



## The Effects of Microwave Thermotherapy for Chronic Prostatitis/Chronic Pelvic Pain Syndrome: A Prospective, Randomized Study

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**Purpose:** Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) causes pain and urinary symptoms that involve the prostate and/or other parts of the male. We analyzed the clinical outcomes of medication and microwave thermotherapy.

**Materials and Methods:** A total of 132 patients with CP/CPPS for at least 3 months were assigned to one of the three study groups (group A: medication; group B: thermotherapy; group C: combination therapy). The NIH-CPSI was recorded at baseline, and at weeks 2, 4, 8, and 12 post-therapy. EPS was evaluated, and semen analysis was performed to assess the changes in prostatic inflammation. Moreover, patient satisfaction questionnaire was completed.

**Results:** Comparisons between groups A and B, as well as between groups B and C showed no significant changes in pain, quality of life, and total scores. At week 12, group C, when compared with group A, had a significantly improved voiding score ( $4.19 \pm 3.02$  vs.  $2.71 \pm 2.30$ ,  $p=0.019$ ) and EPS ( $12.47 \pm 15.91$  vs.  $3.73 \pm 4.82$ ,  $p=0.003$ ). At week 4, the patient satisfaction score in group C was significantly different from that in other groups ( $p=0.043$ ), but there was no difference at week 12 ( $p > 0.05$ ). There was no statistically significant difference in laboratory test results, PSA, and prostate volume between the three groups at baseline and week 12. Complications of thermotherapy resolved with conservative management.

**Conclusions:** Our results showed that a combination of medication and thermotherapy improved NIH-CPSI and patient satisfaction in CP/CPPS more than medication alone. We suggested that thermotherapy could be another treatment option for CP/CPPS.

**Keywords:** Drug therapy; Microwaves; Prostate; Prostatitis

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## INTRODUCTION

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) manifests as pain in the perineum, rectum, prostate, penis, testicles, and/or abdomen for more than 3 of the previous 6 months, or urinary symptoms and painful ejaculation

without documented urinary tract infection by any pathogen. CP/CPPS is the most common urological diagnosis in men over the age of 50 years, and is the third most common urological diagnosis in men younger than 50 years [1]. Prostatitis accounts for 25% of all visits to the urologists and up to 15% to 25% of visits to urologic clinics in Korea

[2]. Cases of CP/CPPS are subdivided by the presence of inflammatory components in expressed prostatic secretions (EPSs) or semen (category IIIA) or its absence (category IIIB). Prostatitis remains to be a significantly underreported and poorly understood disease. Currently, there is much discourse regarding the pathophysiology and optimal therapeutic approach for patients with CP/CPPS. However, there has not been a consensus on the optimal treatment modality. Hence, a multimodal approach has been presumed to demonstrate benefit. Various pharmacologic and nonpharmacologic treatments have been proposed and used [3-5]. Moreover, multiple interventional techniques, including microwave thermotherapy, injection of botulinum toxin, transurethral needle ablation of the prostate, neuromodulation, and extracorporeal shockwave therapy, have been utilized, with each offering varying degrees of benefit. Transrectal microwave hyperthermia of the prostate was developed as a treatment for prostate cancer [6-8], and its application was subsequently extended to benign prostatic hyperplasia and CP [9,10]. Transrectal prostatic hyperthermia has shown efficacy in selected patients with CP who did not respond to conventional therapies [11,12]. This study evaluated the effect of transrectal microwave thermotherapy (TRMT).

## MATERIALS AND METHODS

### 1. Patients

This prospective study was carried out on 132 CP/CPPS patients, who were recruited among men visiting the urology clinics of Konkuk University Chungju Hospital and Eulji University Hospital in Korea between January 2005 and December 2010. This study was performed in accordance with the institutional guidelines and was approved by the Konkuk University Chungju Hospital Institutional Review Board (KU2010-003); all participants provided written informed consent. Patients had symptoms for more than 3 months, and all fulfilled the National Institutes of Health (NIH) diagnostic criteria for CP/CPPS. The NIH Chronic Prostatitis Symptom Index (NIH-CPSI) score was determined in each patient via a questionnaire. Patients with a history of urethritis, epididymitis, varicocele, perianal and rectal disorders, any neurological disease, presence of neurogenic bladder, urethral stricture, and previous urological surgery were excluded. The serum prostate specific antigen (PSA)

level was tested to exclude prostate cancer. None of the patients had received antibiotics or anti-inflammatory agents before enrollment in this study.

