



Clinical Trials Study

Optimized sequential therapy vs 10- and 14-d concomitant therapy for eradicating *Helicobacter pylori*: A randomized clinical trial

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Specialty type: Gastroenterology and hepatology

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Bordin DS, Russia; Cheng H, China

Received: October 6, 2023

Peer-review started: October 6, 2023

First decision: November 12, 2023

Revised: November 26, 2023

Accepted: December 29, 2023

Article in press: December 29, 2023

Published online: February 14, 2024



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Abstract

BACKGROUND

A cure for *Helicobacter pylori* (*H. pylori*) remains a problem of global concern. The prevalence of antimicrobial resistance is widely rising and becoming a challenging issue worldwide. Optimizing sequential therapy seems to be one of the most attractive strategies in terms of efficacy, tolerability and cost. The most common sequential therapy consists of a dual therapy [proton-pump inhibitors (PPIs) and amoxicillin] for the first period (5 to 7 d), followed by a triple therapy for the second period (PPI, clarithromycin and metronidazole). PPIs play a key role in maintaining a gastric pH at a level that allows an optimal efficacy of antibiotics, hence the idea of using new generation molecules.

AIM

To compare an optimized sequential therapy with the standard non-bismuth quadruple therapies of 10 and 14 d, in terms of efficacy, incidence of adverse effects (AEs) and cost.

METHODS

This open-label prospective study randomized 328 patients with confirmed *H. pylori* infection into three groups (1:1:1): The first group received quadruple therapy consisting of twice-daily (bid) omeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg and metronidazole 500 mg for 10 d (QT-10), the second group received a 14 d quadruple therapy following the same regimen (QT-14), and the third group received an optimized sequential therapy consisting of bid rabe-

prazole 20 mg plus amoxicillin 1 g for 7 d, followed by bid rabeprazole 20 mg, clarithromycin 500 mg and metronidazole 500 mg for the next 7 d (OST-14). AEs were recorded throughout the study, and the *H. pylori* eradication rate was determined 4 to 6 wk after the end of treatment, using the ¹³C urea breath test.

RESULTS

In the intention-to-treat and per-protocol analysis, the eradication rate was higher in the OST-14 group compared to the QT-10 group: (93.5%, 85.5% $P = 0.04$) and (96.2%, 89.5% $P = 0.03$) respectively. However, there was no statistically significant difference in eradication rates between the OST-14 and QT-14 groups: (93.5%, 91.8% $P = 0.34$) and (96.2%, 94.4% $P = 0.35$), respectively. The overall incidence of AEs was significantly lower in the OST-14 group ($P = 0.01$). Furthermore, OST-14 was the most cost-effective among the three groups.

CONCLUSION

The optimized 14-d sequential therapy is a safe and effective alternative. Its eradication rate is comparable to that of the 14-d concomitant therapy while causing fewer AEs and allowing a gain in terms of cost.

Key Words: *Helicobacter pylori*; Quadruple therapy; Sequential; Proton-pump inhibitor; Optimization

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Core Tip: *Helicobacter pylori* infection remains a common infection worldwide. The decline in the efficacy of traditional triple therapies since 2010 has required new combinations of antibiotics. The last guidelines of Maastricht VI recommend bismuth quadruple therapies or concomitant quadruple therapies to reach an eradication rate of at least 90%. These values remain higher than those obtained with standard sequential therapy but are associated with a higher cost and more adverse effects (AEs). The results of the present study demonstrate that optimizing sequential therapy by using second-generation proton-pump inhibitors improved eradication rates and reduced AE incidence. This combination can thus be suggested for use in clinical practice.

Citation: Seddik H, Benass J, Berrag S, Sair A, Berraida R, Boutallaka H. Optimized sequential therapy vs 10- and 14-d concomitant therapy for eradicating *Helicobacter pylori*: A randomized clinical trial. *World J Gastroenterol* 2024; 30(6): 556-564

URL: <https://www.wjgnet.com/1007-9327/full/v30/i6/556.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v30.i6.556>

INTRODUCTION

A cure for *Helicobacter pylori* (*H. pylori*) remains a problem of global concern[1]. This bacterium is a well-known cause of peptic ulcer, gastritis, gastric mucosa-associated lymphoid tissue lymphoma and gastric malignancies[2-4]. *H. pylori* eradication is thus an effective strategy in preventing gastric malignancies[5,6].

