Prophylactic Intravesical Instillation of Epinephrine Prevents Cyclophosphamide-Induced Hemorrhagic Cystitis in Rats

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The objective of this study is to investigate the potential protective effects of intravesical instillation of epinephrine in cyclophosphamide-induced hemorrhagic cystitis. In an earlier study, we have shown that epinephrine promotes hemostasis on established hemorrhagic cystitis induced by cyclophosphamide. Female Sprague-Dawley rats were divided into seven groups as follows: group 1: positive control (150 mg/kg, cyclophosphamide, i.p.), group 2: negative control (10 μg/ml, epinephrine, intravesical), co-administration of cyclophosphamide (150 mg/kg, i.p.), group 3: saline (intravesical), groups 4–6: epinephrine (2.5, 5, and 10 μg/ml, intravesical), and group 7: mesna (50 mg/kg, i.p.). Rats were sacrificed on 3 consecutive days and the urinary bladders were removed, weighed, and evaluated. The vesical vascular permeability was determined by wet bladder weight and Evan's blue dye absorbance. After 24 hours of cyclophosphamide administration, severe hemorrhagic cystitis was induced with marked edema, hemorrhage, and inflammation. In the epinephrine-treated groups, symptoms of hemorrhagic cystitis (such as edema, inflammation, and hemorrhage) were reduced significantly. Intravesical instillation of epinephrine prevents edema, hemorrhage, and inflammation in rats with cyclophosphamide-induced hemorrhagic cystitis. Exp Biol Med 232:565–570, 2007

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Introduction

Cyclophosphamide (CYP) is an oxazaphosphorine alkylating agent widely used in the treatment of malignant and nonmalignant diseases such as lymphoproliferative disorders, nephritic syndrome, rheumatoid arthritis, systemic lupus erythematosis, solid tumors, and bone marrow transplantation (1). Hemorrhagic cystitis (HC) is a common dose-limiting side effect of cyclophosphamide with a reported incidence of 40%–75% and mortality rate of 4% (2). Acrolein, the urotoxic metabolite of cyclophosphamide, has been proposed as the main inducing factor. Direct contact of acrolein to the urothelium results in vesical edema, erosion, hemorrhage, inflammation, and ulceration (3). Earlier prophylactic strategies for CYP-induced HC include superhydration, intravesical instillation of saline, prostaglandins E_1 (4) and $F_{2\alpha}$ (1), and hyperbaric oxygen therapy (5). One of the most promising prophylactic agents is the intravenous and oral administration of 2-mercaptoethane sodium sulphonate (mesna) (6). Unfortunately, in mesna-treated patients, a considerable number of HC have been reported. Researchers are now looking for more effective agents of CYP prevention. Recent studies showed that decreased nitric oxide production by antioxidants such as alpha-tocopherol (7), melatonin (7), taurine (8), quercetin, and catechine (9) attenuated CYP-induced HC. Other potential prophylactics against the toxicity of CYP include amifostine (10), keratinocyte growth factor (11), and dexamethasone (12).

Recent works in our laboratory have shown that the

intravesical instillation of epinephrine attenuated established CYP-induced HC significantly (13). Although successful as a therapeutic agent against CYP-induced HC, the protective effect of epinephrine (EPI) has not been examined. In severe cases of hemorrhagic cystitis refractory to mesna or other prophylactics, we hypothesize that the intravesical administration of epinephrine may provide an alternative means of prevention against the toxicity of cyclophosphamide. The objective of this study is to investigate the protective effects of intravesical instillation of epinephrine on CYP-induced HC.

Materials and Methods

Animals. The Animal Care Committee of the Mackay Memorial Hospital approved this study. Female Sprague-Dawley rats (250–350 g) were maintained in a 12:12-hr light:dark cycle with free access to water and food.

Drugs. Cyclophosphamide, epinephrine, mesna, and Evan's blue dye were obtained from Sigma (St. Louis, MO).

Hemorrhagic Cystitis Model. Sprague-Dawley rats were intraperitoneally injected with 150 mg/kg cyclophosphamide according to the methods described by Botta *et al*. (14). Hemorrhagic cystitis was established 24 hours later. The animals were sacrificed and the bladders were removed and evaluated for gross and histological changes.

