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Efficacy and safety of nitazoxanide based quadruple regimen as first line therapy for treating *Helicobacter pylori* infected naïve patients

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Abstract

Background: Eradication of *H. pylori* is a challenging issue in many parts of the world including Egypt.
Aim: To evaluate the safety and efficacy of adding nitazoxanide as an adjuvant drug to the standard clarithromycin-based regimen, a single-center phase 4 prospective superiority parallel open-label randomized controlled trial was conducted.
Methodology: Two hundred naïve *H. pylori*-positive patients were randomly distributed into 4 groups in ratio 1:1:1:1; Group 1: 50 patients were treated by clarithromycin 500mg bid, amoxicillin1gm bid, omeprazole 20 mg, Group 2: 50 patients were treated by clarithromycin 500mg bid, metronidazole 500mg bid, omeprazole 20 mg bid, group 3: 50 patients were treated by clarithromycin 500mg bid, nitazoxanide 500mg bid, omeprazole 20 mg bid, and group 4: 50 patients were treated by clarithromycin 500mg bid, amoxicillin1gm bid, nitazoxanide 500mg bid, omeprazole 20 mg bid. All patients were treated for 14 days and assessed 4 weeks after treatment.
Results: Adding nitazoxanide to standard clarithromycin based triple therapy achieved a high eradication rate of 84% in intention to treat analysis (ITT), and 89.36% in per protocol (PP) analysis with high significant *p* (0.01).
Conclusions: adding nitazoxanide as an adjuvant drug to the standard clarithromycin-based regimen is effective and could be used as a first line regimen in the eradication of *H. pylori*.

Key words: *H. pylori*; nitazoxanide; eradication; resistance.

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Introduction

H. pylori is the most prevalent chronic bacteria which infects 4.4 billion individuals worldwide [1]. The prevalence of *H. pylori* infection in Africa was 70.1% and the estimated prevalence of *H. pylori* infection in Egypt was 54.4% among the general population and 64.6 % among symptomatic children [2-4].

H. pylori has been recognized as the main etiological factor of chronic gastritis, gastric adenocarcinoma, and mucosa-associated lymphoid tissue (MALT) lymphomas. Therefore, eradication of *H. pylori* became a mandatory issue to prevent inflammation and mucosal damage that in turn will reduce the risk of development of gastric adenocarcinoma and MALT [5-7].

According to current guidelines, Treatment of *H. pylori* should be offered to all patients with dyspeptic symptoms who have active *H. pylori* infection to decrease the risk of complications and reduce gastric cancer risk. Also, patients who have any of the following gastric premalignant conditions such as atrophic gastritis, intestinal metaplasia, dysplasia, adenomas, and hyperplastic polyps or patients with active *H. pylori* infection who have a first degree relative with gastric cancer, or persons with gastric mucosa-associated lymphoid tissue (MALT) lymphoma should be treated [8-11].

WHO has classified *H. pylori* as one of the most critical antibiotic-resistant bacteria that require urgent development of new effective antibiotics [12]. Moreover, Global meta-analysis showed that the primary and secondary resistance rate of *H. pylori* to clarithromycin and metronidazole was over 15% in most regions. In the Mediterranean Region, the prevalence of primary resistance to amoxicillin was 14%, 33% to clarithromycin, and 56% to

metronidazole, while secondary resistance to amoxicillin was ≤ 10%, 17% to clarithromycin and 65% to metronidazole [13].

Although current guidelines strongly recommend the use of bismuth quadruple therapy as the first line in the eradication of *H. pylori* infection [11], Clarithromycin-based triple therapy is still used in the treatment of *H. pylori* infected patients in Egypt and many parts of the world including US and Europe [14-18].

Eradication of *H. pylori* became more difficult after the COVID-19 pandemic due to the rise of bacterial resistance antibiotics used to treat *H. pylori*, including clarithromycin and levofloxacin which occurs as a sequence of antibiotics misuse, especially during covid-19 pandemic era [11,19].

As eradication of *H. pylori* is a challenging issue due to the progressive increase in antibiotic resistance so careful selection of therapies and revision of new therapeutic modality of therapeutic strategies become a mandatory issue [20].

