE terms for superficial bladder cancer, non-invasive bladder cancer, transurethral resection, and bladder irrigation. Two researchers reviewed the search details independently to identify eligible articles. The detailed search strategy is provided in Table 1.

Eligibility criteria and study selection

All the references were screened using the titles for the utilization of saline or sterile/distilled water for post-TURBT bladder irrigation. The abstracts with relevant

TABLE 1. **Characteristics of the included studies**

	Study type (Country)	(n)	Group	Material used	RFS (1yr)	RFS (2yr)	Duration of FU	Time to 1st recurrence	Recurrence n (%)	Progressed n (%)	Complications	Newcastle-Ottawa Quality Assessment Scale		
												Selection (4 stars)	Comparability (2 stars)	Outcome (3 stars)
Oosterlinck 1993[15]	Prospective (Netherlands and Belgium)	194	CT	Epirubicine 80 mg in 50 mL (60 min) followed by 24 hrs cont saline irrigation	82	73	Mean 25.1 mo	NR	57 (29%)	7 (3.6%) ≥ PT2	Chemical cystitis: 24 (12.4%) Allergy in 9 (5%) Death due to BC: 3 (1.5%)	★★★★	★★	★★★
		205	Water	Sterile water 50 mL (60 min) followed by 24 hrs cont saline irrigation	74	62	Mean 21.8 mo	NR	84 (41%)	5 (2.4%) ≥ PT2	Chemical cystitis in 4 (2%) Death due to BC: 1 (0.5%)			
Bohle 2009[13]	Double-blind, randomized, PBO-controlled study (Germany and Turkey)	124	CT	30-40-min instillation of GEM (2000 mg/100 mL of saline) followed by cont irrigation of saline ≥ 20 hrs	77.7	64	Median 23.6 mo (0-46)	NR	48 (38.7%)	3 (2.4%) ≥ PT2	Alopecia in 1.2% Procedural pain in 1.2% Pyrexia in 1.2% Death due to BC: 1 (0.8%)	★★★★	★★	★★★
		124	Saline	PBO (100 mL of saline) followed by cont irrigation saline ≥ 20 hrs	75.3	60.7		NR	44 (37.1%	1 (0.8%) ≥ PT2	Pyrexia in 0.4% Death due to BC: 1 (0.8%)			
Onishi 2011[11]	Retrospective (Japan)	115	CT	Mitomycin C in 50 mL Saline (4 weekly instillations followed by 11 monthly instillations)	81%	67	Median 66 mo (42-96)	16 mo	NR	16 (13.9%)	Macrohematuria: 22 (19.1%) Micturition pain: 34 (27.6%) Increased freq: 41 (35.7%) Death due to BC: 4 (4.3%)	★★★★	★★	★★★
		123	Saline	Saline (total of 8.5-9.5 L) for 18-22 hrs	76.7	73	Median 58 mo (32-84)	13.9 mo	NR	9 (7.3%)	Macrohematuria: 9 (7.3% Micturition pain: 15 (12.2%) Increased freq: 13 (10.6%) Death due to BC: 3 (2.4%)			
Grivas 2014[9]	Retrospective (Greece)	239	Water	Water for injection for 18 hrs	75.8	66.2	NR	NR	NR	NR	NR	★★★★	★★	★★★
Bijalwan 2017[14]	Prospective randomized (India)	19	Water	CSWI (sterile water) for 24 hrs	52.6	NA	NR	NR	NR	2 (10%)*	Self-limited hyperkalemia: 2 (10%)	★★★	★★	★★
		17	CT	Mitomycin C (40 mg in 20 mL saline) -- Single	47.1	NA	NR	NR	NR	1 (5.8%)*	Irritative voiding: 7 (36.8%)			
Onishi 2017[12 #]	Prospective unblinded randomized (Japan)	114	Saline	CSBI (saline) for 18 hrs	78.6	76	37 mo	8 mo	NR	5 (4.4%	Macrohematuria: 4 (3.5%) Micturition pain: 1 (0.9%) Dysuria/retention: 2 (1.8%)	★★★★	★★	★★★
		113	CT	MMC (30 mg in 30 mL) -- Single	81	76		8.5 mo	NR	7 (6.2%)	Macrohematuria: 17 (15%) Micturition pain: 8 (7.1%) Increased freq: 5 (1.4%) Dysuria/retention: 8 (7.1%)			

