

ETHANOL INJECTION THERAPY OF THE PROSTATE FOR BENIGN PROSTATIC HYPERPLASIA: PRELIMINARY REPORT ON APPLICATION OF A NEW TECHNIQUE

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ABSTRACT

Purpose: We evaluate the efficacy of a new technique of minimally invasive treatment for benign prostatic hyperplasia involving direct injection of dehydrated ethanol.

Materials and Methods: Dehydrated ethanol was injected transurethraly with lumbar or sacral and urethral anesthesia in 10 patients with prostatic hyperplasia. Endoscopic injection was performed at 4 to 8 sites in the prostate and 3.5 to 12.0 ml. ethanol were used.

Results: There were no intraoperative complications but postoperative urinary retention occurred transiently in all patients which required catheterization for a mean of 8.8 days. Mean symptom score plus or minus standard deviation was 12.2 ± 5.8 at 3 months postoperatively, which was significantly improved from 23.1 ± 7.0 preoperatively ($p < 0.01$). Mean quality of life score also improved significantly from 5.1 ± 0.6 preoperatively to 3.2 ± 1.5 at 3 months postoperatively ($p < 0.01$), mean peak urinary flow rate increased from 8.0 ± 2.2 (9 patients) to 13.1 ± 3.6 ml. per second ($p < 0.05$) and mean residual urine volume decreased from 129.1 ± 55.3 (9 patients) to 49.3 ± 34.7 ml. ($p < 0.05$). There was no significant change in prostate volume. Acute epididymitis and chronic prostatitis occurred in 1 patient each.

Conclusions: This technique can be performed as an outpatient procedure and appears to be safe and cost-effective. Retrograde ejaculation can be avoided.

KEY WORDS: alcohol, ethyl; prostatic hyperplasia; injections

In recent years various methods of minimally invasive surgery have been developed for treatment of benign prostatic hyperplasia (BPH).¹⁻⁴ The ideal method would be effective and without complications when performed on an ambulatory basis. It is important to avoid retrograde ejaculation and to preserve sexual function in sexually active patients. Ethanol injection therapy has previously been used for liver^{5,6} and parathyroid tumors.^{7,8} We report our experience with transurethral injection of dehydrated ethanol in the prostate with local anesthesia in patients with BPH.

MATERIALS AND METHODS

Ethanol injection therapy of the prostate with lumbar or sacral and urethral anesthesia was performed between November 1997 and April 1998 in 10 patients with BPH who gave informed consent. Using an endoscopic injection set and multipurpose continuous flow cystoscope, 0.5 to 2.0 ml. dehydrated ethanol per site were injected transurethraly at 4 to 8 sites in the right and left lobes. Injection was done at 2 (3 and 9 o'clock positions) or 4 (2, 4, 8 and 10 o'clock) sites for patients with mild to moderate BPH. When there was relatively severe BPH as indicated by elongation of the posterior urethra, injection was also done at sites near the bladder neck and seminal colliculus. Injection was done at 1 to 2 sites in the middle lobe for patients with middle lobe hyperplasia. To prevent retrograde ejaculation ethanol was not injected into the bladder neck in patients who wished to preserve sexual function. A urethral balloon catheter was inserted after completion of the procedure. Removal of the catheter on the following day was tried initially but urinary retention occurred in 2 patients, and so it was subsequently done after about 1 week.

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Evaluation to assess operative outcome in all cases included 2 prostate symptom scores, peak urinary flow rate and residual urine volume before, and 1 and 3 months postoperatively, and estimated prostate volume before and 3 months postoperatively. The American Urological Association symptom score (maximum 35 points)⁹ was used to assess urinary symptoms, and quality of life was evaluated using the International Prostate Symptom Score (maximum 6 points).¹⁰ Patient impression of ethanol injection therapy was also evaluated 3 months postoperatively. In response to the question "Are you satisfied with the operation?" patients were asked to choose "satisfied," "equivocal" or "dissatisfied." Prostate volume was measured with ultrasonography.¹¹ The statistical significance of differences was examined with the Wilcoxon signed rank test.

