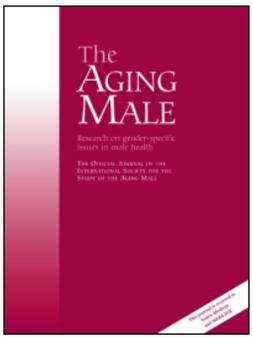

The Aging Male

ISSN: 1368-5538 (Print) 1473-0790 (Online) Journal homepage: www.tandfonline.com/journals/itam20

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To cite this article: B. Pajovic, N. Radojevic, A. Dimitrovski & M. Vukovic (2016) Comparison of the efficiency of combined extracorporeal shock-wave therapy and triple therapy versus triple therapy itself in Category III B chronic pelvic pain syndrome (CPPS), The Aging Male, 19:3, 202-207, DOI: 10.1080/13685538.2016.1197899

To link to this article: https://doi.org/10.1080/13685538.2016.1197899

The Aging Male

http://informahealthcare.com/tam
ISSN: 1368-5538 (print), 1473-0790 (electronic)

Aging Male, 2016; 19(3): 202–207
 DOI: 10.1080/13685538.2016.1197899

Taylor & Francis
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ORIGINAL ARTICLE

Comparison of the efficiency of combined extracorporeal shock-wave therapy and triple therapy versus triple therapy itself in Category III B chronic pelvic pain syndrome (CPPS)

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Abstract

The aim of this study is to determine the effect of combining extracorporeal shock-wave therapy (ESWT) and triple therapy versus triple therapy alone, when treating Category III B chronic prostatitis (CPPS). Study included 60 patients, classified as having CPPS, divided into two groups: the first group numbered 30 patients, who were treated with a combination of an α-blocker, an anti-inflammatory agent and a muscle relaxant; the second group consisted of 30 patients who received a combination of ESWT and the fore-mentioned triple therapy. Patients were treated for 12 weeks. The primary criterion of a response to therapy was scoring 2 or less on the NIH-CPSI quality of life item, while the secondary criterion of a response to therapy was a greater than a 50% reduction in NIH-CPSI pain score. Patients who received triple therapy did not show a significant change neither in post void residual urine (PVR) nor in maximum flow rate (Q_{MAX}), while the second group of patients exhibited significant improvement in both PVR and Q_{MAX} values. Both groups of patients showed statistically significant improvement in all items of the NIH-CPSI score after the treatment, with significantly better results in the second group.

Keywords

Chronic pelvic pain syndrome, chronic prostatitis, extracorporeal shock-wave therapy

History

Received 19 April 2016
Revised 28 May 2016
Accepted 1 June 2016
Published online 4 July 2016

Introduction

Chronic pelvic pain syndrome (CPPS) is the occurrence of chronic pelvic pain in the absence of proven infection or other obvious local pathology which may account for the pain [1]. CPPS is also defined by the National Institutes of Health (NIH) as type III prostatitis, which is the most common urologic diagnosis in men under the age of 50 and its impact on the quality of life is similar to that of myocardial infarction or Crohn's disease [2]. Depending on the presence or absence of inflammatory cells in the semen or prostatic fluid, CPPS is classified into either NIH IIIA or NIH IIIB prostatitis. The treatment of CPPS is difficult because pathogenesis is undefined. Several treatment modalities including antimicrobial drugs, muscle relaxants, α-blockers, biofeedback physical therapy such as monotherapy or combination therapy have been proposed and investigated [3]. Monotherapeutic strategies for the treatment of prostatic pain syndrome can fail, therefore, most patients require multimodal treatment [1]. There is still much controversy regarding triple therapy and its true effects, since although patients showed improvement, the results were associated with side effects [4,5]. Also, there are no contemporary prospective studies showing advantage of triple therapy over other treatment modalities for CPPS. Recently, many reports have indicated that extracorporeal shock-wave therapy (ESWT) for CPPS can significantly improve the symptoms of pelvic pain and urination disorders in CPPS patients and in other chronic conditions, and that the therapeutic effect can be attributed to the inhibition of chronic inflammatory processes and improvement of angiogenesis and the blocking of pain nerves [6]. Therefore, there are many different mechanisms through which ESWT reduces pain: interrupting the flow of nerve impulses by hyperstimulation of nociceptors, healing tissue by revascularisation processes and reductions in muscle tone and spasticity [7,8]. However, the long-term effect of ESWT in patients with CPPS has yet to be confirmed.