*from Ta to T1 or form low grade to high grade; #Onishi 2017 reported; d cystitis manifestations in total in total of 7 and 31 patients in the saline and MMC group respectively

TABLE 2. **Demographics among the three groups: ICT, saline and sterile water**

	Chemotherapy (n = 563)	Saline (n = 361)	Water (n = 463)	p value
n of the studies	5	3	3	
Age: median (IQR)	68 (65, 70)	71 (69, 71)	68 (66.5, 68)	0.548
Grade I: median (IQR)*	51 (36, 62)	46 (31, 56)	89 (79, 99)	0.212
Grade II: median (IQR)*	84 (64, 99)	68 (56, 88)	107 (97, 118)	0.472
Grade III: median (IQR)*	67 (0, 16)	0 (0, 7)	30 (23, 38)	0.170
Stage Ta: median (IQR)*	98 (93, 104)	96 (92, 105)	165 (89, 174)	0.594
Stage T1: median (IQR)*	15 (11, 31)	18 (14, 27)	49 (28, 53)	0.829
RFS 1 YR: median (IQR)	81 (77.7, 81)	76.7 (76, 77.7)	74 (63.3, 74.9)	0.210
REF 2 YRS: median (IQR)#	70 (66.3, 73.8)	73 (66.9, 74.5)	64.1 (63.1, 65.2)	0.488

* = median number of patients across the studies constituting each group (from 5 studies out of 6 excluding Bijalwan 2017[14]; # = from 5 studies out of 6 excluding Bijalwan 2017[14]

titles were reviewed in order to identify the pertinent studies, which were read thoroughly to further select the studies that constituted this review, Table 2. Only comparative studies, which reported recurrence free survival rates, were selected for further analysis, Figure 1.

Quality evaluation of the included studies

Two methods were used in order to evaluate the studies that formed this review including the NewCastle-Ottawa Quality Assessment Scale for cohort studies and the quality assessment tool from the National Heart, Lung and Blood institute was conducted, Table 3.[7] In addition, the GRADE tool was used to generate the level of certainty for the study outcomes,[8] Table 4.

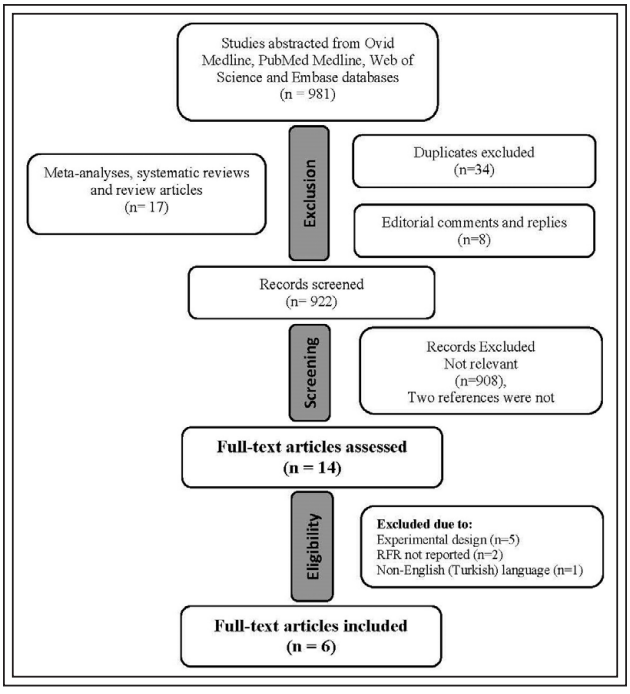

Figure 1. Flow chart of the study.

