The Effect of Intravesical Instillation of Antifibrinolytic Agents on Bacillus Calmette-Guerin Treatment of Superficial Bladder Cancer: A Pilot Study

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Purpose: We determined whether intravesical instillation of antifibrinolytic agents could improve the antitumor effect of bacillus Calmette-Guerin. We also investigated the impact of these antifibrinolytic agents on the dose of bacillus Calmette-Guerin required for a therapeutic effect.

Materials and Methods: In this randomized, prospective, double-blind, controlled pilot study 257 patients with superficial bladder cancer were randomized into groups A through E. They received 100 to 120 mg intravesical bacillus Calmette-Guerin plus 100 mg para-aminomethylbenzoic acid, 50 to 60 mg bacillus Calmette-Guerin plus 100 mg para-aminomethylbenzoic acid, 100 to 120 mg bacillus Calmette-Guerin plus 2.0 gm epsilon aminocaproic acid, 50 to 60 mg bacillus Calmette-Guerin plus 2.0 gm epsilon aminocaproic acid and 100 to 120 mg bacillus Calmette-Guerin alone, respectively. Prothrombin time and activated partial thromboplastin time of each patient were determined at 2 hours after instillation, and adverse events were evaluated. Tumor recurrence was assessed every 3 months postoperatively by cystoscopy. Median followup was 26.0, 25.0, 24.5, 25.0 and 25.5 months, respectively.

Results: No significant change in prothrombin time or activated partial thromboplastin time was observed, and analysis showed no significant difference in prothrombin time or activated partial thromboplastin time among groups A through E ($p = 0.693$, 0.756). Recurrence rates at a minimum of median 2 years were 10.6%, 11.1%, 10.0%, 9.3% and 31.8% in groups A through E, respectively. The log rank test showed that recurrence-free probability was statistically different comparing groups A, B, C and D with group E, respectively ($p = 0.023$, 0.037, 0.031 and 0.020), while pairwise comparisons among groups A, B, C and D showed no significant differences (each $p > 0.05$). The rate of serious adverse events in groups A through E was 9.6%, 3.9%, 15.7%, 5.9% and 13.5%, respectively. However, the differences were not significant ($p = 0.222$).

Conclusions: Intravesical instillation of para-aminomethylbenzoic acid or epsilon aminocaproic acid is a more effective and safer method to improve the bacillus Calmette-Guerin antitumor effect, and can reduce the dose of bacillus Calmette-Guerin with the same effect as the full dose.

Key Words: urinary bladder neoplasms, BCG vaccine, antifibrinolytic agents, recurrence, complications

Intravesical bacillus Calmette-Guerin administered as an adjuvant to transurethral bladder tumor resection is the most efficacious treatment to prevent the recurrence and progression of superficial bladder cancer.[1,2] However, the mechanisms remain unclear. Furthermore, 20% to 53% of patients who received intravesical BCG are still at risk for recurrence,[3] and BCG instillations increase the incidence of AEs.[4] Consequently urologists are still seeking to improve the antitumor effect and reduce the rate of AEs.

Hudson et al retrospectively analyzed patients receiving intravesical BCG after TUR of bladder tumors.[5] They found that the response rate to BCG of patients who concomitantly received drugs inhibiting clot formation was significantly lower than that of the patients who did not, and the former recurrence rate was significantly higher than the latter. In contrast, in a murine bladder tumor model they found enhancement of intravesical BCG when EACA (an antifibrinolytic agent) was injected intravenously.[6] Another clinical study also supported these results.[7] However, in a study conducted by Witjes et al the influence induced by fibrin clot inhibitors could not be confirmed.[8]

Although the aforementioned experiment indicated a potential perspective of improving intravesical BCG effect by systemic administration of antifibrinolytic agents, bladder tumor has a predilection for the middle-aged and the elderly people who often have complications with cardiovascular and cerebrovascular diseases. Systemic administration of antifibrinolytic agents will increase the morbidity and mortality of cardiovascular and cerebrovascular accidents and, therefore, local use (intravesical instillation) of these drugs to improve BCG effects and avoid increased risks of coagulation may be a reasonable strategy.

As a basis for the current study we found that intravesical instillation of EACA or PAMBA in rabbits can enhance BCG attachment to the bladder wall while heparin inhibits it.[9] However, the antitumor effect was not studied in this experiment.

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In this randomized, prospective, double-blind, controlled pilot study, we determined whether intravesical instillation of antifibrinolytic agents could improve the antitumor effect of BCG in patients with SBC postoperatively. The impact of antifibrinolytic agents on the effective dose of BCG was also investigated.