This study compares the long-term effects of combining transperineal ESWT and triple therapy (α-blocker, anti-inflammatory and muscle relaxant), versus triple therapy alone for the treatment of non-inflammatory CPPS (Category III B).

Methods

We performed the prospective study between September 2013 and February 2015, it consisted of 60 patients classified as

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having Category III B chronic prostatitis. The diagnosis of Category III B CPPS included a detailed history, physical examination, PSA measurement, trans-rectal ultrasound, residual urine volume and urine flow measurement, urethral smear along with a sample of semen and standard microbiologic cultures and microscopic analysis of urine (before and after prostatic massage) and prostatic secretions [3]. Patients were randomly divided into two groups. The first group numbered 30 naive patients, who were treated with a combination of an α-blocker, an anti-inflammatory agent and a muscle relaxant. The second group also contained 30 naive patients who accepted the treatment with a combination of ESWT therapy and the above mentioned triple therapy. Every patient had exhibited symptoms for at least three months. We treated both groups for a period of 12 weeks.

Patients were assessed by the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) [9] at the initiation and termination of therapy, as well as 12 and 24 weeks after the cessation of therapy. The primary criterion of a response to therapy was scoring 2 or less (''delighted-to-mostly satisfied'') on the NIH-CPSI quality of life item after 12 weeks [10]. The secondary criterion of a response to therapy was a greater than a 50% reduction in NIH-CPSI pain score [11] and total NIH-CPSI scores after 12 weeks. Other results included and urinary, peak urinary flow rate and post void residual urine (PVR), measured by trans-abdominal ultrasound. The Agency for Healthcare Policy and Research (AHCPR) states that, in general, a PVR of less than 50 mL represents adequate emptying while a PVR of greater than 200 mL represents inadequate emptying. The lower threshold of defining abnormal PVR is in the range of 50–100 mL [12]. The peak urinary flow rate was defined as the maximum flow rate (Q_{MAX}) as measured by a weight transducer flow-meter, with values considered valid only if the voided volume was at least 150 mL [3]. We used an uroflowmeter (MCL-961-A, Mecan Trading Co. Ltd., Guangzhou, China). Patients were also asked if they experienced any adverse effects during each follow-up visit.

Inclusion and exclusion criteria

Eligibility criteria for each patient's inclusion, in either group, were: a diagnosis of Category III B CPPS, aged 30–50; a score of $\geq$5 on items 1 and 2 (pain and discomfort); a score of $\geq$4 on item 9 (quality of life) of the NIH-CPSI; the patient had exhibited symptoms for longer than three months and desired treatment [3].

We excluded patients meeting the following criteria: patients who met the criteria for chronic bacterial prostatitis or Category III A CPPS after lower urinary tract localization studies [13]; those who had previous urinary tract infection documented within the last year, as well as evidence of bacteria in seminal culture tests; those who met any NIH consensus exclusion criteria and those who had been treated or were taking medications that could affect lower urinary tract function (3); patients with a PSA level >4 ng/mL [14].

History and physical examination

The predominant symptom in all patients was pain, most commonly localized to the perineum, but also in the suprapubic area, testes, groin or lower back. Every patient had exhibited symptoms for at least six months. Few of the patients reported erectile dysfunction or sexual disturbances, none of them reported recent sexual transmitted diseases, or any other concomitant urological disease. Patients were not treated forany neurologic, psychiatric, blood or infectious diseases. Patients were carefully examined by inspection and palpation of external genitalia, groin, perineum, coccyx, external anal sphincter (tone), and internal pelvic floor and side walls as prominent areas of pain or discomfort. The digital rectal examination was performed after the patient had produced preprostatic massage urine specimens [15]. All patients reported pain during palpation. Prostate cancer was excluded clinically and serologically [7]. The total PSA was determined in all patients before treatment. PSA levels were not measured post-treatment as the results of a previous study [7] indicated that it would not be required.