Data abstraction, synthesis and analysis

Two standardized forms were used for data collection. The first included the variable study characteristics such as author, year, type of study, country, agent used for irrigation, number of patients, recurrence free survival, duration of follow up, number of recurrences and progressions, time to first recurrence, and number and nature of associated complications (if available). The second form included the baseline demographics for each study and it included median age, grade of tumors, and stage of tumors. All the included six studies had two arms. We merged the similar arms from the selected studies based on the irrigation material used into three groups: ICT, sterile water and saline. We excluded a single arm of the Grivas et al study, in which they were evaluating the outcomes of BCG after water irrigation.[9] For continous data, medians and IQRs were depicited, and Kruskal-Wallis test was used for identifying the correlations of the variables among the different groups. R packages software was used for statistical analysis.[10]

Results

In total, six studies evaluated a total of 1515 patients within this review. Two studies were from Japan,[11,12] additionally one from Germany and Turkey,[13] Greece,[9] India,[14] and the Netherlands and Belgium.[15]

Three studies[11-13] utilized saline as a study group (361 patients), three used sterile water (463 patients),[9,14,15]

TABLE 3. **Quality evaluation of the included studies:**

The quality assessment tool from the National Heart, Lung and Blood institute	Oosterlinck 1993	Bohle 2009	Onishi 2011	Grivas 2014	Bijalwan 2017	Onishi 2017
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes	Yes	Yes	Yes	NR	Yes
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	No	Yes	NA	NA	No	Yes
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	NA	NA	No	Yes
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes	No	Yes
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Yes	Yes	Yes	Yes	Yes	Yes
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	Yes	Yes	Yes	Yes	Yes	Yes
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	No	Yes	No	No	No	No
13. Was loss to follow-up after baseline 20% or less?	Yes	Yes	NA	NA	NR	Yes
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Ye	Yes	Yes	No	Yes	Yes

and five utilized ICT for post TURBT irrigation (563 patients).[11-15] There was no detected significant difference between the three groups regarding the median age, grade or stage of disease, Table 2

Interestingly, there was no significant difference between the three groups with regard to the median recurrence free survival (RFS) at 1 year [ICT: 81%, IQR (77.70, -81.00), sterile water: 74%, IQR (63.3-74.9), saline: 76.7% IQR (76.0, 77.7)], p = 0.21. Five studies out of six have reported RFS at 2 years. While saline irrigation showed the highest median RFS among the groups, there was no significant difference between the three groups [ICT: 70%, IQR (66.25, 73.75), sterile water: 64.1%, IQR (63.05, 65.15), saline: 73%, IQR (66.85, 74.50)], p = 0.49, Table 2, Figure 2. Furthermore, comparing the median RFS in the ICT group versus the sterile water group

TABLE 4. **GRADE evaluation of the evidence level of the outcomes from the included studies**

			Certainty assessment					Certainty
Outcome	**n of studies**	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	
Recurrence free survival	6	Observational studies	Not serious	Serious	Not serious	Not serious	None	⊕⊕◯◯ Very low
Adverse Events	5	Observational studies	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕◯ Low

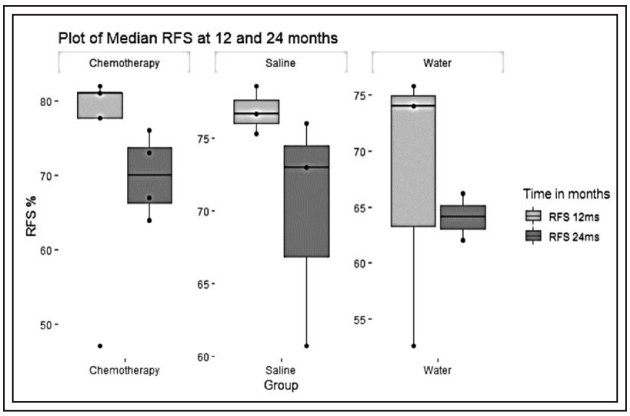

Figure 2. Median RFS among the groups (12 and 24 months).

did not show any significant difference at 1 and 2 years [p = 0.18, p = 0.17 respectively).

