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Review Article

The Safety and Efficacy of Continued Antiplatelet or Anticoagulant Therapy Perioperatively in Patients Performing Transurethral Resection of Bladder Tumors: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction and Objectives: An argument exists between stopping Antiplatelet or Anticoagulant (AP or AC) agents perioperatively to reduce the risk of bleeding complications and continuing the drug to protect against the risk of cardiovascular events during Transurethral Resection of Bladder Tumors (TURBT). And we search a few articles about TURBT in patients receiving AP or AC therapy. We aimed at conducting a systematic review and meta-analysis to evaluate the safety and efficacy of continued AP or AC therapy perioperatively in patients performing TURBT.

Materials and Methods: A literature search was conducted in July 2018 using PubMed (1990- July 2018), EMBASE (1990- July 2018), Cochrane Library (1990- July 2018). All included articles are relevant to the TURBT in patients receiving AP or AC agents. The data was extracted from each study by two reviewers independently. The data was included into a meta-analysis and discussed.

Results: One randomized, prospective study and six retrospective studies among the 1487 included patients were identified for analysis. There was no statistically significant difference in the total complication (OR: 1.70; 95 % CI 0.97-2.97; p=0.06), operating time (WMD, 1.93; 95% CI, -0.66–4.52; P=0.14), median catheter indwelling days after TURBT(WMD, 0.07; 95%CI, -0.15–0.29; P=0.54), blood transfusion (OR: 2.24; 95 % CI 0.72–6.96; p=0.16>0.05), between the stopped group and the continuing group.

Conclusions: The results of our systematic review and meta-analysis revealed that continued AP or AC therapy perioperatively in patients performing TURBT appears safe and effective.

ABBREVIATIONS

TURBT: Transurethral Resection of Bladder Tumors; AP: Antiplatelet; AC: Anticoagulant; UBC: Urothelial Bladder Cancer; ALOS: Average Length of Stay; ASA: Aspirin agents

INTRODUCTION

Bladder tumors are one of the most common urological diseases clinically [1]. Approximately 75% of newly diagnosed Urothelial Bladder Cancers (UBCs) are non-invasive, but they have a high recurrence rate [2]. The other 25% are muscle invasive and requires either radical surgery or radiotherapy [3].

A few lesions can be successfully managed with endoscopic resection in combination with intravesical therapy. TURBT is both diagnostic and therapeutic for patients found to have a bladder tumor [4]. However, TURBT is considered as a surgical procedure associated with a high bleeding risk.

More patients with multiple comorbidities related with the aging process of the population seek help from urologists [5]. Bladder tumors are common urological diseases, espically occurring in elderly [6]. Common lower urinary tract operations for bladder tumors are being increasingly performed in the elderly population, of whom many have cardiovascular comorbidities. AP or AC agents are prescribed widely for primary and secondary prevention for patients with cardiovascular diseases. They are also used after percutaneous vascular interventions with positioning of endovascular stents and prescribed for high-risk patients with multiple cardio vascular risk factors (diabetes mellitus, cigarette smoking, hypercholesterolemia, hypertension) [7]. In the meanwhile, continuation of double platelet anti aggregant therapy for at least 1 year is recommended among patients treated with Bare Metal Stents (BMS) for acute coronary syndrome [8]. A dilemma exists between stopping these AP or AC agents' perioperative to reduce the risk of bleeding complications and continuing them to protect against the risk of cardiovascular events during TURBT [9]. There is currently no consensus among urologists regarding the perioperative management of patients taking AP or AC (AP/AC) agents, and information on this issue is lacking. Current treatment guidelines do not provide useful information about TURBT perioperatively in patients receiving AP/AC therapy [10]. In view of all these facts, we aimed to conduct a systematic review and meta-analysis to evaluate the safety and efficacy of continued AP or AC therapy perioperatively in patients performing TURBT.

