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Eficacy of sulfurous water from Mangalia in Helicobacter Pylori infection: a clinical study

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Abstract: Background: Mangalia balneary resort is situated in the south of the Black Sea and uses sulphurous water springs for rehabilitation therapy. The purpose of this study is to demonstrate the effectiveness of Mangalia sulphurous water on Helicobacter Pylori (H. Pylori) infection. **Methods**: Considering that sulfurous water has a bacteriostatic effect and that most gastritis are caused by H. Pylori infection, we propose that a group of 27 H. Pylori positive patients with or without digestive symptoms ingest sulfurous water daily, for a few days. **Results**: At the end of the study, 15 of the patients tested negative for H pylori antigen. **Conclusions**: The curative effects are due to the bacteriostatic effect of sulfurous water and its stimulating action on the digestive tube.

Keywords: spinal cord injury, high spinal cord lesions, neurological deficit, scales

1. Introduction

Considering that approximately half of the world's population is colonized with Helicobacter Pylori (H. Pylori) [1] and the diversity of pathology induced by it, it is critical to diagnose, eradicate and prevent the spread of this pathogen [2,3].

Classified by the World Health Organization (WHO) as a class I carcinogen [4], H. Pylori is involved in the pathogenesis of chronic gastritis, gastric ulcer and gastric cancer [5,6], by inducing a chronic inflammation and finally a carcinogenic process [7]. There are recent studies that correlate H. Pylori infection with extra-intestinal hematological, metabolic, cardio-vascular, allergic and neurological pathology [8,9].

The reduction of systemic inflammation following the eradication of H. Pylori infection has been proven [10] and implicitly, the risk of developing the mentioned pathology also decreased [11,12].

The drug treatment of H. Pylori infection is chosen based on the local resistance of the bacteria, the availability of drugs and the tolerance to the previously used medication and possible allergies [13,14,15]. Thus, the medication used to treat H. Pylori infection can be of the following type: triple therapy (proton pump inhibitor combination with amoxicillin and clarithromycin), quadruple bismuth-based therapy or combinations with other antibiotics, as second-line therapy [16,17]. According to some recent studies, first-line treatment has different success rate according to geographic area, resistant strains still determining failure to treatment [18,19]. In addition to the effect of drug treatment, the effect of food, plant extracts and supplements on H. Pylori (and inflammation produced by bacteria) was also investigated, for example: Korean red ginseng, garlic extract, omega 3, kimchi and probiotics [20].

The present study is based on the bacteriostatic effect of sulfurous water [21,22] and the fact that its ingestion has effects on the gastrointestinal tract, stimulating gastric secretion, the activity of gastric enzymes and intestinal peristalsis through hydrogen sulfide [23,24].

The purpose of this study is to demonstrate the effectiveness of Mangalia sulphurous water on Helicobacter Pylori infection.

2. Materials and Methods

This study began in February 2023 and was carried out on a group of 27 patients identified with positive Helicobacter Pylori Ag (fecal antigen test - SATs). These patients were either hospitalized in the Mangalia Spa and Recovery Sanatorium or identified as H. Pylori positive by family doctors in Mangalia. Along with the H. Pylori antigen testing, blood tests were performed on the patients regarding the inflammatory status, kidney and liver function and lipid profile. The VAS (Visual Analogic Scale) was applied to assess the pain in all patients complaining of it. These patients drank sulfurous water from the F3 Mangalia spring for 6 -13 days, in an amount calculated individually, according to the Nievre formula (the amount of water ingested in milliliters /24 h = the patient's weight in kilograms x10) [25]. The ingested quantity was distributed in two doses, daily; half an hour before lunch and dinner.

The water from source F3 (spring Callatis) is characterized as sulfurous, chlorinated, bicarbonated, sodium, magnesium, hypothermal, hypotonic mineral water[26,27], with a concentration of hydrogen sulfide (H2S) of 17 mg/l and specific indication in gastric diseases with hyposecretion[28].