In three studies,[11,12,14] authors compared MMC with either saline or sterile water. One year median RFS was slightly higher in the MMC group without any statistically significant difference when compared with the saline/sterile water groups [MMC: 81%, IQR (64.05, 81.00), saline and sterile water: 76.7%, IQR (64.65, 77.65)], p = 0.51. Two out of the three studies[11,12] also evaluated 2 year RFS of MMC versus saline. Saline group showed a slightly higher median RFS than MMC without statistically significant difference [MMC: 71.5%, IQR (69.25, 73.75), saline: 74.5%, IQR (73.75, 75.25)], p = 0.68.

Adverse events were more frequent among patients in the ICT group in comparison to either the saline or sterile water groups, Table 1. Death due to bladder cancer was reported in three studies,[11,13,15] and was comparable among the ICT group 8/433 (1.8%) [by agent: MMC (4), epirubicine (3), and gemcitabine (1)], the saline group 4/247 (1.6%), and the sterile water group 1/205 (0.5%), Table 1.

Discussion

In this systematic review, we present the outcomes of six studies that compared the RFS in NMIBC patients post-TURBT ICT or bladder irrigation with water or saline. There was no statistically significant difference in RFS between ICT versus saline or sterile water post-TURBT at the first and second year follow up (p = 0.21 and p = 0.49, respectively).

The overall RFS at 12 months for patients receiving ICT was 81%, as compared to 76.7% and 74% for saline and water irrigation, respectively. These observations may imply that continuous postoperative intravesical irrigation with sterile water or saline in NMIBC could have comparable efficacy of cancer recurrence as ICT, with reduction of adverse events.

Follow up at 24 months, median RFS for ICT versus saline versus water were 70%, 73% and 64.1%, respectively. These results are comparable with the 12 month recurrence rate, further validating the sustained effect of ICT as well as water and saline bladder irrigation. Bladder tumor recurrence may be attributed to seeding post-TURBT or development of a de novo tumor. If one would expect newly emerging tumors or incipient tumors after resection, this sustained effect would be unlikely to persist. At 2 years post-TURBT, saline demonstrated a more stable and a higher median RFS in comparison to ICT and sterile water. This raises the concern about the utilization of ICT post-TURBT as RFS declines over 24 months.

Recent evaluation of urologic practices demonstrated only 18% and 2% of urologists in Europe, and the USA, respectively, use ICT consistently after resection.[5] In fact, 28% and 66% have never used chemotherapy after TURBT.[5] Possible reasons for why this practice has not permeated globally may be multifactorial.[5] Potential delay in obtaining chemotherapy from pharmacy post resection, rising cost, inadequate training in chemotherapy handling, and uncertainty about the patient's pathology at time of resection are all barriers to the routine use of ICT.[5,16] By establishing water and saline irrigation as an alternative to single use chemotherapy, it may be feasible to eliminate some of the barriers imposed by ICT, such as chemotherapy handling and delay from pharmacy. In addition, with minimal training, the nursing staff can irrigate the bladder for a specified amount of time or volume prior to discharging the patient.

While ICT has multiple disadvantages, cost analysis of bladder irrigation with saline as compared to single installation of MMC has been poorly evaluated. We urge further studies to focus on financial cost evaluation of the aforementioned techniques.

The major limitation of this systematic review study is the limited number of studies. Varying methodologies present other weaknesses, such as the lack of standardization of irrigation, volume infused, and duration of treatment. Another major limitation in our study is the lack of risk stratification. While grade and stage are included in the analysis, the majority of the studies included in this systematic review are prior to European Organization for Research and Treatment of Cancer (EORTC) or the AUA guidelines. Four out of six studies, utilized World Health Organization (WHO) grading, and low grade/high grade was utilized in one.

Conclusions

ICT, saline or water was shown to provide nearly equivalent results in patients with NMIBC. Importantly, irrigation with water or saline showed an improved adverse event profile as compared to chemotherapy. According to the Oxford Center of Evidence, this systematic review is associated with level 3a studies and a grade B recommendation.[17] Evaluating the level of evidence using GRADE, the certainty level of the current study was very low to low. Due to rising cost of healthcare and limited adoption of ICT, bladder irrigation with saline or sterile water may offer a more feasible and equally effective option post-TURBT. Future prospective studies are highly encouraged to further validate the current finding. □

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