Even though *H. pylori* infection management is evolving, no regimen can currently achieve a cure rate of 100%. The most recent Maastricht VI consensus recommends (in the absence of antibiotic susceptibility testing) quadruple Bismuth therapy or non-Bismuth quadruple concomitant therapy to achieve a cure rate of at least 90% despite the association of both regimens with a significant rate of adverse effects (AEs)[7]. Furthermore, the prevalence of antimicrobial resistance is widely rising and becoming a problem of great interest worldwide[8]; in Morocco, a previous study showed clarithromycin resistance of more than 15%[9]. Therefore, the best strategy to increase *H. pylori* eradication rate would be a personalized treatment based on antibiotic susceptibility[10].

However, this strategy is not possible in many developing countries, which is why many studies have instead focused on optimizing the recommended regimens[11]. It can either be an optimization by extending the length of the protocol [12], using a higher dose and/or second-generation proton-pump inhibitors (PPIs) or switching to vonoprazan[13,14], changing the antibiotics used and their posology, or associating other molecules to the eradication protocol, such as probiotics[15].

Optimizing the sequential therapy seems to be one of the most attractive strategies in terms of efficacy, tolerability and cost. The most common sequential therapy consists of a dual therapy (PPI and amoxicillin) for the first period (5 to 7 d), followed by a triple therapy for the second period (PPI, clarithromycin and metronidazole). PPIs play a key role in maintaining a gastric pH at a level that allows optimal antibiotic efficacy[16], hence the idea of using new generation molecules.

The primary aim of this study was to compare the efficacy of the 14-d sequential therapy (optimized by using a second-generation PPI) and standard non-bismuth quadruple therapies of 10 and 14 d. The secondary aims were to compare the tolerability and AEs among the groups, as well as their cost-effectiveness.

MATERIALS AND METHODS

Study design and patient selection

This was a single center, prospective, open-label, randomized study, conducted between January 2018 and March 2020, at the Mohammed V Military Teaching Hospital of Rabat. We included adult patients with *H. pylori* infection confirmed by histological analysis of gastric biopsies performed during upper endoscopy. Five gastric biopsy samples were taken systematically according to the recommended Sydney system (antrum, incisura, greater and lesser curvature)[17], and then studied for the presence of *H. pylori* using Hematoxylin and eosin staining at the pathology laboratory of our hospital. Patients who previously received an eradication therapy, PPI, H₂-blockers, non-steroidal anti-inflammatory drugs or Bismuth containing compounds 4 wk prior to the study, and/or patients who were allergic to the prescribed antibiotics were excluded from the study. Pregnant and breastfeeding females, patients with history of gastric surgery, kidney or liver failure, or severe psychiatric conditions were also excluded. All patients provided written informed consent to be included in the study. The protocol followed Helsinki Declaration guidelines and was approved by our local scientific committee at Mohammed V Military Teaching Hospital of Rabat. Our clinical trial was registered in the Pan African Clinical Trial Registry (www.pactr.org) on December 7, 2021, registration number: PACTR202112632957229.

Randomization and treatment

Patients were randomly assigned into three groups in a 1:1:1 ratio, using a computer-generated table: QT-14, QT-10 and OST-14. Allocations were concealed in a sealed opaque envelope which was to be opened during the consultation day. The QT-14 and QT-10 groups received omeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg and metronidazole 500 mg, all twice daily for 14 and 10 d, respectively. The OST-14 group received an optimized sequential therapy consisting of twice daily rabeprazole 20 mg and amoxicillin 1 g during 7 d, followed by rabeprazole 20 mg, clarithromycin 500 mg and metronidazole 500 mg, all twice daily for the remaining 7 d. PPI was administered 30 min before breakfast and supper, whereas antibiotics were administered every 12 h after meals.

Follow-up and outcomes

The *H. pylori* eradication was assessed at least 4 wk after the last day of the treatment using the 13C-urea breath test (UBT), which was performed blindly at the same laboratory for all patients. The cut-off value for the UBT was 2.5 per thousand. The patients did not undergo additional therapy with PPI after completion of eradication therapy.