MATERIALS AND METHODS

Search strategy and study selection

The search strategy was conducted to find relevant studies from PubMed (1990- July 2018), EMBASE (1990-July 2018), Cochrane Central Register of Controlled Trials - CENTRAL (in The Cochrane Library - Issue 1, 2018).

The following search terms were used for the search: (Transurethral resection of bladder tumors OR TURBT) AND (anticoagulant OR antiplatelet OR antithrombotic). Reference lists of previous reviews and previous trials were included; papers in languages other than English such as Japanese were included, references of searched papers were evaluated for potential inclusion, and recently published versions were included if the publication was duplicated.

Two reviewers (Yang Pan and Han Chen) identified all studies that appeared to fit the inclusion criteria for full review. Each reviewer independently selected studies for inclusion in the review. Disagreement between the two extracting authors was resolved by consensus. If consensus between the two reviewers could not be reached, a third author (Gang Chen) was deferred to for arbitration and consensus.

Data extraction and analysis

Studies reporting on the treatment of transurethral resection of bladder tumors in patients receiving AP or AC therapy perioperatively were included. The following variables were extracted from each study: period of the study; country of origin of the study; study population demographics; type of anticoagulant or antiplatelet therapy used; follow up; change in hemoglobin; the total complication; operating time; median catheter indwelling days after TURBT; blood transfusion; cardiovascular events and the average length of stay. The data of each study was grouped into a meta-analysis to allow a numerical representation of the results. The methodologic quality of the studies was evaluated according to the Jadad scale for randomized, prospective study and Newcastle-Ottawa Scale for retrospective study. The assessments were processed independently by two reviewers, and the final decision was determined by a discussion between them.

Statistical analysis

The odds ratio (OR) and mean difference were used for the binary and continuous variables, respectively. The mean values and standard deviations are applied to pool data for continuous parameters. The Q and I2 statistics were used to evaluate the heterogeneity among studies if the published literature only presents continuous data as means and range. Homogeneity was rejected when the Q statistic P value was < 0.10 or the I2 value was >50%. The fixed effect model or the random effect model were applied to estimate the combined ORs (or weighted mean differences) and the 95% Confidence

Intervals (CIs). The pooled effects were computed by the z test, and statistical significance was set at $P < 0.05$. The statistical analysis was conducted by Rev-Man 5.3 statistical software.

RESULTS

The characteristics of the included studies

39 studies were incorporated through the literature search, 32 of them were excluded by title or abstract which did n't conform to the aims of our review. After rigorous assessment, 7 trials, including 1 Random Controlled Trial (RCT) [11] and 6 retrospective studies [5,12-16] were selected for further analysis (Figure 1).

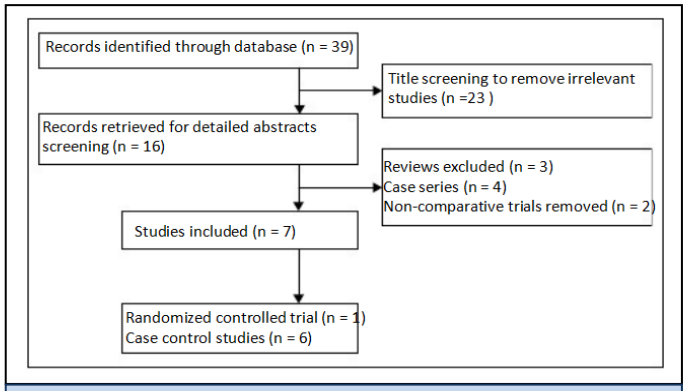

Figure 1: Flowchart for article selection process of the review.

Table 1: Study characteristics and quality assessments.

