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Intraprostatic Ethanol Injection in the Treatment of Lower Urinary Tract Symptoms Associated with Benign Prostatic Hyperplasia: A Safer and Less Invasive Alternative?

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Abstract

Gold standard surgical therapies for Benign Prostatic Hyperplasia (BPH) are invasive and associated with complications and long-term side effects. The need for the development of safer and less invasive alternatives has been recognized and, as a result, significant progress has been made in recent years in the development of minimally invasive treatment options for male lower urinary symptoms associated with BPH. Intraprostatic injection has been evaluated as a potential minimally invasive treatment for BPH. Four agents have been tested during the past two decades. Absolute Anhydrous Ethanol (EtOH) has been tested most extensively in both preclinical and clinical studies, however, a randomized controlled trial has not been published to date and EtOH use as a BPH treatment has been abandoned by many due to rare, but serious complications involving extraprostatic tissue damage caused by EtOH. This review summarizes preclinical and clinical studies published to date and presents outcomes of research aimed at improving the safety and efficacy of intraprostatic EtOH injection.

Keywords: Ethanol; Intraprostatic injection; Prostate disease

Introduction

When pharmacotherapy fails, and general anesthesia is not an option due to co-morbidities, intraprostatic injection therapy can be a viable, alternative treatment for male patients suffering from Lower Urinary Tract Symptoms (LUTS) associated with Benign Prostatic Hyperplasia (BPH). Four agents have been tested for use as intraprostatic injection therapies – absolute ethanol, botulinum toxin, NX1207 and PRX302. In phase III randomized controlled trials, both botulinum toxin and NX1207 showed no improvements when compared to placebo [1]. Intraprostatic injection of PRX302 – proaerolysin activated by prostatic-specific antigen – showed significant improvements in both LUTS and peak flow rate in a phase IIb double blind study involving 92 patients, published in 2013 [2,3]. The results of the phase III randomized placebo controlled study are not yet available.

Absolute anhydrous (>95%) ethanol (EtOH) has been widely studied for in situ tissue ablation. Currently, a percutaneous injection of EtOH is considered the standard of care for intralesional treatment of hepatocellular carcinomas and parathyroid adenomas [4-6]. In urology, EtOH injection is being used in sclerotherapy of renal cysts [7] and has been investigated for renal angioinfarction

and subtrigonal injection for the treatment of detrusor instability [8-12].

Mechanism of action

Intraparenchymal injection of EtOH causes coagulative necrosis with protein denaturation and cell membrane lysis. We have investigated the effects of intraprostatic injection of EtOH in preclinical studies on canines. Two hours following injection, these experiments showed well-delineated tissue lesions, characterized histologically by complete cellular ablation, cell membrane lysis, loss of normal acinar architecture, and vascular occlusion. Seven days post-injection, hemorrhagic and coagulative necrosis surrounded by both acute and chronic inflammation was documented, with evidence of demarcation and sloughing of the necrotic tissue [13]. Four weeks post EtOH injection formation of cysts lined by epithelium was noted. The volume of cysts was proportionate to the volume of EtOH injected. The cysts were surrounded by fibroblasts, a varying amount of collagen, and sparse macrophages. The fibrotic area was regular, and, to a high degree, it followed the couture of the cyst. In some instances, the necrotic tissue surrounded by a fibrotic capsule was identified. (Unpublished data) Twelve weeks' post-injection, the re-epithelization of the defect was complete, with stromal fibrosis adjacent to the tissue defects [14]. The prostatic pseudocapsule remained intact, acting as a barrier to EtOH diffusion outside the prostate. We found similar acute (2 hour) histological findings in human prostates from cadaveric organ donors [15]. Chronic effects on the human prostate were examined in a prostate obtained during the autopsy of a single patient who died 8 months after receiving an intraprostatic injection of EtOH and also prostate biopsies from patients 1 month after the procedure [16]. Cavities within the prostate, confirming tissue ablation, were documented using transrectal ultrasound (TRUS) [17].