The inclusion criteria was the presence of Helicobacter Pylori infection detected by fecal Ag.

Exclusion criteria from the study:

- previous or current treatment with proton pump inhibitors
- altered liver function (increased transaminases and gamma glutamyl transpeptidase).

The patients included in the study were 8(29,63%) males and 19(70,37%) females, aged between 51 and 76 years, of which 11(40.74%) were aged in the 7th decade. Their environment of origin was predominantly urban (20 patients -74,07%).

Regarding the personal history of digestive diseases, only 2 patients (7,41%) were aware of any digestive disease; 14 (51.85%) of the patients included in the study describing epigastric pain.

The statistical analysis was performed using IBM SPSS statistics software version 25. Data are presented as mean ± standard deviation (SD) for continuous variables in case of symmetric distributions, median and IQR (Interquartile range IQR = P75-P25) for numerical discrete variables or for continuous variables in case of skewed distributions, or as frequencies and percentages for categorical variables (Table 1). The normality of the continuous data was estimated with Shapiro-Wilk Tests of Normality. For hypotheses testing: Paired Samples t-Test, Related Samples Wilcoxon Signed Rank Test, Chi-Square Test of association and McNemar's Test, were used depending on the

type of analyzed variables. The significance level α was set at 0.05. If the test statistic for every conducted test was in the critical region, and the p-value was less than or equal to the significance level, we decided to reject the null hypothesis in favour of the alternative hypothesis.

Statistics

	N	Mean	SD	Min	Max	Percentiles P25	Median	P75
Age (years)	27	63.70	7.52	51.00	76.00	57.00	64.00	68.00
VAS (1)	13	7.52	.39	7.00	8.00	7.15	7.50	7.95
VAS (2)	13	2.06	.67	1.00	3.00	1.60	2.00	2.70
ESR (1) mm/h	27	15.81	10.70	3.00	42.00	5.00	16.00	25.00
ESR (2) mm/h	27	15.44	10.77	3.00	38.00	4.00	15.00	23.00
Fibrinogen (1) mg/dL	27	386.33	68.65	258.00	550.00	343.00	372.00	419.00
Fibrinogen (2) mg/dL	27	369.22	67.91	238.00	543.00	334.00	368.00	394.00
Glucose (1) mg/dL	27	101.39	12.31	82.00	130.00	94.45	97.00	104.00
Glucose (2) mg/dL	27	99.93	11.54	80.00	127.00	92.00	97.00	106.00
Total cholesterol (1) mg/dL	27	193.70	40.55	133.00	281.00	170.00	192.00	223.00
Total cholesterol (2) mg/dL	27	185.93	43.73	100.00	276.00	161.00	172.00	218.00
Triglycerides (1) mg/dL	27	118.89	43.28	44.00	193.00	82.00	118.00	154.00
Triglycerides (2) mg/dL	27	124.04	48.62	50.00	240.00	93.00	113.00	157.00
AST (1) UI/L	27	22.90	6.93	13.00	38.00	18.00	22.00	25.00
AST (2) UI/L	27	21.44	4.83	11.00	29.00	18.00	22.00	25.00
ALT (1) UI/L	27	24.69	7.73	14.00	41.00	18.00	23.00	28.00
ALT (2) UI/L	27	24.59	6.93	12.00	36.00	18.00	23.00	28.00
GT range (1) UI/L	27	20.59	8.46	9.00	40.00	15.00	18.00	24.00
GT range (2) UI/L	27	19.52	8.08	10.00	37.00	13.00	19.00	23.00
Uric acid (1) mg/dL	27	4.93	1.10	2.40	6.50	4.20	4.80	5.86
Uric acid (2) mg/dL	27	4.83	1.13	2.10	6.60	4.00	4.90	5.70
Serum urea (1) mg/dL	27	23.50	6.94	9.00	38.00	17.00	23.00	30.00
Serum urea (2) mg/dL	27	19.48	5.54	8.00	29.00	15.00	20.00	24.00
Creatinine (1) mg/dL	27	.86	.23	.50	1.30	.70	.80	1.00
Creatinine (2) mg/dL	27	.85	.22	.50	1.30	.70	.90	1.00

