USE OF CYCLOOXYGENASE-2 INHIBITOR FOR PREVENTION OF URETHRAL STRICTURES SECONDARY TO TRANSURETHRAL RESECTION OF THE PROSTATE

ALESSANDRO SCIARRA, STEFANO SALCICCIA, LUCA ALBANESI, ANTONIO CARDI,
GIUSEPPE D'ERAMO, AND FRANCO DI SILVERIO

ABSTRACT

Objectives. To analyze whether the addition of a cyclooxygenase (COX)-2 inhibitor after transurethral resection of the prostate (TURP) offers an advantage compared with TURP alone in reducing postoperative urethral strictures. At urethroscopy, stenosis of the urethra with a circumference of less than 19 mm was defined as stricture.

Methods. This was a prospective, unblinded, randomized, single-center study. Between December 2001 and December 2003, 96 consecutive men with benign prostatic hyperplasia underwent TURP. After TURP, patients were randomly assigned to receive or not receive a COX-2 inhibitor (rofecoxib 25 mg/day). In the group given the COX-2 inhibitor, the therapy was started at catheter removal and continued for 20 days. Follow-up was performed on an outpatient basis after 1 month. A diagnosis of postoperative urethral stricture was assessed during a follow-up of 12 months.

Results. At the 1-month visit, the mean and median improvement in the peak urinary flow rate from preoperative values was $+6.25 \pm 3.76$ mL/s (median 7.30) in the no COX-2 inhibitor group and $+9.42 \pm 3.06$ mL/s (median 8.75) in the COX-2 inhibitor group. The improvement was significantly ($P < 0.0001$) greater for the group treated with the COX-2 inhibitor. At 1 year of follow-up, a urethral stricture had been diagnosed in 8.3% of all cases; in particular, in 17% and 0% of cases in the no COX inhibitor group and COX-2 inhibitor group, respectively. Post-TURP COX-2 inhibitor therapy was significantly ($P = 0.0039$) and inversely ($r = -0.2876$) associated with urethral stricture development.

Conclusions. We suggest that limited postoperative treatment with a COX-2 inhibitor can effectively prevent post-TURP urethral stricture development by specifically interfering with the inflammatory processes that can precede scar formation. UROLOGY **66:** 1218–1222, 2005. © 2005 Elsevier Inc.

Generally, transurethral resection of the prostate (TURP) for benign prostatic hyperplasia (BPH) is a highly successful operation with low morbidity and low mortality. More than 90% of the patients claim their voiding is normal or improved after TURP.[1] The occurrence of urethral strictures after TURP is well recognized and has been reported as one of the major complications. The incidence of post-TURP urethral stricture varies between 4% and 29%.[1–3] Urethral instrumentation

during the operative procedure or the presence of a transurethral catheter in the postoperative period and/or a combination of these factors are the most plausible causes.[2] Several invasive measures have been introduced to prevent stricture formation, including preoperative urethral dilation,[4] internal urethrotomy,[5] and instillation of steroid ointment in the urethra immediately postoperatively.[6]

Cyclooxygenase-2 (COX-2) is a pro-inflammatory and inducible enzyme that can be induced in different cell types.[7] Several studies have demonstrated the expression of COX-2 mRNA in human prostatic tissue.[8,9] COX-2 was expressed in epithelial cells with 60% BPH and 94% peripheral zone of the prostate.[10,11] The mechanisms through which COX-2 may play a role in the prostate gland are multiple. Some of these mechanisms are likely to result from a COX-2-induced increase in prosta-

glandin synthesis.[9] Moreover, COX-2 has been shown to upregulate bcl-2 expression with an associated decrease in apoptosis in prostatic tissue.[11]

The aim of this study was to analyze whether the combination of a COX-2 inhibitor after TURP procedure offers an advantage compared with TURP alone in improving postoperative flow rates and reducing the incidence of postoperative urethral strictures.

The rationale of combining a COX-2 inhibitor with TURP is that by adding an anti-inflammatory effect with a specific target on prostatic tissue in the short term, urinary flow rates may improve more and urethral strictures may be better prevented.

In particular, we analyzed differences in the short-term urinary flow rate improvement between those treated with TURP alone and those treated with TURP combined with postoperative COX-2 inhibitor; differences in the long-term incidence of urethral strictures between the two groups (TURP alone versus TURP plus COX-2 inhibitor); and associations in the incidence of urethral stricture and age, prostate volume, urinary flow rate, operative time, postoperative catheterization, and use of COX-2 inhibitor therapy.