Epinephrine Instillation Model. Epinephrine (0.1%) solution was diluted with normal saline to concentrations of 2.5 (1:400,000), 5 (1:200,000), or 10 (1:100,000) μg/ml. After anesthesia, a PE-10 catheter was inserted into the urethra for bladder evacuation of residual urine and drug administration. The intravesical solutions were retained until the animals voided spontaneously.

Experimental Protocol. The animals were divided into 7 groups of 15 rats each. On Day 0, group 1 (CYP; positive control) animals were given an intraperitoneal injection of CYP (150 mg/kg), while group 2 (EPI; negative control) animals received a 0.5 ml bolus of epinephrine (10 μg/ml) intravesically. Rats in groups 3 to 7 underwent intraperitoneal CYP (150 mg/kg) on Day 0. On the same day, groups 3 to 6 were concomitantly given a 0.5 ml intravesical bolus of saline (vehicle), or epinephrine, 2.5, 5, or 10 μg/ml, respectively; group 7 received a concomitant intraperitoneal injection of mesna, 50 mg/kg.

Gross Evaluation. Five rats per group were sacrificed for 3 consecutive days (Days 1, 2, and 3). All the bladder specimens were removed at the bladder neck by an urologist (Y.C.C.) and reviewed by a designated pathologist (C.Y.T.), blinded to the study groups. Using the criteria described by Gray *et al*. (4), gross and histologic changes in the bladder were evaluated with half grades allowed in crossover from mild to severe groups. The gross appearance of the bladders was graded by a bladder damage score: Gross edema: 3—severe (fluid within and external to bladder wall); 2—moderate (fluid confined to internal mucosa); 1—mild (between moderate and normal); 0—none (normal). Gross hemorrhage: 3—severe (intravesical clots); 2—moderate (mucosal hematomas); 1—mild (telangiectasia or dilatation of bladder vessels); 0—none (normal).

Histologic Evaluation. The bladders were excised, embedded in paraffin, and stained with hematoxylin and eosin. A pathologist reviewed each histologic section using the following scoring system: 0—normal (normal epithelium, no inflammatory cell infiltrate or ulcers); 1—mild (diminished epithelial cells, flattening with submucosal edema, mild hemorrhage, few ulcerations); 2—moderate (mucosal erosion, inflammatory cell infiltrate, fibrin deposition, hemorrhage, and multiple ulcerations); 3—severe (mucosal erosion, inflammatory cell infiltrate, fibrin deposition, multiple ulcerations, and transmural hemorrhage with severe edema).

Measurement of Vesical Edema. Vesical vascular edema was quantified by wet bladder weight (WBW) and Evan's blue extravasation (EBE) using different sets of animals. On Day 0, the animals underwent treatment as described above in the experimental protocol. On the following day (Day 1), five animals in each group were sacrificed to examine vesical vascular permeability. Evan's blue dye (25 mg/kg) was injected into the right femoral vein 1 hour before sacrifice. The bladders were dissected, placed in glass tubes containing 1.5 ml of formamide and incubated at 56°C overnight. The optical density of the extracted dye absorbance was measured at 600 nm on a spectrophotometer and expressed as mean ± SEM Evan's blue/g of the body weight (15). Wet bladder weights (mg) were reported as mean ± SEM tissue/100 gm animal weight (16).

Statistical Analysis. The results were expressed as mean ± SEM or as median values (macroscopic and histologic scores). Statistical significance ($P < 0.05$) was assessed by one-way analysis of variance (ANOVA). For morphologic data, statistical evaluation was performed by Kruskal-Wallis non-parametric analysis of variance followed by the Mann-Whitney U-test.

Results

Control Animals. Grossly, all the bladders in the control group showed severe distention, edema, and hemorrhage with a damage score 3 within 24 hours after cyclophosphamide administration.

Gross Evaluations. The damage score of edema and hemorrhage in the positive control (CYP) group was significantly higher than the score of 0 in the negative control (EPI) group. In groups 4 to 6 administered with epinephrine, there was a dose-dependent reduction of gross hemorrhage and edema. Mesna showed better outcome in the prevention of edema than 10 μg/ml epinephrine, while epinephrine yielded a greater hemostatic effect than mesna. Compared to the negative control (EPI) group, both the 10 μg/ml epinephrine and mesna groups showed equivalent attenuation of CYP toxicity (Table 1).

