

Original article

Ozonated olive oil, a new alternative in the treatment of *Helicobacter pylori*

Yanisley Martin Serrano M.D
Javier Cecilio Cespedes Suarez M.D
Isidro Hernández Ramos M.D
Cardiozono Medical center, Luanda, Angola

Key words

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Summary

There are multiple treatments to eradicate *Helicobacter pylori*. However, the infection caused by it is a problem not yet resolved. According to existing schemes, the resistance rates keep on increasing. Globally, the standard triple therapy has lost the efficacy that had in the past and the sequential therapy is not equally effective on all sites.

For these reasons, we took advantage of the biological effects of ozonated oils and conducted this trial. The experimental design included 48 patients with positive diagnosis for *H. pylori* (Respiratory urease test and Antigen fecal test) and treated them with soft capsules (Ozonated olive oil) made of ozonized sunflower oil with peroxide index of 500 mEqO₂/kg. The softgels were given to the patients 3 times a day for 30 days. At the end of the treatment the diagnosis test was repeated and a new cycle of treatment was performed to patients who continued to have a positive test.

The results of the study in terms of eradication (> 93%) of *H. pylori* were similar to the efficacy of triple standard antibiotic therapy (~80%). In addition, it has huge advantages in terms of the absence of collateral symptoms and antimicrobial resistance. Therefore, Ozonated olive oil is considered an alternative in the treatment of *H. pylori* infection and symptoms that accompany it, such as heartburn, chronic gastritis and peptic ulcer.

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Introducción

Infection with *Helicobacter pylori* is a problem not solved yet. In the last 13 years, more than 6000 works have been published on *Helicobacter pylori*,¹ data that clearly expresses the enormous interest that this microorganism has aroused in the international scientific community. At least 13 species are currently accepted within this genus, with *Helicobacter cholecystus* being the latest proposal.² The type species is *Helicobacter pylori*, described by Marshall and Warren in 1983,³ considered the agent that produces active chronic gastritis, gastroduodenal ulcer, and has recently been included as a type 1 biological carcinogen.⁴ It should be remembered that These microorganisms have been known as such since 1989,⁵ but until that date and since 1983 they were known as *Campylobacter pyloridis* / *pylori*.

The *Helicobacter pylori* is a gram-negative bacterium that colonizes the stomach and is probably the most common chronic bacterial infection in the world,^{six} more than 50% of the world 's population is infected with *H. pylori*. In Africa, Mexico, South and Central America, *H. pylori* infection reaches a prevalence of 70-90%.

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The use of antibiotics to eradicate *H. pylori* has greatly altered the incidence and natural history of peptic ulcer.⁹ The resistance of *H. pylori* to macrolides, fluoroquinolones, and nitroimidazoles has increased due to the widespread use of these antibiotics with multiple indications. Increased resistance to antibiotics diminishes the efficacy of current triple therapy regimens and makes our ability to treat peptic ulcer with antibiotics increasingly difficult.¹⁰

The *Helicobacter pylori* is sensitive to many antibacterial agents *in vitro*; however, in clinical practice it is difficult to eradicate the stomach bacteria,¹¹ the ideal strategy has not yet been found, not only in terms of the antimicrobials to be used, but also with regard to the doses and duration of treatment.¹² Currently, the need to use a combination of at least two or three drugs, including antimicrobials and substances used to treat ulcers, such as bismuth salts, H₂ receptor antagonists or proton pump inhibitors, seems to be established. gastric parietal cells. These compounds act synergistically with antimicrobials, although the reasons for this are not known. There are *in vitro* studies that show synergy in some combinations of antibiotics and compounds such as omeprazole, lansoprazole and bismuth salts,¹³ and this effect seems to correlate with the possibility of better eradicating the bacteria when antimicrobials are used together with other compounds in the clinical practice.¹⁴ The truth is that therapeutic regimens are under continuous development and an ideal formula for their eradication has not yet been found.¹⁵