Author	Year	Period	Place	Design	Age mean(years)		No. of patients		Newcastle-Ottawa score
					study group	control group	study group	control group	
Hiroki	2017	2011-2015	Japan	Retrospectively	77	80	24	25	★★★★★
Tsuzumi	2017	2013-2016	Japan	Retrospectively	77	81	19	155	★★★★★
Antonio	2015	2008-2013	Rome	Retrospectively	62	62	287	287	★★★★★★★
Naoki	2014	2007-2013	Japan	Retrospectively	75	73	105	171	★★★★★★
Stefano	2013	2007-2012	Italy	Retrospectively	74	68	83	50	★★★★★★
Ehrlich	2007	2004-2006	Israel	RCT	72	72	23	24	4 scores (Jadad)
Prader	2017	2013-2015	France	Retrospectively	74	66	117	117	★★★★★★

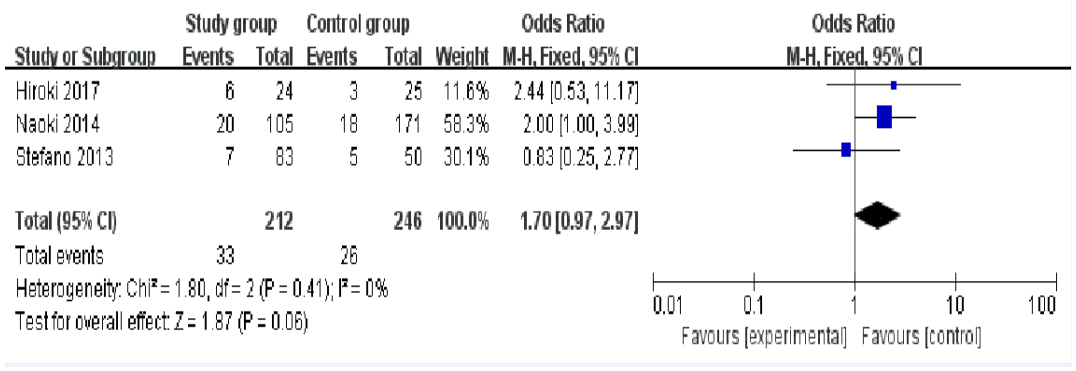

Figure 2: Forest plot comparing total complication rates.

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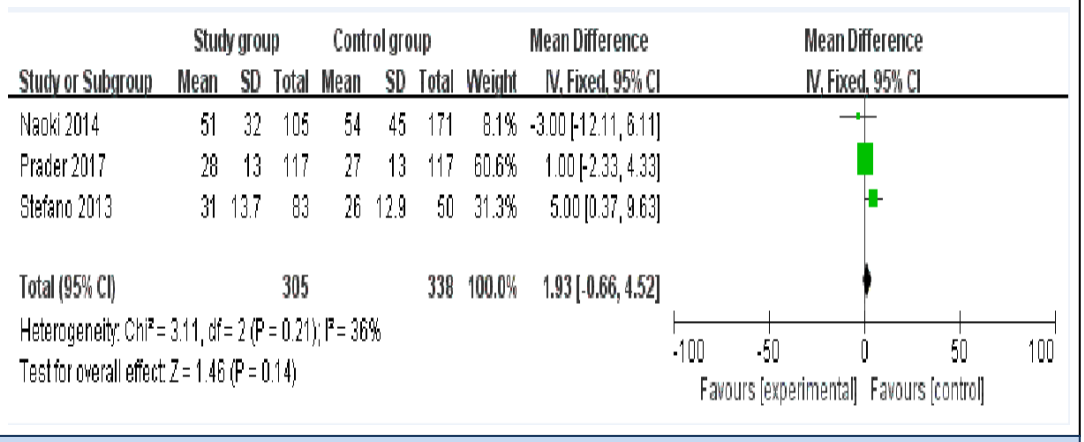

Figure 3: Forest plot comparing operating time.

