A RANDOMISED COMPARATIVE TRIAL OF SEVEN VERSUS FOURTEEN DAY TRIPLE THERAPY FOR HELICOBACTER PYLORI ERADICATION AT THE AGA KHAN UNIVERSITY HOSPITAL, NAIROBI

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Introduction

- Helicobacter pylori (H. pylori), a gram-negative micro-aerophilic bacillus.

- Recognized to be associated with diverse upper gastrointestinal pathologies such as chronic gastritis, peptic ulceration, mucosal associated lymphoid tissue (MALT) lymphoma and gastric carcinoma

Introduction

- Infection with H. pylori occurs worldwide, but the prevalence varies greatly among countries.

- It is more common in developing countries where prevalence is over 80% in middle-aged adults as compared to 20-50% in industrialised countries.

H Pylori in Kenya

In Kenya a study done by Ogutu et al showed all cases of peptic ulcer disease had evidence of H. pylori infection while dyspeptic patients with normal endoscopic mucosal findings had H. pylori in 80.5% of cases

H Pylori in Kenya

- A study done by Kalebi et al in 2004 at the Kenyatta National Hospital looking at the rate of H pylori gastritis was 91% in dyspeptic patients

- World J Gastroenterol 2007 August 14; 13(30): 4117-4121
Indications for Diagnosis and Treatment of H. pylori

- Active peptic ulcer disease (gastric or duodenal ulcer)
- Confirmed history of peptic ulcer disease (not previously treated for H. pylori)
- Gastric MALT lymphoma (low grade)
- After endoscopic resection of early gastric cancer
- Uninvestigated dyspepsia (depending upon H. pylori prevalence)

Benefits Of Treating H Pylori

- Healing of peptic ulcers and the prevention of recurrence. Eradication also prevents recurrent bleeding from peptic ulcers.
  


- Prevention of development or recurrence of non-cardia gastric cancer. Wong BC JAMA 2004;291:244-5.
First Line

- Standard first-line treatment is based on clarithromycin, amoxicillin, or metronidazole combined with proton-pump inhibitor (PPI).

Effective Eradication

- Effective eradication treatment should be successful in more than 80% of intention-to-treat and 90% per-protocol treated patients

Uncertainty

- Treatment strategies for Helicobacter pylori have evolved rapidly in the last decade, but there is still uncertainty about the optimal duration of therapy.
In Europe, a 7-d triple therapy is still recommended because 14-d therapy had an insignificant advantage in terms of treatment success rate.

Guidelines from North America recommend 10-d to 14-d therapy, as some studies have reported superior cure rates with prolonged therapy using triple regimens.

Korea

- Comparison of 7-day and 14-day proton pump inhibitor containing triple therapy for Helicobacter pylori eradication

- Neither treatment duration provides acceptable eradication rate in Korea of 90% in per-protocol analysis

*Kim BG Helicobacter 2007; 12: 31-35*
In Asia, an Indian study reported that prolonged triple therapy with lansoprazole, amoxicillin and tinidazole achieved a significant increase in eradication rates: 47.6% vs 80% vs 91.3% for 1 wk, 2 wk and 3 wk of therapy, respectively.

Chaudhary A, Helicobacter 2004; 9: 124-129
2-Week Triple Therapy for *Helicobacter pylori* Infection is Better Than 1 Week in Clinical Practice: a Large Prospective Single-Center Randomized Study

Paoluzi et al Helicobacter 2006;11:562–8. ( Italy )

<table>
<thead>
<tr>
<th></th>
<th>ITT analysis% (95% CI)</th>
<th>PP analysis% (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OAC-1</strong> 117</td>
<td>57 (48–66)</td>
<td>66 (57–76)</td>
</tr>
<tr>
<td><strong>OAC-2</strong> 126</td>
<td>70 (62–78)</td>
<td>77 (69–85)</td>
</tr>
</tbody>
</table>

**Difference** 13% 11%

OAC-1, -2, omeprazole + amoxicillin + clarithromycin for 1 week or 2 weeks
**Helicobacter pylori** Eradication Therapy Success Regarding Different Treatment Period Based on Clarithromycin or Metronidazole Triple-Therapy Regimens


<table>
<thead>
<tr>
<th>Treatment protocol</th>
<th>Eradication success ITT (%)</th>
<th>Eradication success PP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACI7</td>
<td>92/120 (76.7)</td>
<td>92/113 (81.4)</td>
</tr>
<tr>
<td>PACI10</td>
<td>98/118 (83.1)</td>
<td>98/109 (89.9)</td>
</tr>
<tr>
<td>PACI14</td>
<td>55/57 (96.5)</td>
<td>55/56 (98.2)</td>
</tr>
</tbody>
</table>
In Kenya

- Standard first-line treatment in Kenya is based on Clarithromycin, Amoxicillin, or Metronidazole combined with proton-pump inhibitor (PPI) for 7 - 14 days.