### 2. Study Design and Interventions

Men were randomly assigned in equal proportions to three groups: group A, receiving ciprofloxacin 500 mg twice daily and nonsteroidal anti-inflammatory drugs (NSAIDs); group B, receiving TRMT alone; and group C, receiving a combined therapy of ciprofloxacin 500 mg twice daily, NSAIDs, and TRMT (group C). Patients were treated for 12 weeks, at which time the primary endpoint was assessed. Symptoms were assessed to evaluate a longer-term treatment response at weeks 4, 8, and 12. The NIH-CPSI scores were recorded at baseline, and at weeks 2, 4, 8, and 12. EPS, semen analysis, and cytokine levels were used to evaluate inflammation. A patient satisfaction questionnaire, which consisted of 5 scales, was completed. A single TRMT treatment was performed with a URO-DR™ device (Somang Medical, Gangneung, Korea), at an intrarectal temperature of 43°C for 30 minutes, at a medium heating rate (Fig. 1). This system included a 6-ring electrode mounted on a silicone-coated 16-Fr latex Foley catheter, and incorporated a computer-controlled radiofrequency generator that enabled bipolar treatment. The treatment area was chosen according to the prostatic urethral length, measured by transrectal ultrasound (TRUS); localized treatment was performed by applying an energy to the different catheter electrodes.



Fig. 1. URO-DR™ (Somang Medical, Gangneung, Korea).

We also measured the prostate volume by TRUS and the PSA level before treatment. Patient follow-up at week 12 included TRUS and PSA level.

### 3. EPS and Semen Collection

Expressed prostatic secretion (EPS) and semen samples were collected after 3-5 days of abstinence. The penis and meatus were cleaned and disinfected. Urine was collected before and after prostate massage for routine examination and bacterial culture. Digital rectal examination and EPS collection were carried out with the subject in the knee-chest position. Semen was collected in a 1.5-ml cryotube after centrifugation at 3,000g for 10 minutes and stored at  $-20^{\circ}\text{C}$  for approximately 2 hours, which was then transferred for storage at  $-70^{\circ}\text{C}$  until thawed for analysis. The EPS was smeared on a glass slide and examined promptly with a high-power microscope ( $\times 400$ ) for cells and lecithin bodies.

### 4. Efficacy Calculation and Patient Satisfaction Questionnaire

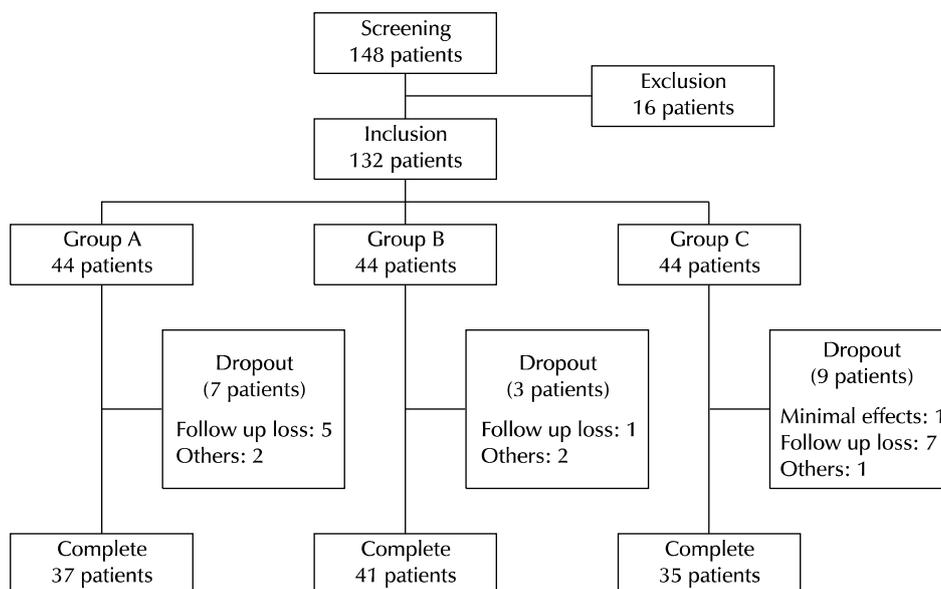
We used a self-reported patient satisfaction questionnaire at baseline, and at weeks 4 and 12. Patient satisfaction after treatment was determined using a visual analogue scale (category IIIA: 0 to 15, category IIIB: 0 to 30). Efficacy was calculated with a formula, including questionnaire results. Patients in category IIIA showed a decrease in EPS white blood cell (WBC) counts.