Vesical Vascular Edema. In the negative control

Table 1. Bladder Damage Scores of Gross Edema, Gross Hemorrhage, and Histologic Evaluation[a]

Groups (range)[b]	Time interval	CYP[c]	EPI[d]	NS[e]	2.5 Epi[f]	5 Epi [f]	10 Epi[f]	MES[g]
Gross edema	Day 1	3	0 (0–0.5)*	3 (2.5–3)	1.5 (1–2)*	1.5 (1–1.5)*	1 (1–1.5)*	1 (1–1.5)*
	Day 2	3 (2.5–3)	0 (0–0.5)*	2.5 (2.5–3)	1.5 (0–2)*	1 (0–1)*	0.5 (0–1)*	0.5 (0–0.5)*
	Day 3	3 (2.5–3)	0 (0–0.5)*	3 (2.5–3)	0.5 (0–1.5)*	1 (0.5–1)*	1 (0.5–1)*	0 (0–0.5)*
Gross hemorrhage	Day 1	3 (2.5–3)	0 (0–0.5)*	3 (2.5–3)	1.5 (−2)*	1 (0–1.5)*	0.5 (0–1)*	1 (1–1.5)*
	Day 2	3 (2.5–3)	0*	3 (2.5–3)	1 (1–1.5)*	0.5 (0–1)*	1 (0–1)*	0 (0–0.5)*
	Day 3	3	0 (0–0.5)*	3 (2.5–3)	1.5 (1–2)*	1*	0.5 (0–1)*	0.5 (0–1)*
Histology	Day 1	3 (2.5–3)	0*	3 (2.5–3)	2 (1.5–2)*	1.5 (1–1.5)*	1 (0.5–1)*	1 (0–1)*
	Day 2	3	0 (0–0.5)*	3 (2.5–3)	1.5 (1–1.5)*	1*	0.5 (0–1)*	1 (0–1)*
	Day 3	3 (2.5–3)	0*	3 (2.5–3)	1 (0–1)*	1*	0.5 (0–0.5)*	0*

[a] See Materials and Methods for an explanation of scoring method.
[b] Values represent median (range) of the results in 5 animals sacrificed over 3 consecutive days.
[c] CYP, cyclophosphamide.
[d] EPI, epinephrine-treated group.
[e] NS, normal saline.
[f] Epi, μg/ml epinephrine.
[g] MES, mesna-treated group.
* Significantly different from positive control, cyclophosphamide (CYP) group ($P < 0.05$).

(EPI) group, the WBW was 43.1 mg/100 g body weight and the EBE was 1.2 g/body weight. Compared to the EPI group, the positive control (CYP) and vehicle-treated groups had significant increases in WBW (128% and 122%, respectively) and EBE (1138% and 1148%, respectively). The 2.5, 5, and 10 μg/ml epinephrine-treated and mesna-treated groups exhibited smaller increases in WBW (38%, 23%, 8%, and 2%, respectively) and EBE (340%, 143%, 5% and 3% respectively). In the groups treated with epinephrine and mesna, all showed significantly better results than the positive control (CYP) group (Fig. 1A and B).

Histologic Evaluations. Histologic analysis demonstrated that epinephrine produced dose-dependent attenuation of HC (Fig. 2). Compared to the score of 3 in the vehicle (NS) and positive control (CYP) groups, the scores of the 2.5, 5, and 10 μg/ml epinephrine-treated and mesna-treated groups decreased significantly (Table 1).

Discussion

In a recent study, the therapeutic effect of intravesical instillation of epinephrine surpassed mesna in the attenuation of established CYP-induced HC (13), however the protective effect of intravesical instillation of epinephrine on CYP-induced HC has not been investigated. In this study using different sets of animals and protocol, the hemostatic effect of prophylactic epinephrine was statistically significant when compared to the positive control, CYP group. Epinephrine not only induces hemostasis on established hemorrhage, but also prevents and protects the bladder from CYP-hemorrhagic cystitis.