Table 1. The centralization of the monitored parameters

3. Results

After performing the crenotherapy treatment, the initial tests were repeated. Also, after repeating the H. Pylori antigen, it was found that 15 patients (55,56%) tested negative, a statistically significant difference between the proportion of patients who presented Ag HP – Positive pre-treatment (27 out of 27) 100.00% and the proportion of patients who presented Ag HP Positive post-treatment (12 out of 27) 44.44 % ($\chi 2$ calc = 15,000 > $\chi 2$ critical = 3.841, df = 1, $p < 0.001 < \alpha = 0.05$); there is a significant statistical difference between the number of patients who pre-treatment presented AG HP Positive, and post-treatment presented Ag HP Negative (15 out of 27; 55.56%) and the number of patients who pre-treatment presented Ag HP Negative and post-treatment presented AG HP Positive (0 out of 27; 0.00%), the difference that cannot be attributed to chance (McNemar's test).

Regarding the antibodies against H. Pylori (Ac H. Pylori), before crenotherapy 12 (44.44%) of the patients had antibodies, suggesting that for them the present condition represented a reinfection with H. Pylori. After the crenotherapy treatment, 20 of the patients (74.04%) had Ac H. Pylori ($\chi 2$ calc = 8.000 > $\chi 2$ critical = 3.841, df = 1, $p = 0.0046 < \alpha = 0.05$). A statistically significant difference is found between the number of patients who pre-treatment presented Ac H. Pylori positive, and post-treatment presented Ac H. Pylori negative (0 out of 27; 0.00%) and the number of patients who pre-treatment presented Ac H. Pylori negative and post-treatment presented Ac H. Pylori positive (8 out of 27; 29.63%), the difference that cannot be attributed to chance (McNemar's test).

The inflammation samples monitored in the study were erythrocyte sedimentation rate (ESR) (Figure 1), fibrinogen (Figure 2) and C-reactive protein (CRP).

The normality assumption estimated with Shapiro-Wilk Test was not met for ESR (mm/h) at both admission and discharge moments ($p_{(1)} = 0.009$, $p_{(2)} = 0.021 < 0.05$). A Wilcoxon signed-rank test showed that for Crenotherapy group ($Z = -1.307$, $p = 0.191$) the treatment did not elicit a statistically significant change in the ESR (mm/h) values between admission (1) and discharge (2): Median $ESR_{(1)} = 16.00$, $IQR_{(1)} = 20.00$, Median $ESR_{(2)} = 15$, $IQR_{(2)} = 19.00$.

