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ORIGINAL CLINICAL ARTICLE

Nonablative transurethral Erbium:YAG laser treatment for chronic prostatitis/chronic pelvic pain syndrome: A prospective comparative study

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Abstract

Aims: This prospective study aimed to compare the clinical outcomes between the use of Erbium:YAG (Er:YAG) laser in a nonablative mode, to the use of the pharmacological treatment of oral tadalafil for the treatment of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).

Methods: The laser group received two sessions of Erbium:YAG laser, administered intraurethrally in a long, nonablative train of long pulses (SMOOTH™ mode), applied at the level of the male prostatic urethra. Tadalafil group received oral tadalafil at a dose of 5 mg/day, consecutively for 2 months. Effectiveness was assessed using the International Prostate Symptom Score (IPSS) questionnaire, VAS (visual analogue scale) pain score, and maximum urethral flow at follow-up visits up to 12 months after initiating treatment. Adverse effects were recorded after each treatment and follow-up sessions.

Results: The results show a significant decrease in the IPSS score in both groups up to the 12-month follow-up. The increase in Q-max was evident up to 3-months follow-up in the tadalafil group and up to 6 months in the laser group. The decrease in the VAS pain score was also significant in both treatment groups, lasting up to 3 months in the tadalafil group and up to 6 months in the laser group.

Conclusions: The nonablative Er:YAG SMOOTH™ laser seems to be a promising treatment for this widely occurring condition. More studies are needed to confirm its safety and efficacy.

KEYWORDS

chronic prostatitis with chronic pelvic pain syndrome, nonablative Er:YAG laser therapy, tadalafil

1 | INTRODUCTION

Chronic prostatitis is very common among adult men, with a prevalence of up to 14% of the entire male population.[1,2] Prostatitis is the most common diagnosis (>50%) in men visiting outpatient urological clinics.[3]

Although category III or chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is the most prevalent form of prostatitis,[4] its causes are largely unknown and treatments often fail to alleviate symptoms in the long term. In contrast, patients suffering from type I and II prostatitis are successfully treated with antibiotics, as a uropathogen or an infectious agent is usually identified as the cause.[2]

CP/CPPS is characterized by pain in the perineum and tenderness in the prostate along with various urological symptoms (urgency, frequency, and low urethral pressure) and sometimes also ejaculatory symptoms, such as painful ejaculation. More than 20% of patients affected by CP/CPPS also suffer from depressive symptoms, illustrating the highly debilitative nature of the condition.[1]

Currently used treatments for CP/CPPS are mainly pharmacological, including α-blockers, 5-α reductase inhibitors, anti-inflammatories, antibiotics, phytotherapy, allopurinol, botulinum toxin, and traditional Chinese medicine.[5] Nonpharmacological therapies include acupuncture, prostatic massage, extracorporeal shockwave therapy, pulsed magnetic field therapy, transrectal and transurethral thermotherapy, and others.[6] Some of the abovementioned therapies alleviate symptoms by improving vascularization and blood flow of the prostate and periprostatic area. In this study, we aimed to evaluate a new approach to the treatment of CP/CPPS—using the transurethral application of the Erbium:YAG (Er:YAG) laser with nonablative SMOOTH™ mode. It works by the thermal pulsing of the treated surface, with pulses in the microseconds-range combined into long (several hundred milliseconds) sequences. Each laser micropulse sharply increases tissue temperature and acts as a stimulative trigger.[7,8] Long pulse trains cause slower diffusion of heat to deeper layers of the skin or mucosa, up to several hundred micrometers in depth. Initially, the trigger vasodilation and then stimulation of fibroblasts and collagen remodeling.[9,10] It has been shown to improve vascularization and alleviate symptoms of genitourinary syndrome of menopause (GSM) in women, including irritation, dryness, and pain.[11,12] It has also been used intraurethrally in women to alleviate urinary symptoms of GSM.[13,14] Transurethral thermal therapy using microwaves has previously been shown to be promising in the treatment of CP/CPPS in men.[6] In this study, we aimed to assess the safety and effectiveness of transurethral nonablative Er:YAG laser therapy applied at the level of the male prostatic urethra and to compare it with pharmacological treatment (5 mg oral tadalafil) for the treatment of CP/CPPS.