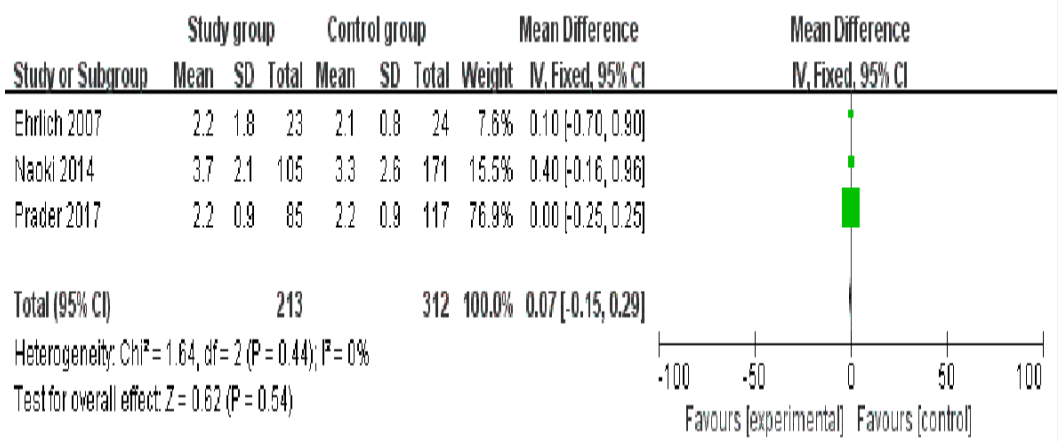

Figure 4: Forest plot comparing median catheter indwelling days after TURBT.

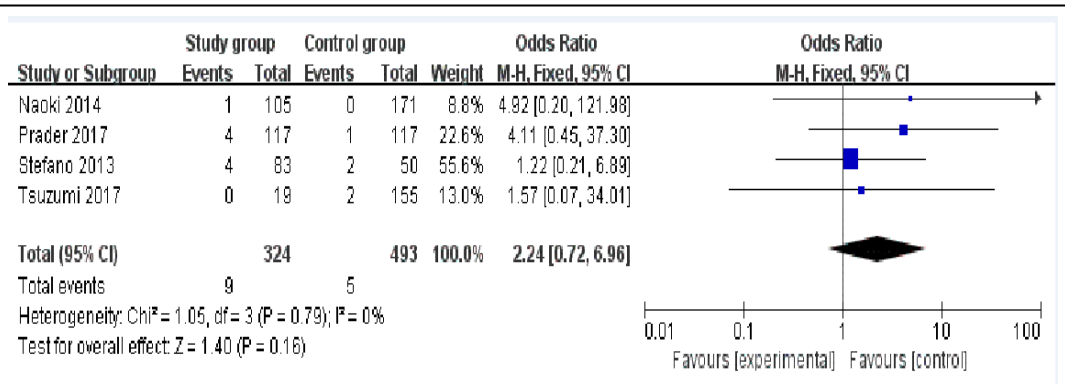

Figure 5: Forest plot comparing blood transfusion.

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All the studies were conducted in the 5 different countries. And they were published between 2007 and 2017, reflecting the debate of whether to continue AP or AC therapy perioperatively in patients receiving TURBT.

The 7 trials reported data on 1487 patients: 658 patients with continued AP or AC therapy during TURBT perioperatively was regarded as the study group. And 829 patients with stopping AP or AC therapy perioperatively during TURBT perioperatively was regarded as the control group, respectively. The time of AP or AC drug withdrawal was ranged from 24 hours to 7 days preoperatively. And all patients began to resume AP or AC drugs one day postoperatively. The base characteristics and quality assessment were summarized on Table 1. We compared the baseline information between two groups. Some continuous data were presented as medians and ranges.

Methodological quality assessment of the included studies

Two authors conducted the quality assessment according to the Jadad scale for one randomized, prospective study and the Newcastle-Ottawa Scale for six retrospective studies. In the modified Newcastle-Ottawa scale, a score of 1–9 stars were allocated. And in the modified Jadad scale, 4 scores were given for only 1 RCT study.