As mentioned earlier, in many patients undergoing cyclophosphamide therapy, hemorrhagic cystitis persists despite prophylactic measures of mesna. The clinical relevance of this study is that in cases of recurrent hematuria induced by cyclophosphamide toxicity intractable to current forms of hemostasis and prevention, our method provides the clinician with an additional treatment option. In our medical center, we successfully controlled intractable bleeding induced by radiation cystitis in over 20 patients suffering from cervical, bladder, and colon cancer by intravesical instillation of epinephrine.[1] Hence, further studies on the effect of epinephrine on dilemmas such as interstitial cystitis or other forms of hemorrhagic cystitis should also be warranted.

Epinephrine (adrenaline), a catecholamine originating from the adrenal medulla, acts as a vasopressor and vasoconstrictor used in various conditions such as shock, hypotension, arrhythmia, congestive heart failure, local hemostasis, nasal decongestant, asthma, and allergy. Epinephrine has been used successfully for hemostasis in many clinical applications such as gastrointestinal surgery, proctology, radiology, orthopedic surgery, endodontic surgery, and plastic surgery. Vaeusorn *et al*. injected epinephrine into the renal artery and rapidly controlled an intractable post-biopsy renal bleeding (17). From our earlier works, we postulated that the hemostatic effect of intravesical epinephrine is the result of vasoconstriction induced by α_1-adrenergic stimulation. Adrenergic receptors are divided into two types, α (α_1 and α_2) and β (β_1, β_2, and β_3); in the vascular smooth muscle, only α_1, α_2, and β_2 adrenoceptors are found. The α_1 postsynaptic adrenoreceptors are found in smooth muscles in the body, genitourinary system and blood vessels near sympathetic nerves. Located on the presynaptic nerve terminals, the α_2 adrenoreceptors respond to circulating catecholamines. Under the stimulation of epinephrine, α_1 and α_2 adrenoceptors induce smooth muscle vasoconstriction by increasing the intracellular calcium concentration, whereas β_2 adrenoceptors cause vasodilatation (18).

[1]Chow Y-C, Hsu J-M, Lin W-C, Chang H-K, Yang Y-C, Yang S. Intravesical instillation of epinephrine in patients with intractable hemorrhagic cystitis. Unpublished study. 2007.