Clinical trials

Transurethral intraprostatic injection

Two multicenter clinical trials on transurethral EtOH ablation of the prostate (TEAP) have been reported. The first trial, published in 2004, included 94 patients at 15 European sites, with a 12-month follow-up period [18]. The second trial, published in 2006, included 79 patients at 15 sites in the US, with a 6-month follow-up [17]. These studies were similar in design and injection technique used, although the EU study included patients with hypertrophy of the median lobe, while the US study did not. Injections were performed with a 22-gauge axially deflecting hollow-core needle specifically designed for transurethral intraprostatic injection. The needle was deployed into the lateral lobes of the prostate at the 3 and 9 o'clock positions under direct visual control, using an injection device attached to a rigid cystoscope. The depth of deployment was determined based on the maximum transverse dimension of the prostate (D1) with a 1 cm safety margin. The number of injection planes was determined by the length of the prostatic urethra, with the first plane of injection being 1 cm distal to the bladder neck. If the distance between the verumontanum and the bladder neck was more than 2 cm, an additional injection plane was added 0.5 – 1.0 cm distal to the first. All procedures were performed on an outpatient basis, with most cases using regional anesthesia with a periprostatic anesthetic block, with or without intravenous (i.v.) sedation.

Both EU and US trials documented significant improvements in the International Prostate Symptom Score (IPSS), Quality of Life Index (QoL), and maximum flow rate (Q_{max}). Post-procedure prostate volume decreased by 16.1% at 12 months in the EU trial and by 15% at 6 months in the US trial. The US trial recorded a significant 22% reduction in prostate-specific antigen (PSA) levels 6 months after the procedure. Patients in the US trial were randomized into three groups receiving different EtOH doses, but no correlation was found between the volume injected and the outcome. The most commonly reported adverse events were bothersome, irritative voiding symptoms in 26% (EU) and 39.2% (US), urinary retention requiring re-catheterization following catheter removal after a minimum of three days' post procedure in 17% (EU) and 21.5% (US), hematuria in 16% (EU) and 41.8% (US), and erectile dysfunction in 2.5% (EU) and 4.1% (US). In addition, 27.8% of patients in the US trial reported pain or discomfort. None of the subjects reported retrograde ejaculation. In the EU trial, two serious adverse events involving bladder necrosis developed. Both patients developed long-lasting urinary retention and had undergone TURP. In the first case, the patient underwent urinary diversion for gross urinary leakage during the TURP. The second patient required a ureteral re-implantation due to distal stenosis. One patient in the US trial developed a small area of bladder necrosis, which healed 12 months following the procedure. The dropout rate was not reported in the US trial but was 9.6% in the EU trial. In the EU and US trials, 7.0% and 2.5% of patients, respectively, had to undergo TURP due to inadequate efficacy of TEAP (Table 1).