Trans-rectal and trans-abdominal ultrasound

After performing a trans-rectal ultrasound, there were no significant differences in ultrasound patterns of patients the two groups. The prostates showed slightly enlarged volumes with dilatation of periprostatic venous plexuses and thickening of the inner septae. The trans-abdominal ultrasound was used to determine PVR values.

Microbiological analysis of semen

The microbiological assessment entailed taking a urethral smear along with a sample of the semen. We used the PCR (polymerase chain reaction) nucleic acid amplification technique, the sensitivity of which is 90%, with a specificity of 98% [16], on a real-time PCR system (7300 Real Time PCR System; Applied Biosystems, Foster City, CA), for antigen detection. A five day abstinence rule was used when providing the samples.

Pre-massage and post-massage urine test (PPMT)

Segmented urine collection was used and the PPMT was made according to the ''2-glass test'' method [17]. Expressed prostatic secretion (EPS) was available and microscopy and culture of secretion were performed as described by Maeres and Stamey [13].

Medicamentous and ESWT therapy

The first group of patients were treated in accordance with the recommendations of the European Association of Urology (EAU) [1]. They received triple therapy which consisted of the combination of an α-blocker (doxazosin 4 mg/day), an anti-inflammatory (ibuprofen 400 mg/day) and a muscle relaxant (tiocolchicoside 12 mg/day) for 12 weeks [3]. During treatment, patients were advised to use ranitidine in case of gastrointestinal complaints. The second group of patients were treated with the same dose of triple therapy in combination with ESWT, where patients, while in supine position, received one perineally applied ESWT treatment weekly, for 12 weeks; in each session 3000 impulses were applied, with a total energy flow density of 0.25 mJ/mm^2, 3 Hz [18]. The duration of ESWT was 12 min each. The type of shock wave used was focus, applied with an electric SW

device (Lubisone, KM-2000 S, K1 Med Co. Ltd., Seoul, Korea). Use of an additional transducer positioning system was unnecessary, according to previous research [18]. Patients were treated as outpatients and anaesthesia was not required. Patients were evaluated after the treatment and followed up for another 24 weeks post-treatment, with evaluation after 12 and 24 weeks post-treatment to evaluate the long-term effects of the treatment protocol. The study protocol was approved by the Ethics Committee of Medical faculty, University of Montenegro.

Statistical methodology

Following the customary methods of statistical description, the Student T test was applied in order to assess statistical significance. The difference of the obtained values was considered to be significant when $p<0.05$ and highly significant when $p<0.01$.

Ethics

This clinical study was conducted in accordance with the principles laid down in the WMA Declaration of Helsinki along with the strict respect of patient's rights and clinical study protocol. Patient confidentiality and data security is guaranteed. They all signed the written consent form.

Results

The average age of the patients was 39.4 ± 4.4 years (ranging from 30 to 50). In the majority of examinees, the prostate was slightly enlarged and tender with average volume in first (32 ± 4.31 mL) and second group (33 ± 3.42 mL); nevertheless, none of the patients had a PSA level >4 ng/mL. During rectal palpation, patients reported on degree and location of the pain. The grade of pain was evaluated using a visual analoque scale (VAS, 1–10) [19], and first group of patients reported on moderate pain (5.4 ± 1.7), while the second group exhibit moderate to severe pain (7.2 ± 1.3) during palpation. Majority of the patients reported on pain localised to the prostate during palpation, but seven patients from the first group and 11 from the second reported on ano-rectal and perineal pain during rectal examination. First group of patients: microbiologic cultures and microscopic analysis of urine confirmed the absence of inflammation and infection before and after prostatic massage. There was no significant difference in regard to initial disease duration between groups. During the 12 weeks treatment period, nine patients from the first group (30%) had side effects compared to 11 (36.6%) in the second group. Side effects included dizziness (three versus five patients), gastrointestinal complaint (two versus one patient) and postural hypotension (four versus five patients) (Table 1). The ESWT was well tolerated, with no anaesthesia, and no side effects were apparent. None of the patients were excluded from the study, and everybody completed the study protocol during the follow-up period. Using the primary criterion, 15 of 30 subjects (50%) responded in the first group compared to 20 of 30 (66.6%) in the second group. Using the secondary criterion, 10 of 30 subjects (33.3%) responded in the first group compared to 26 of 30 (86.6%) in the second group (Table 2). Group 1 and group 2 showed statistically significant improvement ($p<0.05$) in all items of the NIH-CPSI score after the treatment. Patients who received triple therapy alone did not show a statistically significant change neither in PVR (30.93 ± 4.83 versus 28.83 ± 5.64, $p>0.05$) nor in Q_{MAX} (12.13 ± 2.12 versus 13.05 ± 2.16, $p>0.05$) while the group of patients who received a combination of ESWT and triple therapy showed significant improvement in both PVR and Q_{MAX} values (32.58 ± 3.68 versus 26.3 ± 4.79, $p<0.05$ and 12.93 ± 2.04 versus 15.55 ± 2.72, $p<0.05$).