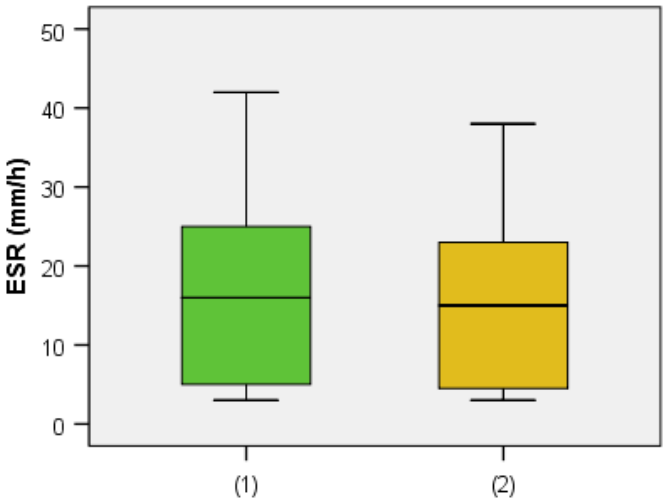

Figure 1. Box-Plot Chart – ESR (mm/h) at *admission (1)* and *discharge (2)*

A Paired samples t-test was conducted to determine the effect of treatment on *Fibrinogen* (score). The results indicate a not significant difference between *Fibrinogen* (score) before treatment (M=386.33 *mg/dL*; SD=68.65 *mg/dL*) and *Fibrinogen* (score) after treatment (M=369.22 *mg/dL*; SD=67.91 *mg/dL*); [t(26) = 1.637, p = 0. 114, with a95% confidence interval of the difference between the means ranged from [-4.375 to 38.597] *mg/dL.*

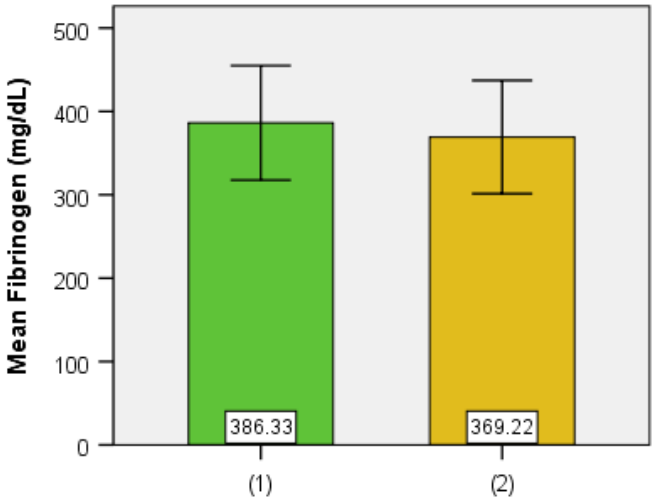

Figure 2. Bar-Error Bar Chart – Fibrinogen at *admission (1)* and *discharge (2)*

There was a statistically significant difference between the proportion of patients who presented CRP Positive pre-treatment (19 out of 27) 70.37% and the proportion of

patients who presented CRP Positive post-treatment (6 out of 27) 22.22 % (χ2calc = 3.000 < χ2critical = 3.841, df = 1, p = 0.0332 > α = 0.05) or, with other words, there was statistically significant difference between the number of patients who pre-treatment presented CRP Positive, and post-treatment presented CRP Negative (13 out of 27; 48.14%) and the number of patients who pre-treatment presented CRP Negative and post-treatment presented CRP Positive (0 out of 27; 0.00%), the difference that cannot be attributed to chance (McNemar's test).

The markers used to evaluate liver function were transaminases (AST and ALT) and gamma glutamyl transpeptidase (GT).