All patients were evaluated 2 wk after the start of the treatment and at its end to assess AEs and compliance. Drug compliance was defined by taking at least 90% of the prescribed protocol drugs and was assessed at the end of the protocol. AEs were assessed using a pre-established structured questionnaire consisting of dichotomous questions about the occurrence and intensity of AEs including diarrhea, nausea and/or vomiting, gastralgia, metallic taste, dysgeusia, symptoms related to an allergic reaction, headache, dizziness, asthenia, or any other AE.

Cost-effectiveness analysis was assessed by comparing the overall cost of each protocol. The cost of every drug was calculated using a national website: www.medicament.ma. The cost-effectiveness ratio for each regimen was calculated by dividing the total cost for 100 patients treated by the percent of patients treated.

Statistical analysis

This study sample size was determined as follows. We presumed the eradication rate of OST-14 to be 95% and the eradication rate of QT-10 to be 83% (lowest eradication rate of the three treatment regimens). By setting the bilateral significance level to 0.05, the power to 80% and the drop-out rate to 5%, at least 104 patients were required in each group. Our hypothesis on the QT-10 eradication rate was based on a previous meta-analysis[18].

The primary endpoint of the study was the eradication rate of *H. pylori*, which was assessed by intention to treat (ITT) and per-protocol (PP) analyses. The safety population included all randomized patients who received at least one treatment dose during the study, ITT population included all patients who received at least one treatment dose during the study and who were examined during the first visit, while the PP population included only patients who completed the study. Therapeutic failure was recorded as outcome for patients with missing data due to incomplete treatment. The secondary outcomes were the incidence of AEs, the therapeutic compliance and the cost-effectiveness of the protocols.

Descriptive and inferential statistical analyses were performed using Software Package Social Science SPSS® for mac OS version 22.0 (IBM Corp, Armonk, NY, United States). For all statistical analyses, *P* value less than 0.05 was considered statistically significant. Qualitative variables (eradication rates of the three groups) were compared using χ^2 test and Fisher's exact test. Continuous variables were compared between the three groups using a one-way ANOVA test.

RESULTS

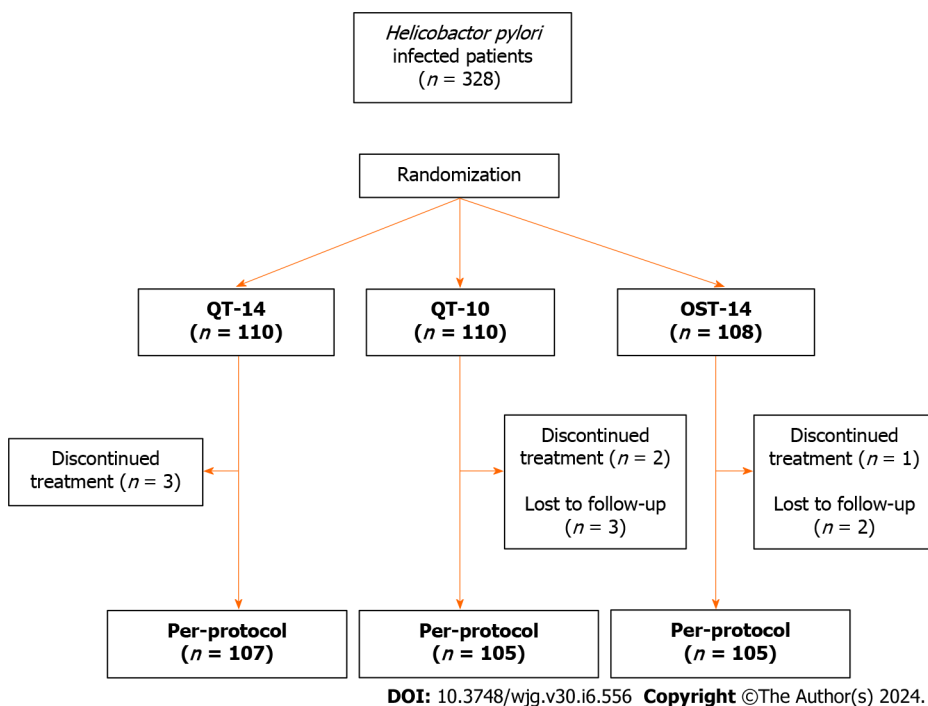
Population characteristics

A total of 328 patients were enrolled in the study. They were included in the ITT analysis and randomized into the three groups. After eliminating the dropped-out patients from the study, the PP analysis included 317 patients. The study flow chart is shown in Figure 1. Demographic and clinical characteristics of the three groups are shown in Table 1 and were not significantly different between the groups.

