RESEARCH ARTICLE

Vitamin D as an Adjuvant Therapy for Eradication of H. pylori. A Randomized Controlled Clinical Trial

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Received: 18th July, 2024; Revised: 5th Aug, 2024; Accepted: 9th Aug, 2024; Available Online: 31st August, 2024

ABSTRACT

Background: Helicobacter pylori shows high rate of antibiotic resistance and declining eradication rates; thus, a salvage therapy is needed. Vitamin D is known to have antimicrobial and immune modulatory properties. Observational studies linking Vitamin D serum levels to H pylori eradication have paved a way for interventional clinical trials. **Aim**: To study the effect of adding Vitamin D to the standard clarithromycin based triple therapy on eradication rates of H pylori. Subsidiary aim was to detect vitamin D serum levels among Egyptian Children infected with H pylori. **Methods**: A randomized controlled clinical trial including 200 children with an age range between 5-15 years, presenting to pediatric gastrointestinal endoscopy, and diagnosed as having H pylori infection based on histopathology of their gastric biopsy specimens, they were randomly allocated to 2 groups, one group received the standard clarithromycin based triple therapy, while the other group received 1000 IU Vitamin D 3 in addition to the triple therapy. Fecal antigen was done 1 month after stopping the medications to diagnose success of eradication. **Results**: The eradication rate of H pylori was significantly higher (82 %) among the group receiving Vitamin D supplementation , in comparison to the other group (51%). Also, Vitamin D intake was an independent factor for predicting the success of eradication (odds ratio: 5.08, CI: 2.51-10.98, P value=0.0001). **Conclusion**: Vitamin D supplementation improves eradication rates of H pylori among children especially at communities with prevalent Vitamin D deficiency.

Keywords: HPylori ; vitamin D ; Children

How to cite this article: Yosra Mohamed Mohsen Awad, Ahmed Mohamed Hamdy, Gihan Mohamed Bebars, Shaimaa Mohamed Yasin*, Chrestina Monir Fekry Hanna, Samir M Mounir. Vitamin D as an Adjuvant Therapy for Eradication of H. pylori. A Randomized Controlled Clinical Trial .International Journal of Pharmaceutical Quality Assurance. 2024;15(3): 2011-2016. DOI: 10.25258/ijpqa.15.3.135

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

The prevalence of Helicobacter pylori (H pylori) exceeds 30% among children worldwide and this prevalence was significantly higher in low and middle income countries than in high-income countries. [1]. It is known to cause gastric or duodenal ulcers or erosions, as well as extra-gastric manifestations as refractory iron deficiency anemia. [2]

The treatment is based on the triple therapy for 10-14 days, which consists of a proton pump inhibitor and amoxicillin plus clarithromycin or metronidazole based on each country's local susceptibility tests [3]. The primary eradication rates are targeted to exceed 95% [4], however the eradication rates are not satisfactory mostly due to antibiotic resistance or poor patients' compliance [5]. In the United States eradication rates of the standard triple therapy in children reached as low as 60% [6]. In Africa, the eradication rates varied widely from 90% to 22.3% across the countries of the continent. [7]

Thus, various modifications have been proposed to improve the eradication rates of H pylori, either through sequential therapy, quadriple therapy, increasing doses of therapeutics, adding bismuth compounds, or changing antibiotics [3]. Due to the growing need to elaborate alternative eradication regimens, some researchers have drawn attention to probiotics and immunomodulators as adjuvant therapies. [8]

Vitamin D (Vit D) is known of its immunomodulatory and anti-inflammatory properties. Studies have shown that vitamin D plays a vital part in the expression of genes coding for antimicrobial proteins (AMPs), which then modulate immune responses to various infections [9, 10]. Vitamin D is also involved in T-cell antigen receptor maturation and mediates T-cell immune response [11]. Therefore, the deficiency of vitamin D may be implicated to hamper the normal immunological response to infectious agents [10]. A number of studies provide evidence that vitamin D plays a role in eradicating H. pylori [12-15] all of these studies were in adults. In this study we aimed to study the effect of adding Vitamin D to the standard clarithromycin based triple therapy among a group of Egyptian children in comparison to the standard triple therapy. Subsidiary aim was to detect vitamin D serum levels among Egyptian Children infected with H pylori.