- There are no studies in Kenya looking at the eradication rates of the first line treatment.
Consensus

- For PPI, clarithromycin, amoxicillin or metronidazole 14 day treatment is more effective than seven days.

- A seven day treatment may be acceptable where local studies show that it is effective.

This variation of the results could be a consequence of many factors such as:-
Bacterial virulence
Environmental factors
Antibacterial resistance, which are peculiar for each country.
Recent study at AKUHN

All the *H. pylori* investigated in this study were largely sensitive to

- Clarithromycin (100%)
- Amoxicillin (100%)
- Metronidazole (95.4%).

Justification for the study

- The optimal duration of triple therapy to obtain eradication of H. pylori is still a matter of debate.

- No studies have been done in Kenya to find out the H pylori eradication rates using the first line triple therapy.

- The duration for adequate eradication using triple therapy is not known in Kenya.
Null Hypothesis

- There is no difference between 7 day and 14 day triple therapy on H pylori eradication rates in Kenya
Aim

- To compare the efficacy and safety of 7- and 14 day regimens of esomeprazole, amoxicillin and clarithromycin triple therapy for *H. Pylori* eradication
Primary Objective

1. To determine and compare the *H. pylori* eradication rates of 7 and 14 day triple therapy.
Secondary objectives

- To compare the side-effects between seven and fourteen day triple therapy
- To compare the compliance rates between 7 and 14 day triple therapy.
Methodology Study design

- A prospective randomised comparative trial of 7 and 14 day *H. pylori* eradication triple therapy at the Aga Khan University Hospital Nairobi

- Patients were recruited from A/E, wards and gastroenterology clinics
Study Population

- All patients who presented with dyspepsia and *H. pylori* positive on stool antigen were randomised to receive either 7 day or 14 day triple therapy (Clarithromycin 500mg BD + Amoxicillin 1g BD + Esomeprazole 20mg BD).
Study Period

- The patients were studied during the period from December 2009 through to May 2010 at The Aga Khan University Hospital, Nairobi.
Inclusion Criteria

- Male and female patients aged 18yrs and above.
- Helicobacter Pylori positive on stool antigen
- Signed informed consent
Exclusion Criteria

- The use of antimicrobials or gastrointestinal medication like PPIs or bismuth compounds within 4 weeks prior to study entry.

- Known allergy or adverse drug reaction to amoxicillin (penicillin), clarithromycin or PPI.

- Pregnancy or Lactation

- Alarm features.
**Outcome measures and definition of variables**

- *H. pylori* infection was defined by stool *H. pylori* antigen positive. A Rapid Strip HpSA™ (Meridian Bioscience Europe), monoclonal anti *H. pylori* antibody was used. Sensitivity and specificity are 94% (95% CI: 93–95) and 97% (95% CI: 96–98). *Am J Gastroenterol.* 2006 Aug;101(8):1921-30.

- Alarm features were defined by age > 45, gastrointestinal bleeding, anemia, early satiety, unexplained weight loss, progressive dysphagia, odynophagia, recurrent vomiting, family history of GI cancer, previous esophagogastric malignancy. *Am J Gastroenterol.* 2007 Aug;102(8):1808-25.
Sample Size

\[ N = 2 \left[ Z_{1-\alpha/2} \frac{\sqrt{2p\Psi(1-p\Psi)}}{\sigma^2} + Z_{1-\beta} \frac{\sqrt{p_1(1-p_1)+p_2(1-p_2)}}{\delta^2} \right]^2 \]

Where;
- \( N \) = Sample size for both groups
- \( P_1 \) = the hypothesized proportion of patients who have \( H. pylori \) cleared in 7 days (76%) Filipec Kanizaj et al.
- \( P_2 \) = the hypothesized proportion of patients who have \( H. pylori \) cleared in 14 days (96%) Filipec Kanizaj et al.
- \( p\Psi = \frac{P_1 + P_2}{2} = 0.86 \)
- \( Z_{1-\alpha/2} \) = Normal deviate corresponding to a 95% confidence interval in a two tailed test (=1.96)
- \( Z_{1-\beta} \) = z score for power of the test 80% = 0.842
- \( \delta \) = Minimum difference between the two proportions
N = 86
In each arm 86/2 = 43
Approximately 30% logistical errors + drop out

Each arm 60 patients

Dypepsia + H pylori stool antigen positive n = 120

7 day therapy (EAC 7) N = 60
14 day therapy (EAC 14) N = 60
Randomization and Blinding

- Patients were randomly assigned to the two treatment arms using simple random sampling.