Table 1 Basic overall population and group characteristics

Characteristic	Overall, <i>n</i> = 317	QT-14, <i>n</i> = 107	QT-10, <i>n</i> = 105	OST-14, <i>n</i> = 105	<i>P</i> value
Age in yr, mean ± SD	44.13 ± 15.30	43.37 ± 14.40	43.36 ± 15.9	45.67 ± 15.53	0.46
Sex ratio as male/female	0.98	1.03	1	0.92	0.91
Smoking habit	49 (14.9)	18 (16.4)	14 (12.7)	17 (15.7)	0.62
Gastroduodenal ulcer	47 (14.3)	22 (20)	13 (11.8)	12 (11.1)	0.16
Gastric atrophy	51 (15.5)	14 (12.7)	18 (16.4)	19 (17.6)	0.58
Gastric metaplasia	18 (5.5)	7 (6.4)	8 (7.3)	3 (2.8)	0.26
HP antral density					0.30
+	114 (34.9)	37 (33.9)	37 (33.6)	40 (37)	
++	170 (52)	58 (53.2)	56 (50.9)	56 (51.9)	
+++	35 (10.7)	11 (10.1)	12 (10.9)	12 (11.1)	
HP fundic density					0.74
+	147 (44.8)	54 (49.1)	46 (41.8)	47 (43.5)	
++	62 (18.9)	20 (18.2)	22 (20)	20 (18.5)	
+++	7 (2.1)	1 (0.9)	2 (1.8)	4 (3.7)	

All values are expressed as *n* (%) unless otherwise stated. +: Sparse; ++: Moderate; +++: Marked. HP: *Helicobacter pylori*; SD: Standard deviation.

**Figure 1 Flow-chart of study patients.**

Eradication rates

In the ITT analysis, *H. pylori* eradication was achieved in 85.5% of patients in the QT-10 group, 91.8% of patients in the QT-14 group, and 93.5% of patients in the OST-14 group. In the PP analysis, the results were as follows: 89.5%, 94.4%, and 96.2% in the QT-10, QT-14, and OST-14 groups, respectively.

Comparison of eradication rates

The eradication rate in the OST-14 group was higher compared to the QT-10 group in the ITT analysis ($P = 0.04$) and in the PP analysis (0.03). However, there was no statistically significant difference between the eradication rate of OST-14 and QT-14 groups (in ITT analysis: $P = 0.34$, in PP analysis $P = 0.35$).

Safety

The treatment tolerance was better in the OST-14 group, with an incidence of AEs of 24.7% compared to 42.7% and 39% in the QT-14 and QT-10, respectively ($P = 0.03$) (Table 2). However, the treatment was globally well tolerated among the three groups, and AEs were mild to moderate in all patients. The drug compliance was excellent among the three groups: 97%, 95% and 98.9% in the QT-10, QT-14 and OST-14, respectively ($P = 0.48$).

Cost-effectiveness

The overall cost was lower in the OST-14 group [427.10 Moroccan dirhams (MAD)], compared to QT-14 and QT-10 groups (691.90 MAD and 587.10 MAD, respectively). The cost-effectiveness ratio was lower in the OST-14 group, as shown in Table 3.

DISCUSSION

According to the Maastricht VI consensus, the most recommended empirical regimens for *H. pylori* infection are Bismuth quadruple therapy and non-Bismuth quadruple concomitant therapy[7]. However, eradication rates widely vary geographically due to varying antimicrobial resistance, especially to clarithromycin and metronidazole[19].

It is important to note that the *H. pylori* eradication rate is significantly influenced by antibiotic resistance. Furthermore, the bismuth agent is not available in all areas. Therefore, in areas where *H. pylori* is highly resistant to clarithromycin, non-bismuth quadruple therapies are still recommended when the bismuth agent is not available.

Several non-bismuth regimens have been tested to improve the management of *H. pylori* infection[20,21]. One of them is modified sequential therapy[12,22]. In the present study, we aimed to compare the results of the standard 10- and 14-d non-bismuth quadruple therapies to an optimized sequential therapy by using a second-generation PPI.