Transurethral intraprostatic ethanol injection						
Outcome measure mean (SD)	**Pre-op**	**6 Mo**	**12 Mo**	**24 Mo**	**36 Mo**	**48 Mo**
Grise et al. 2004	N = 114	N = 93	N = 93			
IPSS	20.6 (5.9)	10.6 (6.3)	10.3 (6.2)			
Q max (mL/sec)	9.9 (2.9)	13.4 (8.6)	13.4 (5.8)			
Post void residual (mL)	NA	NA	NA			
Prostate volume (cc)	45.9 (19.9)	39.2 (20.4)	38.5 (17.9)			
Magno et al. 2008	N = 36	N = 36	N = 36			
IPSS	28.8 (5.0)	17.8 (0.7)	15.5 (1.4)			
Q max (mL/sec)	6.0 (2.4)	14.2 (1.1)	15.2 (0.1)			
Post void residual (mL)	290.6 (14.1)	5.1 (21.2)	4.2 (14.1)			
Prostate volume (cc)	66.1 (3.5)	NA	53.4 (3.5)			
Arslan et al. 2014	N = 52	N = 36	N = 35			
IPSS	22.6 (8.9)	11.8 (NA)	12.8 (NA)			
Q max (mL/sec)	6.4 (6.6)	10.1 (6.6)	9.7 (6.6)			
Post void residual (mL)	160.1 (NA)	66.0 (NA)	68.0 (NA)			
Prostate volume (cc)	49.5 (NA)	39.0 (NA)	38.8 (NA)			
Sakr et al. 2009	N = 35		N = 32	N = 29	N = 25	N = 25
IPSS	22.0 (3.9)		6.4 (1.8)	7.5 (2.1)	8.7 (2.1)	9.9 (2.2)
Q max (mL/sec)	5.9 (3.7)		18.7 (3.9)	18.2 (3.8)	17.1 (3.9)	16.9 (4.1)
Post void residual (mL)	68.6 (50.0)		31.9 (19.0)	32.5 (18.1)	34.7 (15.3)	36.0 (20.9)
Prostate volume (cc)	52.7 (20.4)		43.9 (18.7)	44.8 (20.6)	46.6 (19.5)	49.9 (21.3)

Transrectal intraprostatic ethanol injection				
Outcome measure mean (SD)	**Pre-op**	**6 Mo**	**12 Mo**	**24 Mo**
Li et al. 2014	N = 70	N = 70	N = 69	N = 67
IPSS	29.3 (6.7)	11.0 (4.1)	10.1 (3.0)	9.8 (2.4)
QoL	5.3 (1.7)	2.2 (1.1)	2 (0.9)	1.9 (0.7)
Q max (mL/sec)	4.7 (3.1)	14.6 (3.5)	15.2 (3.7)	15.3 (3.2)
Post void residual (mL)	130.8 (71.5)	27.3 (10.6)	26.5 (12.1)	25.9 (12.0)
Prostate volume (cc)	55.9 (16.7)	47.7 (8.3)	46.9 (7.9)	46.8 (8.1)
Espinoza et al., 2018	N = 60			N = 60
IPSS	23.3 (2.0)			12.1 (1.7)
QoL	5.4 (0.1)			3.1 (0.2)

Q max (mL/sec)	8.0 (0.8)			14.5 (1.9)
Post void residual (mL)	170.0 (30.3)			70.0 (16.8)
Prostate volume (cc)	67.5 (2.9)			43.9 (2.8)

Table 1: Outcome measures from trials evaluating ablation of the prostate using intraprostatic injection of absolute ethanol. Only trials with follow-up ≥12 months and drop-out rate <10% were included.

A number of smaller, single-institution studies using TEAP have been reported [19,20]. Two of these studies, by Arslan et al. and Magno et al., provided 12-month follow-up data from 35 and 36 patients, respectively [21,22]. Depending on prostate size, the authors of these latter studies injected 6 – 16 ml of EtOH. At 12 months' post treatment, the corresponding studies reported a 42% and 46% improvement in IPSS, 11.6% and 19.2% decreases in prostate size, 49% and 98.6% reductions in PVR, and 52% and 154% increases in Q_{max}. No severe adverse events occurred. Minor complications were recorded, including irritative symptoms in 0% and 33.3%; transient postoperative hematuria in most patients, with two requiring bladder irrigation due to clot retention; urinary tract infection in 0% and 11.1%, and epididymoorchitis in 2.8% and 0% in patients in the Arslan et al. and Magno et al. studies respectively. The drop-out rates in the two studies were 9% and 0%. Seven patients (20%) needed further surgical treatment in the study by Arslan et al., while the study by Magno did not report a need for re-operation (Table 1).