MATERIAL AND METHODS

This was a prospective, unblinded, randomized, single-center study. Between December 2001 and December 2003, 96 consecutive men with BPH who were on the waiting list for TURP were considered for inclusion in the study. All patients provided written informed consent. Men with a history of uncontrolled hypertension, congestive heart failure, unstable angina, cerebrovascular accident, bleeding diathesis, or sensitivity to COX-2 inhibitors were excluded. Moreover, none of the included patients had a history of recurrent urinary tract infection, urethral stricture, or indwelling catheter. All patients underwent TURP performed by a single surgeon (A.S.), and the diagnosis of BPH was histologically confirmed. None of the patients had a preoperative stricture at the urethral cystoscopic examination performed during TURP.

EQUIPMENT AND TECHNIQUE

TURP was performed with a standard loop using 145 W for the cutting current and 60 W for coagulation. TURP was performed under continuous mannitol irrigation and spinal anesthesia. At the end of the procedure, a 20F, three-way silicone Foley catheter with irrigation was placed in the bladder, homogeneously in all cases. Postoperative irrigation was discontinued when the bleeding had stopped.

RANDOMIZATION

After TURP, patients were randomly assigned to receive or not receive rofecoxib 25 mg/day. In the group given the COX-2 inhibitor, the therapy was started at catheter removal and continued for 20 days.

CLINICAL EVALUATION

The preoperative prostate volume was measured at transrectal ultrasonography using the ellipsoid method. Urinary flow was assessed using the Dantec Urodyn 1000 rotating uroflowmeter. Standard laboratory testing and International Pros-

TABLE I. *Patient characteristics*

Characteristic	COX-2 Inhibitor After TURP		P Value*
	No	Yes	
Baseline			
Patients (n)	48	48	
Age (yr)	66.47 ± 3.40, 67.0, 57.0–75.0	66.14 ± 3.76, 65.51, 57.0–74.0	0.6521
Prostate volume (cm³)	59.92 ± 9.53, 60.0, 43.0–75.0	59.45 ± 8.39, 60.0, 43.0–80.0	0.7985
Qmax (mL/s)	11.03 ± 1.84, 10.60, 7.40–14.70	11.11 ± 2.68, 11.50, 4.0–15.70	0.8713
Operative time (min)	46.86 ± 6.63, 50.0, 30.0–60.0	47.50 ± 6.91, 45.0, 30.0–60.0	0.8357
Catheterization after TURP (days)	3.27 ± 0.56, 3.0, 2.0–4.0	3.12 ± 0.53, 3.0, 2.0–4.0	0.2424
Follow-up			
Qmax at 1 mo	17.20 ± 4.17, 18.40, 7.40–27.50	20.56 ± 3.58, 19.55, 15.40–29.50	<0.0001
Qmax improvement (preoperative to 1 month) (mL/s)	+6.25 ± 3.76, 7.30, −2.20 to +17.10	+9.42 ± 3.06, 8.75, +4.10 to +17.80	<0.0001
Urethral stricture (%)	8 (17.0)	0 (0)	<0.0001

KEY: COX = cyclooxygenase; TURP = transurethral resection of prostate; Qmax = maximal urinary flow rate.
Data presented as mean ± SD, median, and range, unless otherwise noted.
* Student's t test.

TABLE II. *Characteristics of urethral strictures*

Stricture Cases Total (n)	8
Site (n)	
Bladder neck	3
Bulbar	4
Submeatal	1
Interval from TURP (mo)	
Mean ± SD	1.75 ± 0.88
Median	1.50
Range	1.0–3.0

TABLE III. *Association between urethral stricture development and other clinical parameters*

Association	r*	P-Value
Urethral stricture and age	0.0561	0.5813
Urethral stricture and prostate volume	0.1181	0.2441
Urethral stricture and preoperative Qmax	−0.1675	0.1011
Urethral stricture and operative time	0.0060	0.9527
Urethral stricture and postoperative catheterization	0.1331	0.0902
Urethral stricture and analise of COX-2 inhibitor	−0.2876	0.0039

Abbreviations as in Table I.
* Spearman's correlation coefficient.

tate Symptom Score determination were also performed. The follow-up examinations were started 1 month after surgery on an outpatient basis. The presence of postoperative urethral stricture was assessed during a 12-month follow-up period (1, 2, 3, 6, 9, and 12-month visits). During follow-up, patients with a maximal urinary flow rate (Qmax) of less than 15 mL/s (a cutoff of less than 15 mL/s was chosen on the basis of previous reports[1,2]) underwent urethroscopy to confirm the diagnosis. As in previous studies,[1,2] at urethroscopy, stenosis of the urethra with a circumference of less than 19 mm was defined as stricture.

STATISTICAL ANALYSIS

Descriptive statistics were used to characterize the variables in the population and in each treatment group (mean ± SD, median, and range). Mean changes adjusted for baseline are presented and were tested using the Student *t* test and Wilcoxon signed-rank test. Pair-wise treatment comparisons were made. Associations between the incidence of urethral stricture and the other clinical parameters were assessed by Spearman coefficients. All statistical tests were two-tailed, with a 5% level of significance for treatment effects.