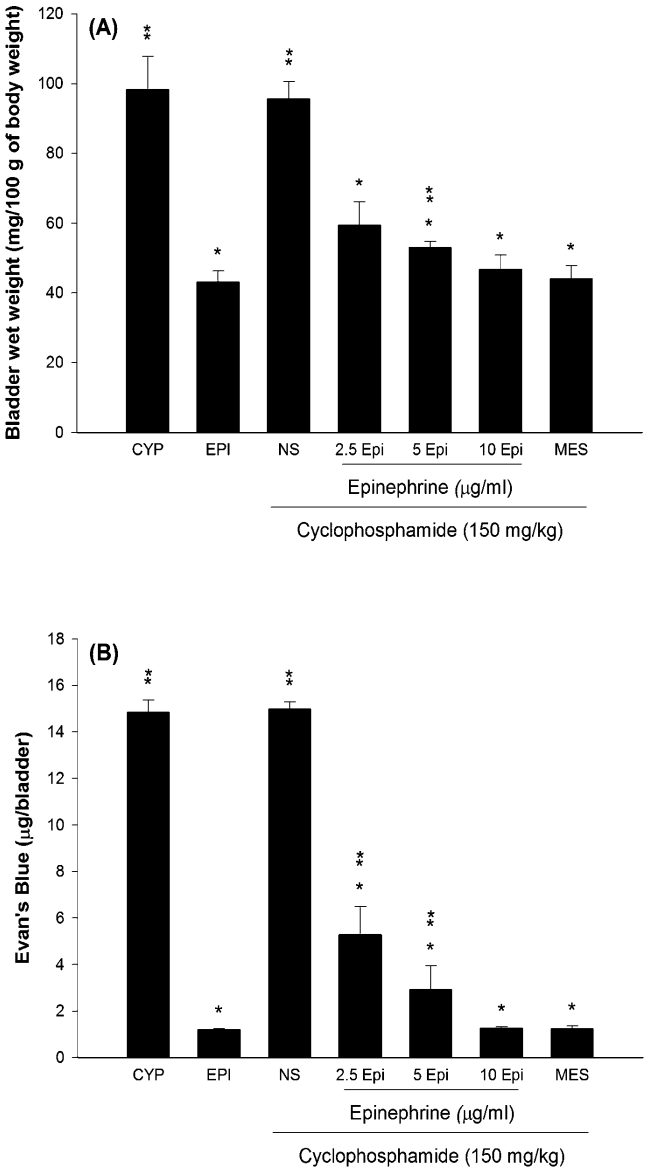

Figure 1. (A) Wet bladder weight (mg; mean ± SEM tissue/100 g animal weight). (B) Evan's blue dye (g; mean ± SEM Evan's blue/g of the body weight). CYP, cyclophosphamide (positive control); EPI, epinephrine (negative control); NS, normal saline (vehicle); 2.5, 5, 10 Epi, 2.5, 5, 10 μg/ml epinephrine, respectively; MES, Mesna. Each bar is the mean ± SEM of 5 animals. Vertical bars represent standard errors of the means. * Significantly different from CYP or positive controls with $P < 0.05$. ** Significantly different compared with EPI or negative control with $P < 0.05$.

In another ongoing preliminary study[2] using similar procedures as previously described (150 mg/kg cyclophosphamide, intraperitoneal injection), α_1-adrenergic agonist, L-phenylephrine (0.1–1 mg/kg), and α_2-adrenergic agonist, clonidine (0.1–1 mg/kg) induced hemostasis in CYP-induced HC. Severe urine retention and blood clots were noted under high (10–100 mg/kg) doses of both agents, presumably due to their actions on the bladder neck and smooth muscles. Under low doses (0.001 mg/kg), both phenylephrine and clonidine showed poor hemostasis. Alpha-adrenergic antagonists were used to block the vasoconstrictive effects of epinephrine. Concomitant use of epinephrine (10 μg/ml) and high doses of prazosin (50 mg/kg, α_1-adrenergic blocker) and also yohimbine (100 mg/kg, α_2-adrenergic blocker) yielded severe hemorrhage and edema. However, lowered concentrations (0.01–1 mg/kg) of prazosin and clonidine were unable to block the vasoconstriction and hemostasis produced by epinephrine. Interestingly, relatively low doses of phenoxybenzamine (1 mg/kg, mixed α-adrenergic blocker) were required to inhibit the hemostatic effects of epinephrine. Since this is only a preliminary study on the actions of epinephrine, we think that the vasoconstrictive effects of epinephrine are the result of synergistic actions on both α_1 and α_2 adrenergic receptors; however, more extensive studies should be conducted in the near future to determine the exact mechanism.

In this study, significant gross and microscopic edema reduction and prevention of CYP-induced HC was observed in epinephrine-treated rats. Quantified measurements of edema using the wet bladder weight and Evan's Blue dye extravasation further demonstrated that epinephrine-treated groups contained significantly less fluid contents when compared with the positive control (CYP) groups. Rey and coworkers studied the effects of vasoconstriction induced by epinephrine in rats for skin flap hematoma (19). Contrary to most beliefs, hematoma was not observed after the initial vasoconstrictive effect waned, indicating that the reflex vasodilatation had minimal impact on the flap. The death rates of the rats declined significantly after combining epinephrine with lidocaine. The authors proposed that epinephrine slowed the systemic absorption of lidocaine, a highly toxic substance for rats. In this study, we postulated that epinephrine not only induced vasoconstriction but also slowed acrolein absorption in the bladder resulting in reduced tissue edema, hemorrhage, inflammation, and ulceration.

Since the acrolein contact with the urothelium requires no vascular support to induce cystitis, other effects of epinephrine other than vasoconstriction are postulated. One plausible explanation might be the decrease of inflammation and ulceration involving deep layers of the bladder wall. Hence other important functions of catecholamine stimulation of α- and β-adrenergic receptors might provide us with some insight. These functions include enhanced platelet-neutrophil adhesion and platelet aggregation, decreased neutrophil adherence, chemotaxis, and phagocytic activity. Epinephrine also affects cytokine regulation, such as inhibition of tumor necrosis factor and interleukin (IL)-1, activation of IL-8 and IL-10 production, and enhancement of L-selectin (monocytes) and P-selectin (platelets) expressions (20). Recent studies showed that cytokines such as NO are also released in CYP-induced cystitis (21). During inflammatory states, lipopolysaccharides activate monocytes resulting in the production of interleukin-8 (IL-8), a member

[2]Chow Y-C, Yang S, Huang C-J, Wang T-Y, Su Y-H, Wang P-S. Unpublished study. 2006.