2 | MATERIALS AND METHODS

This was a prospective study, conducted between April and September of 2017. The study was performed according to the Helsinki declaration and was approved by the institutional medical ethics committee (No. 03/2017) and recorded in the Clinicaltrials.gov register (identification No NCT04446598). All patients had signed informed consent for participation in the study.

The inclusion criteria were: Clinical diagnosis of CP/CPPS with characteristic symptoms of perineal pain and urinary symptoms of dysuria and urinary frequency; negative urine culture after a prostatic massage; prostatic volume less than 50 cc in prostatic ultrasound; and obstructive uroflowmetric pattern with a Q-max value between 10 and 15 ml/s. Only patients without any previously existing conditions that could result in pelvic pain/urinary issues were included in the study.

Thirty-six patients were enrolled in the study, arbitrarily allocated into two groups—the laser group, comprising 16 patients and the tadalafil group, comprising 20 patients. In the laser group, patients received two sessions of Er:YAG intraurethral laser in nonablative SMOOTH™ mode with a 1-month interval between sessions. The tadalafil group was treated with daily oral administration of tadalafil at a dose of 5 mg/day, consecutively for 2 months.

Follow-up assessments were scheduled at 1, 3, 6, and 12 months after the first laser session in the laser group; whereas, in the tadalafil group the follow-up assessments were performed at 1, 3, 6, and 12 months from the start of the oral administration of the drug. Outcome measures were used to evaluate pain and urinary symptoms. Patient assessment of pain on the 0–10 VAS (visual analogue scale) was used to measure chronic pelvic pain at baseline and at each follow-up. Urinary symptoms were evaluated using different outcome measures: Objectively, by measuring the maximum urethral flow value (Q-max) using uroflowmetry; and subjectively, using the International Prostate Symptom Score (IPSS) questionnaire, which consists of seven questions concerning urinary symptoms and one question concerning quality of life.[15] The IPSS total score range is from 0 to 35, from asymptomatic (score 0), mildly symptomatic (1–7), moderately symptomatic (8–19) to severely symptomatic (20–35).

The impact of the symptoms on quality of life was also assessed using a single question to determine the patients' satisfaction with the treatment results; the patients had to choose a grade from a 7-point Likert scale

with grading as follows: 0—"Very Satisfied," 1—"Mostly Satisfied," 2—"Somewhat Satisfied," 3—"Neither Satisfied nor Unsatisfied," 4—"Somewhat Unsatisfied," 5—"Mostly Unsatisfied," and 6 —"Very Unsatisfied"). Patient satisfaction was assessed in both groups at the 6- and 12-month follow-ups.

Adverse effects were recorded after each treatment and follow-up sessions.

2.1 | Laser procedure

The procedure was performed using an SP Dynamis laser device (Fotona), with a special intraurethral cannula which was used to deliver the laser beam to circumferentially cover the urethral wall.

An endoscope with a camera was inserted inside the urethra to enable the controlled placing of the sterile cannula along the whole length of the urethra. The endoscope was then removed. Laser parameters used were: 4-mm spot size, 1.5 J/cm^2, 1.4 Hz, in the nonablative SMOOTH™ mode. Four SMOOTH™ pulses were delivered at each location throughout the urethra. The sterile cannula was moved from the proximal to distal direction, towards the urethral orifice, and laser energy was delivered along the prosthetic part of the urethra in 2.5-mm intervals. After the completion of the first pass, five more passes were made, as described above. The procedure was performed under sedation and was typically completed in about 15 min. All patients left the doctor's office within an hour and returned to normal activities on the same day. The patients received two laser procedures, with a 1-month interval between treatments.

2.2 | Statistical analysis

Descriptive and comparative analyses were performed using Prism software (GraphPad). The Friedman test with multiple comparisons was used in comparing the values at baseline to the follow-up values inside each group. The values between groups were compared using the Kruskal–Wallis test with multiple comparisons.