Nitazoxanide has antimicrobial characteristics similar to metronidazole, but nitazoxanide appears to be a potent agent against metronidazole-resistant strains because it has anti-vacuolating toxin activity which prevents against development of antimicrobial resistance [21,22].

Nitazoxanide has a wide-spectrum antimicrobial effect against viruses, and anaerobic bacteria, as well as against helminths and protozoa [23-25]. Moreover, Nitazoxanide has been used as a part of eradication therapy of *H. pylori* in adult and pediatric populations with a cure rate of 94.6% and 89.2% respectively [22,26].

The study aimed to evaluate the safety and efficacy of adding nitazoxanide to clarithromycin-based therapy versus standard clarithromycin-based triple therapies in naïve patients infected with *H. pylori* after the COVID-19 pandemic.

Patients and Methods

This single-center phase 4 prospective superiority parallel open-label randomized controlled trial was conducted on two hundred naïve *H. pylori*-positive patients presented with dyspeptic symptoms who were diagnosed to have *H. pylori* infection by stool antigen test. The study was done at the outpatient clinic of Hepatology and Gastroenterology Department, Al-Azhar-Assiut University Hospital, in the period from December 2021 to December 2022 to evaluate the efficacy and safety of adding nitazoxanide to the standard triple regimens in patients infected with *H. pylori*.

Ethics consideration

This trial is registered to the Pan African Clinical Trials Registry, (PACTR202112686695509, https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=19250) after obtaining ethics approval from Al-Azhar-Assiut-Faculty of Medicine Ethics Committee. It is conducted in accordance with the World Medical Association Declaration of Helsinki as revised in 2013, Edinburgh, UK, and in agreement with CONSORT criteria of clinical trials. Informed written consent was signed by all patients enrolled in the trial.

Eligibility Criteria

The eligibility of enrolled patients was evaluated in the baseline visit. It included 200 consecutive naïve patients above the age of 18 years with dyspeptic symptoms. Diagnosis of *H. pylori* infection based on stool antigen test (SAT) (one-step *H. pylori* Antigen test Device) manufactured by (Abon Biopharm, Hangzhou, China).

Patients were excluded from the study if they refused to participate or had any of the following: 1) aged less than 18 years; 2) experienced *H. pylori* eradication therapy; 3) intake of any of the following medications within the last 6 weeks: antibiotics, anticoagulant, antacids including histamine (H2) receptor blockers and proton pump inhibitor (PPI), or nonsteroidal anti-inflammatory drugs; 4) known allergy to any of the used drugs; 5) active gastrointestinal bleeding; 6) recent gastric surgery; 7) gastrointestinal malignancy; 8) pregnant or lactating women; 9) hepatic or renal impairment.

Randomization, enrollment, and intervention

Two hundred consecutive patients were enrolled in this study. A computerized random table was used to randomly distribute the enrolled patients into one of four groups in a ratio of 1:1:1:1.

Regarding the categorization and used regimens, we thought that we must use two different groups for the standard triple therapy (amoxicillin-based regimen in group 1 and metronidazole-based regimen in group 2). As Nitazoxanide has antimicrobial characteristics similar to metronidazole [21,22], we thought that using both nitazoxanide and metronidazole in a single regimen is of no additional therapeutic benefits so instead of studying metronidazole-based standard triple therapy plus nitazoxanide (PPI + clarithromycin + metronidazole + nitazoxanide), we removed metronidazole from this group and used PPI +

clarithromycin + nitazoxanide in the third group. Moreover, we studied one group for amoxicillin-based standard triple therapy and nitazoxanide (PPI + amoxicillin + clarithromycin + nitazoxanide) in the fourth group.

Group 1 (amoxicillin based triple therapy)

Included 50 patients who were treated with clarithromycin (Klacid®; Abbott Laboratories, Cairo, Egypt) 500 mg bid, amoxicillin (Amoxil®; GlaxoSmithKline, Cairo, Egypt) 1000 mg bid, and omeprazole (Pepzol®; Hikma Pharmaceuticals, Giza, Egypt) 20 mg bid for 14 days.