Ozone has a very high germicidal power, its great disadvantage is that it is extremely unstable, so it must be generated practically before being used. However, a controlled reaction of ozone with unsaturated fatty acids present in vegetable oils produces oxidized derivatives with high germicidal, immunostimulating and tissue repairing activity, being able to be stabilized for a period of up to 2-3 years,^{16, 17} a fact that they link it with the chemical, pharmaceutical and cosmetic industries. Its stability and biological benefits allow its use in multiple pathologies, which is supported by pre-clinical and clinical studies; The use of ozonated oils has been effective in the treatment of viral,

bacterial, fungal and protozoal diseases.^{18, 19} The first evidences on the clinical use of ozonated oils appear in the scientific literature since 1859.¹⁶

Inspired by these facts and taking advantage of the biological effects of ozonated oils, we carried out this work in order to evaluate the effectiveness of the administration of ozonated sunflower oil in the eradication of *Helicobacter pylori*.

Materials and method

A monocentric retrospective clinical study was carried out that included the period from March 2015 to February 2016, in a total of 48 patients who attended the Luanda Cardiozono Medical Center, Angola. All selected patients underwent a thorough physical examination which was accompanied by non-invasive analytical tests (respiratory urease test and fecal antigen test), confirming the diagnosis of *Helicobacter pylori* infection, the results of which were included in the clinical history. The patients included in this study signed the informed consent, not exposing themselves to additional risks in any case.

The research protocol was submitted for discussion by the participating researchers, for review and approval by the ethics and institutional review committee of the Centro Medico Cardiozono. The protocol was executed only after its approval, complying with the ethical procedures for medical research on human beings established in the Declaration of Helsinki issued by the World Medical Assembly.²⁰

Formulation used : Soft gelatin capsules: Ozonated olive oil capsules is a food supplement, each capsule contains 1.2 g of a mixture of vegetable oils with a high content of omega 3 and monounsaturated fatty acids (omega 9), an ozonated sunflower oil fraction with a peroxide index of 500 meqO₂ / kg and a natural mixture of tocopherols and other antioxidants is also part of this supplement.

Inclusion criteria : Patients of both genders older than 12 years of age, having lived in Angola during the last two years, not having received therapy with antibiotics, bismuth compounds, proton pump inhibitors or other treatments, during the three months previous. The presence of *H. pylori* was demonstrated in all patients by means of the respiratory urease test, together with the detection of specific *H. pylori* antigens in the feces of the patients. Of the 48 patients, there were 32 who presented clinical symptoms of chronic gastritis, the rest were asymptomatic.

Exclusion criteria : Children under 12 years of age, pregnancy and lactation. Participation in another clinical study or use of a drug in the experimental phase, The unwillingness of the subject to participate in the study. The exit criteria were: Refusal of the subject to continue in the study, death or appearance of psychiatric illness.

Treatment: The treatment protocol consisted of the oral administration of Ozonated olive oil for 30 days, 1 capsule thirty minutes before breakfast, lunch and dinner to promote its direct action on the bacteria and delivered to the 48 patients infected with *H. pylori*. The patients were monitored weekly with

medical visits during the thirty days of treatment, all patients were asked to voluntarily indicate if they presented adverse effects to the treatment.

Eradication control : To determine the eradication of *H. pylori* , the analytical tests (respiratory urease test and fecal antigen test) were repeated, both immediately after finishing the treatment and 30 days after it ended. *H. pylori* was considered eradicated when *laboratory* tests 30 days after the end of treatment were negative. A second 30-day cycle of treatment was considered in patients where the *H. pylori* assay continued to be positive.

The information was processed statistically: A descriptive analysis was made in which the mean or median and the standard deviation or maximum and minimum value (depending on the type of data) were calculated for each sample. Analysis to detect aberrant points (*outliers*). Levene's test of homogeneity of variance. Simple classification ANOVA. To determine statistical differences between the proportions of patients before and after treatment, the McNemar test was used. The data were processed using the statistical package STATISTICA Version 4.5 for WINDOWS

Results

Of the total sample (48 patients), 36 were male and 12 female. The average age was 40 years (minimum value 21 years, maximum 62 years).