RESULTS

Clinical data are presented in table 1. Mean patient age was 68.8 ± 6.7 years (range 62 to 81). An old cerebral infarction was noted in 2 patients, 1 had undergone surgery for a thoracoabdominal aortic aneurysm, 1 had undergone aortic coronary bypass surgery and was being treated with ticlopidine hydrochloride and aspirin, and 1 had the myelodysplastic syndrome with a history of surgery for chronic subdural hematoma. One patient with a cerebral infarction had a residual left hemiparesis and was on warfarin therapy, and 1 had only mild paresis of the left hand. A hypotonic bladder was also noted in 1 of these patients.

Intraoperative finds are shown in table 1. The procedure was done with sacral plus urethral anesthesia in 7 patients and urethral anesthesia alone in 1. Lumbar anesthesia was used for our first patient and 1 who also underwent transurethral resection of a bladder tumor. Since ethanol injection

TABLE 1. Clinical profile and intraoperative data

Pt. — Age No. (yrs.)	Preop. Complications (anticoagulant therapy)	Prostate Vol. (ml.)	Anesthesia	Injection Site	(No.)	Total Ethanol Dose (ml.)	Hospital Stay (days)	Duration Urethral Catheterization (days)
1 — 75	Cerebral infarction due to atrial fibrillation (warfarin)	41.0	Lumbar	Middle, rt. + lt. lobes	(6)	8.5	4	3
2 — 62		63.1	Sacral + urethral	Rt. + lt. lobes	(8)	12.0	2	8
3 — 76		39.6	Sacral + urethral	Rt. + lt. lobes	(4)	6.0	0	15
4 — 72	Surgery for thoracoabdominal aortic aneurysm	49.2	Sacral + urethral	Rt. + lt. lobes	(4)	6.5	0	8
5 — 66		52.0	Sacral + urethral	Rt. + lt. lobes	(4)	4.0	1	7
6 — 66	Bladder tumor (recurrent) + cerebral infarction (ticlopidine)	71.6	Lumbar	Rt. + lt. lobes	(6)	6.0	5	7
7 — 81	Aortic coronary bypass grafting (ticlopidine, aspirin)	57.3	Sacral + urethral	Rt. + lt. lobes	(4)	4.0	0	7
8 — 63	Osteomyelodysplasia syndrome, surgery for chronic subdural hematoma	50.7	Urethral	Rt. + lt. lobes	(4)	4.0	1	22
9 — 62		33.6	Sacral + urethral	Middle, rt. + lt. lobes	(4)	3.5	1	6
10 — 65		49.0	Sacral + urethral	Rt. + lt. lobes	(4)	5.0	1	5

therapy did not seem to cause severe intraoperative or postoperative pain, we subsequently changed to a less invasive method of anesthesia.

Mean estimated prostate volume was 50.7 ± 11.3 ml. (range 33.6 to 71.6) before ethanol injection therapy. Mean total volume of ethanol injected was 6.0 ± 2.6 ml. (range 3.5 to 12.0), mean volume injected per site was 1.2 ml. and the total ethanol volume per patient accounted for 7.0 to 20.7% of the prostatic volume. There were no changes in blood pressure or pulse rate, or symptoms of alcohol toxicity in any patient during the procedure. Minor bleeding occurred in most patients without a significant decrease in hematocrit. However, due to bleeding from the injection sites in 2 patients it was necessary to perform retraction and continuous irrigation of the bladder briefly using a urethral balloon catheter. The endoscopic appearance before and during ethanol injection therapy is shown in figure 1. Postoperative pain caused by ethanol injection and the indwelling urethral catheter could be controlled with simple analgesics. The urethral balloon catheter was removed after 3 to 22 days (mean 8.8 ± 5.6).

The plasma ethanol concentration was evaluated after injection at 30, 60 and 120 minutes in patient 2; at 15, 30, 60 and 120 in patient 3; at 15 and 60 in patient 5; at 15, 30 and 120 in patient 9; and immediately, and at 30 and 60 in patient 10. No ethanol was detected in these patients. The first 2 patients were hospitalized for 4 and 2 days, respectively, to monitor the postoperative course. Subsequently 4 patients were hospitalized for 1 day and 3 underwent treatment on an ambulatory basis, excluding the patient who also underwent bladder tumor resection.