Table 1. Side effects between two groups of patients during treatment period.

Side-effects during treated period	Group I – triple therapy (α-blocker, anti-inflammatory agent and muscle relaxant)	Group II – combination of triple therapy and transperineal ESWT
Dizziness	3	5
Gastrointestinal complaint	2	1
Postural hypotension	4	5
Palpitation	0	0

Table 2. Differences in primary and secondary criterion of a response between two groups of patients 12 weeks after the treatment initiation.

Mean	Primary criterion of a response[a]	Secondary criterion of a response[b]
Group I		
Response number	15	10
Total number	30	30
%	50	33.3
Group II		
Response number	20	26
Total number	30	30
%	66.6	86.6

[a]The primary criterion of a response to therapy was coring 2 or less on the NIH-CPSI quality of life item after 12 weeks.
[b]The secondary criterion of a response to therapy was a greater than 50% reduction in NIH-CPSI pain score after 12 weeks.

Table 3 displays the mean values and standard deviations of the measured parameters of the two groups of patients, prior to beginning the treatment, as well as the parameters at the end of the treatment period and during the 24 week post-treatment follow-up period. Initial values of NIH-CPSI, PVR and Q_{MAX} parameters, before therapy, among the two groups of patients did not show a significant difference. The table also indicates some statistically significant differences between the two groups in PVR, Q_{MAX} and items of the NIH-CPSI score, after the treatment has finished and during the follow-up period.

Discussion

According to previous comprehensive randomized control studies [7,18], ESWT can be used safely, with no side effects and repeated as often as required. Also it requires little time or personnel costs, which was of particular importance to this research. Our data clearly reveals improvement in all items of NIH-CPSI scores both in group 1 and group 2, after period of 12 weeks of treatment, with significantly better results in the second group regarding total score, pain score and impact on

Table 3. Changes in NIH-CPSI scores, Q_{MAX} and PVR values in both groups of patients.

Mean (SD)	NIH-CPSI total score (items 1–9)	NIH-CPSI pain score (items 1–4)	NIH-CPSI urinary (items 5 and 6)	NIH-CPSI quality of life impact (items 7–9)	Q_{max} (mL/s)	PVR (mL)
Group I						
Initial	29.3 (6.38)	14.5 (3.22)	5.76 (3.04)	9.1 (1.51)	12.13 (2.12)	30.93 (4.83)
12 weeks	16.8 (9.03)[a]	8.66 (5.61)[a]	2.1 (1.34)[a]	5.36 (3.8)[a]	13.05 (2.16)	28.83 (5.64)
24 weeks	16.1 (6.48)[a]	10.9 (3.7)[a]	2.83 (1.51)[a]	6.06 (3.64)[a]	12.61 (3.1)	31.06 (6.59)
36 weeks	22.46 (5.96)[a]	13.56 (4.66)	3.33 (1.47)[a]	7.96 (3.68)	12.45 (3.06)	35.21 (4.51)[a]
Group II						
Initial	31.06 (7.75)	15.9 (3.31)	5.03 (2.41)	9.96 (1.8)	12.93 (2.04)	32.58 (3.68)
12 weeks	10.16 (3.99)[a,b]	4.83 (2.54)[a,b]	2.2 (0.84)[a]	2.9 (1.64)[a,b]	15.55 (2.72)[a,b]	26.3 (4.79)[a,b]
24 weeks	11.63 (5.86)[a]	6.63 (3.73)[a]	2.1 (0.86)[a]	4.03 (2.55)[a]	13.99 (2.89)	29.8 (6.07)[a]
36 weeks	13.66 (4.90)[a,c]	6.7 (2.98)[a,c]	1.86 (0.77)[a,c]	4.43 (2.23)[a,c]	13.26 (2.57)	32.03 (5.06)[c]