PATIENTS AND METHODS

Patient Population

From October 1999 to December 2004, 257 consecutive patients including 180 men and 77 women with SBC (Ta, T1 and CIS) were enrolled in this study at 2 academic institutions (the Department of Urology, Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, and the Department of Urology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China). Median patient age was 58.5 years (range 28 to 80). All study patients were confirmed to have transitional cell carcinoma by histology, represented all tumor grades (G1, G2 and G3) and those without a history of BCG instillations or vaccination, and excluded those with hematological disease or tuberculosis. Of the 257 cases 188 were primary tumor cases and 69 were recurrent tumor cases, and 209 had single tumors and 48 had multiple tumors.

A total of 257 patients underwent TUR of bladder tumor or partial cystectomy and were randomized into 5 groups (A through E) according to a completely random design. Clinical and pathological characteristics are shown in table 1. The majority of patients were in the low to intermediate risk category. The double-blind method was used in this study. The protocol was reviewed and approved by the ethics committee at each hospital. All patients provided written informed consent before entering the trial.

Dose and Treatment Procedures

The first instillation was given 1 week after TUR of bladder tumor or 2 weeks after partial cystectomy. The instillation regimen was administered once weekly for 6 consecutive weeks and then once monthly beginning 6 weeks later, continuing for 2 years. Group A received intravesical instillation of 100 to 120 mg BCG plus 100 mg PAMBA, group B 50 to 60 mg BCG plus 100 mg PAMBA, group C 100 to 120 mg BCG plus 2.0 gm EACA, group D 50 to 60 mg BCG plus 2.0 gm EACA and group E received 100 to 120 mg BCG alone. The drug was retained in the bladder for 2 hours. The BCG (Pasteur's vaccine) was provided by the Shanghai Institute of Biological Products, China, and 50 to 60 mg or 100 to 120 mg BCG powder was dissolved in 30 ml sodium chloride. The PAMBA and EACA were produced by Zhangjiagang Pharmacy Company, China.

Followup

PT (normal laboratory value 11.0 to 15.3 seconds) and APTT (normal laboratory value 31.5 to 43.5 seconds) of each patient were determined 2 hours after completing BCG instillation. The AEs induced by BCG were evaluated by the investigator and those which resulted in discontinuation of BCG instillation were defined as serious AEs in this study. Tumor recurrence was assessed every 3 months postoperatively by cystoscopic inspection and microscopic examination of biopsies taken at the original tumor site, exfoliative cytology as needed.

Statistical Analysis

The chi-square test or Fisher's exact test was used to compare the rates among groups. Descriptive results of continuous variables were expressed as mean ± SE and assessed by 1-way ANOVA. The Kaplan-Meier method was used to calculate time dependent outcomes and differences were assessed with the log rank statistic. Statistical significance in this study was set as $p < = 0.05$. All reported p values are 2-sided. All analyses were performed with SPSS® version 10.0.

RESULTS

Of 257 patients 219 (85.2%) completed all study procedures and 38 (14.8%) withdrew. A total of 25 patients discontinued during early treatment because of serious AEs. In addition, 13 patients were lost during followup including 4 (Ta/G1, T1/G1×2 and T1/G2) in group B, 3 (Tis/G2, Ta/G1 and T1/G1) in group C, 5 (Ta/G1 × 2 and T1/G1 × 3) in group D and 1 patient (Tis/G2) in group E. Median followup for all patients was 25.0 months (range 4 to 66), and median followup for patients in groups A, B, C, D and E was 26.0, 25.0, 24.5, 25.0 and 25.5 months, respectively.

As seen in table 2 the cessation rates were not statistically different among groups A through E (chi-square test $p = 0.493$). The reasons for not completing the study included serious irritative symptoms (14 of 257), fever (greater

TABLE 1. *Distribution of patients and tumor characteristics*

	Group A	Group B	Group C	Group D	Group E	p Value
No. pts	52	51	51	51	52	
No. sex (%):						0.533
Men	40 (76.9)	36 (70.6)	38 (74.5)	32 (62.7)	35 (67.3)	
Women	12 (23.1)	15 (29.4)	13 (25.5)	19 (37.3)	17 (32.7)	
No. T (%):						0.462
Tis	1 (1.9)	3 (5.9)	4 (7.8)	2 (3.9)	6 (11.5)	
Ta	12 (23.1)	9 (17.6)	8 (15.7)	8 (15.7)	13 (25.0)	
T1	39 (75.0)	39 (76.5)	39 (76.5)	41 (80.4)	33 (63.5)	
No. grade (%):						0.986
G1	37 (71.2)	34 (66.7)	36 (70.6)	38 (74.5)	35 (67.3)	
G2	9 (17.3)	9 (17.6)	10 (19.6)	8 (15.7)	11 (21.2)	
G3	6 (11.5)	8 (15.7)	5 (9.8)	5 (9.8)	6 (11.5)	
No. resection (%):						0.689
TUR	42 (80.8)	45 (88.2)	46 (90.2)	43 (84.3)	44 (84.6)	
Partial cystectomy	10 (19.2)	6 (11.8)	5 (9.8)	8 (15.7)	8 (15.4)	