### 5. Data Analysis

Data were analyzed using SPSS ver. 14.0 for Windows (SPSS Inc., Chicago, IL, USA). Single-factor analysis of variance was used to compare age, WBC counts, NIH-CPSI scores, and patient satisfaction between the three groups. Pearson's correlation was used to analyze the relationship between WBC counts and NIH-CPSI scores. A p-value of less than 0.05 was considered statistically significant.

## RESULTS

We screened 148 patients in 2 hospitals, and 16 were excluded due to urethritis, urethral stricture, or other relevant medical history. A total of 132 patients with CP/CPPS for at least 3 months were randomly assigned to one of the three groups (Fig. 2). There was no statistically significant difference in routine laboratory tests, PSA, or prostate volume between the three groups at baseline and at week 12 (Table 1). After 12 weeks of treatment, all groups showed signs of improvement compared with the baseline (Fig. 3;  $p < 0.05$ ). Comparisons between groups A and B, as well as between groups B and C showed no significant changes in pain, quality of life (QoL), and total scores. At week 12, group C, when compared with group A, had a significantly improved voiding score ( $4.19 \pm 3.02$  vs.  $2.71 \pm 2.30$ ,  $p = 0.019$ ; Table 2) and EPS findings (category IIIA,  $12.47 \pm 15.91$ /high-power field [HPF] vs.  $3.73 \pm 4.82$ /HPF,  $p = 0.003$ ). At week 4, the patient satisfaction score in group C was significantly different from that in other groups ( $p = 0.043$ );



**Fig. 2.** Study flow diagram. Group A: medical therapy, group B: microwave thermotherapy, group C: medication and microwave thermotherapy.

**Table 1.** Patient characteristics

Characteristic	Group A (n=37)	Group B (n=41)	Group C (n=35)
Age (y)	31.5±6.7	35.1±8.9	38.1±8.0
Height (cm)	168.8±6.56	169.5±4.5	170.4±4.55
Body weight (kg)	67.5±9.07	68.5±9.84	69.5±8.91
Category			
IIIA (VAS 0 to 15)	13	21	13
IIIB (VAS 0 to 30)	24	20	22
Duration of symptoms (mo)	24.95±27.15 (3-120)	24.59±7.10 (2-168)	23.94±5.92 (3-240)
Previous treatment history of CP/CPPS	21 (56.8)	20 (48.8)	19 (54.3)
Prostate specific antigen (ng/ml)			
Baseline	0.9±0.8	1.1±0.8	1.0±0.8
Week 12	0.8±0.6	1.5±1.6	1.0±0.4
Prostate volume (TRUS, ml)			
Baseline	19.2±5.9	22.7±5.6	21.5±5.1
Week 12	19.6±5.1	24.6±6.6	20.6±5.7
White blood cells (/μl)			
Baseline	6,236±1,597	6,632±1,480	7,043±1,554
Week 12	6,306±2,012	6,657±1,635	6,320±1,376

Values are presented as mean±standard deviation, number only, or number (%).

Group A: medical therapy, group B: microwave thermotherapy, group C: medication and microwave thermotherapy, VAS: visual analogue scale, CP/CPPS: chronic prostatitis/chronic pelvic pain syndrome, TRUS: transrectal ultrasound.