Overall, we found that the optimized 14-d sequential regimen using rabeprazole (OST-14) achieves a higher cure rate than the standard quadruple therapy without bismuth for 10 d (85.5% and 93.5%, respectively, $P = 0.04$), while there was no statistically significant difference between OST-14 and the 14-d quadruple therapy (93.2% and 91.8%, respectively, $P = 0.34$). OST-14 allowed a greater tolerance with fewer AEs compared to quadruple therapies ($P = 0.01$), and there was no difference in term of drugs compliance between the three groups. Furthermore, the cost-effectiveness ratio was lower in the OST-14 group.

The sequential therapy was introduced for the first time in 2000 in Italy by Zullo *et al*[23]. We personally demonstrated its superiority compared to the standard triple therapy in a previous study[24]. A recent metanalysis by Wang *et al*[18] showed that there is no difference in terms of eradication rate between a 14-d sequential and a 14-d concomitant therapy. Another study showed that a 14-d sequential therapy is equivalent to 10 d bismuth quadruple therapy in terms of eradication rate (91.3% and 91.6%, respectively), but bismuth therapy led to more AEs[25]. In a metanalysis, the same team demonstrated that a 14-d sequential therapy is more effective than a 14-d triple therapy[26].

In the present study, the gain in terms of eradication rate can be explained by the use of a second generation PPI (rabeprazole 20 mg bid) in the OST-14 group. In fact, the last Maastricht consensus states that switching omeprazole 20 mg twice daily to rabeprazole 20 mg bid or esomeprazole 40 mg bid may increase eradication rate by 8%-12%[7]. The advantage of PPIs lies in the fact that the majority of proposed regimens are pH-dependent and become less effective when the intragastric pH is low[27], hence the use of higher dose PPIs and second-generation substances. A possible explanation for the superiority of second-generation PPIs (rabeprazole and esomeprazole) may be their metabolism, which is less dependent on CYP2C19 genetic variables and their higher acid inhibition power[28]. A further metanalysis by McNichol *et al*[29] confirmed that both esomeprazole and rabeprazole led to higher eradication rates compared to first generation PPIs (omeprazole, lansoprazole and pantoprazole). High doses of PPIs also improved the efficacy of eradication therapy. In strains resistant to clarithromycin, the eradication rate can be increased using PPI-amoxicillin dual therapy[30].

All therapeutic regimens currently recommended are associated with gastrointestinal AEs[31]. Herein, OST-14 allowed a gain in terms of AE incidence compared to quadruple concomitant therapies. These findings confirm those of previous studies[32-34]. The 14-d sequential therapy consists of the same antibiotics as the 14-d concomitant regimen but for a shorter duration. It should therefore lead to fewer AEs. This was the case in our study with a benefit of 18% in terms of AE occurrence (31.3% *vs* 49.5%; $P = 0.03$). Because treatment cost is a determining factor, especially in developing countries, we carried-out cost- effectiveness analysis and showed that OST-14 is the most cost-effective among our study's groups. The same result was previously reported by Farhoud *et al*[33], who found that 14-d sequential therapy is cheaper than 14-d triple therapy. Further, Kate *et al*[35] confirmed in a metanalysis that sequential therapies are cheaper than standard therapies. Other cost-analysis studies have shown the same results and found that sequential therapy is the most economically attractive option[36,37]. This benefit can be explained by the fact that clarithromycin is the most expensive drug used in different protocols, and it is used for a shorter duration in sequential therapy.

One of the limitations of this study is that we did not perform *H. pylori* cultures and did not have any data about antibiotic susceptibility. However, a recent study showed that in Morocco, the local primary resistance to clarithromycin was 29%, 40% to metronidazole and 0% to amoxicillin[9]. Another potential limitation is that second line treatments were not included, which makes it difficult to interpret the cost effectiveness analysis. Additionally, it is difficult to generalize our results to other areas, as the study was conducted in a single center. Nonetheless, the sample size was reasonable to allow for correct statistical analysis. However, our results should be validated by further studies in different geographic areas. Other studies could further compare these eradication regimens to others containing vonoprazan. For the moment, this molecule is still not available in Morocco.

Table 2 Incidence of adverse effects among the study groups

Analysis	QT-10	QT-14	OST-14	P value ¹
ITT	39%	42.7%	24.7%	0.03
PP	45.1%	49.5%	31.3%	0.01

¹P value of χ^2 test.

ITT: Intention to treat; PP: Per-protocol.