Subjects and methods

This study included 200 children whose age ranged between 5-15 years and endoscopically diagnosed as having H pylori related disease and were planned to start

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Table 1: Comparisons between the intervention group "group A" and the control group "Group B" regarding demographic characteristics, clinical presentations and vitamin D status.

Variables	Group A Received vitamin D and triple therapy. N=100	Group B Received triple therapy only. N=100	Significance
Age (mean± SD)	9.01±2.1	9.45± 2.03	P=0.13*
Gender N (%)			
Male	46 (46%)	51 (51%)	P=0.48†
Female	54(54%)	49(49%)	
Vomiting	74 (74%)	71 (71%)	P=0.64†
Hematemesis	20 (20%)	12 (12%)	P=0.12†
Dyspepsia	59(59%)	69(69%)	P=0.27†
Abdominal distension	14(14%)	13(13%)	
Both	27(27%)	18(18%)	
Serum vitamin D (Mean±SD)	14.78±6.3	15.93±7.2	P=0.24*
Sufficient vitamin D (≥30 ng/ml)	5 (5%)	7 (7%)	P=0.48†
Insufficient vitamin D(20-29ng/ml)	5 (5%)	10 (10%)	
Deficient vitamin D (10-20 ng/ml)	85 (85%)	77 (77%)	
Severe <10 ng/ml	5(5%)	6(6%)	
Eradication rates at follow up			
Eradicated	82 (82%)	51 (51%)	
Not eradicated	18(18%)	49(49%)	P=0.001†

*: Independent t test, †: Chi square test.

eradication therapy . We included children presented to gastroenterology endoscopy unit at Minia University Children Hospital, Egypt. The patients suffered from upper gastrointestinal symptoms in the form of vomiting, hematemesis, dyspepsia, persistent upper abdominal pain which necessitated upper GI endoscopy. The diagnosis of H pylori was based on histopathology of the gastric biopsies and rapid urease test . We excluded children who had received previous treatment of H pylori, as well as those who received proton pump inhibitors or antibiotics one month prior to endoscopy. Patients also on current vitamin D supplementation were excluded. Patients suffering from chronic renal, or hepatic illness or malabsorption syndromes were also excluded. The study had the approval of the Ethical Committee of Minia University, and was registered on the clinical trials.gov number NCT05879237 prior to initiation. The study follows the declaration of Helsinki and informed consent was taken from parents or guardians of the children.

Sample size

Our sample size was estimated using online epitools programme for "Prospective, cohort, and randomized clinical trials studies". Using the_following parameters: Percent of exposed with outcome: 80.96% [15], Confidence interval: 95 %, Desired power: 80%, Alpha: 0.05. Minimal required sample size was (186). We chose (200) as nearby correct number. Randomly allocated (divided) into (2) groups, each group contains (100) case. At the time of enrollment sociodemographic and clinical data were collected from the patients and caregivers . Complete blood picture was done, and a blood sample for measuring 25(OH) D3 was collected and kept frozen at -20 . Upper GI endoscopy was then performed under general anesthesia using propofol for sedation , and four gastric biopsies from gastric antrum (one from the distal lesser curvature and one from the distal greater curvature),and the two from corpus (from greater curvature). were taken for histopathology. Patients were randomly allocated into two groups by simple random method depending on the odd and even number of their files, where group A "intervention group"received clarithromycin based triple therapy of H pylori for 2 weeks (Clarithromycin , amoxicillin and proton pump inhibitor), and additional daily 1000IU Vitamin D3 supplementation (oral vitamin D drops; 100 IU per drop) for 1 month, while group B " control group "received the triple therapy only (Clarithromycin , amoxicillin and proton pump inhibitor) for 2 weeks as per guidelines [3]. The dose of Vitamin D was chosen based on the international recommendations that high-risk patients were required to receive Vitamin D in a dose ranging from 600-2000 IU/day [16, 17]. Additionally, the use of 1000 IU/day for 4 weeks was not recorded to result in any significant rise in serum, level of Vitamin D for Vitamin D sufficient persons [18]

Compliance to medication was checked and confirmed with patients that if they have completed their treatment regime and no dose was missed. Only those participants who completed the study were included in the final analysis, Whatever about 25 patients were dropped out in our study

Table 2: Comparison between patients successfully eradicated to those who failed H pylori eradication.