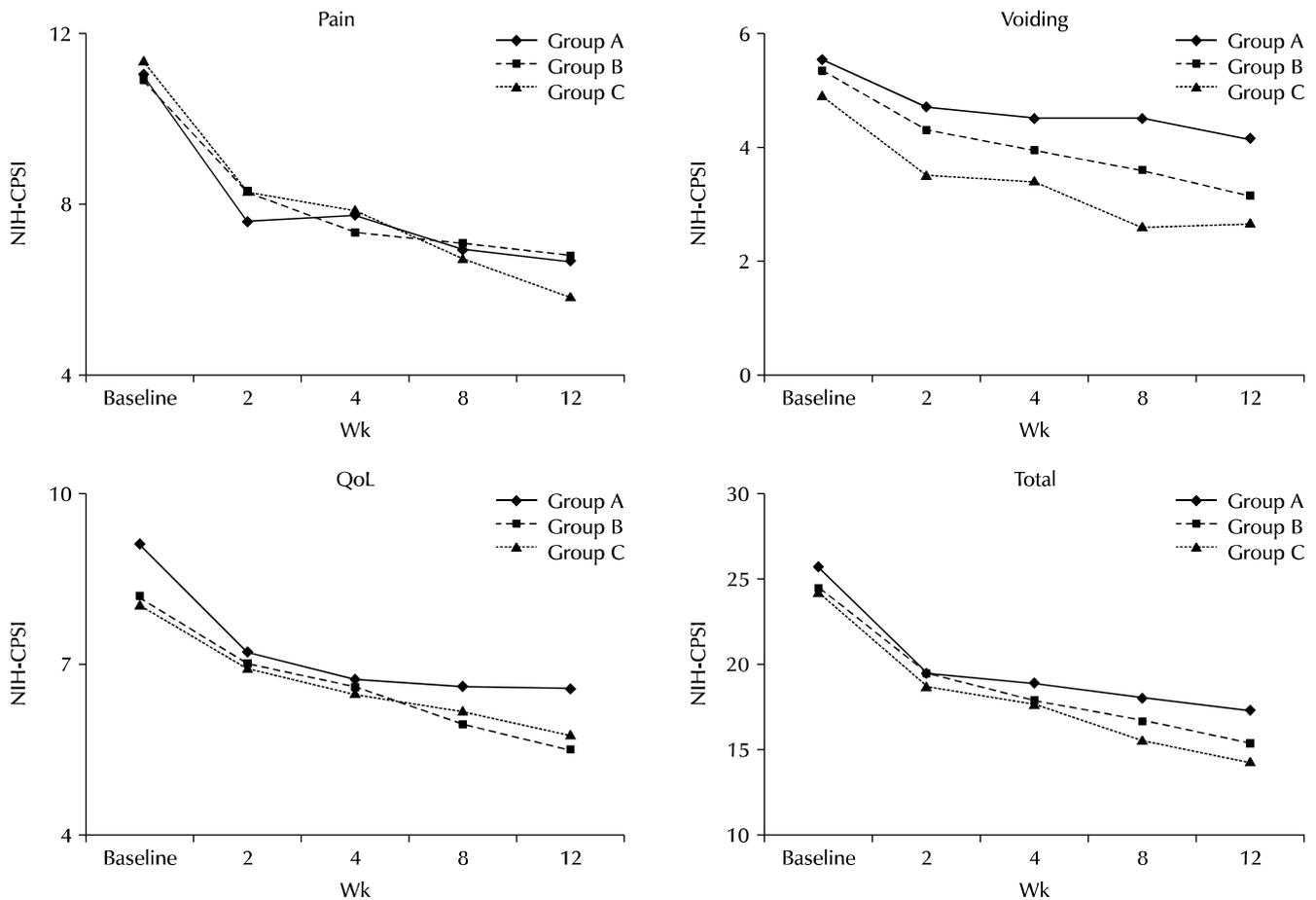
All parameters were no statistically significant difference compared with each groups.

however, there was no difference at week 12 ( $p > 0.05$ ). Group C had improved NIH-CPSI and patient satisfaction scores compared with group A (Tables 2, 3, Fig. 3). Nineteen patients dropped out due to minimal effect, loss to follow-up, or other reasons. One patient in group C was dissatisfied because of minimal effect. Minor complications were noted with URO-DR<sup>TM</sup>, such as anal itching and tenesmus, but these improved with conservative management.