- A computer generated list of 120 numbers randomly assigned ‘7’ and ‘14’ for 7 day and 14 day eradication therapy respectively was printed.

- This list was kept in the pharmacy and each consecutive patient referred was entered in a continuous fashion.
Randomization and Blinding

- By using this method the primary physician did not in any way determine the duration of the drugs the patient received and neither did he know the duration during follow up of the patient.

- The register was made available to the principle investigator at the end of the study.

- All the patients whether in the 7 day group or 14 day group were called for reviews at 2 and 6 weeks after starting of therapy to avoid unblinding the investigators.

- The laboratory technicians who were doing the *H. pylori* stool antigen test did also not know whether the patient will receive or has received 7 or 14 day triple therapy.
Ethical approval

- The study protocol was approved by the Aga Khan University Hospital research committee and the hospital ethics board after review by the department of medicine and the participating consultants.
Data collection

- A questionnaire was filled on first contact with the patient after consent.
- The patient was explained the study and the patient's contact details were taken as part of the questionnaire.
- The patient was then sent to the pharmacy with a special prescription printed for the study which the pharmacists were informed about.
Follow up

- All patients returned after 2 weeks of start of therapy to assess side affects and compliance.

- All patients returned 6 weeks after start of therapy and a repeat stool antigen was done to determine eradication.
Compliance

- Compliance was assessed by counting the pills returned by the patients.

- Good compliance was defined as consumption of more than 90% of the prescribed drugs. Helicobacter. 2009 Feb;14(1):29-35.

- Patients who had low compliance were excluded for per-protocol analysis.
Adverse events

- Type and severity of adverse events during treatment was reported by patients and recorded in the questionnaire.

- Adverse effects were defined as
  1. Mild - when not interfering with normal daily activity
  2. Moderate - when frequently interfering but allowing treatment to be completed
  3. Severe when withdrawal will be necessary

Statistical analysis

- Data were analysed using SPSS version 15.0 for Windows.

- Analysis of baseline characteristics and eradication success between different treatment protocols were performed using the Chi-square test.

- The t-test was used to analyze the age distribution between the different patients groups.

- Data were analyzed according to intention to treat (ITT) and per protocol (PP) criteria. The ITT analysis included all patients randomized to a treatment group, whereas in the PP analysis, patients lost during follow-up or showing low compliance were excluded.

- The incidences and severity of adverse events between two groups were also compared using the chi-square test.
Results
Flow of participants through each phase of the study

Dyspepsia + H. pylori Stool antigen positive N = 146

Randomized Patients N = 120

7 days EAC N = 60 ITT

14 days EAC N = 60 ITT

3 pregnant
4 breastfeeding
3 allergic to Penicillins
7 use of PPI within 4 weeks
4 alarm features
5 did not give consent

10 lost to follow up

N = 50 PP

N = 47 PP

12 lost to follow up
1 low compliance
### Baseline characteristics of study patients

<table>
<thead>
<tr>
<th></th>
<th>EAC 7 ( n = 60 )</th>
<th>EAC 14 ( n = 60 )</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25 (41.7%)</td>
<td>24 (40%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Female</td>
<td>35 (58.3%)</td>
<td>36 (60%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age years mean (SD)</strong></td>
<td>34 (10)</td>
<td>36 (11)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 (8.3%)</td>
<td>2 (3.3%)</td>
<td>0.24</td>
</tr>
<tr>
<td>No</td>
<td>55 (91.7%)</td>
<td>58 (96.7%)</td>
<td></td>
</tr>
</tbody>
</table>
# Baseline characteristics of study patients