RESULTS

A total of 96 men who underwent TURP by a single surgeon (A.S.) were entered into the study and were randomized to treatment. The baseline characteristics of this population were not significantly different statistically between the two treatments groups (Table I). In contrast, at the 1-month visit, the mean and median Qmax and Qmax improvement were significantly ($P <0.0001$) greater in the group treated with the COX-2 inhibitor (Table I).

During 1 year of follow-up, a urethral stricture was diagnosed in 8.3% of all patients; in particular, in 17% and 0% of patients, respectively, in the no COX-2 inhibitor group and the COX-2 inhibitor group. The characteristics of the urethral strictures are summarized in Table II. The development of a post-TURP urethral stricture was not significantly associated with the preoperative prostate volume ($P = 0.1181$), Qmax ($P = 0.1011$), operative time ($P = 0.9527$), or time of catheterization after TURP ($P = 0.0902$). In contrast, post-TURP COX-2 inhibitor therapy was significantly ($P = 0.0039$) and inversely ($r = -0.2876$) associated with urethral stricture development (Table III).

Treatment with the COX-2 inhibitor was gener-

ally well tolerated. None of the patients discontinued the treatment, and no serious adverse events were reported.

COMMENT

The incidence of urethral stricture after TURP has been the subject of much discussion. Attempts to reduce the stricture incidence have included several invasive methods such as preoperative urethrotomy.[5] Many urologists believe the size of the sheath and movement of the sheath during surgery are the main causes of stricture formation.[3] Hart and Fowler[3] underlined that, in their experience, no correlation with stricture formation was found concerning the size of the operating sheath, size and material of the catheter, and the presence of an infected urine or a positive urethral swab. In contrast, Hammarsten *et al.*[2] showed that the choice of urethral catheter plays a more important role than other factors during the operative procedure. Some investigators[2,12] presented a hypothesis concerning the etiology of stricture formation after TURP, stating that the initial damage is a mucosal lesion that leads to a leakage of urine and causes inflammation and scar formation. Trauma to the urethra is undoubtedly a significant factor. On re-instrumentation of the urethra several days after resection, isolated erythematous areas in the urethral mucosa can be visualized.[1] Nielsen and Nordling[1] also underlined the role of urine extravasation into the subepithelial space causing increased inflammation and subsequent scar formation. This process may be progressive, with urethral stenosis from edema and subsequent stricture formation causing increased intramural voiding pressure, which leads to further leakage across the mucosal barrier. Myofibroblasts are probably responsible for the formation of the stricture, and giant cells may be involved in continued collagen synthesis.

Steroids have been used in the treatment of urethral strictures,[1,6] administered either systemically or by local injection into the stricture.[13]

All these aspects represent the basis and rationale for our study. We specifically tested the role of a COX-2 inhibitor to prevent (not treat) the development of post-TURP urethral strictures. Our purpose was to add a COX-2 inhibitor postoperatively after TURP to add an anti-inflammatory effect that can prevent the process that is conducive to scar formation.

A COX-2 inhibitor was chosen because of several points: greater expression of COX-2 mRNA in human BPH tissue; COX-2 activity in prostaglandin production; and COX-2 activity in modulating inflammation in the microenvironment around cells.[14–16] Moreover, some investigators[17,18] have shown that, in mice, COX-2 expression at the bladder and urethral level is stimulated by outlet obstruction.

The baseline characteristics and extension of our population are comparable to those reported in previous experiences.[2,3] In particular, to reduce the differences at baseline between the two randomization groups, all patients were homogeneously treated by a single surgeon using a standard TURP technique, and the surgical instrumentation and type and size of postoperative catheter were similar for all cases included.

Patients were prospectively evaluated and randomized to receive or not receive a COX-2 inhibitor. The lack of blinding and lack of a placebo in this study may have allowed for a bias in the interpretation of the results. However, the objective definition of stricture at the urethroscopic assessment and the determination of an objective parameter, such as the uroflow rate, to decide who should undergo urethroscopy, limited the influence of the surgeon's interpretation on our results. The use of a flow rate cutoff of less than 15 mL/s may be not highly sensitive in revealing strictures in all cases. However, it has been already used in published reports,[1,2] and no other parameters (eg, the International Prostate Symptom Score) have demonstrated greater sensitivity.