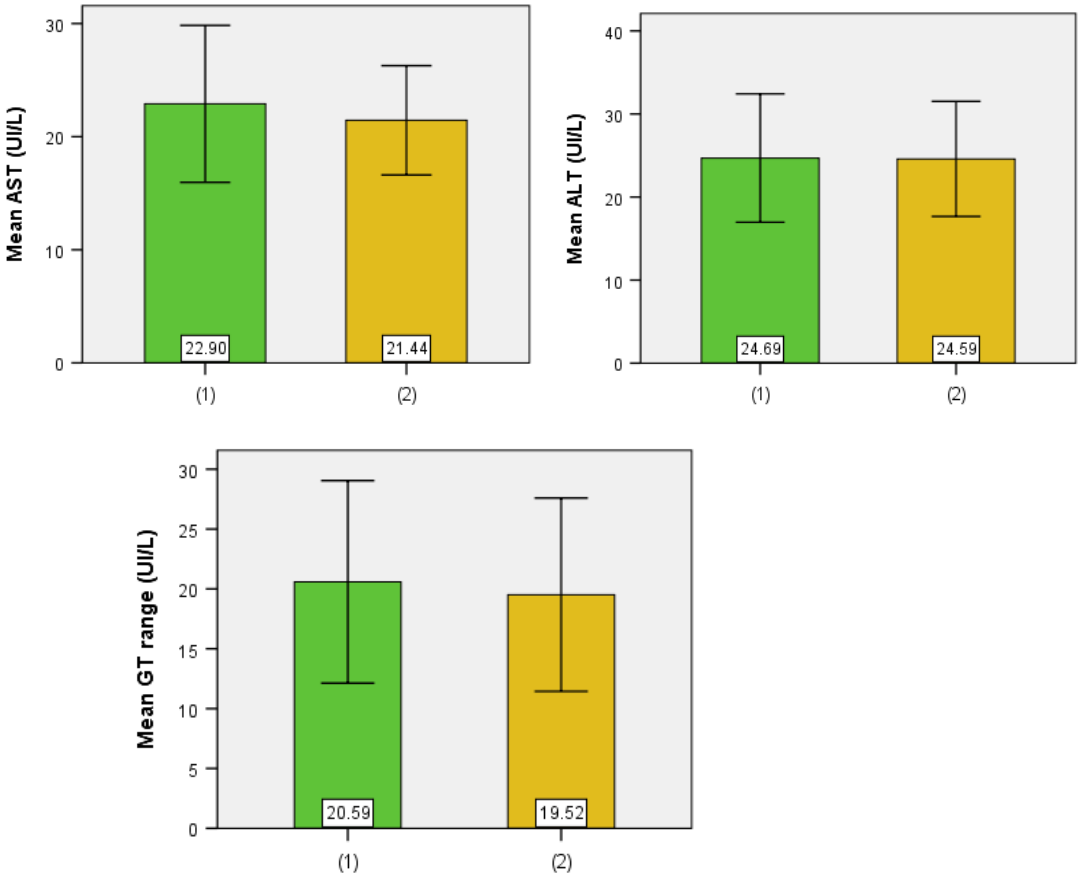

Figure 3. Bar-Error Bar Chart – AST, ALT and GT at admission (1) and discharge (2)

A Paired samples t-test was conducted to determine the effect of treatment on *AST, ALT and GT* (Figure 3).

The results indicate an insignificant difference between *AST* before treatment (M=22.90 *UI/L*; SD=6.93 *UI/L*) and *AST* after treatment (M=21.44 *UI/L*; SD=4.83 *UI/L*); [t(26) = 1.549, p = 0. 134, with a 95% confidence interval of the difference between the means ranged from (-0.477 to 3.388) *UI/L]*. The test also indicate an insignificant difference between *ALT* before treatment (M=24.69 *UI/L*; SD=7.73 *UI/L*) and *ALT* after treatment (M=24.59 *UI/L*; SD=6.93 *UI/L*); [t(26) = 0.080, p = 0.937, with a 95% confidence interval of the difference between the means ranged from (-2.511 to 2.714) *UI/L].*

For GT the result was the same. There is an insignificant difference between *GT* before treatment (M=29.59 *UI/L*; SD=8.46 *UI/L*) and *GT* after treatment (M=19.52 *UI/L*; SD=8.08 *UI/L*); [t(26) = 1.445, p = 0.160, with a 95% confidence interval of the difference between the means ranged from (-0.454 to 2.602) *UI/L].*

A Wilcoxon signed-rank test showed that for Crenotherapy group (Z = -3.182, p = 0.001) the treatment did elicit a statistically significant change in the VAS score between admission (1) and discharge (2) (Figure 4): Median VAS Score $_{(1)}$ = 7.50, IQR $_{(1)}$ = 0.80, Median VAS Score $_{(2)}$ = 2, IQR $_{(2)}$ = 1.10.