Group 2 (metronidazole-based triple therapy)

Included 50 patients who were treated with clarithromycin (Klacid®; Abbott Laboratories, Cairo, Egypt) 500 mg bid, metronidazole (Flagyl®, SANOFI, Cairo, Egypt) 500mg bid, and omeprazole (Pepzol®; Hikma Pharmaceuticals, Giza, Egypt) 20 mg bid for 14 days.

Group 3 (nitazoxanide based triple therapy)

Included 50 patients who were treated with clarithromycin (Klacid®; Abbott Laboratories, Cairo, Egypt) 500 mg bid, nitazoxanide (Nanazoxid®, UTOPIA pharmaceuticals, Cairo, Egypt) 500 mg bid, and omeprazole (Pepzol®; Hikma Pharmaceuticals, Giza, Egypt) 20 mg bid for 14 days.

Group 4 (concomitant nitazoxanide with standard clarithromycin based triple therapy)

Included 50 patients who were treated with clarithromycin (Klacid®; Abbott Laboratories, Cairo, Egypt) 500 mg bid, amoxicillin (Amoxil®; GlaxoSmithKline, Cairo, Egypt) 1000 mg bid, nitazoxanide (Nanazoxid®, UTOPIA pharmaceuticals, Cairo, Egypt) 500 mg bid and omeprazole (Pepzol®; Hikma Pharmaceuticals, Giza, Egypt) 20 mg bid for 14 days.

Baseline data and characteristics

Baseline data and investigations were collected before randomization and before enrollment to any of the study groups. These data included full history taking, clinical examination, and investigation: 1) complete blood count (CBC), renal function (urea and creatinine), liver functions (aspartate transferase (AST), alanine transferase (ALT), serum bilirubin, international normalized ratio (INR), and albumin), fasting blood sugar (FBS), lipid profile (including cholesterol and triglycerides), and erythrocyte sedimentation rate (ESR).

Diagnosis of H. pylori

Stool antigen test (SAT) (one-step *H. pylori* Antigen test Device) was used for diagnosis of *H. pylori* infection of suspected patients before being enrolled in the study and for evaluation of *H. pylori* infection eradication 4 weeks after treatment. A stool antigen test (SAT) (manufactured by Abon Biopharm, Hangzhou, China) was used in accordance with manufacturer instructions.

Follow up

All participants were followed up for at least 6 weeks: two weeks of treatment and 4 weeks post-treatment to assess eradication, compliance, and side effects of treatment. Regular weekly follow-up was applied with either hospital-based visits or phone-based questionnaires. Patients were instructed not to take any antibiotics, PPIs, or H2 blockers for at least 4 weeks after the end of treatment and during the follow-up period.

Outcomes

Primary outcome: eradication rate in each group.

Secondary outcomes: side effects of used regimens.

Statistical Analysis and Sample Size

The collected data were statistically analyzed by Statistical Package for Social Sciences (SPSS) version 28 (IBM SPSS Inc., Chicago, US) for Windows 10. Categorical data were expressed as numbers and percentages while continuous data were expressed as Mean ± standard deviation (SD). The categorical variables were compared using chi-square (χ^2). The Student's T-test was used for comparisons in numerical parametric data. A $p < 0.05$ was considered significant. The eradication rate was calculated by dividing cured

Table 1. Baseline demographics data of patients enrolled in the trial.

Parameters	All cases (N = 200)	G1 (N = 50)	G2 (N = 50)	G3 (N = 50)	G4 (N = 50)	*p*
Age (Mean ± SD)	32.22 ± 11.8	33 ± 13.16	33.46 ± 12	32 ± 10.88	30.4 ± 11.2	0.21
Male	56 (28%)	18 (36%)	13 (26%)	17 (34%)	8 (16%)	0.06
Female	144 (72%)	32 (64%)	37 (74%)	33 (66%)	42 (84%)	
Smoker	18 (9%)	5 (10%)	5 (10%)	4 (8%)	4 (8%)	0.6
Non smoker	182 (91%)	45 (90%)	45 (90%)	46 (92%)	46 (92%)	

G1: Group 1; G2: Group 2; G3: Group 3; G4: Group 4.

Table 2. Baseline laboratory investigations of studied groups.