Our hypothesis was to use a COX-2 inhibitor as preventive medicine against stricture development. For this reason, treatment with the COX-2 inhibitor was limited to the first 20 days after TURP. We followed up patients after TURP for 12 months. As described in previous reports,[1] all strictures developed within 6 months postoperatively. The stricture site was mainly in the bladder neck and bulbar urethra. The percentage (8.3%) of strictures reported in our population is within the range described in published studies.[1,2] In our study, the difference in the stricture incidence between the two randomized groups suggests a preventive effect of COX-2 inhibitor therapy on the development of post-TURP strictures. Moreover, COX-2 inhibitor treatment also produced greater improvement in Qmax at the 1-month visit ($P < 0.0001$; Qmax improvement 9.42 ± 3.06 versus 6.25 ± 3.76 mL/s, respectively, in the COX-2 inhibitor and no COX-2 inhibitor groups). It is possible that the specific anti-inflammatory activity of the COX-2 inhibitor can also improve post-TURP results in terms of short-term uroflow parameters.

The development of urethral stricture was not related to patient age, prostate volume, operative time, or postoperative catheterization time. The only factor that influenced stricture development negatively was COX-2 inhibitor therapy.

On September 30th, 2004, rofecoxib was recalled worldwide, halting sales of the drug. However, the effect described in this study could be referred to the entire class of COX-2 inhibitors (ie, celecoxib, etoricoxib), but additional studies are needed to verify our hypothesis.

CONCLUSIONS

On the basis of the results of our randomized analysis, we suggest that limited postoperative treatment with a COX-2 inhibitor can effectively prevent post-TURP urethral stricture development, specifically by interfering with the inflammatory processes that can precede scar formation. This treatment may represent a noninvasive method to reduce the incidence of postoperative urethral stricture. We emphasize that any conclusions regarding the usefulness of this therapy should only be drawn from larger, controlled clinical trials.

REFERENCES

1. Nielsen KK, and Nordling J: Urethral stricture following transurethral prostatectomy. Urology 34: 18–24, 1990.
2. Hammarsten J, Lindqvist K, and Sunzel H: Urethral strictures following transurethral resection of the prostate: the role of the catheter. BJU Int 63: 397–400, 1989.
3. Hart AJL, and Fowler JW: Incidence of urethral stricture after transurethral resection of prostate. Urology 18: 588–591, 1981.
4. Lentz HC, Mebust WK, Foret JD, et al: Urethral strictures following transurethral prostatectomy: review of 2223 resections. J Urol 117: 194–201, 1977.
5. Bailey MJ, and Shearer RJ: The role of internal urethrotomy in the prevention of urethral stricture following transurethral resection of the prostate. BJU Int 51: 28–34, 1979.
6. Roll WA, and Waller JI: The prevention of postoperative urethral stricture. J Urol 81: 289–295, 1959.
7. Hla T, Bishop D, Liu CH, et al: Cyclooxygenase 1 and 2 isoenzymes. Int J Biochem Cell Biol 31: 551–557, 1999.
8. O'Neill GP, and Ford AW: Expression of mRNA for cyclooxygenase 1 and 2 in human tissues. FEBS Lett 330: 156–160, 1993.
9. Hussain T, Gupta S, and Mukhtar H: Cyclooxygenase 2 and prostate carcinogenesis. Cancer Lett 191: 125–135, 2003.

10. Kirschenbaum A, Klaisner AP, Lee R, *et al:* Expression of cyclooxygenase 1 and 2 in the human prostate. Urology **56:** 671–676, 2000.

11. Tsujii M, and DuBois RN: Alterations in cellular adhesion and apoptosis in epithelial cells overexpressing prostaglandin endoperoxide synthase 2. Cell **83:** 493–501, 1995.

12. Lentz HC, Mebust WK, and Foret JD: Urethral strictures following transurethral prostatectomy. J Urol **117:** 194–197, 1977.

13. Sharpe JR, and Finney RP: Urethral strictures: treatment with intralesional steroids. J Urol **116:** 440–448, 1976.

14. Di Silverio F, Bosman C, Monti S, *et al:* Combination therapy with rofecoxib and finasteride in the treatment of men with LUTS and BPH. Eur Urol **47:** 72–79, 2005.

15. Tsuji S, Tsujii M, Kawano S, *et al:* Cyclooxygenase 2 upregulation as a perigenetic change in carcinogenesis. J Exp Clin Cancer Res **20:** 117–129, 2001.

16. Zha S, Gage WR, Sauvageot J, *et al:* Cyclooxygenase 2 is up-regulated in proliferative inflammatory atrophy of the prostate, but not in prostate carcinoma. Cancer Res **61:** 8617–8623, 2001.

17. Park JM, Yang T, Arend LJ, *et al:* Cyclo-oxygenase-2 is expressed in bladder during fetal development and stimulated by outlet obstruction. Am J Physiol **273**(4 Pt 2): 538–544, 1997.

18. Luo C, Strauss L, Ristimaki A, *et al:* Constant expression of cyclooxygenase 2 gene in prostate and the lower urinary tract of estrogen-treated male rats. Z Naturforsch **56:** 455–463, 2001.