Three long-term studies of TEAP have been published. Two of these studies, one by Goya et al. and one by El-Husseiny et al., reported 3- and 4.5-year follow-ups, respectively, on patients suffering from BPH with multiple comorbidities. The study by Goya et al. included 17 patients with BPH and the El-Husseiny et al. study included 14 patients with BPH, 41% of whom experienced chronic urinary retention [23,24]. The dose of injected EtOH was 3 – 14 ml (mean, 6.4 ± 2.9 ml) in the study by Goya et al.; El-Husseiny et al. reported injecting up to 26 ml. A significant improvement in symptoms was maintained for the duration of the monitoring period in both studies. The same was true for flow parameters, except for PVR, which decreased by 74% in the El-Husseiny trial, while it did not change in the trial by Goya et al. Complications in the Goya trial included acute epididymitis (1 patient), chronic prostatitis (2 patients), postoperative bleeding (2 patients), and retrograde ejaculation (1 patient); no complications were reported in the trial by El-Husseiny. Additional treatment was necessary in 41% of patients in the Goya trial and 23% of patients in the El-Husseiny trial. A significant limitation of these studies was the high drop-out rate, 50% and 75% in the Goya and El-Husseiny trials, respectively.

Sakr et al. performed TEAP in 35 patients with BPH and concomitant medical conditions, 32 of whom completed a 4-year follow-up [25]. Injections were performed under spinal anesthesia using an endoscopic, flexible, 6-gauge injection needle (50 cm in length with a 1-cm long injection tip), a 19-Fr continuous-flow rigid cystoscope, and a short bridge with a side channel and a 30° lens. EtOH injections (2 ml each) were performed at the 2, 4, 8, and 10 o'clock positions in either one or two planes. The enlarged medial lobe was treated with one or two injections. A permanent urethral catheter was removed 7 days' post procedure. Of the 32 patients who completed the 4-year follow-up, 25 required no further therapy. Their IPSS dropped by 70% 1-year post procedure but increased slightly to 45% of pre-treatment values at 4 years. The Q_{max} improved by 218% and PVR decreased by 53.5% 1-year post treatment. Both remained unchanged for the remainder of the study. Prostate volume decreased by 16.7% 1 year after procedure, but then increased to a volume only 5.3% smaller than pre-treatment values 4 years following the procedure. A significant correlation was documented between the volume of EtOH injected and the decrease in PVR, but no correlation was found between the volume injected and symptoms or flow parameters. No further treatment was necessary in 91.4% and 74.3% of patients one- and four-years post injection, respectively. Of the 7 patients who required further surgical therapy, three opted for repeated EtOH injection (Table 1).

A single study used a gel composed of 97% alcohol combined with a polymer to increase the viscosity, with the aim of reducing backflow along the needle tract [26]. Transurethral injection was used in 36 patients, transperineal in eight patients, and transrectal in 21 patients. Aside from hematuria, there were no complications reported, with beneficial effects observed in the IPSS and QoL scores as well as the flow parameters. These improvements lasted throughout the entire 12-month follow-up period. Mataguchi et al. published 6-month follow-up data on patients with BPH and advanced prostate cancer with chronic urinary retention [27]. Fourteen of the 16 BPH patients (87.5%) and three out of five patients with advanced prostate cancer (60%) regained the ability to void spontaneously. The authors of this study reported that the procedure, performed under sacral (4 patients) and lumbar (17 patients) anesthesia, was well tolerated by these patients, despite their advanced age, comorbidities, and the high risk associated with general anesthesia.

TRUS-guided intraprostatic injection

A number of recent studies have evaluated intraprostatic injection using real-time TRUS. This delivery method provides real-time control of the exact position of the needle in the prostate.