Results of the preoperative and postoperative assessments are shown in table 2. The symptom and quality of life scores were not significantly altered postoperatively at 1 month but were significantly improved at 3 months compared to baseline values ($p < 0.01$). The peak urinary flow rate and residual urine volume were evaluated in 9 patients, excluding the patient with urinary retention preoperatively. The peak urinary flow rate showed no significant change postoperatively at 1 month but was increased significantly at 3 ($p < 0.05$). The residual urine volume was significantly decreased postoperatively at 1 ($p < 0.05$) and 3 ($p < 0.05$) months. No significant change in prostate volume was evident before and 3 months after the procedure.

Postoperative infection consisted of acute epididymitis in 1 patient and chronic prostatitis in 1. Pyuria persisted in the latter patient for a long period, and the pain was considered to be caused by tissue degeneration associated with ethanol injection and bacterial prostatitis. Retropubic prostatectomy was performed after 6 months in patient 2. Histological ex-

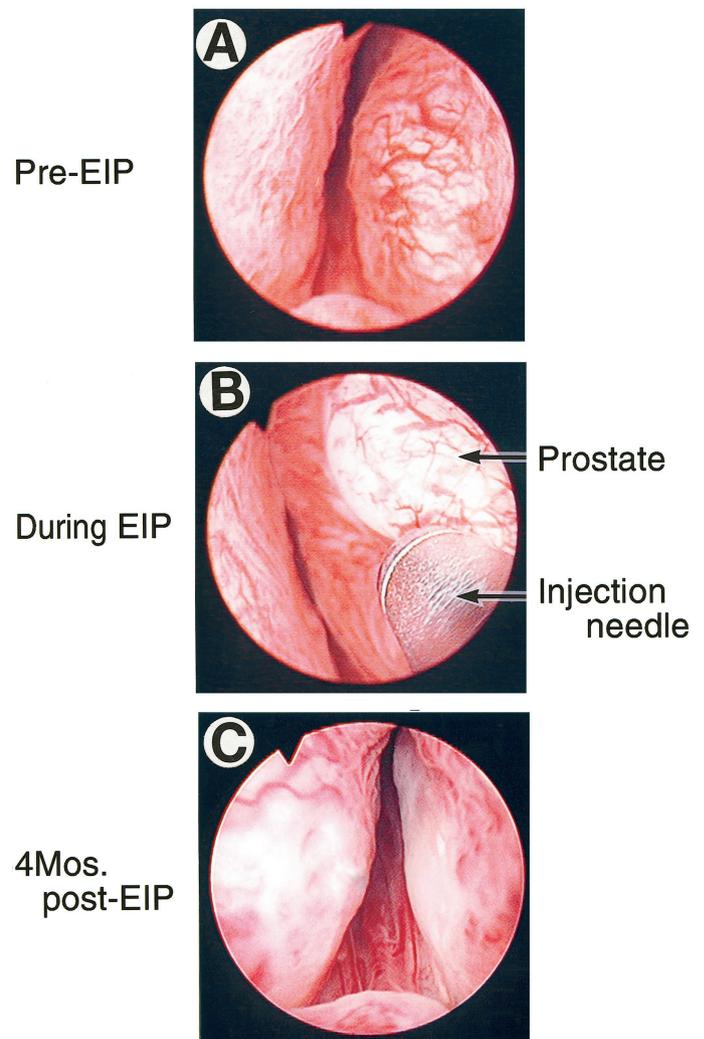


FIG. 1. Endoscopic findings in patient 3. A, before ethanol injection therapy of prostate (EIP). B, during injection. C, prostate has decreased in size around injection sites 4 months postoperatively and white suggests scarring. Protrusion of prostate into urethra is reduced.

amination of the resected prostate revealed severe tissue damage, including coagulative necrosis, hyalinization and scarring (fig. 2, A), and glandular atrophy was seen around the directly involved area (fig. 2, B). No patient had urinary incontinence or urethral stenosis. Antegrade ejaculation was

