Peptik Ülser Kanamasında Tedavi Yaklaşımı

Prof.Dr. Ömer ŞENTÜRK

1

Plasebo ?
&
H_2RA ?
&
PPİ ?
&
H.pilori eradikasyonu ?
&
Endoskopik tedavi ?

2

- Her 100 000 yatıştan 10-50 üst gis kanama
- En sık neden p.ülser
- Mortalite oranı %7-10
- Şiddetli hemoraji veya tekrar hemoraji riskleri
  - Prezentasyonda hemodinamik instabilite
  - Tekrarlayan hematemetez veya hematokezya ile kanamanının manifestasyonu
  - Gastik aspirasyonda aspiratın temiz gelmemesi
  - > 60 yaş
  - İlave ciddi hastalıkların olması
  - Aktif kanamalı ülserin >1-2cm
  - Visible vessel bulunması

Holtmann G,Howden CW.Aliment Pharma Ther 2004

3

- Endoskopik tedavinin amacı;
  - Aktif kanamanın durdurulması
  - Tekrar kanamanın önlenmesi
- Uzun süreli tedavi hedefi;
  - Ülserin iyileştirilmesi
  - Ülser rekürrensinin önlenmesi

4

Kanayan Ülserde Tedavi Stratejisi

- Kan kaybı derecesinin değerlendirilmesi
- Endoskopik değerlendirme (hemorajinin kaynağı?)
- Endoskopik sonuca göre tedavi seçenekleri;
  - Elektrokoagülasyon
  - Heater probe
  - İnjeksiyon (vazoaktif ajanlar)

  } +

  - Medikal tedavi (antisekretuvar)
- Ülser tabanına “adherent clot” ?
- Cerrahi tedavi

5

Endoskopik Değerlendirme

- Üst endoskopi;
  - Kanama yerini
  - Kanamanın ciddiyetini
  - Akut kanamanın kontrol altına alınmasını SAĞLAR
- Endoskopik tedaviler;
  - Tekrar kanama oranını
  - Cerrahi gereksinimi ve
  - Mortaliteyi AZALTIR
- Kanamanın “initial” endoskopik yaklaşımla kontrolü sonrası “follow-up” veya “second look” endoskopi gerekir mi ?

6

Endoskopik Değerlendirme

- "second look" endoskopi ;
  - Rekürren kanamayı anlamlı derecede azaltır
  - Cerrahi gereksinim ve
  - Mortalite azaltmada etkisi anlamlı değil

Marmo R.Gastrointest Endosc 2003

7

	Recurrent bleeding		Surgery		Mortality	
	RT n (%)	No RT n (%)	RT n (%)	No RT n (%)	RT n (%)	No RT n (%)
Villanueva[5]	11 (21)	15 (29)	4 (8)	8 (15)	1 (2)	2 (4)
Saeed[6]	0 (0)	5 (24)	0 (0)	0 (0)	1 (5)	2 (11)
Rutgeerts[7]	27 (10)	42 (16)	9 (3)	12 (5)	12 (4)	15 (6)
Messmann[8]	11 (21)	9 (17)	3 (6)	2 (4)	3 (6)	2 (4)
Overall	49 (12)	71 (18.2)	16 (4)	22 (5.7)	17 (4.3)	21 (5.2)
ARR [95% CI]	6.2 [1.3, 11.1]		1.7 [–1.6, 4.0]		1.0 [–4, 1.9]	
NNT [95% CI]	16 [9, 75]		58 [–64, 28]		97 [–25, 53]	
p Value	<0.01		NS		NS	

RT, Second look with retreatment; *No RT*, second look only if clinical suspicion of recurrent bleeding; *ARR*, absolute risk reduction; *NNT*, number needed to treat; *NS*, not significant.

8

"second look" endoskopi : kime yapalım ?

- Hipotansiyon
- <10g/dl hemoglobin
- Midede taze kan
- Aktif kanama
- Büyük ülserler

9

Farmakolojik Tedavi

H_2RA & PPİ

10

Farmakolojik Tedavi

- PPİ & H_2RA
  - Rekürren kanamanın önlenmesinde PPİ'leri daha etkili
  - Cerrahiye olan gereksinim ve mortalite üzerine olan etkiler benzer
  - Endoskopik tedavi uygulanmayan hastalarda persistan veya rekürren kanama PPİ hasta gurubunda daha az (%4,3 & %12)
  - Endoskopik tedavi uygulanan hastalarda fark daha az anlamlı (%10,3 & %15,2)

Gisbert JP.Aliment Pharmacol Ther 2001

11

İV H_2RA peptik ülser kanamasında etkisi

"METAANALİZ"

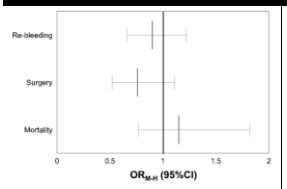


Figure 2. Pooled Mantel–Haenszel odds ratio (OR_{M-H}) and 95% confidence interval (CI) for re-bleeding, surgical intervention and mortality from a meta-analysis of randomized controlled trials comparing intravenous H_2-receptor antagonists with placebo in bleeding duodenal ulcer.