TRUS-guided transrectal intraprostatic injection

Li et al. reported long-term follow-up data for a trial that included 70 elderly patients suffering from BPH with significant comorbidities who underwent TRUS-guided intraprostatic EtOH injection [16]. Twenty-five of the study subjects had a long-term indwelling catheter due to chronic urinary retention. Sixty-seven completed the 24-month follow-up. EtOH was injected using a 25-cm percutaneous transhepatic cholangiography needle, which was directed using a TRUS probe with a needle guide channel. A single injection into each lateral lobe, 0.5 – 1 cm from the bladder, was performed. The hyperplastic middle lobe was injected in some patients as well. Five patients whose prostate volumes were greater than 75 cm^3 underwent two treatments. The initial 36 patients received an injection volume that was one-third of the calculated prostate volume, with the subsequent patients receiving an injection volume of one-quarter of the prostate volume. Flow parameters and PVR improved significantly. IPSS improved by 67% one-year post procedure. All the positive effects were maintained throughout the entire follow-up period (Table 1). Prostate volume decreased by 16% 6-months following the procedure and remained unchanged for the duration of the study. Twelve patients from the high-dose group experienced pain during the procedure. Two developed severe cystitis and an additional two developed bladder necrosis, which healed in 40 and 45 days with the use of an indwelling catheter. Only one patient from the lower-dose group reported pain, and none developed serious complications. Minor complications were not reported.

Recently, Espinoza et al evaluated 60 male patients treated with TRUS-guided intraprostatic injection [28]. The dosage of ethanol was 25% of the calculated prostate volume (7.5 – 33 ml), divided into 3 injections in each lateral lobe (upper, middle and lower segment). Ethanol was instilled from the periurethral area to the periphery using a 25-cm long 18-gauge needle. The follow-up period was 12 months. At 3 and 12 months, IPSS, QoL, and an ultrasound measurement of PVR were performed. Twenty-four patients (40%) reported mild pain after the procedure, 28 (46.6%) moderate pain and 8 (13.3%) severe pain. Other complications assessed were hematuria (26.7%), irritative symptoms (15%), urinary infection (13.3%), acute urinary retention (8.3%) and erectile dysfunction (5%). Approximately one quarter of the patients required re-treatment. Open surgery was difficult due to fibrosis between the adenoma and surgical capsule. Three patients who were not able to undergo surgical treatment underwent intraprostatic re-injection of ethanol or received medical treatment with alpha-blockers of 5-alpha reductase inhibitors. Between the second and the eighth week post-injection, 19 patients (31.6%) reported elimination of prostate fragments through the urethra with urination. Five patients required urethrocystoscopy with extraction of slings, one patient needed a cystotomy to remove tissue from the bladder cavity. The average prostate volume decreased by 35% at 12 months' post-procedure. The average IPSS decreased by 47.6%. The average Q_{max} increased by 84.8% (Table 1).

TRUS-guided transperineal intraprostatic injection

A study by Chiang et al. reported a six-month follow-up of 11 patients with prostatic obstruction due to BPH and advanced prostate cancer, treated using the TRUS-guided transperineal approach under local anesthesia [29]. These researchers used a low volume of EtOH (<15% of total prostate volume) and did not report any severe adverse events. Patients were not catheterized. One patient developed acute retention post-procedure that resolved after three days of catheterization. The symptoms subsided significantly, and flow parameters improved in all study subjects three and six months after the procedure.

Preclinical studies evaluating intraprostatic injection using a microporous needle

Pre-clinical studies using transurethral intraprostatic injection using a hollow core needle showed a weak correlation between the injected volume and size of the lesion [14]. In an experiment, using fluoroscopy and by quantifying the EtOH content in the irrigation fluid, it was documented that this is likely due to EtOH backflow along the needle tract and an unpredictable volume of EtOH retained in the prostate [30]. To avoid the backflow of injectate along the needle tract seen with the classical hollow core needle, injection using a microporous needle was introduced. The microporous needle is like a standard needle, but the injection is performed through a 1 – 3 cm porous segment rather than a single opening at the tip. In experiments performed in canine and ex vivo human prostates, it was demonstrated that this technology eliminates backflow of EtOH along the needle tract and results in diffusion into a significantly larger area. When the microporous needle is used, the volume of EtOH injected correlates well with the size of the necrotic lesion and that the prostatic pseudocapsule acts as a barrier preventing extraprostatic effects [15,31].