3 | RESULTS

The average age of patients was 41.3 (31–47) years in the laser group and 40.6 (30–45) in the tadalafil group. There were no statistically significant differences between groups at baseline values of any diagnostic or outcome measures. All the evaluated symptoms showed a statistically significant improvement in the follow-ups at one month and at 3 months in both groups (Table 1). The improvement in chronic pelvic pain measured by VAS showed a significant decrease in both groups—the highest decrease in VAS pain score was evident after 3 months from initiating therapy. In the laser group, the decrease in pain was still significant at the 6-month follow-up, whereas the value at 12 months did not

TABLE 1 Outcome measures in laser and tadalafil group at baseline and at follow-ups

	Baseline	1 month	3 months	6 months	12 months
Laser group ($N = 16$)					
Pain (0–10 VAS)	7.75 (0.44)	**3.56** (0.62)*	**1.38** (0.58)*	**2.31** (0.83)*	5.88 (0.38)
Dysuria (0–10 VAS)	6.75 (0.67)	**3** (0.64)*	**1.44** (0.7)*	**2.44** (0.77)*	3.62 (0.49)
IPSS score	26 (1.59)	14.88 (2.31)	**4.69** (2.19)*	**5.88** (2.23)*	**9.69** (1.68)*
Q flow max (ml/min)	12.94 (0.43)	**15.06** (0.64)*	**16.63** (0.69)*	**16.94** (0.64)*	/
Patient satisfaction (Likert scale: From 0 [*very satisfied*] to 6 [*very unsatisfied*])	/	/	/	1.62 (0.27)	1.87 (0.30)
Tadalafil group ($N = 20$)					
Pain (0–10 VAS)	7.6 (0.39)	**2.85** (0.35)*	**1** (0.28)*	5.4 (0.51)	5.7 (0.38)
Dysuria (0–10 VAS)	6.45 (0.51)	**3.35** (0.47)*	**1.05** (0.25)*	**2.5** (0.32)*	**3.1** (0.29)*
IPSS score	19.15 (1.59)	**10.2** (1.71)*	**4.15** (2.11)*	**4.75** (0.77)*	**8.9** (1.07)*
Q flow max (ml/min)	12.95 (1.85)	**16.2** (0.5)*	**16.75** (0.54)*	**15.55** (0.47)*	/
Patient satisfaction (Likert scale: From 0 [very satisfied] to 6 [very unsatisfied])	/	/	/	2.65 (0.30)	2.95 (0.23)

Note: Numbers represent means with standard error in parentheses. Descriptive and comparative analyses were performed using Prism software (GraphPad). The Friedman test with multiple comparisons was used in comparing the values at baseline to the follow-up values inside each group. The bold values represent statistical significant difference compared to baseline.

Abbreviations: IPSS, International Prostate Symptom Score; VAS, visual analogue scale.

*$p < .05$, statistical significance of the measurement compared with baseline.

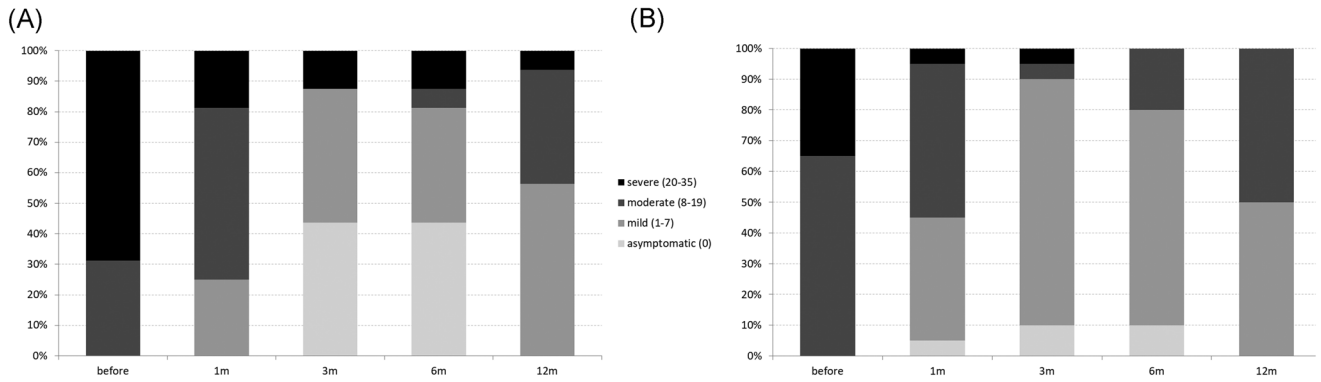

FIGURE 1 (A) International Prostate Symptom Scores (IPSS) of the laser group. The graph shows the proportions of laser group patients ($N = 16$) in each IPSS severity category at baseline and at follow-ups. (B) IPSS of the tadalafil group. The graph shows the proportions of tadalafil group patients ($N = 20$) in each IPSS severity category at baseline and at follow-ups

significantly differ from baseline (Table 1 and Figure 3A). In the tadalafil group, the decrease in pain was significant at the 1- and 3-month follow-ups after initiating therapy. At 6 and 12 months, the decrease in pain was not significant. The decrease in dysuria (Table 1 and Figure 3B) was significant in both groups, and the effects were long-lasting; in the tadalafil group, there was a significant decrease at all follow-ups, including at 12 months after initiating treatment, whereas, in the laser group, a significant decrease was evident after 6 months, whereas, at 12 months the decrease was still marked, although not statistically significant ($p = .06$).