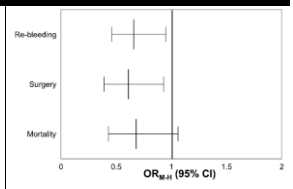


Figure 3. Pooled Mantel–Haenszel odds ratio (OR_{M-H}) and 95% confidence interval (CI) for re-bleeding, surgical intervention and mortality from a meta-analysis of randomized controlled trials comparing intravenous H_2-receptor antagonists with placebo in bleeding gastric ulcer.

Levine JE.Alimenter Pharmacol Ther 2002

12

İV H_2RA peptik ülser kanamasında etkisi

"METAANALİZ"

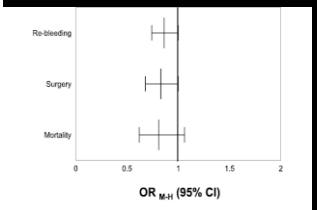


Figure 1. Pooled Mantel–Haenszel odds ratio (OR_{M-H}) and 95% confidence interval (CI) for re-bleeding, surgical intervention and mortality from a meta-analysis of randomized controlled trials comparing intravenous H_2-receptor antagonists with placebo in bleeding ulcer (duodenal and gastric ulcer combined).

- İV H_2RA'leri kanayan DÜ'lerde etkisiz, GÜ'lerde hafif etkili

Levine JE.Alimenter Pharmacol Ther 2002

13

Farmakolojik Tedavi

- Endoskopik olarak "sign of recent bleeding" olan peptik ülserli 220 hastanın ORAL PPİ & plasebo tedavi sonuçları;
  - Endoskopik tedavi yapılmayanlarda PPİ'leri
    - Kanamanın devamı,
    - Cerrahi gereksinim,
    - Transfüzyon gereksinimi ve
    - Mortalite oranını (plaseboya göre) anlamlı derecede AZALTIR

Khuroo MS.N Engl J Med 1997

14

Farmakolojik Tedavi

Peptik ülser kanamasında re-bleeding'in azaltılmasında oral omeprazolun etkisi

	Omeprazole group ($n = 71$)	Placebo group ($n = 78$)	P value
Death (%)	0	1 (1)	N.S.
Operation (%)	1 (1)	1 (1)	N.S.
High-risk ulcers on re-endoscopy* (%)	2/23 (9)	9/26 (35)	0.039
Ulcer with visible vessel	0/2	2/9	
Ulcer with oozing of blood	2/2	4/9	
Ulcer with spurting artery	0/2	3/9	
Clinical re-bleeding (%)	12 (17; 95% CI. 12.7–39)	26 (33; 95% CI. 29.6–57.6)	0.022
Hospital stay (h) (mean ± s.d.)	62.8 ± 28.6	75 ± 39	0.032
Hospital stay > 5 days (%)	1 (1)	8 (10)	0.034
Need for blood transfusion (%)	40 (56)	56 (72)	0.049
Amount of blood transfused (bag) (mean ± s.d.)	1.13 ± 1.36	1.68 ± 1.68	0.029
Hb on discharge (g/dL) (mean ± s.d.)	10.31 ± 1.88	10.29 ± 1.78	N.S.
Hb on discharge − Hb 6 h after admission (g/dL) (mean ± s.d.)	+ 0.63 ± 2.2	+ 0.36 ± 1.9	N.S.
Need for ≥ 3 bags of blood (%)	14 (20)	20 (26)	N.S.

95% CI. 95% confidence interval; Hb, haemoglobin; N.S., statistically not significant.
* Re-endoscopy was performed in 49 patients.

Kaviani MJ. Aliment Pharmacol Ther 2003

15

Farmakolojik Tedavi

Peptik ülser kanamasında re-bleeding'in azaltılmasında oral omeprazolun etkisi

- Yüksek riskli ülser kanamalı hastalarda endoskopik enjeksiyon tedavisi sonrası oral omeprazol tedavisi hastanede kalış süresini, tekrar kanama ve kan transfüzyon oranını belirgin derecede azaltır

Kaviani MJ. Aliment Pharmacol Ther 2003

16

Farmakolojik Tedavi

- İV PPİ kullanımı
  - ABD'de yapılmış
  - Randomize kontrollü klinik çalışma YOK
- Endoskopik hemostaz sağlandıktan sonra İV PPİ (80 mg bolus, 8mg/saat infüzyon 72 saat) & Plasebo
  - 30 gün içerisinde rekürren kanama PPİ grubunda %6.7, plasebo grubunda %22.5 (her iki grupta 120 hasta arasında tedavi grubunda 8, kontrol grubunda 27 hastada kanama mg)

Lau JYW.N Engl J Med 2000
(Hong Kong çalışması)

17

Table 2. Outcomes after Endoscopic Therapy.