NIH-CPSI = National Institutes of Health Chronic Prostatitis Symptom Index; PVR = post void residual; Q_{max}=maximum urinary flow rate.
[a]Statistically significant difference compared with initial values between corresponding groups.
[b]Statistically significant difference between Group I and Group II after 12 weeks treatment period.
[c]Statistically significant difference between Group I and Group II after 36 weeks (24 weeks after treatment cessation).

quality of life. Prior to treatment there was no significant difference in NIH-CPSI urinary scores between the two groups. At the end of 36 weeks NIH-CPSI urinary scores were significantly better in the second group, indicating the benefits of including ESWT in the therapy protocol, even over longer follow-up periods. The study made by Moaydenia et al. [19] indicates no significant differences between ESWT and sham groups in any aspect of NIH-CPSI after a 24-week follow-up period. However, they applied ESWT treatment for only four weeks, which is, in our opinion, too short for definite positive effect of ESWT. Nevertheless, Zimmermann et al. [18] have proved that only after two weeks and six ultrasonographically controlled ESWT treatments, patients symptoms of pain and quality of life were significantly improved, while voiding conditions were only temporary improved. The reason for this huge difference in ESWT effect could be in placement of the shock-wave focus, which, in latter study, was placed intraprostatically, under real-time US guidance and moved to scan virtually the whole gland [18]. In our study, patients received one perineally applied ESWT treatment weekly (with no use of an additional transducer positioning system), for 12 weeks, which could be the main reason for long-term positive effects. Also, we combined ESWT and triple therapy, which may be influential factor in positive results over a longer period of time, although there is no evidence that combination of ESWT with triple therapy explains the advantage of ESWT. Moreover, study by Vahdatpour et al. [8] showed positive effect in pain domain scores after four weeks of treatment with ESWT, transperineally applied. Also, QoL and total NIH-CPSI scores were significantly improved too, at the first and 12-th week after the treatment. All those studies confirm positive treatment tendency of ESWT, especially after longer treatment period and proper energy application. Hellstrom et al. [20] stated that patients with Category III B CPPS have significantly lower urinary tract symptoms, related to poor relaxation of the bladder neck during voiding. A combination of α-blockers and muscle relaxants may improve outflow obstruction, but contemporary studies show conflicting results. Tugcu et al. [3] besides improving the parameters of NIH-CPSI score, did not show any significant difference between triple, monotherapy and placebo group regarding PVR and Q_{MAX}. A similar outcome of triple therapy on PVR and Q_{MAX} was obtained in our study, where group 1 did not show a significant difference before and after the treatment. Group 2 patients however, who received a combination of triple therapy and ESWT showed a statistically significant improvement in PVR and Q_{MAX} values after 12 weeks of treatment, which may be an indication of positive influence of ESWT on neck bladder relaxation during voiding. This is supported by the fact that almost every item of NIH-CPSI score is significantly improved after receiving a combination of ESWT and triple therapy compared with triple therapy alone. Also, many investigators feel that CPPS is the ultimate reflection of a smooth and skeletal neuromuscular dysregulatory phenomenon in the perineum or pelvic floor [3]. Two recent studies made by Zimmermann et al. [7,18] demonstrated statistically significant improvements in pain and quality of life (QOL) after ESWT, however voiding conditions improved without statistical significance. Unlike this research, we evaluated our patients urodynamically, before and after ESWT, where we studied patients urinary flow and residual urine as parameters of urinary disorder, which could be essential in achieving objective results about local perineal changes which could have effects on urination behavior in patients with CPPS. This study showed that, in the second group, patients had significantly improved voiding conditions; PVR decreased significantly after 12 weeks of treatment as well as 24 weeks after the initiation of therapy, however by 36 weeks levels rose to initial, pretreatment values. Q_{MAX} showed improvement only after treatment has finished, and only in the second group. Also, after cessation of treatment it is clearly visible that both PVR and Q_{MAX} are significantly more improved in the second group compared to the first one, which implies that the combination of triple therapy and ESWT is crucial for the improvement of voiding conditions. However the long follow-up period showed improvement only in PVR values which is not enough to conclusively confirm the positive effect of combined therapy over a longer period of time. A study performed by John et al. [21] indicates that urethra-anal afferent electrostimulation, applied twice a week, for five weeks, has a positive effect on various chronic prostatitis symptoms including prostatic pain, micturition complaints and total symptom score, which confirm our