## DISCUSSION

Many treatments have been investigated and tested in patients with CP/CPPS, but none have shown significant long-term benefit [13]. Recently, a combination treatment for CP/CPPS has been suggested as a preferred method due to its synergistic effect, showing superiority over monotherapy [14,15]. Combination therapy was based on the UPOINT system of domains (urinary, psychosocial, organ-specific, infection, neurologic/systemic, and tenderness) [16]. Many patients are involvement with more than one UPOINT domain and require multimodal therapy. There has recently been an increase in the use of hyperthermia to treat prostatic diseases, although with controversial results [9,17,18]. In 1996, Nickel and Sorensen [19] reported that transurethral microwave thermotherapy showed greater benefit than those receiving therapy. They suggested that

transurethral microwave thermotherapy was effective and safe to treat patients with CP/CPPS. However, transurethral treatments have been associated with increased risk of urinary tract infection. The aim of this study was to validate TRMT with URO-DR<sup>TM</sup> in a prospective randomized trial. The transrectal approach has minimal complications, such as anal itching and tenesmus. This improve with conservative management. Our results showed that a combination therapy with TRMT, using URO-DR<sup>TM</sup> and medication, improved NIH-CPSI and patient satisfaction scores for CP/CPPS compared with medical therapy alone (Table 2, Fig. 3). Additionally, the patient satisfaction scores in group C were significantly different from scores in other groups at week 4 ( $p=0.043$ ), but not at week 12 ( $p > 0.05$ ). Thakkinstian et al. [20] reported significant improvement in voiding symptoms with antibiotics and/or NSAIDs compared with the placebo. At week 12, voiding symptoms significantly improved in group C compared with group A ( $p=0.019$ ). Additionally, voiding symptoms, pain, and QoL were significantly improved in all groups (Fig. 3). There were no significant differences in PSA, WBC counts, and prostate volume following TRMT with URO-DR<sup>TM</sup>, compared with the results with medical therapy (Table 1). In this study, 19 patients dropped out due to minimal effect, loss to follow-up, and other reasons (Fig. 2). One patient in group C was dissatisfied due to minimal effect.



**Fig. 3.** Changes of pain, voiding, quality of life (QoL), and total score. Group A: medical therapy, group B: microwave thermotherapy, group C: medication and microwave thermotherapy, NIH-CPSI: The National Institutes of Health Chronic Prostatitis Symptom Index.

**Table 2.** NIH-CPSI score at the baseline and at week 12

NIH-CPSI	Group A (n=37)		Group B (n=41)		Group C (n=35)	
	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12
Pain	11.24±3.92	6.51±4.23	11.02±3.06	6.76±3.55	11.49±3.30	5.91±4.05
Voiding	6.11±2.58	4.19±3.02	5.29±3.03	3.17±2.52	4.66±3.10	2.71±2.30
QoL	8.97±2.92	6.49±2.67	8.27±2.66	5.46±2.25	7.80±2.17	5.83±2.62
Total	26.27±5.45	17.19±8.23	24.59±7.10	15.39±6.51	23.94±5.92	14.46±7.34

Values are presented as mean±standard deviation.

Group A: medical therapy, group B: microwave thermotherapy, group C: medication and microwave thermotherapy, NIH-CPSI: The National Institutes of Health Chronic Prostatitis Symptom Index, QoL: quality of life.

**Table 3.** Changes of patient satisfaction questionnaire

Patient satisfaction	Group A (n=37)				Group B (n=41)				Group C (n=35)			
	IIIA (n=13)		IIIB (n=24)		IIIA (n=21)		IIIB (n=20)		IIIA (n=13)		IIIB (n=22)	
	Week 4	Week 12	Week 4	Week 12	Week 4	Week 12	Week 4	Week 12	Week 4	Week 12	Week 4	Week 12
Very satisfied	-	3	-	1	-	3	2	-	1	2	3	4
Satisfied	5	3	7	8	8	5	8	10	6	8	8	8
Neutral	7	5	15	12	10	12	9	9	5	3	10	10
Dissatisfied	2	2	1	2	3	-	1	1	-	-	1	-
Very dissatisfied	-	-	1	1	-	1	-	-	-	-	-	-

Group A: medical therapy, group B: microwave thermotherapy, group C: medication and microwave thermotherapy. Visual analogue scale: category IIIA, 0 to 15; category IIIB, 0 to 30.