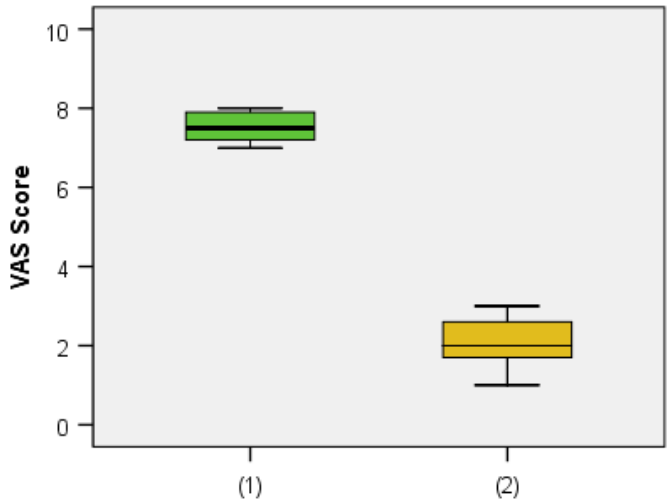

Figure 4. Box-Plot Chart – VAS Score at *admission (1)* and *discharge (2)*

Regarding the values of the other monitored parameters regarding blood sugar, renal function and lipidogram, there were no significant changes (Table 2).

Paired Samples Test

	Paired Differences	Mean	SD	95% CI of the Diff. Lower	Upper	t	df	p
1	Fibrinogen (1)-(2) mg/dL	17.111	54.315	-4.375	38.597	1.637	26	0.114
2	Glucose (1)-(2) mg/dL	1.465	8.471	-1.886	4.816	.899	26	0.377
3	Total cholesterol (1)-(2) mg/dL	7.770	24.813	-2.046	17.586	1.627	26	0.116
4	Triglycerides (1)-(2) mg/dL	-5.146	33.262	-18.304	8.012	-.804	26	0.429
5	AST (1)-(2) UI/L	1.456	4.885	-.477	3.388	1.549	26	0.134
6	ALT (1)-(2) UI/L	.101	6.604	-2.511	2.714	.080	26	0.937
7	GT range (1)-(2) UI/L	1.074	3.862	-.454	2.602	1.445	26	0.160
8	Uric acid (1)-(2) mg/dL	.102	.449	-.075	.280	1.184	26	0.247
9	Serum urea (1)-(2) mg/dL	4.017	4.796	2.120	5.914	4.352	26	0.000
10	Creatinine (1)-(2) mg/dL	.014	.122	-.034	.062	.585	26	0.563

Table 2. The evolution of the monitored parameters

4. Discussions

There are studies that show that the rate of reinfection with H. Pylori after eradication varies from 4.3% to 3.5% or 2.2% in the first year after treatment [29-33] depending on the specific risk factors of the region; with an annual reinfection rate of 1.5% per year [34]. These data cannot be correlated with the rate of patients in the study who presented Ac H. Pylori prior to treatment with sulfurous water (44.44%), because the age of H. Pylori infection of the people included in the study is not known.

In other studies, is proven a decrease in chronic and acute inflammation, indicated by the increase in the release of IL-10, a powerful anti-inflammatory cytokine, after ingestion of sulfur water [35]; therefore, the monitoring of inflammatory factors was important for the study. In our study, CRP was the only inflammatory test realized who showed significant decrease after sulfurous water ingestion, IL-10 being subject for further exploration. CRP demonstrated a significant decrease

Given that sulfurous waters with concentrations of hydrogen sulfide above 20 mg/l are considered cytotoxic to the liver {36, 37], even if the sulfurous water used for crenotherapy has H_2S values of 17 mg/dl, it was important to monitor liver function during the study.

There are studies that demonstrate that H_2S influences the perception of visceral and somatic pain in several ways, through the transient receptor ankyrin 1 (TRPA 1) [38] or through various ion channels, including calcium channel, Cav 3.2 [39-45]; ways that could be acted upon by other means to decrease the pain.

5. Conclusions

Following the results of treatment with Mangalia sulfurous water for H. Pylori infection, we can conclude that it represents a safely alternative to pharmacological therapy, with benefit on symptoms improvement.

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