Effect of Helicobacter pylori eradication on platelet count in Idiopathic Thrombocytopenic Purpura

Thesis

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Abstract

Background:

Helicobacter pylori infection has been implicated in the pathogenesis of extra-digestive disorders, such as idiopathic thrombocytopenic purpura (ITP), since partial or even complete remission of thrombocytopenia has been reported in some patients after eradication of H.pylori .

Objective:

The aim of the study was to assess the effect of anti-H. pylori treatment on chronic ITP patients and its effect on blood platelet count & clinical outcome.

Methodology:

A total of 25 chronic ITP patients diagnosed as having H. pylori infection by Urea Breath Test (UBT) and received the standard therapy for H. pylori eradication were assessed clinically and laboratory 1 month after treatment & over one year duration on 3 monthly intervals.

Results:

According to results of UBT after H. pylori treatment; 22 patients (88%) of group (A) responding to treatment (responders), 3 patients (12%) still had H. pylori infection (non-responders).

During follow up; significant increase in platelet count and clinical improvement was observed in group (A) in relation to group (B) with the peak of this increase in platelet count at 6^{th} month.

Group (A); showed significant and sustained increase in platelet count on comparing before and after H. pylori treatment which continued till the end of follow up at 3, 6, 9& 12 months respectively.

Among group (A); significant increase in platelet count occurred in responders, while in non responders non significant increase occurred in platelet count during the period of follow up.

No correlation between platelet counts with age & sex detected before and after H. pylori treatment.

Conclusion:

H. pylori treatment in chronic ITP patients can increase the blood platelet count and improve the clinical outcome.

Further studies with large number of patients are recommended.

Key words:

*ITP: chronic Idiopathic thrombocytopenic purpura.

* H. pylori: Helicobacter pylori.

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List of Abbreviations

ACTH	Adrenacorticotropic hormone
BabA	Blood group antigen binding adhesion
CagA	Cytotoxin associated gene A
CD	Cluster of differentiation
CDT	Cytolethal distending toxin
cITP-csITP	Chronic ITP, Chronic severe ITP
DC	Dendritic cell
DOB	Delta over base line
EHS	Enterohepatic Helicobacter species
ERK1	Extracellular signal regulated kinase 1
FRET	Fluorescence resonance energy transfer
GC-MS	Gas chromatography-mass spectrometry
GM-CSF	Granulocyte-macrophage-colony stimulating factor
GP	Glycoprotein
H. pylori	Helicobacter pylori
HDMP	High dose methyl prednisolone
HLA	Human leukocytic antigen
HSP	Heat shock protein
HUS	Hemolytic uremic syndrome
IceA	Induced by contact with epithelial gene
ICH	Intracranial hemorrhage
ICP-MS	Inductively coupled plasma mass spectrometry
IFN	Interferon
IG	Immunoglobulin
IL	Interleukin
IRMS	Isotope ratio mass spectrometer
ITAM	Immunoreceptor tyrosine-based activation motifs
ITIM	Immunoreceptor tyrosine-based inhibitory motifs
ITP	immune thrombocytopenic purpura
IVIG	Intravenous immunoglobulin
LDH	lactate dehydrogenase
LPS	Lipopolysaccharide
MAHA	Microangiopathic hemolytic anemia
MALT	Mucosa associated lymphoid tissue
MAP	Mitogen activated protein kinase
MDMP	Medium dose methyl prednisolne
MMIF	Macrophage migratory inhibitory factor
MM-RAP	Mutidimensial scale recurrent abdominal pain
NaPA	Neutrophil activating protein A
NASPGN	North American Society for Pediatric Gastroenterology and Nutrition

NF-B	Nuclear factor Kappa B
NK	Natural killer
NUD	Non ulcer dyspepsia
PA IgG	Platelet- associated Ig G
PCR	Polymerase chain reaction
PCR-SSCP	Polymerase chain reaction-single strand conformation polymorphism
PLT	Platelet
PN	Peripheral neuritis
PPI	Proton pump inhibitor
PTP	Post transfusion purpura
PUD	Peptic ulcer disease
RAP	Recurrent abdominal pain
RELP	Restriction fragment length polymorphism
RES	Reticuloendothelial system
SH2	Rous-sarcoma-oncoprotein-homology-2
SHIP1	SH inositol 5 phosphate
SLE	Systemic lupus erythrematosis
TH	T-helper cell
TIMS	Thermal ionization mass spectrometry
TLR	Toll-like receptor
TMA	Thrombotic microangiopathies
TNF	Tumor necrotic factor
TTP	Thrombotic Thrombocytopenic purpura
UBT	Urea breath test
VacA	Vaculating cytotoxin A
vW	von Willebrand's factor