CP/CPPS is the most common urological diagnosis in men younger than 50 years, accounting for 8% of all office visits to urologists. CP/CPPS is characterized by pelvic or perineal pain, with or without detectable inflammatory changes in the prostate tissue and secretions. Men with CP/CPPS also have urinary symptoms and sexual dysfunction, both of which have a negative effect on QoL. Most prostatitis cases are classified as CPPS (NIH category III). Traditionally, inflammation in CPPS cases has been considered synonymous with leukocytes in EPS. However, there is no correlation between leukocytes and CPPS symptoms in men or leukocytes in EPS and histological inflammation. As shown in a Reduction by Dutasteride of Prostate Cancer Events study, histological inflammation in CPPS cases showed a slight correlation with the overall NIH-CPSI score, but no correlation with pain [21,22]. In contrast, numerous studies showed increased proinflammatory cytokines and chemokines, which in some instances correlate with NIH-CPSI [23-25].

Although the etiology of CP/CPPS is uncertain, it may include inflammatory or non-inflammatory etiologies. An inciting agent may cause inflammation or neurological damage in or around the prostate, leading to pelvic floor neuromuscular and/or neuropathic pain. Predisposing factors for CP/CPPS may include heredity, infection, voiding abnormalities, hormone imbalance, intraprostatic reflux, immunological or allergic triggers, or psychological traits. A wide variety of therapies, including  $\alpha$ -blockers, antibiotics, anti-inflammatory medications, and other agents (e.g., finasteride, gabapentinoids), are routinely used. The findings of several placebo-controlled trials suggest that a treatment with  $\alpha$ -blockers may be effective for reducing symptoms in men with CP/CPPS, in those who have not previously been treated with these drugs, and in those who have had symptoms for a relatively short time. Alternative treatments for CP/CPPS, such as phytotherapy, physical therapy, biofeedback, and thermotherapy, have shown some success in ameliorating the symptoms of CP/CPPS. Evidence is increasing for a role of cytokines as inflammation mediators in CP/CPPS. Different cytokines, such as interleukin (IL)-2, IL-8, IL-10, and tumor necrosis factor alpha (TNF- $\alpha$ ), have been found in prostate secretion fluids of CP/CPPS patients and presumably play an important role in the process of CP/CPPS [23-26]. Pro-inflammatory, anti-inflammatory, and regulatory cytokines have been tested for their diagnostic

usefulness. IL-6 and IL-8 are representative pro-inflammatory cytokines with greater levels in seminal plasma [27]. According to our results, IL-1b, IL-6, IL-8, IL-10, and TNF- $\alpha$  in the seminal fluid did not change after treatment (all groups, data not shown). Further studies of prostate cytokines may help to characterize the different types of CP/CPPS, and improve our understanding of prostate immune responses in patients with CP/CPPS.

Our study has some limitations to consider when interpreting the results. First, we used self-reported "patient satisfaction questionnaires" without validation. Indeed, patient satisfaction in group C was significantly different from that in other groups after 4 weeks ( $p=0.043$ ), but not at week 12 ( $p>0.05$ ). Second, other reports showed that changes in cytokines were useful as diagnostic tools. Although we examined seminal fluid after centrifugation, cytokine levels did not change in all groups. We surmise that seminal fluid samples could have been contaminated.

## CONCLUSIONS

A combined therapy of medical therapy and thermotherapy using URO-DR<sup>TM</sup>, compared with medical therapy along, resulted in an improvement of NIH-CPSI and patient satisfaction scores for CP/CPPS. Thermotherapy using URO-DR<sup>TM</sup> resulted in no significant differences in laboratory findings compared with other treatments, and had minimal complications. Thermotherapy using URO-DR<sup>TM</sup> can be another treatment option for CP/CPPS. However, further clinical trials are necessary to clarify the role of thermotherapy for CP/CPPS.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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