Parameters	All cases (N = 200)	G1 (N = 50)	G2 (N = 50)	G3 (N = 50)	G4 (N = 50)	*p*
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Red blood cells (10^6/mm^3)	4.32 ± 2.96	5.2 ± 5.79	4.01 ± 0.63	4.07 ± 0.54	4.01 ± 0.65	0.06
Hemoglobin concentration (g/dL)	11.93 ± 1.86	11.9 ± 2.3	11.82 ± 1.65	12.25 ± 1.6	11.76 ± 1.81	0.8
Mean corpuscular hemoglobin (pg)	30.1 ± 20.04	34.76 ± 39.2	28.59 ± 2.87	28.70 ± 7.11	80.79 ± 4.82	0.1
Mean corpuscular volume (fL)	79.32 ± 8.63	77.85 ± 12.75	80.74 ± 5.38	80.79 ± 4.8	77.93 ± 8.9	0.9
White blood cells (10^3/mm^3)	5.66 ± 1.18	6.13 ± 1.33	5.71 ± 1.17	5.38 ± 0.96	5.38 ± 1.11	0.8
Platelets (10^3/mm^3)	269 ± 69.68	268.7 ± 81.1	253.48 ± 68.98	273.34 ± 73.9	280.88 ± 50.83	0.2
Alanine transferase (μ/L)	14.6 ± 7.56	15.46 ± 8.06	15.64 ± 9.15	13.06 ± 6.52	14.28 ± 6.03	0.2
Aspartate transferase (μ/L)	20.6 ± 7.32	19.96 ± 8.77	21.52 ± 7.4	19.72 ± 6.81	21.24 ± 6.1	0.6
Total Protein (g/dL)	7.18 ± 0.41	7.43 ± 0.35	7.07 ± 0.43	7.09 ± 0.38	7.14 ± 0.37	0.5
Albumin (g/dL)	3.79 ± 0.2	3.75 ± 0.23	3.81 ± 0.21	3.79 ± 0.5	3.8 ± 0.18	0.2
Urea (mg/dL)	13.64 ± 3.7	13.88 ± 3.15	13.89 ± 0.55	13.6 ± 0.55	13.5 ± 3.86	0.2
Creatinine (mg/dL)	0.68 ± 0.17	0.67 ± 0.18	0.67 ± 0.16	0.69 ± 0.19	0.71 ± 0.14	0.2
International normalized ratio	1.008 ± 0.02	1.01 ± 0.37	1 ± 0.007	1.009 ± 0.03	1.006 ± 0.01	0.1
Erythrocyte sedimentation rate (mm/h)	13.39 + 6.029	14.74 ± 6.009	11.44 ± 4.44	12.34 ± 5.7	15.04 ± 6.9	0.6
Fasting blood sugar (mg/dL)	91.72 ± 8.98	93.62 ± 12.033	91.52 ± 7.37	89.46 ± 7.3	92.28 ± 8.1	0.2
Total cholesterol (mg/dL)	90.96 ± 0.039	87.06 ± 28.36	98.14 ± 34.88	92.08 ± 28.39	86.56 ± 26.32	0.6
Triglycerides (mg/dL)	146.23 ± 32.33	142.54 ± 32.74	152.18 ± 27.12	154 ± 32.37	136 ± 34.17	0.3

G1: Group 1; G2: Group 2; G3: Group 3; G4: Group 4.

patients by the number of enrolled patients in each group (calculated as the intention to treat and per protocol analyses). Effect size using odds ratios (with their confidence intervals, CI) of cured and failed patients in each group and the number needed to treat were also calculated. The sample size was calculated for RCTs with dichotomous outcomes using a power of 80%, type 1 error of 0.05, cases control ratio of 1:1, drop-out ratio of 10%, and margins of risk differences of 0.3 [27].

Results

Baseline characteristics

In this trial, 200 patients were enrolled, of which 56 (28%) were males, and 144 (72%) were females. Mean age was 32.22 + 11.8 years, and 18 (9%) patients were smokers, with no significant differences between the studied groups regarding their ages and their special habits as shown in baseline demographics (Table 1).

Regarding the presenting symptoms among the studied groups, epigastric pain (59%), heartburn (28%), early satiety (11%), and urticaria (2%) were the presenting symptoms of patients with no significant difference between the studied groups *(p* > 0.05 for each).