Urinary symptoms were evaluated using an IPSS questionnaire. The results have shown a statistically significant improvement in both groups, which was most pronounced at follow-up 3 months after initiating treatment, but still remained statistically significant at the 12-month follow-up (Table 1 and Figure 1A,B).

The maximum urethral flow–Q-max, measured by uroflowmetry, showed a significant improvement in both groups, ranging from approximately 2–4 ml/s improvement with respect to the starting values, and was maintained after 6 months (Table 1).

Patient satisfaction with the treatment was measured at the 6- and 12-month follow-ups. The satisfaction following treatment at the 12-month follow-up was significantly better in the laser group compared to the tadalafil group. At the 6-month follow-up, the difference was not statistically significant.

4 | DISCUSSION

CP/CPPS is highly prevalent and causes physical and psychological distress. The majority of patients presenting with CP/CPPS symptoms do not have a proven bacterial infection or prostatic hyperplasia and the etiology of the condition is still largely unknown. The need for effective treatments with a good safety profile is high.

This prospective parallel cohort study has shown that the innovative nonablative transurethral Er:YAG laser treatment with thermal SMOOTH™ mode is equally as effective as tadalafil in relieving symptoms of CP/CPPS, with significant improvement of symptoms lasting for up to a year after only two treatment sessions.

This is the first completed study that has investigated the use of transurethral CP/CPPS treatment using nonablative Er:YAG SMOOTH™ laser, offering a completely new approach to the treatment of this difficult-to-treat condition. Intraurethral Er:YAG SMOOTH™ mode has already been shown to be successful in prospective trials for treating female intrinsic sphincter deficiency and also in menopause-related urinary incontinence.[14,16] Intravaginal SMOOTH™ Er:YAG has been shown to improve clinical symptoms as well as tissue histology. The results have shown an increase in the thickness of the vaginal wall and improved tissue structure and vascularization of the vaginal mucosa.[17–20]

The proposed mechanism of action of the nonablative Er:YAG SMOOTH™ mode is heat-pulsing of the urethral mucosa, which achieves a dual tissue regeneration effect[7]: first, microsecond heat pulses act as triggers of paracrine signaling pathways that stimulate tissue regeneration. Second, bulk heating of the mucosa causes a strong effect of vasodilation in the prostatic portion of the urethra that markedly increases oxygenation and nutrition at the loco-regional level, as well as activation of fibroblasts and stimulation of new collagen formation.[21] The result is better tissue architecture with increased thickness of the epithelium and better vascularization, resulting in an anti-inflammatory and angiogenic effect.[11,14,18] By improving the vascularization of the prostatic portion of the urethra, the prostatic parenchyma is indirectly improved, explaining the improvement of voiding symptoms and pelvic pain.

Although they are not yet standardly used, there are existing somewhat analogous approaches of transurethral thermotherapy, using different methods of heating the tissue. Transurethral therapy using microwaves has been shown effective in published clinical trials.[22–24] Thansrectal thermotherapy using radiofrequency was also shown to be effective in the study by Gao et al.[25] They have also shown a significant decrease in the production of reactive oxygen species, which often accompanies inflammatory processes. Decreasing the generation of reactive oxygen species and production might be a consequence of better vascularization and an influx of immunomodulatory factors. Still, although there is proof of clinical effectiveness, the exact mechanisms behind thermal therapy for CP/CPPS remain largely unknown.

We believe that the main advantage of the transurethral nonablative Er:YAG laser treatment for CP/CPPS is its minimally invasive nature. Compared to microwave energy or radiofrequency, nonablative Er:YAG laser is an inherently safer form of thermal therapy, as it enables precise control of reached temperature and more importantly, the depth of heat diffusion. Erbium:YAG laser light of 2940 nm is very highly absorbed in water, so it is optically completely absorbed at the tissue surface, with only heat being diffused below the tissue surface. The depth of penetration and the achieved temperature can be precisely controlled by the properties of the SMOOTH™ pulse train, which are preprogrammed in the device for achieving the optimal amount of pulsed heating. Therefore, the heating is superficial and controlled, reaching a maximum of 60–65°C in short pulses, without damaging the tissue surface or the possibility of injuring underlying structures.