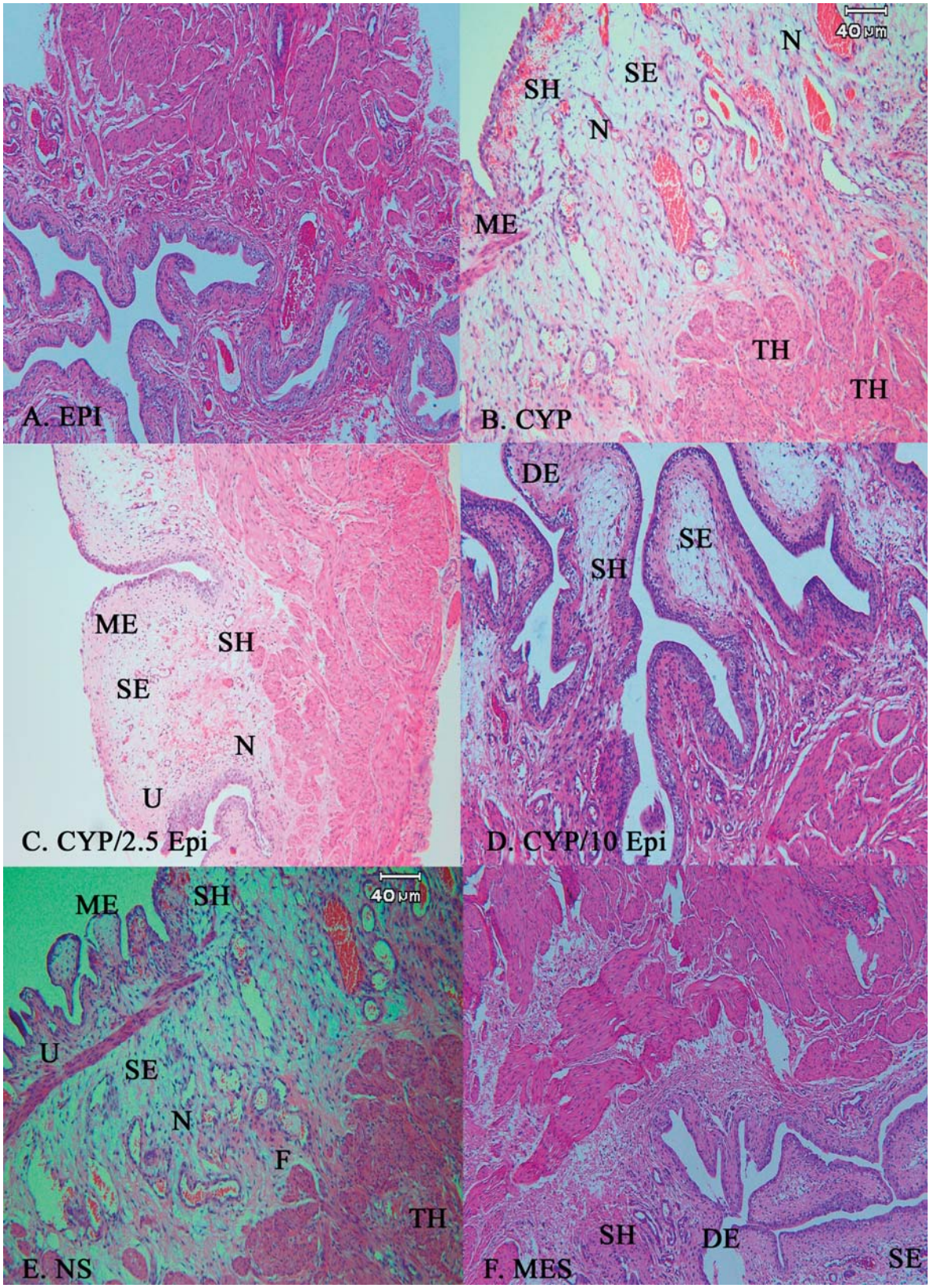

Figure 2. Histological analysis of representative bladder walls in cross-section. (A) EPI (epinephrine or negative control group): Score of 0 with absence of edema, hemorrhage, or inflammation. H&E, ×100. (B) CYP (cyclophosphamide or positive control group): severe hemorrhagic cystitis with a score of 3 for severe edema, transmural hemorrhage, mucosal ulceration, and neutrophil infiltration. H&E, ×100. (C) 2.5 Epi: 2.5 μg/ml epinephrine group, score of 2 for mucosal erosion, submucosal edema, and hemorrhage and ulcerations. H&E, ×100. (D) 10 Epi: 10 μg/ml epinephrine group, score of 1 with mild submucosal edema, minimal hemorrhage, few diminished epithelial cells, and no inflammation. H&E, ×100. (E) NS: normal saline or vehicle group, score of 3 with severe edema, transmural hemorrhage, mucosal erosion, multiple ulcerations, fibrin deposition, and neutrophil infiltration. H&E, ×100. F MES: mesna group, score of 0–1 with diminished epithelial cells, submucosal edema, and hemorrhage. H&E, ×100 (SE: submucosal edema; SH: submucosal hemorrhage; TH: transmural hemorrhage; N: neutrophil infiltration; F: fibrin deposition; U: ulceration; ME: mucosal erosion; DE: diminished epithelial cells).

of CXC chemokines. IL-8 attracts inflammatory cells to areas of infections (22). Loll and Lowry showed that epinephrine upregulates the LPS-induced IL-8 production by beta-adrenergic receptors. In their study, the effects of epinephrine on IL-8 production were blocked after using propranolol, a