Regarding baseline laboratory investigations of patients (Table 2), there were no significant differences between the studied groups *(p* > 0.05 for each).

Endpoints and efficacy

In total, 185 out of 200 included patients completed the study. In group 1, 46 patients completed the trial (3 patients excluded due to non-compliance and one missed patient), 44 in group 2 (2 missed and 4 with non-compliance), 48 in group 3 (2 non-compliance), and 47 in group 4 (2 non-compliance and one missed patient).

In this prospective randomized controlled trial, all enrolled patients were tested by stool antigen test 4 weeks after completion of treatment to evaluate eradication rates among enrolled patients. Our trial showed that patients in group 4 who were treated with clarithromycin, amoxicillin, nitazoxanide, and omeprazole had achieved the highest eradications rate 84% in intention to treat analysis (ITT), and 89.36% in per protocol (PP) analysis, followed by group 1 which achieved eradication rate of 64% in ITT and 69.56% in PP, while in group 3 the eradication rate was 56% in ITT, and 56.25% in PP, and finally, group 2 achieved the least eradication rate 36% in ITT and 40.90% in PP, with significant difference between the studied groups (p = 0.01) (Table 3).

Secondary outcome

Minor adverse effects occurred in 94 (ITT: 47%, 50.81% PP) patients in the form of epigastric pain, nausea, urine discoloration, diarrhea, and metallic taste as shown in (Table 4).

Effect sizes of used regimens

By using group 1 as a comparison group, we used the odds ratio (OR) to calculate the effect size for each used regimen in comparison to group 1. The effect size for group 2 is 0.3029 (CI; 127- 0.7224), for group 3 is

Table 3. Eradication rates among the studied groups.

Eradicated rate	All cases (N = 185)	G1 (N = 46)	G2 (N = 44)	G3 (N = 48)	G4 (N = 47)	*p*
ITT	120 (60%)	32 (64%)	18 (36%)	28 (56%)	42 (84%)	0.01
PP	64.86%	69.56%	40.90%	56.25%	89.36%	

ITT: intention to treat; PP: per protocol. G1: Group 1; G2: Group 2; G3: Group 3; G4: Group 4.

Table 4. Side effects of treatment among patients enrolled in the trial.

Side effects		All cases (N = 185)	G1 (N = 46)	G2 (N = 44)	G3 (N = 48)	G4 (N = 47)
Epigastric pain	ITT	22 (11%)	10 (20%)	6 (12%)	5 (10%)	1 (2%)
	PP	11.89%	21.73%	13.6%	10.41%	2.12%
Nausea	ITT	18 (9%)	5 (10%)	6 (12%)	1 (2%)	6 (12%)
	PP	9.72%	10.86%	13.63%	2.08%	12.76%
Urine discoloration	ITT	14 (7%)	0 (0%)	0 (0%)	7 (14%)	7 (14%)
	PP	7.56%	0%	0%	14.58%	14.89%
Diarrhea	ITT	12 (6%)	8 (16%)	0 (0%)	0 (0%)	4 (8%)
	PP	6.48%	17.36%	0%	0%	8.51%
Metallic taste	ITT	8 (4%)	0 (0%)	8 (16%)	0 (0%)	0 (0%)
	PP	4.32%	0%	18.18%	0%	0%

ITT: intention to treat; PP: per protocol. G1: Group 1; G2: Group 2; G3: Group 3; G4: Group 4.

0.6125 (CI; 0.2616- 1.434), and for group 4 is 3.675 (CI; 1.1992- 11.2623). Hence, the Clarithromycin, Amoxicillin, nitazoxanide, and Omeprazole regimen (group 4) showed the highest significant effect size (3.675) with the highest CI. The number needed to treat group 4 is 5.