In this study, we have used a pharmacological tadalafil treatment as a comparator because of a somewhat comparative proposed mechanism of action with respect to increasing vascularity and blood flow. Tadalafil is a drug inhibitor of the enzyme phosphodiesterase type 5, responsible for deactivating the nitric oxide vasodilator.[26] It has been proven effective in several randomized drug trials for treating benign prostate hyperplasia.[27–29] Benelli et al.[30] have shown that a 5-mg dose of tadalafil was also effective in reducing the symptoms of CP/CPPS after 4 weeks of daily administration, the same dose that was used in our study.

Our results have shown that Er:YAG SMOOTH™ transurethral therapy of CP/CPPS is effective in alleviating pain and urinary symptoms of CP/CPPS and that the effectiveness is similar to that of tadalafil administered in a daily dose of 5 mg, which was the primary endpoint of the study.

Both treatments have shown beneficial for reducing pelvic pain, but the effect of the laser treatment lasted longer and was more pronounced. As pain is often the most disturbing of all symptoms of CP/CPPS, it is very important to emphasize the large improvement of the VAS pain score seen up to 6 months after the laser treatment. The patient satisfaction with the procedure was high, probably reflecting the magnitude of the pain reduction.

Both treatments have shown a very similar effect in alleviating the symptoms of dysuria, the effect lasted up to 6 months for both treatments. The IPSS scores were very significantly decreased after both treatments and the results have persisted up to the 12-month follow-up. Hiramatsu et al.[31] have recently found that tadalafil administration led to a larger decrease of IPSS scores in patients with benign prostatic hyperplasia that also had more severe pain scores, compared to those that did not experience high levels of pain. That is consistent with our results, as all of the patients in our study had high pain scores and have shown very pronounced IPSS improvement after both treatments (Figure 2). Lee et al.[32] have recently shown that patients with

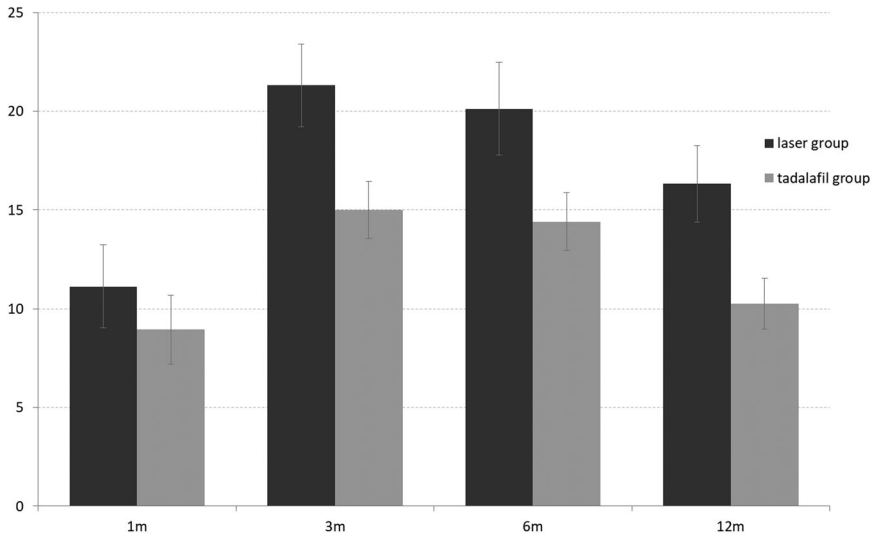

FIGURE 2 Decrease in International Prostate Symptom Scores (IPSS). The graph shows the mean decrease (±SEM) of IPSS scores in both groups (laser group, $N = 16$; tadalafil group, $N = 20$) at each follow-up session in relation to the baseline IPSS score