Meta-analysis outcomes

1) The total number of complications

For the analysis of total number of complications, 3 articles [12,14,16] with 458 patients were included. The total complication rate was 15.6 % (33/212) in the study group versus 10.6 % (26/246) in the control group (OR: 1.70; 95 % CI 0.97–2.97; p=0.06) (Figure 2).

2) Operating time

For the analysis of operating time, 3 articles [14-16] with 643 patients were included (WMD, 1.93; 95% CI, -0.66–4.52; P=0.14) (Figure 3).

3) Median catheter indwelling days after TURBT

Catheter indwelling days are regarded as a parameter to reflect urine excretion situation postoperatively. For the analysis of median catheter indwelling days after TURBT, 3 articles [11,14,15] with 525 patients were included(WMD, 0.07; 95%CI, -0.15–0.29; P=0.54) (Figure 4).

4) Blood transfusion

For the analyses blood transfusion, 4 articles [5,14-16] with 717 patients were included. The blood transfusion rate was 2.78 % (9/324) in the study group versus 1.01 % (5/493) in the control group (OR: 2.24; 95 % CI 0.72–6.96; p=0.16) (Figure 5).

5) Cardiovascular events

There are 3 articles [5,11,16] to make mention of the cardiovascular events. Two of them don't occur the cardiovascular events in study group or control group. One article reported two case of the cardiovascular events, one case in study group and another one case in control group.

DISCUSSION

Bladder tumor is one of the most common diseases in urological department, and TURBT is regarded as a diagnostic and therapeutic way [10]. TURBTs are being increasingly performed in the elderly population, many of whom have cardiovascular comorbidities [11]. AP or AC agents are needed in primary and secondary prevention of vascular and coronary artery diseases for patients with cardiovascular comorbidities [14]. The problem is that the surgery cannot be postponed for the patients with cancer who are receiving the antithrombotic treatment at the same time. As a result, it increased the operating risk from both the surgical and the cardiological point of view. The surgical point included increased bleeding, need for transfusions and repeating interventions. The reasons of increased risk of thrombosis of the stent from the cardiological point were not only by suspension of the antiplatelet drugs but also by the operation itself [7].

The management of perioperative AP or AC therapy during TURBT is an important and daily challenge faced by both surgical and anesthesia teams because antithrombotic drugs are commonly used among aging populations [17]. As a result, we conduct a systematic review and meta-analysis to evaluate the safety and efficacy of continued AP or AC therapy perioperatively in patients performing TURBT.

In our meta-analysis for the complications, we found that there was no statistically significant difference between two groups for the total number of complications included 3 articles [12,14,16] with 458 patients (OR: 1.70; 95 % CI 0.97–2.97; p=0.06) (Figure 1). And in the other 4 articles, some common complications such as fever and urinary injury are described.

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However, the number of these complication events is low and has no statistically significant difference. These results indicate that there is no difference between two groups. And the safety of continued AP or AC therapy perioperatively in patients performing TURBT was supported.

One study [5] described that the incidence of clot retention was significantly increased in the continuing group (21%) compared with the discontinuing group (5%). All four patients with aspirin monotherapy resulted in clot retention, however, it didn't occurred in patients taking AC agents or combined AP/AC agents [5]. Luca et al. [18] also reported that there was a high proportion of complications such as clot-related acute urinary retention. And it was mainly caused by bladder overdistension when the urinary catheter was removed early. It is suggested that keeping the catheter in situ for at least 5-7 days after TURBT to prevent distension of the resection bed and the bleeding at this site. For the blood transfusion, we found that there was no statistically significant difference between two groups for blood transfusion rate included 4 articles [5,14-16] with 717 patients (OR: 2.24; 95 % CI 0.72–6.96; p=0.16) (Figure 5). The result indicates that the study group would not need more blood transfusion than control group, which also reflects that the study group won't cause more bleeding when compared with control group.