Discussion

Nitazoxanide has antimicrobial characteristics against *H. pylori* like metronidazole and has been used as part of the eradication therapy of *H. pylori* [26,28]. Moreover, unjustified antimicrobial using during the COVID-19 pandemic has exacerbated antimicrobial resistance [28]. *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Acinetobacter baumannii* were the most frequent pathogens with levels of antimicrobial resistance identified by the Centers for Disease Control and Prevention (CDC) [29,30]. Also, Kamal *et al.* reported after 2 years of the COVID-19 pandemic, there is an increase in the resistance rate of *H. pylori* to both clarithromycin and levofloxacin [19]. In light of the previous studies, we aimed to evaluate the safety and efficacy of synergistic adding nitazoxanide to the standard clarithromycin-based triple therapy versus other standard clarithromycin-based triple regimens in patients infected with *H. pylori* after Covid-19 pandemic.

In this trial, patients within group 4 who were treated with clarithromycin 500mg bid, amoxicillin 1gm bid, nitazoxanide 500 mg bid, and omeprazole 20 mg bid for 14 days had the highest eradication rate of 84% in ITT and 89.36% in PP than other studied groups with significant *p* (0.01). Our results are in line with the findings of Waheeb *et al.* who reported that adding nitazoxanide to standard clarithromycin-based triple therapy improves the eradication rate (92%) [31]. Also, our results agree with Jha *et al.* who reported that the patients who were treated with nitazoxanide 500mg bid, clarithromycin 500 mg bid, amoxicillin 1gm bid, and esomeprazole 40mg bid for 14 days achieved optimal eradication rate (93.7%) [28].

Moreover, patients within group 1 who were treated with clarithromycin 500mg bid, amoxicillin 1gm bid, and omeprazole 20 mg bid for 14 days had a suboptimal eradication rate of 64% in ITT and 69.56% in PP. This agrees with previous studies that showed most *H. pylori* infected patients who were treated by clarithromycin-based triple therapy had achieved a suboptimal cure rate [18,19,32]. Based on the Maastricht V/Florence consensus report, previous studies in Egypt, and these current results, we do not recommend clarithromycin-based triple therapy anymore as the first line in Egypt [9,18-20,33].

In group 3, the eradication rate in patients who were treated with clarithromycin 500mg bid, nitazoxanide 500 mg bid, and omeprazole 20 mg bid for 14 days was 56% in ITT, and 56.25% in PP, while patients within group 2 who were treated with clarithromycin 500mg bid, metronidazole 500 mg bid and omeprazole 20 mg bid for 14 days had achieved the least eradication rate 36% in ITT and 40.90% in PP.

In comparison, Shehata *et al.* reported that patients who were treated with clarithromycin 500 mg b.i.d, and nitazoxanide 500mg b.i.d, omeprazole 40mg b.i.d for 14 days had achieved eradication rate of 94.6% while patients who received (clarithromycin, metronidazole and omeprazole for 14 days) had achieved eradication rate of 60.6% [26]. This dramatic decrease in eradication rates of *H. pylori* may have occurred due to increased bacterial resistance to antibiotics especially macrolide and levofloxacin [19,34].

Regarding to adverse effects of different regimens used in the trial, minor adverse effects were reported Minor adverse effects occurred in 94 (ITT: 47%, 50.81% PP) patients in the form of epigastric pain, nausea, urine discoloration, diarrhea, and metallic taste. Urine discoloration occurred in patients who were treated with nitazoxanide, diarrhea in patients treated with amoxicillin, and metallic taste in patients treated with metronidazole.

Conclusions

Concomitant use of nitazoxanide with clarithromycin based triple therapy is safe, effective, and significantly improves the eradication rate of *H. pylori*. Concomitant use of nitazoxanide with standard clarithromycin based triple therapy could be used as the first line for eradication of *H. pylori*. Moreover, after the COVID-19 era all clarithromycin-based triple regimens achieved suboptimal eradication rates, so we did not recommend using clarithromycin-based triple therapies anymore as first-line therapy for eradication of *H. pylori*.

Study limitations and future recommendations

This trial had some limitations of being a single-center study with a small sample size so we recommend further multi-center studies with larger sample sizes in different areas.

Authors' contributions

Hassan AM and Mohammed FM created the research idea. Hassan AM, Mohammed FM, and Abdel-Gawad M designed the study. Hassan AM, Mohammed FM, and Mahmoud MM performed the clinical examination. All authors shared in analyzing and interpreting the patient data and in writing the manuscript drafting. All authors read and approved the final manuscript.

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Conflict of interests

No conflict of interests is declared.

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