Variable	Successful eradicated N=133	Failed eradicated N=67	Significance
Age (mean ± SD)	9.14±2.1	9.40±2.05	P=0.41*
Gender			
Male	65 (48.9%)	32 (47.8%)	P=0.88†
Female	68 (51.1%)	35 (52.2%)	
Vitamin D intake			
Yes	82 (61.7%)	18(26.9%)	P=0.001†
No	51 (38.3%)	49 (73.1%)	
Hb (mean ± SD)	10.39±1.4	10.46±1.16	P=0.72*
Initial Serum vitamin D	15.83±7.1	14.43±6.1	P=0.18*
Hematemesis			P=0.92†
Yes	17 (14.3%)	12 (14.8%)	
No	102 (85.7%)	69 (85.2%)	
Vomiting			P=0.17†
Yes	93 (69.6%)	53 (79.1%)	
No	40(30.1%)	14(20.9%)	
Pain site			P=0.39†
Epigastric	111 (83.5%)	59 (88.1%)	
Generalized	22 (16.5%)	8 (11.9%)	
Serum vitamin D			
Sufficient vitamin D	11(8.3%)	1 (1.5%)	P=0.18†
Insufficient vitamin D	8(6%)	7(10.4%)	
Deficient vitamin D	106(79.7%)	56(83.6%)	
Severe deficiency	8(6%)	3(4.5%)	

*: Independent t test, †: Chi square test.

due to non compliance and another 25 cases were taken instead. Follow up of patients one month after stopping the triple therapy where fecal antigen of H pylori was tested ,to assess the success of the eradication therapy. Serum 25 (OH) D_3 was measured using ELISA . Patients with Vitamin D level ≥ 30 ng/ml were considered as Vitamin D sufficient, while levels ranging from 20-29 ng/ml were considered vitamin D insufficient, those with serum Vit D levels <20 ng/ml were considered deficient and those < 10 were considered as severely deficient. [19] The dose of Vitamin D was chosen based on the international recommendations that high risk patients were required to take Vitamin D in a dose ranging from 600-2000 IU/day [16, 17].. Additionally, the use of 1000 IU/day for 4 weeks was not recorded to do any significant rise in serum, level of Vitamin D for Vitamin D sufficient persons [18]

Statistical analysis

Data was analyzed using Statistical Package of Social Science (SPSS) version 22. Quantitative data were presented by mean and standard deviation also by range, while qualitative data were presented by number and percentages. Independent sample t test was used to compare means of two groups. Chi –square test was performed to show significance between qualitative variables. The probability of less than (0.05) was used as a cut off point for all significant tests.

RESULTS

This study included 200 children of age ranging from 5-15 years, with a mean age of 9.33±2.1 years. Nearly half of them (48.5%) were males. Clinical presentation included abdominal pain which was present in 47.5% of patients , dyspepsia 65.5% ,vomiting 73% and hematemesis in 17%. Mean Hemoglobin was (Hb) 10.41±1.3 (mean ± SD) gm/dl Range: (6-13.6 gm / dl), The most common endoscopic finding was gastric nodularity (96%) followed by gastric erosions (49.5%). None of included children had gastric or duodenal ulcers. The mean level of serum vitamin D among studied population was (15.36±6.8) ng/ml, ranged from (6-47) ng/ml. Most of the patients were Vitamin D deficient 173 (86.5%), of whom 11 (5.5%) were severely deficient, while 15 (7.5%) had Vitamin D insufficiency, and only 12 (6%) were sufficient. Both study groups; the intervention and the control groups; were comparable regarding age, gender, clinical presentations and serum vitamin D and vitamin D status as shown in table (1) Successful eradication was achieved in 123 children (61.5%) with a significantly higher frequency among the intervention group (82%) compared the control group (51%), (p= P=0.001) as shown in table (1) Then comparisons were done between those with successful eradication and those

Table 3: Multivariate logistic regression for factors associated with H. pylori eradication

Variable	Odds ratio	Confidence interval	Significance
Age	0.95	(0.81-1.12)	0.55
Gender (male)	1.13	(0.59-2.15)	0.72
Vitamin D (intake)	5.08	(2.51-10.29)	0.0001
Hb	1.12	(0.86-1.45)	0.40
Serum vit D	1.05	(0.99-1.11)	0.11

who failed H pylori eradication, as shown in table (2). It showed that mean serum level of Vitamin D was not significantly different between those with successful or failed eradication. Then multivariate regression analysis was performed including the most important factors of eradication success and this is shown in table (3) where patients who received vitamin D had a chance of successful eradication 5 times higher than those who did not receive vitamin D.