claims of potential positive influence of transperineal applied energy for improving outflow obstruction and urinary flow, as with α-blockers, whose effects are already confirmed. Nevertheless, Cheah et al. [10] stated that α-blockers improved urinary symptoms without improving the relatively poor peak urinary flow with NIH IIIB CP/CPPS, thus suggesting the presence of a structural rather than a functional obstruction.

Since pain has more impact on quality of life than urinary symptoms, the importance of our results is clearly visible. In a recent randomized controlled trial, a triple combination of a muscle relaxant (tiocolchicoside), an anti-inflammatory drug (ibuprofen) and an α-blocker (doxazosin) was effective in treating naïve patients, but not superior to an α-blocker alone [3]. This study also indicates significant improvement in all parameters of NIH-CPSI scores after a six-month treatment with triple therapy and showed no advantages over monotherapy. However, their study did not include ESWT therapy, therefore the comparison is not entirely valid. Several studies [7,18,19,22] reported positive effects on pain and QOL scores after ESWT treatment, but long-term effects have rarely been confirmed [22].

Our study demonstrated similar positive results in the second group of patients, with the most significant improvements found in prostatic pain and total NIH-CPSI scores. It is evident that 36 weeks after initiation of treatment, the second group of patients showed significantly better results than the first group in all aspects of NIH-CPSI scores; additionally, in comparison to initial NIH-CPSI score values, significant improvements after 36 weeks is visible in almost every score, excepting urinary and QOL scores, this confirms better long-term effects of combined therapy over triple therapy alone. Our study encompassed only patients with CPPS and no signs of infection, this focussed our research on structural and physiological issues, rather than infective. Considering all these facts together, we conclude that both triple therapy and its combination with ESWT showed significant improvement of symptoms in patients with NIH IIIB CP/CPPS, while combined therapy achieved much better results over the longer time period. Thus ESWT can have a significant influence in improving urinary flow and decreasing PVR, which is of significant importance to those patients. Possible weaknesses in the results of our study are the absence of standard protocols for ESWT therapy and the absence of control groups or placebo therapy.

ESWT therapy in combination with triple therapy is highly effective for NIH IIIB CP/CPPS, especially in relieving prostate pain, reducing total NIH-CPSI score, PVR and Q_{MAX} volume. ESWT deserves a wider clinical application and may in particular be interesting because of its easy operation and high acceptability, the lack of any side effects, and the potential for repetition of the treatment at any time. Our result is essential because according to literature review, no study was found about the efficacy of ESWT on CPPS with long-term, 24 weeks follow-up period; in combination with triple therapy, it could be possible. Hence, according to our result, this positive tendency of symptoms improvement over six months' time could signify positive effectiveness of combined therapy even for longer period of time. More comprehensive future, long-term, randomized, controlled trials could estimate its real potential and ultimate use in patients with chronic prostatic pain syndrome.

Conclusion

ESWT could be of significant importance in the treatment of patients with CPPS. Longer treatment period and proper device application are crucial. Combination with triple therapy could improve the treatment outcome. Thus our study generates new hypotheses, which should be pursued. More randomized-controlled studies are necessary to support our results.

Declaration of interest

No part of this paper has been presented, published, or submitted for publication elsewhere in this or in any other language.

This clinical study was conducted in accordance with the principles laid down in the WMA Declaration of Helsinki along with the strict respect of patient's rights and clinical study protocol. Patient confidentiality and data security are guaranteed.

Authors did not have any support in funding of the paper. The authors of this paper hereby declare that have not received nor shall receive any financial benefits from publishing the paper, neither have they received any financial incentive from a third party. We, the author and coauthors, hereby solemnly declare that we are not in any situation which could give rise to a conflict of interest.

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