Of the 32 patients with clinical symptoms of chronic gastritis (66% of the total), it completely disappeared in 25 patients and in the rest (7 patients), their symptoms improved (Table 1). Side effects associated with the treatment were not observed in any of the patients.

Table 1. Evolution of chronic gastritis symptoms with treatment.

GENDER	Patients with clinical symptoms of chronic gastritis prior to the treatment	Patients with total disappearance of symptoms after the 1st cycle of treatment.	Patients with clinical improvement of symptoms after both treatment cycles .	Patients with persistence of symptoms of chronic gastritis after both cycles.
MALE	15	11	4	0
FEMALE	17	14	3	0
TOTAL	32	25	7	0

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The analytical examination performed on all 48 patients immediately after completing the treatment according to the protocol, was negative in 39 patients, that is, 81.25%, only in 9 patients both tests remained positive (respiratory urease test and fecal antigen test). 30 days after finishing the treatment, we repeated the tests again on all patients, observing the same results. It was decided to repeat 30 more days of treatment in those patients who tested positive for *H. pylori* , it was carried out under strict medical control, obtaining complete negativization of the complementary tests in 6 more patients, for a final

result of 93.75% of Healing, a result that exceeds 80% that until now are considered favorable with the usual triple therapy (Table 2).

Table 2. Evolution of the presence of *H. pylori* with treatment.

GENDER	Patients with both positive diagnostic tests for <i>H. pylori</i> prior to the treatment	Patients with both negative diagnostic tests after the 1st treatment cycle.	Patients with both test diagnostics negative after the 2nd cycle of treatment.	Patients with both positive diagnostic tests after both cycles.
MALE	25	19	4	2
FEMALE	23	20	2	1
TOTAL	48	39	6	3

Discussion

There is no doubt that triple antibiotic therapy against *Helicobacter pylori* continues to be the treatment of choice for the entire medical community, but even the eradication rates are still insufficient, so it is reasonable to delve into the subject.²¹

Today the use of proton pump inhibitors (PPIs) such as omeprazole, lansoprazole, pantoprazole among others, is part of all antimicrobial formulations against *H. pylori* however its effectiveness is still controversial, some *in vitro* studies allege that it has a synergistic effect with antibiotics,¹³ others suggest that it could improve the damage caused to the gastric mucosa by the bacteria itself or by the indiscriminate use of antibiotics, thus favoring its repair or healing process; However, something that is very well demonstrated is that PPIs increase the pH of the stomach making it less acidic, conditions similar to those created by the bacteria itself for its survival, it is known that *H. pylori* is endowed with an enzyme called urease, which converts urea into CO₂ and ammonia, the latter decreases local acidity, favoring its development and growth; However, we must highlight the importance of keeping the pH of the stomach within its normal values (between 1.5 and 3.5), this acidity creates an ideal environment for pepsin, which is the main digestive enzyme to break down food and promote the digestive process, this acidity also helps to maintain the balance of the intestinal microbiota.

Another no less important aspect is that the presence of *H. pylori* causes, to a certain extent, an iron deficiency anemia, a situation similar to that caused by all PPIs by reducing iron absorption.

The effectiveness of the recommended schemes for the eradication of *H. pylori* infection has decreased over time, a decrease in the effectiveness of the eradication schemes recommended in international consensus has been documented, since, to consider them effective, These must achieve an eradication rate greater than 80.00%.^{22, 23} This is attributed in part to an increase in resistance to any of the antibiotics included in the regimens.^{24, 25}

There are several hypotheses that try to explain the mechanism of action of ozonated oils, one of them suggests that it is likely that stable triozoneides when in contact with exudates from wounds that are at a temperature of approximately 37°C, decompose and generate ozone, this ozone would form hydrogen

peroxide and lipoperoxides that would be responsible for the regenerative and disinfectant effects.²⁶ It is suggested that the slow release of ozone in wounds favors the healing process, not only due to local disinfection but also by promoting the release of cytokines with reparative effects at the local level.^{27, 28}