Table 3 Cost-effectiveness ratio in the three protocols costs, expressed in Moroccan dirhams

Therapeutic protocol	Overall cost of 100 patients	Effectiveness	Cost-effectiveness ratio
QT-10	58710	89.5%	655
QT-14	69190	94.4%	732
OST-14	42710	98.1%	435

CONCLUSION

In conclusion, the results of the present study showed that the 14-d sequential therapy using rabeprazole appears to be an optimal therapy that is comparable to 14-d concomitant therapy while causing fewer AEs and allowing a gain in terms of cost.

ARTICLE HIGHLIGHTS

Research background

A cure for *Helicobacter pylori* (*H. pylori*) remains a problem of global concern and none of the currently available treatments can achieve a cure rate of 100%. With the global rising issue of antibiotic resistance and the difficulty to establish personalized treatments according to antibiotic susceptibility in developing countries, optimizing sequential therapy seems to be one of the most attractive strategies in terms of efficacy, tolerability and cost.

Research motivation

H. pylori eradication rate is significantly influenced by antibiotic resistance. According to the Maastricht VI consensus, the most recommended empirical regimens for *H. pylori* infection are Bismuth quadruple therapy and non-Bismuth quadruple concomitant therapy when the Bismuth agent is not available. Many studies showed that switching to high doses of second-generation proton-pump inhibitors (PPIs) and using a PPI-amoxicillin dual therapy can improve the eradication rate and could lead to fewer adverse effects (AEs). The cost of treatment is also a determining factor, especially in developing countries.

Research objectives

In the present study, we aimed to compare the results of the standard 10- and 14-d non-bismuth quadruple therapies to an optimized sequential therapy by using a second-generation PPI, in terms of efficacy, tolerability and cost-effectiveness. The 14-d sequential therapy using rabeprazole appears to be an optimal therapy that is comparable to 14-d concomitant therapy while causing fewer AEs and allowing a gain in terms of cost. Other studies could further validate the standard eradication regimens vs the 14-d sequential therapy using rabeprazole vs other regimens containing vonoprazan. For the moment, this molecule is still not available in Morocco.

Research methods

We conducted a single center, prospective, open-label, randomized study with patients randomly assigned into three groups in a 1:1:1 ratio using a computer-generated table: QT-14, QT-10 and OST-14. Allocations were concealed in a sealed opaque envelope to be opened during the consultation day.

Research results

This study showed that the 14-d sequential therapy using rabeprazole appears to be an optimal therapy that is comparable to 14-d concomitant therapy while causing fewer AEs and allowing a gain in terms of cost.

Research conclusions

According to the Maastricht VI consensus, the most recommended empirical regimens for *H. pylori* infection are Bismuth

quadruple therapy and non-Bismuth quadruple concomitant therapy. This study suggests the use of an optimized 14-d sequential regimen using rabeprazole to achieve the same eradication rate as the non-bismuth quadruple concomitant therapy while leading to fewer AEs and being more economically attractive.

Research perspectives

Given our study's limitations, these are several future research perspectives: (1) Conduct a multicenter trial (in different geographical areas) to validate our results; (2) Compare the sequential therapy to other therapies containing vonoprazan; and (3) Compare the use of esomeprazole and rabeprazole in a sequential therapy in terms of efficacy, tolerability and cost-effectiveness.

FOOTNOTES

Author contributions: Seddik H was responsible for study concept and planning and supervised the statistical analysis and manuscript revision; Benass J and Boutallaka H were involved in performing the statistical analysis and writing the manuscript, with input from all authors; Berrag S, Sair A, and Berraida R were involved in patient enrollment and data collection and were involved in manuscript preparation; All authors reviewed the manuscript.

Institutional review board statement: An Institutional Review Board (Scientific committee at Mohammed V Military Teaching Hospital of Rabat) reviewed and approved the trial protocol. Our study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Clinical trial registration statement: Our clinical trial has been retrospectively registered in the Pan African Clinical Trial Registry (www.pactr.org) on December 7, 2021, Registration No.: PACTR202112632957229.

Informed consent statement: All patients included in the study provided written informed consent before being enrolled in the trial.

Conflict-of-interest statement: The authors report having no relevant conflicts of interest for this article.

Data sharing statement: The datasets generated and/or analyzed during the study are available from the corresponding author on reasonable request.

CONSORT 2010 statement: The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

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S-Editor: Wang JJ

L-Editor: Filipodia

P-Editor: Yuan YY

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