What's more, there are 3 articles [5,14,15] described the cardiovascular events. In two of these articles, we didn't find the occurrence of the cardiovascular events in study group or control group. One article reported two case of the cardiovascular events, one in study group and another one in control group. As a result, we could indicate that the incidence of cardiovascular events was and similar between two groups. At the same time, the safety of continued AP or AC therapy in patients performing TURBT was confirmed again.

4 articles [5,11,14,15] mentioned perioperative median hemoglobin change. We found that the study groups had a lager perioperative median hemoglobin change than control groups (WMD, 0.21; 95% CI, 0.05–0.37; P=0.01). We may explain it by some aspects. Firstly, there are many reasons for perioperative hemoglobin changes, such as anesthesia and blood volume changes. Secondly, the operation itself can also cause bleeding and make changes in hemoglobin. In the meanwhile, there is also one article in our study reported perioperative median hemoglobin change, but it didn't record the value of MD, and the perioperative median hemoglobin change was the same between the study group (n=19) and the control group (n=137) [5]. Therefore, perioperative median hemoglobin change was uncontrollable and affected by all kinds of reasons. And we can't deny the safety of continued AP or AC therapy in patients performing TURBT because of larger perioperative median hemoglobin change in study group.

For the operating time, 3 articles [14-16] with 643 patients were included. There was no statistically significant difference between two groups in operating time (WMD, 1.93; 95% CI, -0.66–4.52; P=0.14) (Figure 2). One of another 4 articles also reported the operating time, but it didn't record the value of MD, so we didn't include this data in our meta-analysis for operating time. But the conclusion is the same: the operating time is similar and has no statistically significant difference (p>0.05) in this article between the study group and the control group [12]. The operating time has not been affected by whether the patients has the AP/AC treatment or not.

There was no statistically significant difference between two groups in median catheter indwelling days after TURBT (WMD, 0.07; 95%CI, -0.15–0.29; P=0.54) (Figure 3). At the same time, another two articles in our study also recorded the median catheter indwelling days, and the study group had a longer median catheter indwelling days than the control group both in that two articles [5,12]. One reasonable cause may be that leaving the catheter in situ for a longer period can prevent distension of the resection bed. Because they didn't record the value of MD in those two study, we couldn't include this data into our statistically analysis. And it is evident that the difference of median catheter indwelling days is low between two groups. According to the result, we find that continued AP or AC therapy perioperatively in patients performing TURBT won't influence catheter indwelling days. Furthermore, we may speculate that the continued therapy wouldn't affect urine excretion situation postoperatively.

Three articles [5,12,15] had recorded the median days of hospital stay after TURBT, and the data was as follow: 4 vs 3.5, 5 vs5, 2.9 vs 2.5 (days) in the study group and control group. From these data, we found the study group had an

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similar result with the control group. We could surmise that there was no significant difference in the median days of hospital stay after TURBT. The result also shows that there is no statistical difference in postoperative complication rate and postoperative recovery time. It proves the safety and efficacy of continued AP or AC therapy in patients performing TURBT once again.

There are several limitations to our study. First, only one prospective, randomized trial is included in our study and the other 6 trials are retrospective study. Obviously, the retrospective study increases the risk of patient selection bias. And the risk of taking AP or AC agents undergo in TURBT may be underestimated because of the small sample size. Second, there are inevitable differences in the judgment and standards of the authors of these studies, which are conducted in different districts and at different institutions.

In conclusion, through our meta-analysis, there was no statistically significant difference in the total complication, operating time, median catheter indwelling days, blood transfusion, cardiovascular events and the average length of stay between the continuing group compared to the control group. The results of this systematic review and meta-analysis suggest that continued AP or AC therapy perioperatively in patients performing TURBT appears safe and effective.

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Not applicable.

CONFLICTS OF INTEREST

The authors declare that they have no financial interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the Declaration of Helsinki, and the use of data/material only for research purposes. Approval was obtained from the Institutional Ethics Committee from the first affiliated hospital of Chongqing medical university with IRB ID: 2018-003.

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