Regarding the antimicrobial effects, it has been shown that not only ozonides are responsible for these effects, but also other components of the oils.¹⁷ When ozonated oil is put in contact with a microorganism, severe damage to its cytoplasm can be seen.²⁹ In addition to causing a reduction in the content of nucleic acids that corresponds to a reduction in lipase, amylase, keratinase and urease activity.³⁰

In summary, the antimicrobial and healing mechanisms of ozonized oils could respond to:

- 1) **Direct oxidation** : the release of ozone, trioxolanes and lipoperoxides could directly destroy microorganisms through oxidation.^{27, 29}
- 2) **Cytotoxicity** : compounds such as trioxolanes, lipoperoxides and aldehydes, are cytotoxic for microorganisms and can inactivate key enzymatic pathways for their survival.³⁰
- 3) **Release of growth factors** : Various components of ozonated oils can release growth factors such as PDGF, TGF- β and VEGF that can influence tissue remodeling.³¹
- 4) **Oxidative pre-conditioning** : local oxidation of tissues by ozonated oil components can stimulate endogenous antioxidant mechanisms^{32, 33} and promote tissue repair.³⁴

Studies carried out at the Ozone Research Center in Havana, Cuba, demonstrated the effectiveness of ozonated sunflower oil on *Helicobacter pylori*. An *in vitro* study was carried out on samples of the mucosa of the digestive system contaminated with *Helicobacter pylori* and treated with ozonized sunflower oil. Through the urease test, the effectiveness of the ozonized sunflower oil was evaluated. *Helicobacter pylori* growth was not observed in any of the samples treated with ozonated sunflower oil.³⁵

If we analyze the above all the details and results obtained in this study with the administration of Ozonated olive oil, it is very easy to realize the enormous advantages that the use of ozonated sunflower oil has over the usual triple antibiotic therapy.

- Ozonated oil does not modify the pH of the stomach, which is very important for the proper digestion of food and the maintenance of the balance of the intestinal microbiota.
- Ozonated sunflower oil does not interfere with iron absorption, so it is not related to iron deficiency anemia that could occur in these patients as a cause of prolonged use of PPIs and the presence of *H. pylori*.
- The mechanism of action by which it eliminates the bacteria is by direct oxidation and cytotoxicity; It is known that *H. pylori* possesses an antioxidant mechanism that is capable of neutralizing the reactive oxygen species generated by neutrophils and macrophages as a result of the local inflammatory response, but apparently this antioxidant system is insufficient to neutralize the oxidative power of the peroxide species present in Ozonated olive oil capsules
- The disappearance of symptoms such as gastritis and heartburn could be related on the one hand by the *release of growth factors*; various

components of ozonated oils can release growth factors such as PDGF, TGF- β and VEGF that can influence tissue remodeling.³¹ On the other hand, by an *oxidative re-conditioning* mechanism : the local oxidation of tissues by the components of ozonated oils can stimulate endogenous antioxidant mechanisms^{32,33} and promote tissue repair.³⁴

- We cannot say that the results exceed those obtained so far with triple antibiotic therapy, but we can highlight the safety of the use of Ozonated olive oil in terms of side effects and antimicrobial resistance .

Conclusions

The results of the study regarding the eradication of *H. pylori* are similar to those obtained with the usual triple antibiotic therapy, however, it has enormous advantages in terms of the absence of collateral symptoms and antimicrobial resistance, therefore, we consider that Ozonated olive oil it constitutes an alternative in the treatment of *H. pylori infection* , and in accompanying symptoms such as heartburn, chronic gastritis, and peptic ulcer.

Recommendations

Due to the complexity of *H. pylori infection* and its treatment, we must continue in the continuous search for a 100% effective treatment, being perhaps the development of a vaccine probably the only strategy that can make a difference in the incidence and prevalence of *H. pylori infection* around the world. As long as a solution of this kind is not reached, the administration of therapies such as ozonated oils, with high efficacy and a low rate of adverse events, could be a solution. Larger clinical studies are required in this regard.

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