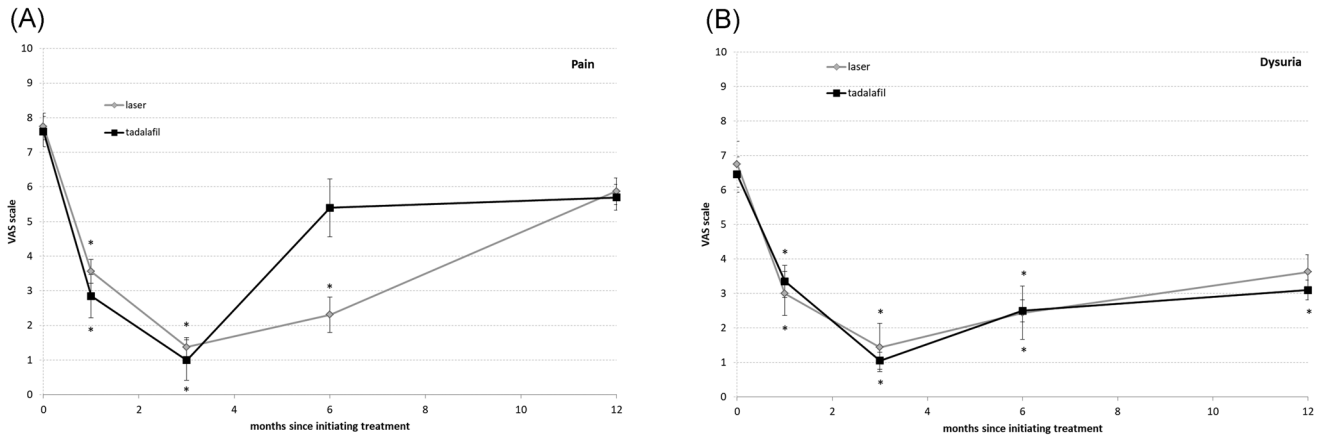

FIGURE 3 (A) The graph shows mean (±SEM) VAS (visual analogue scale) pain scores at baseline and follow-ups in both groups (laser group, $N = 16$; tadalafil group, $N = 20$). (B) The graph shows mean (±SEM) VAS dysuria scores at baseline and follow-ups in both groups (laser group, $N = 16$; tadalafil group, $N = 20$); $^*p < .05$ statistical significance from the baseline value

higher pain scores on the NIH-CPSI questionnaire also had higher total IPSS scores. The magnitude of the improvement might be also connected with the fact that the study participants were younger men, with a median age of 41, whereas most of the other reported studies included significantly older men.

The secondary endpoint of the study is to evaluate the safety of the Er:YAG treatment in comparison with tadalafil. Our study has shown that the treatment has an excellent safety profile, as there have been no reported adverse events. The same was true for the tadalafil group. This corroborates the results of previous studies on the urogynecological application of Er:YAG SMOOTH™ laser in women, which have also found the treatment to be safe. Other advantages of this therapy are that it achieves long-term effects without daily administration (eliminating issues with patient compliance) and the fact that the treatment is ambulatory, without any downtime needed.

The limitations of this study are: The absence of the placebo group; the small sample sizes; the allocation of patients to groups being arbitrary and not systematically randomized, therefore, selection bias was still possible, although the demographic parameters did not significantly differ between groups. Larger randomized controlled trials are needed to further evaluate the clinical effectiveness of this promising therapy.

5 | CONCLUSION

This study indicates that innovative nonablative transurethral Er:YAG laser treatment with thermal SMOOTH™ mode is a promising minimally invasive therapy for relieving symptoms of CP/CPPS.

Prospective randomized studies with a larger number of patients are needed to confirm our initial findings.

CONFLICT OF INTERESTS

Irena Hreljac and Zdenko Vižintin are currently employed at Fotona d.o.o.

AUTHOR CONTRIBUTIONS

Conceptualization: Adrián Gaspar and Zdenko Vižintin. *Supervision*: Adrián Gaspar. *Methodology and investigation*: Adrián Gaspar, Joaquín Silva, Gustavo Silva, Raúl Anchelerguez, Jorge Prats, Alejandro Sagaz, Eduardo Rovere, Mauricio Alastra, Juan Pino, Alejandro Jauregui, Marcos Farrugia, Fabricio Villaroel, Jonathan Guareschi, Maximiliano Vega, Emanuel Biasiori, Emanuel Moyano, and Antonio La Rosa. *Formal analysis*: Irena Hreljac. *Writing original draft*: Adrián Gaspar and Irena Hreljac. *Writing review and editing*: Adrián Gaspar, Zdenko Vižintin, and Irena Hreljac.

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