Outcome	Omeprazole Group (N= 120)	Placebo Group (N= 120)	Relative Risk (95% CI)*	P Value
Recurrent bleeding — no. of patients				
By day 3	5	24	4.80 (1.89–12.2)	<0.001
By day 7	7	26	3.71 (1.68–8.23)	<0.001
By day 30	8†	27†	3.38 (1.60–7.13)	<0.001
Recurrent bleeding within 30 days — no. of patients/total no.				
Actively bleeding ulcers	3/64	10/58	4.24 (1.10–16.3)	0.04
Ulcers with nonbleeding visible vessels	5/56	17/62	3.85 (1.31–11.3)	0.02
Endoscopic retreatment successful — no. of patients	6	23	3.83 (1.62–9.08)	<0.001
Surgery — no. of patients	3	9	3.00 (0.83–10.8)	0.14
Median hospital stay <5 days — no. of patients (%)	56 (46.7)	38 (31.7)		0.02
Duration of hospitalization — days				
Patients admitted for bleeding peptic ulcers				
Median	4	5		0.006
Range	3–65	3–64		
Patients in whom bleeding developed in the hospital				
Median	13	9		0.33
Range	3–40	4–46		
Units of blood transfused‡	2.7±2.5	3.5±3.8		0.04
Before endoscopic therapy	1.0±1.3	1.1±1.5		0.46
After endoscopic therapy	1.7±1.9	2.4±3.2		0.03
Death within 30 days — no. of patients	5	12	2.40 (0.87–6.60)	0.13
Ulcer healing at 8 wk — no. of patients/total no. assessed endoscopically	72/85	77/83	1.10 (0.98–1.22)	0.14

*Values indicate the relative risk of an outcome in the placebo group as compared with the omeprazole group. CI denotes confidence interval.
†This number is the total number of patients in the group who had recurrent bleeding within 30 days after treatment.
‡Plus–minus values are means ±SD.

18

Lau JYW.N Engl J Med 2000

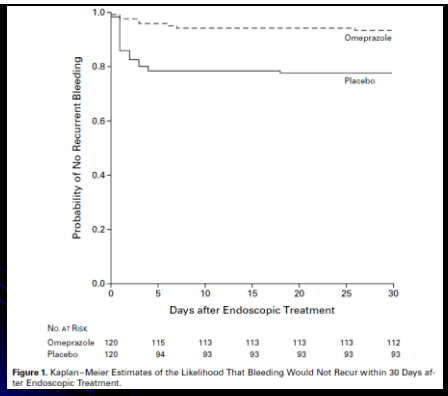


Figure 1. Kaplan–Meier Estimates of the Likelihood That Bleeding Would Not Recur within 30 Days after Endoscopic Treatment.

Lau JYW.N Engl J Med 2000

19

Farmakolojik Tedavi

- Farklı farmakolojik tedavilerin uygulandığı akut ülser kanamalı 30 RCCT (toplam 3530 hasta)
  - Yüksek doz PPİ
  - PPİ
  - H_2RA
  - Somatostatin + octreotit

  } & Plasebo
- Tüm farmakolojik grupta tekrar kanama ("re-bleeding") ve mortalite anlamlı derecede az
- Yüksek doz PPİ grubunda re-bleeding ve mortalite H_2RA ve plaseboya göre anlamlı derecede daha az

Bordou M.Gastroenterology 2003

20

Farmakolojik Tedavi

- Endoskopik tedaviden sonra yüksek doz oral tedavi (pantoprozol 2x40 mg/gün 5 gün) ve İV tedavi (80 mg bolus, takiben 8 mg/saat 3 gün) "re-bleeding" üzerine etkiler AYNI

Barkun AN. Gastroenterology 2003

21

H.Pilori enfeksiyonu p.ülser kanaması

Table 3. Eradication and re-bleeding rates for trials comparing treatment of *H. pylori* infection with ulcer healing treatment alone

	Treatment group			Control group		
Trial (reference)	*n*	Eradication rate (%)	Re-bleeding (*n*)	*n*	Eradication rate (%)	Re-bleeding (*n*)
Graham *et al.*[13]	17	77	0	14	0	4
Rokkas *et al.*[14]	16	81	0	15	13	5
Jaspersen *et al.*[15]	40	83	0	40	3	7
Lai *et al.*[16]	60	85	6	60	2	12
Pooled	133	83	6 (4.5%)	129	4	28 (22%)