TABLE 2. Results of preoperative and postoperative assessments

	No. Pts.	Mean \pm SD			
		Preop.	1 Mo. Postop.	3 Mos. Postop. (p value*)	
Symptom score	10	23.1 \pm 7.0	17.9 \pm 8.4	12.2 \pm 5.8	(<0.01)
Quality of life score	10	5.1 \pm 0.6	4.1 \pm 1.2	3.2 \pm 1.5	(<0.01)
Peak flow rate (ml./sec.)	9	8.0 \pm 2.2	11.5 \pm 4.2	13.1 \pm 3.6	(<0.05)
Residual urine (ml.)	9	129.1 \pm 55.3	75.9 \pm 31.9	49.3 \pm 34.7	(<0.05)
Prostate vol. (ml.)	10	50.7 \pm 11.3		48.6 \pm 12.6 (not significant)	

* Significance before versus 3 months after ethanol injection therapy of the prostate.

confirmed postoperatively in all 6 patients with sexual function preoperatively, including patient 2 who eventually underwent prostatectomy, although he had ejaculatory pain. Of the patients 8 were satisfied, 1 dissatisfied and 1 equivocal postoperatively.

DISCUSSION

Various new approaches have been developed for the treatment of BPH and, considering the likely increase in BPH incidence with the aging of society, an effective form of minimally invasive therapy is needed.¹⁻⁴ Ethanol injection therapy has already been performed in a limited number of patients with small hepatic and abdominal tumors^{5,6} or secondary hyperparathyroidism,^{7,8} and has been confirmed to produce tumor regression. Pure ethanol causes coagulative necrosis of tissue through dehydration and its fixative effect. Fujimoto injected pure ethanol into normal, cirrhotic and carcinomatous rat livers, and confirmed a rapid cytotoxic action.⁶ Clinically he observed the angiographic disappearance of tumor stains in 14 of 16 patients (88%) with liver tumors less than 3 cm. in diameter treated with injection of pure ethanol. Complete necrosis of the carcinoma was observed in 2 of 4 patients who subsequently underwent tumor resection. He also reported that 11 of 12 patients followed remained disease-free more than 1 year after percutaneous ethanol injection therapy.

Based on such findings we hypothesized that ethanol could be used to produce tissue necrosis and atrophy in the prostate, which is also a glandular and stromal structure, and we tried prostatic injection of dehydrated ethanol in dogs. Coagulative necrosis with inflammation was observed histologically 1 week after ethanol injection, and fibrosis and scarring with ductal atrophy were seen after 6 months. Since this treatment seemed to be safe and effective in dogs, we performed the present clinical study.

Transurethral ethanol injection therapy was done with sacral and urethral anesthesia on an ambulatory basis. The treatment caused little bleeding in most patients and there were no hemodynamic changes. However, bleeding from the ethanol injection site may be a problem. If massive bleeding occurs, a ball electrode may be useful for pinpoint coagulation. In patients on anticoagulant therapy it would seem necessary to suspend medication before ethanol injection therapy.

We evaluated the blood ethanol level in 5 cases but detected none. Therefore, ethanol injection therapy may be feasible even in an ethanol intolerant patient if monitored closely. Postoperative urinary retention occurred in all patients and the urethral catheter could be removed after 3 to 22 days (mean duration 8.8). Urination improved gradually from weeks 2 to 4 after ethanol injection therapy and improved significantly after 3 months compared to preoperative data.

Epididymitis occurred postoperatively in 1 patient who had been catheterized for a long period preoperatively. In patient 6 white coating was observed on the urethral mucosa endoscopically after 3 months, suggesting that necrosis of the urethral mucosa had been caused by ethanol injection. Accordingly, injection should be performed deep enough inside the prostate to avoid damage to the urethral mucosa. In addition, care should be taken to avoid postoperative urinary tract infection. Antegrade ejaculation was maintained in all patients who had normal ejaculatory function preoperatively. It was considered possible to prevent retrograde ejaculation by avoiding injection near the bladder neck.