DISCUSSION

Due to high rates of antibiotic resistance and declining eradication rates of H pylori, [20] a salvage therapy is needed. In Egypt this problem is even more pronounced where the eradication rates of the standard triple therapy reached as low as 59%, which totally unsatisfactory. [21] A number of studies provide evidence that vitamin D plays a major role in eradicating H. pylori. A study showed that vitamin D3 decomposition product (VDP1) selectively affects H. pylori where it induces a collapse of cell membrane structures of *H. pylori* and ultimately lyses the bacterial cells [22, 23] Vitamin D is also known to regulate
the expression of antimicrobial peptides – cathelicidin and β-defensin, which kill the bacteria. The hormonal form of vitamin D (3), 1,25-dihydroxyvitamin D (3), is an immune system modulator and it signals through the vitamin D receptor, and it directly regulates the antimicrobial innate immune responses. [24] On clinical grounds, Vitamin D has been studied in relation to H pylori , where some studies included patients who received treatment for H pylori and compared the serum level of Vitamin D among those with successful eradication to others who failed eradication, and it showed that those with failed eradication had lower serum levels of vitamin D and that the vitamin D deficient persons were more among the non-eradicated group. [12-14, 25]. This was not the case in our study, since there was no significant difference between mean serum levels among both groups with successful and failed eradication, maybe because 86.5% of our patients were Vitamin D deficient. However, their observational studies paved the way for interventional studies. In an interesting study by Bashir et al in 2016[18] where volunteers were asked to do upper GI endoscopy to study their gastrointestinal inhabitant microbiome, and the effect of vitamin D supplementation on these organisms. After baseline assessment, H. pylori infection was detected in three volunteers. All three volunteers showed an overall decline in Helicobacter after 8 weeks of vit D3 supplementation. each volunteer received a weekly dose of 980 IU/kg body weight of vitamin D3 for 4 weeks which was then halved for the remaining 4 weeks.[18] Recently, randomized controlled clinical trials involving the use of Vitamin D as an adjuvant therapy to the triple therapy of H pylori were published, few studies of them showed higher eradication rates among the group receiving vitamin D. However, those studies were performed on adult population and have not stated the dose of vitamin D used. [15, 26] This study shows that the group which received vitamin D had much higher eradication rates (86%), compared to the standard clarithromycin based triple therapy which had an eradication rate of 51% in our study. Regression analysis of the factors predicting eradication of H pylori showed that adding vitamin D to the standard triple therapy improved the eradication rates (Odds ratio 5.08 (CI: 2.5-10.29, P value = 0.0001)) And this is the first study to be done on children ,To the best of our knowledge.

Limitation

Our study showed that most of the patients had vitamin D deficiency (86.5%) or insufficiency (7.5%), this comes in accordance with a survey done on Egyptian adolescents prevailing a very high prevalence of Vit D deficiency (94.8%) and Vit D insufficiency (4.2%) while only (1%) of participants had Vit D sufficiency [27]. This may question this marvelous effect of adding Vitamin D to the standard triple therapy among communities with sufficient vitamin D.

Conclusion

Adjuvant therapy with Vitamin D to triple therapy of H .pylori improves eradication rates of H.pylori among children especially at communities with prevalent vitamin D deficiency .

Recommendation

Supplementation of vitamin d 1000 IU/day for one month with the triple therapy of H.pylori .

ACKNOWLEDGMENTS

Conflict-of-interest statement: The authors declare that they have no competing interests.

Funding: This research has not received grants from any public, commercial, or not-for-profit agency.

Data availability: All data generated during this study are included in this article. Further inquiries can be directed to the corresponding author.

Consent for publication : Not applicable.

Ethical approval: This study approved by ethics committee of the faculty of medicine, Minya University ((approval number 42:2021) and consent to participate was taken from authors.

clinical trials: NCT05879237

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