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Introduction

Idiopathic thrombocytopenic purpura (ITP) is a disorder characterized by thrombocytopenia with a shortened platelet survival, normal to increased numbers of bone marrow megakaryocytes,and elevated levels of platelet- associated IgG **(McMillan ., 1981)**

Helicobacter pylori are a Gram-negative microaerophilic bacterium that colonizes the human stomach of more than 50% of world population. It is recognized as the causative agent of active chronic gastritis and the predominant cause of peptic ulceration. **(Suerbaum et al., 2002)**

Recently, it has been suggested that Helicobacter pylori may contribute to the pathogenesis of chronic idiopathic thrombocytopenic purpura (ITP), since partial or even complete remission of thrombocytopenia has been reported in some patients after eradication of H.pylori .A cross molecular mimicry between the highly antigenic H.pylori CagA (cytotoxin-associated gene A) protein and platelet antigens has been indicated as the possible pathophysiological mechanism of this subset of ITP. **(Emilia et al., 2005)**

A causal relationship between H.pylori infection and ITP has been suggested by studies showing platelet count improvements following H.pylori eradication in infected ITP patients. **(Kurtoglu et al., 2004)**

Researchers from Italy and Japan investigated the relationship between H pylori infection and chronic ITP in recent 10 years and found significant platelet count increase and platelet- associated IgG (PAIgG) decrease after eradication of H pylori in chronic ITP patients with H pylori, while those whose H pylori infection were not successfully eradicated, the platelet count and PAIgG changed little. They concluded that H pylori is a causative agent of chronic ITP, eradication of H pylori can increase platelet count in chronic ITP patients. On the other side,

some subsequent studies disagreed with the conclusion. The relationship between H pylori and chronic ITP remains controversial. **(Russo, et al., 2011)**

Aim of work

To identify the effect of eradication of Helicobacter pylori on platelet count in chronic idiopathic thrombocytopenic purpura patients and follow up of their clinical status and platelet count throughout a period of one year .

CHAPTER 1

Idiopathic Thrombocytopenic Purpura

General Background

Platelets are small; a nucleate blood elements, a disk-shaped structure, 2 to 4 μm in diameter lack a nucleus and DNA but contain active enzymes and mitochondria, and under normal conditions constitute a small fraction of the circulating cells. Classically they were thought to be derived from megakaryocytes in the bone marrow by the process of Fragmentation **(Saunders. 2007)**

Megakaryocytes and megakaryocytopoiesis produce the circulating platelet of the blood that is comprised of fragments of megakaryocyte cytoplasm and functions in both normal hemostasis and abnormal thrombosis. **(Shirley., 2004)**

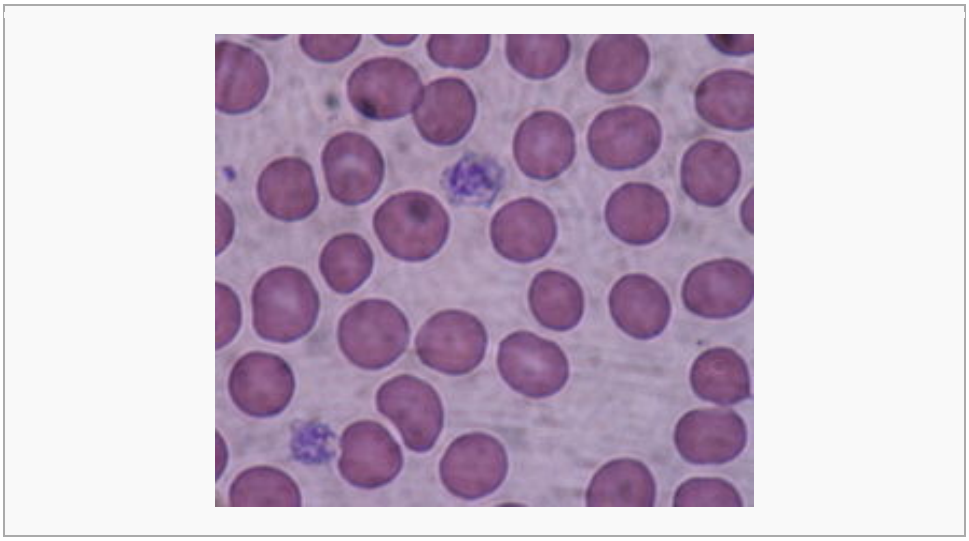

Figure (1) Platelets: Image from a light microscope (40×) from a peripheral blood smear. (**Campbell, Neil A. (2008).**