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alcohol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21 (35%)</td>
<td>22 (36.7%)</td>
<td>0.85</td>
</tr>
<tr>
<td>No</td>
<td>39 (65%)</td>
<td>38 (63.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Endoscopy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not done</td>
<td>49 (81.7%)</td>
<td>47 (78.3%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Gastritis</td>
<td>11 (18.3%)</td>
<td>13 (21.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Compliance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;90%</td>
<td>50 (100%)</td>
<td>47 (97.9%)</td>
<td>0.53</td>
</tr>
<tr>
<td>&lt;90%</td>
<td>0</td>
<td>1 (2.1%)</td>
<td></td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>10 (16.7%)</td>
<td>12 (20%)</td>
<td>0.24</td>
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</table>
*H. pylori* eradication rates calculated according to intention to treat (ITT) and per protocol (PP) analysis

<table>
<thead>
<tr>
<th>Regimen</th>
<th>EAC 7</th>
<th>EAC 14</th>
<th>p-value</th>
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<tbody>
<tr>
<td>No. patients</td>
<td>60</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Lack of compliance</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Loss to follow up</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Number eradicated</td>
<td>46</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>ITT analysis, n %</td>
<td>46/60</td>
<td>44/60</td>
<td>0.67</td>
</tr>
<tr>
<td>% eradicated (95% CI)</td>
<td>76.7%</td>
<td>73.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(66 to 87.4)</td>
<td>(62.1 to 84.5)</td>
<td></td>
</tr>
<tr>
<td>PP analysis, n %</td>
<td>46/50</td>
<td>44/47</td>
<td>0.76</td>
</tr>
<tr>
<td>% eradicated (95% CI)</td>
<td>92%</td>
<td>93.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(84.5 to 99.5)</td>
<td>(86.6 to 100)</td>
<td></td>
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</tbody>
</table>
Comparison of eradication rates of 7 day and 14 day therapy as per Per protocol analysis (PP) and Intention to treat analysis (ITT)
Eradication rates amongst different variables

<table>
<thead>
<tr>
<th></th>
<th>Repeat stool test N = 98</th>
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<tbody>
<tr>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>38</td>
</tr>
<tr>
<td>Female</td>
<td>52</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
</tr>
<tr>
<td>No</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
</tr>
<tr>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32</td>
</tr>
<tr>
<td>No</td>
<td>58</td>
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<tr>
<td></td>
<td>Endoscopy</td>
</tr>
<tr>
<td>Not done</td>
<td>70</td>
</tr>
<tr>
<td>Gastritis</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Compliance</td>
</tr>
<tr>
<td>&gt;90%</td>
<td>90</td>
</tr>
<tr>
<td>&lt;90%</td>
<td>0</td>
</tr>
</tbody>
</table>
Comparison of frequency and severity of adverse events in the two treatment groups

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>EAC 7 ( n = 50 )</th>
<th>EAC 14 ( n = 47 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Headache</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adverse event</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
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<tr>
<td>------------------------</td>
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<td>--------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Loss of appetite</strong></td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Taste disturbance</strong></td>
<td>17</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Abdominal pain</strong></td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Graph showing percentage compliance in both treatment groups
Dypepsia + H. pylori stool antigen positive N = 146

Randomised Patients N = 120

3 pregnant
4 breastfeeding
3 allergic to Penicillins
7 use of PPI within 4 weeks
4 alarm features
5 did not give consent

ITT 1 week EAC N = 60

10 lost to follow up

N = 50 PP

Repeat test negative N = 46
92% PP
76.7% ITT

Repeat test positive N = 4

ITT 2 week EAC N = 60

N = 47 PP

Repeat test negative N = 44
93.6% PP
73.3% ITT

Repeat test positive N = 3

12 lost to follow up
1 low compliance
Patients with H pylori positive after completion of therapy were referred to Gastroenterology clinic for second line therapy
Conclusion

- One week esomeprazole with amoxicillin and clarithromycin based triple therapy regimen is highly effective in eradicating H. pylori infection (92%). This is in agreement with Maastricht consensus recommendations (PP > 90%).

- 1-week and 2-week triple therapy for H pylori eradication are similar in terms of efficacy, safety and patient compliance.
Study limitations

- Endoscopy was not done for all our patients to determine the type of disease caused by the *H. pylori* and the affect of *H. pylori* eradication on the disease.

- Stool antigen test was used to diagnose *H. pylori* infection and confirm its eradication instead of the urea breath test.
Recommendations

- One week triple therapy is adequate for *H. pylori* eradication as it is equally efficacious to two week therapy.

- A Large multi centre trial should be carried out within Kenya to confirm our findings as antibiotic resistance rates can vary with different regions.
Thank you