The optimum method of ethanol injection therapy still remains to be established. We injected ethanol at 1 or 2 sites in the right and left lobes of the prostate as well as at proximal and distal sites if there was elongation of the posterior urethra. Middle lobe hyperplasia seems to respond well to ethanol injection therapy. Although none of our patients had urinary incontinence, it is necessary to avoid injection of ethanol into the external urethral sphincter. In patient 2, 12.0 ml. ethanol were injected into the prostate, which was estimated to have a volume of 63.1 ml., and chronic prostatic pain developed postoperatively, which may have been partly due to prostatitis. The relatively large dose of ethanol also may have been a factor.

With reference to the procedures already established for hepatoma and parathyroid tumors, 0.5 to 2.0 ml. ethanol were initially injected per site.⁵⁻⁸ In our series the total volume of ethanol injected eventually ranged from 7.0 to 20.7% of the prostate volume. The results obtained with high doses were not always favorable. When extensive tissue degeneration occurred, severe symptoms were caused by local irritation and improvement in voiding was delayed in some patients. After performing a detailed evaluation in individual patients, it was determined that the volume of ethanol

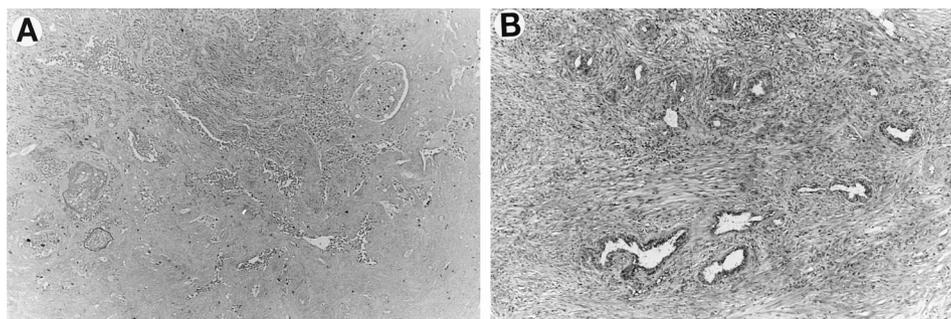


FIG. 2. Histological findings of prostate in patient 2 at 6 months postoperatively. A, severe tissue damage. B, glandular atrophy. H & E, reduced from $\times 20$.

injected did not necessarily correlate with the prostate volume.

Using prostate glands obtained during total prostatectomy in patients with prostatic cancer, we infused 0.5 and 1.0 ml. ethanol mixed with indigo carmine to perform a preliminary study of the distribution of ethanol in prostatic tissue. In general, the tissue volume infiltrated was about twice that of the ethanol infused, although the volume of distribution seemed to depend on the histological composition of the prostate. Ethanol should be infused at a dose that will affect tissues as far as the transitional zone. From 7 to 15% of the prostate volume should be selected for ethanol treatment, and the total dose of ethanol should not exceed 10 ml. If it is necessary to infuse a larger volume, the dose should be divided into portions and administered in 2 or 3 sessions. Another study needs to be performed to find the optimum dose of ethanol and to determine whether ethanol injection therapy is best completed at a single session or is more effective when repeated. In the present series ethanol was injected transurethrally under endoscopic vision. However, we are considering transperineal injection under transrectal ultrasonographic guidance as a less invasive alternative.

The mechanism underlying the effect of ethanol injection therapy is unknown but vascular damage induced by ethanol may cause tissue necrosis and a decrease in prostate volume. However, no significant decrease in prostate volume occurred after 1 session of ethanol injection therapy. Another possible mechanism is that α 1-receptors may be destroyed by ethanol, thus decreasing the tone of the prostatic urethra. The long-term outcome of this therapy also needs to be determined by following a larger series of patients. However, since ethanol injection therapy of the prostate is minimally invasive, maintains ejaculatory function and improves urinary symptoms, it seems to be a potentially useful technique for treatment of BPH.

CONCLUSIONS

There was significant improvement of the symptom and quality of life scores, peak urinary flow rate and residual urine volume 3 months after ethanol injection therapy of the prostate, although the decrease in prostate volume was not significant. Since this technique seems to have few complications and can be done as an outpatient procedure, it has the potential to become a useful and highly cost-effective treatment for BPH.

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