Platelets play an important role in both the formation of a primary plug as well as the coagulation cascade. **Platelet factors** important in hemostasis which are contained in or attached to the platelets: platelet factor 1 is adsorbed COAGULATION FACTOR V from the plasma; platelet factor 2 is an accelerator of the thrombin-fibrinogen reaction; platelet factor 3 is a lipoprotein with roles in the activation of both coagulation factor X and prothrombin; platelet factor 4 is capable of inhibiting the activity of heparin. **Saunders, 2003**

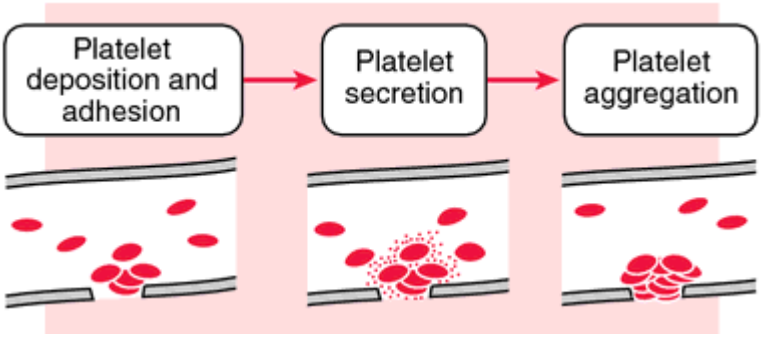

Figure (2) Platelet response to vascular injury . From Malarkey and McMorrow, 2000

The platelet lifespan has been estimated at 8-12 days by a variety of radioisotopic labeling techniques. Destruction of effete platelets is accomplished by macrophages of the reticulo-endothelial system in the spleen, liver and bone marrow. **(Castellone, 2007)**

Thrombocytopenia defined as a subnormal number of platelets in the circulating blood. It is the most common cause of abnormal bleeding**. (Shirley, 2004)**
The term idiopathic thrombocytopenic purpura usually refers to thrombocytopenia in which apparent exogenous etiologic factors are lacking and in which diseases known to be associated with secondary thrombocytopenia have been excluded **(Shirley., 2004)**

Idiopathic thrombocytopenic purpura (ITP) is also known as immune thrombocytopenic purpura and autoimmune thrombocytopenic purpura. **(Blanchette, 1998)**

Immune thrombocytopenic purpura (ITP) was initially recognized by astute clinicians who noted an acquired, isolated thrombocytopenia in the absence of disseminated intravascular coagulation or an underlying disorder characterized by immune activation. **(Chanock et al, 2003)** ITP can be classified based on patient age (adult or childhood ITP), and duration of thrombocytopenia (acute or chronic). The clinical features of ITP in adults are different from the clinical features seen in childhood. **(Stasi et al, 2008)**

It is characterized by a low platelet count (platelet count <150, 000/ml) which is the result of both increased platelet destruction and insufficient platelet production. Auto- antibodies against platelet surface glycoproteins can commonly be detected (60-70%), but are of no

prognostic significance and this is not a useful diagnostic test **(Bolton Maggs et al, 2000)-**

Over the past few years several of the antigens recognized by the auto antibodies that cause ITP have been identified. This has enabled new tests to be developed that may facilitate the diagnosis of ITP and its differentiation from other causes of thrombocytopenia. Several important new treatment modalities have also been introduced into practice, each of which is effective in some patients. However, each of these also has important potential side effects and some have considerable cost. **(Bussel et al., 2000)**

Recent advances in our understanding of the role of individual genetic risk factors and immune dysregulation in immune thrombocytopenic purpura(ITP) have opened the door to new avenues of research in the most common form of hematological auto -immune diseases in adults and children**.(Nugent., 2006)**

Incidence:

Childhood immune thrombocytopenic purpura (ITP) is an uncommon condition, with an incidence of about 1 in 25,000 children. It is usually a benign self-limiting condition without serious bleeding problems and recovery of platelet count within 2 months. The main problems surround the diagnosis and management **(Bolton-Maggs, 2003)**

The incidence peaks in the winter and spring, following the incidence of viral infections. Acute ITP is most common between 2 and 6 years of age. Approximately 7 to 28% of children with acute ITP develop the chronic variety. The ratio of females to males is nearly 1:1 in acute ITP and 2 to 3:1 in chronic ITP **(Shirley, 2004)**

Only 5% or fewer children experience serious bleeding, most commonly from the nose or gastrointestinal tract. While intracranial hemorrhage is the most feared and serious complication, it is rare, occurring in about 0.3% of cases, and if treated promptly usually has a good outcome**. (Bolton-Maggs, 2003)**