beta-adrenergic antagonist. However, they stressed that the effects of epinephrine on cytokines are not solely based on beta-adrenergics (23). The stimulatory effect of epinephrine on IL-8 production does not reflect or support the anti-inflammatory effects of epinephrine, but shows one of the many actions of epinephrine with cytokines.

In our study, histologic evaluations demonstrated that epinephrine reduced neutrophil infiltration. The inhibition of inflammatory cells was also postulated through actions mediated by α_2-adrenoceptors. Nordling *et al*. discovered that the severity of urethral inflammation in female rats was suppressed by high doses (100 μg/day) and enhanced by low doses (10μg/day) of epinephrine. Low-dose epinephrine increases sympathetic post-ganglionic neurotransmission mediated by β_2-adrenoceptors, whereas high-dose epinephrine inhibits sympathetic neurotransmission and inflammation through the α_2-adrenoceptors (24). From these points, we can logically deduce that the temporary and transient vasoconstrictor effects of epinephrine are local actions on alpha-adrenergic receptors in the bladder as shown in day 1 results. Long-term (day 3) results and more systemic actions may involve the anti-inflammatory effects of epinephrine in inducing cytokine release or synthesis or blocking these cytokines from arriving to their targets. Intravesical instillation of epinephrine can effectively promote protection against vesical edema, inflammation, and hemorrhage induced by cyclophosphamide in rats.