Comparison of intraprostatic EtOH injection to some recently approved and emerging minimally invasive treatments

Intraprostatic EtOH injection is an outpatient procedure that can be performed in less than 25 minutes, using periprostatic block, oral or intravenous sedation, or spinal anesthesia. All available clinical data come from single-arm studies. Because of the significant differences in study design in terms of the number of injections and total dose delivered, pooling the data from these trials is not feasible. Studies reported varying improvements in both

symptoms and objective parameters (IPSS improvement ranged from 10 to 14 points and Q_{max} improvement ranged rom 2 to 30 ml/s) at 12 months [1]. Long-term data are sparse, and their reliability is limited in some studies by high drop-out rates. Significant variability in long-term outcomes and retreatment rates were reported. Despite this limitation, the values from existing trials favorably compare to newly approved minimally invasive therapies and, in some instances, are comparable to those of TURP.

The Prostatic Urethral Lift (PUL) is an FDA-approved, minimally invasive BPH treatment that, like an intraprostatic EtOH injection, is an outpatient procedure performed under regional anesthesia with or without i. v. sedation. It utilizes mechanical separation of lateral prostatic lobes to relieve obstruction without the need for tissue removal. Roehrborn et al. performed the largest multicenter trial evaluating PUL procedure [32]. In the randomized controlled study published in 2017, these authors assessed five-year outcomes of PUL. Randomization assigned 140 subjects to PUL and 66 subjects to a sham treatment. Patients undergoing the PUL procedure had an 88% greater reduction in IPSS when compared to the sham treatment group at 3 months' post-procedure (PUL -11.1 ± 7.7, sham -5.9 ± 7.7). The difference in QoL and Q_{max} improvements were also significant (Table 2). Throughout the 5 years' observation period, an improvement of IPSS, QoL and Q_{max} was found to be 36%, 50% and 44% respectively. The authors reported a cumulative rate of surgical re-intervention for recurrent BPH symptoms to be 10.7% after 3 years and 13.6% after 5 years. PUL was shown to be free from adverse effects of BPH surgery (stress urinary incontinence, need for a transfusion) and was associated with low postoperative catheter requirement. Only lateral lobe enlargement was treated in the study.

Aquablation

Outcome measure mean (SD)	Pre-op	24 Mo
Gilling et al. 2019	N = 116	N = 110
IPSS	22.9 (6.0)	14.7 (7.1)
QoL	4.8 (1.1)	3.2 (1.7)
Q max improvment (mL/sec)		11.2 (11.0)
Post void residual (mL)	78.0 (0.0)	57.0 (0.0)

Prostatic Urehtral Lift

Outcome measure mean (SD)	Pre-op	3 Mo	12 Mo	24 Mo	60 Mo
Roehrborn et al. 2017	N = 140	N = 139	N = 139	N = 139	N = 139
IPSS	22.3 (5.4)	11.3 (7.7)	12.4 (7.5)	13.3 (8.0)	14.5 (8.4)
QoL	4.6 (1.1)	2.4 (1.7)	2.4 (1.7)	2.5 (1.7)	2.5 (1.8)
Q max (mL/sec)	7.9 (2.4)	11.7 (5.3)	11.5 (5.2)	11.5 (5.2)	11.1 (4.7)

Table 2: Outcome measures from the two largest trials evaluating aquablation and prostatic urethral lift.