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1. Levine LA, Jarrard DF. Treatment of cyclophosphamide-induced hemorrhagic cystitis with intravesical carboprost tromethamine. J Urol 149:719–723, 1993.
2. Levine LA, Richie JP. Urological complications of cyclophosphamide. J Urol 141:1063–1069, 1989.
3. Cox PJ. Cyclophosphamide cystitis—identification of acrolein as the causative agent. Biochem Pharmacol 28:2045–2049, 1979.
4. Gray KJ, Engelmann UH, Johnson EH, Fishman IJ. Evaluation of misoprostol cytoprotection of the bladder with cyclophosphamide (Cytoxan) therapy. J Urol 136:497–500, 1986.
5. Shameem IA, Shimabukuro T, Shirataki S, Yamamoto N, Maekawa T, Naito K. Hyperbaric oxygen therapy for control of intractable cyclophosphamide-induced hemorrhagic cystitis. Eur Urol 22:263–264, 1992.
6. Hows JM, Mehta A, Ward L, Woods K, Perez R, Gordon MY, Gordon-Smith EC. Comparison of mesna with forced diuresis to prevent cyclophosphamide induced haemorrhagic cystitis in marrow transplantation: a prospective randomised study. Br J Cancer 50:753–756, 1984.
7. Yildirim I, Korkmaz A, Oter S, Ozcan A, Oztas E. Contribution of antioxidants to preventive effect of mesna in cyclophosphamide-induced hemorrhagic cystitis in rats. Cancer Chemother Pharmacol 54: 469–473, 2004.
8. Abd-Allah AR, Gado AM, Al-Majed AA, Al-Yahya AA, Al-Shabanah OA. Protective effect of taurine against cyclophosphamide-induced urinary bladder toxicity in rats. Clin Exp Pharmacol Physiol 32:167–172, 2005.
9. Ozcan A, Korkmaz A, Oter S, Coskun O. Contribution of flavonoid antioxidants to the preventive effect of mesna in cyclophosphamide-induced cystitis in rats. Arch Toxicol 79:461–465, 2005.
10. Srivastava A, Nair SC, Srivastava VM, Balamurugan AN, Jeyaseelan L, Chandy M, Gunasekaran S. Evaluation of uroprotective efficacy of amifostine against cyclophosphamide induced hemorrhagic cystitis. Bone Marrow Transplant 23:463–467, 1999.
11. Ulich TR, Whitcomb L, Tang W, O'Conner Tressel P, Tarpley J, Yi ES, Lacey D. Keratinocyte growth factor ameliorates cyclophosphamide-induced ulcerative hemorrhagic cystitis. Cancer Res 57:472–475, 1997.
12. Vieira MM, Brito GA, Belarmino-Filho JN, Macedo FY, Nery EA, Cunha FQ, Ribeiro RA. Use of dexamethasone with mesna for the prevention of ifosfamide-induced hemorrhagic cystitis. Int J Urol 10: 595–602, 2003.
13. Chow YC, Yang S, Huang CJ, Tzen CY, Huang PL, Su YH, Wang PS. Epinephrine promotes hemostasis in rats with cyclophosphamide-induced hemorrhagic cystitis. Urology 67:636–641, 2006.
14. Botta JA, Jr., Nelson LW, Weikel JH, Jr. Acetylcysteine in the prevention of cyclophosphamide-induced cystitis in rats. J Natl Cancer Inst 51:1051–1058, 1973.
15. Gomes TN, Santos CC, Souza-Filho MV, Cunha FQ, Ribeiro RA. Participation of TNF-alpha and IL-1 in the pathogenesis of cyclophosphamide-induced hemorrhagic cystitis. Braz J Med Biol Res 28: 1103–1108, 1995.
16. Philips FS, Sternberg SS, Cronin AP, Vidal PM. Cyclophosphamide and urinary bladder toxicity. Cancer Res 21:1577–1589, 1961.
17. Vaeusorn N, Viranuvatti J, Singchoovong L. Post-biopsy haematuria successfully treated by selective transcatheter epinephrine injection. Br J Radiol 54:425–426, 1981.
18. Sinnott CJ, Cogswell IL, Johnson A, Strichartz GR. On the mechanism by which epinephrine potentiates lidocaine's peripheral nerve block. Anesthesiology 98:181–188, 2003.
19. Rey RM, Jr., Smoot EC, III, Nguyen D, Lesavoy MA. A study of the effects of epinephrine infiltration on delayed bleeding in a rat flap model. Ann Plast Surg 37:406–410, 1996.
20. Horn NA, Anastase DM, Hecker KE, Baumert JH, Robitzsch T, Rossaint R. Epinephrine enhances platelet-neutrophil adhesion in whole blood in vitro. Anesth Analg 100:520–526, 2005.
21. Xu X, Cubeddu LX, Malave A. Expression of inducible nitric oxide synthase in primary culture of rat bladder smooth muscle cells by plasma from cyclophosphamide-treated rats. Eur J Pharmacol 416:1–9, 2001.
22. Kikuchi T, Hagiwara K, Honda Y, Gomi K, Kobayashi T, Takahashi H, Tokue Y, Watanabe A, Nukiwa T. Clarithromycin suppresses lipopolysaccharide-induced interleukin-8 production by human monocytes through AP-1 and NF-kappa B transcription factors. J Antimicrob Chemother 49:745–755, 2002.
23. van der Poll T, Lowry SF. Lipopolysaccharide-induced interleukin 8 production by human whole blood is enhanced by epinephrine and inhibited by hydrocortisone. Infect Immun 65:2378–2381, 1997.
24. Nordling L, Lundeberg T, Liedberg H, Theodorsson E, Ekman P. The contribution of epinephrine to experimentally induced urethral inflammation in the rat. Neurosci Lett 139:169–172, 1992.