Another FDA approved minimally invasive BPH therapy is aquablation. It uses a robotic-assisted, high-velocity saline stream to selectively ablate prostatic glandular tissue while preserving the capsule. It is a procedure which could be performed in the outpatient setting, however it requires general anesthesia. The largest study using aquablation was performed by Gilling et al. and published in 2019 [33]. The authors reported two-year results. One hundred eighty-one patients with BPH were assigned at random to either aquablation or TURP (2:1 ratio). At 2 years' post-procedure, IPSS scores were seen to have improved by 14.7 points in the aquablation group and 14.9 points in the TURP group and Q_{max} improvement was measured to be 11.2 and 8.6 ml/sec for aquablation and TURP, respectively ($p = 0.188$, 95% CI for difference - 1.3 to 6.4) (Table 2). Sexual function decreased slightly in the TURP group and was stable in the aquablation group. Surgical re-treatment rates for aquablation were 1.7% and 4.3% after 12 months and 2 years, respectively. For TURP, retreatment rates were 0% and 1.5%, respectively.

Discussion

EtOH has been proven to ablate prostate tissue and improve voiding function. Improvement in the symptom score after intraprostatic EtOH injection often exceeds the functional benefits, which could possibly be attributed to the effects of EtOH on the sensory nerves and suppression of afferent activity [34]. A high number of male patients suffering from BPH-related LUTS have been treated with intraprostatic EtOH injection in the clinical trial setting, however, a phase III randomized trial has not been completed to date. The absence of a phase III trial and existence of two severe and several mild adverse events caused by extraprostatic tissue damage, led to the designation of intraprostatic EtOH injection as an experimental therapy in the 2015 EAU Guidelines [35]. It is not mentioned in the latest EAU guidelines [1,35].

EtOH is highly corrosive, therefore development of a safe and reproducible method for intraprostatic injection, which would guarantee targeted delivery, of this agent and prevention of extraprostatic leak is critical. The prostate contains glandular tissue, smooth muscle, and fibrous stroma. When a standard single core needle is used, the type of tissue that the singular needle opening is placed in has a large effect on intraprostatic EtOH diffusion. Backflow along the needle, which is a path of least resistance, has been frequently observed with the transurethral EtOH injection and objectively quantified in canine model [30]. This could explain the poor correlation between improvement in symptoms and flow rate and the injected volume found in clinical trials using transurethral ethanol ablation [17,18,25] Even more importantly, with transrectal or transperineal injection, backflow could result in extraprostatic tissue leakage, which likely was a reason for the pain recorded in 17% of patients receiving transrectal TRUS-guided EtOH injection of a volume equivalent to one-third of the prostate volume in the study by Li et al. [16] The development of a porous needle could be a significant advancement in preventing the backflow.

Another aspect that could advance the safety of this procedure is optimizing the needle track. This could be achieved using precise control of needle deployment, using a transrectal ultrasound. Recently, due to rare but often catastrophic complications of transrectal prostate biopsies, transperineal prostate biopsies are being adopted by an increasing number of urologists and precise and user-friendly equipment for transperineal biopsy have become available [36]. Transperineal deployment of the needle for intraprostatic EtOH injection could be safer as the position of the entire porous segment during injection will be deep in the prostatic tissue and parallel to the prostatic capsule which stops the spread of EtOH outside the prostate. At this time, EtOH is the only agent that has been confirmed to induce prostate tissue ablation in both preclinical (necrosis documented on whole mount sections of canine prostate) and clinical trials (22% decrease in PSA, documentation of defects in the prostatic tissue and reduction in the size of the prostate) [13,17,37]. The current development of a method for precise targeted intraprostatic delivery of ethanol injection therapy facilitates the use of ethanol as a safer and less invasive alternative in the treatment of lower urinary tract symptoms.

Conclusion

All published studies regarding EtOH intraprostatic injection reported significant improvement in symptoms and some reported significant improvement in objective parameters. The precise comparison to the medical therapy of BPH and approved minimally invasive therapies is not possible until a properly designed randomized trial is conducted. EtOH is highly cytotoxic, which with the old techniques of injection raised concerns about possible complications. The current development of a method for precise targeted intraprostatic delivery of injection therapy addresses this problem and facilitates the use of ethanol or other prostate tissue-specific ablation agents once they become validated.

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