Table 5. Eradication and re-bleeding rates for trials comparing treatment of *H. pylori* infection with initial ulcer healing treatment and subsequent maintenance therapy

	Treatment group			Control group		
Trial (reference)	*n*	Eradication rate (%)	Re-bleeding (*n*)	*n*	Eradication rate (%)	Re-bleeding (*n*)
Riemann *et al.*[19]	47	89	2	48	NR	4
Sung *et al.*[20]	126	86	0	124	6	3
Santander *et al.*[21]	84	79	2	41	NR	5
Pooled	257	84	4 (1.6%)	213	6	12 (5.6%)

NR, not reported.

Sharma VK.Aliment Pharmacol Ther 2001

Table 6. Probability and range for sensitivity analysis for ulcer recurrences with bleeding, or with pain but without bleeding

	Probability (%)	Range for sensitivity analysis (%
Treatment of *H. pylori* infection		
Ulcer recurrence with bleeding	2.5	0–10
Ulcer recurrence with pain but without bleeding	2.5	0–10
Ulcer healing with maintenance H_2-receptor antagonist		
Ulcer recurrence with bleeding	6	2–13
Ulcer recurrence with pain but without bleeding	10	5–20
Ulcer healing with no maintenance therapy		
Ulcer recurrence with bleeding	22	18–33
Ulcer recurrence with pain but without bleeding	30	20–40

- H.pilori tedavisi ülser kanamasının tekrarlamasını önlemede sadece ülser tedavisi uygulananlara (idame tedavi yapılsa dahi) göre daha etkili
- Ülser kanaması olan hastalar H.pilori açısından taranmalı, pozitifler eradike edilmeli

Sharma VK.Aliment Pharmacol Ther 2001

23

Uzun Süreli Tedavi

- Peptik ülser hemorajili hastalarda H.pilori eradikasyonu rekürren kanamayı %17 ↓
- H.pilori prevalansı kanamalı hastalarda daha sık
- H.pilori durumu erken tekrar kanama oranını etkilemez ("initial rate of early re-bleeding")

Lin HJ. Am J Gastroenterol 1999

24

Peptik ülser kanaması
Low-dose aspirin / H.pilori / PPİ

- Uzun süreli düşük doz aspirin kullanımına bağlı ülser komplikasyonunun tedavisinde H.pilori eradikasyonuna ilaveten lansoprazol ile tedavi ülser komplikasyonu (örn.kanama) rekürrensini azaltır

Lai KC.N Engl J Med 2002

25

Table 3. Characteristics of Patients with Recurrences of Ulcer Complications or Clinical Rebleeding.*

Variable	Lansoprazole Group (N=62)	Placebo Group (N=61)
Patients with recurrences of complications		
Total — no. (%)	1 (1.6)	9 (14.8)
Site of relapse — no.		
Gastric ulcer	1	8
Duodenal ulcer	0	1
Time to relapse — no.		
<6 mo	0	2
≥6 mo	1	7
Recurrence of *H. pylori* infection — no.	0	4
Deaths — no.	1	0
Patients with clinical rebleeding†		
Total — no.	0	8
Age — yr	—	66.5±8.5
Female sex — no. (%)	—	4 (50.0)
Transfusion required — units	—	1.13±1.46
Range		0–4
Location of ulcer — no.		
Gastric	—	8
Duodenal	—	0
Range of ulcer size — mm	—	5–15
Hemoglobin level on admission — g/dl	—	10.34±2.09
Pulse >100 beats/min on admission — no. (%)	—	3 (37.5)
Systolic blood pressure <100 mm Hg on admission — no. (%)	—	2 (25.0)
Shock at presentation — no. (%)‡	—	2 (25.0)
Serum urea level >10 mmol/liter — no. (%)	—	5 (62.5)
Endoscopic hemostasis required — no. (%)	—	2 (25.0)

*Plus–minus values are means ±SD.

†Two patients are not included, because their rebleeding was identified only by a decrease in hemoglobin levels.

‡Shock was defined as a systolic blood pressure of less than 100 mm Hg with a pulse of 100 beats per minute or more.

Lai KC. N Engl J Med 2002

26

Farmakolojik Tedavi & Endoskopik Tedavi

27

"adherent clots" saptanan hastalarda rekürren ülser hemorajisini önlemede medikal veya endoskopik tedavi ?

Table 1. Study Criteria for Distinguishing Nonbleeding Adherent Clots and Nonbleeding Visible Vessels

	Visible vessel	Adherent clot
Size[a]	≤4 mm	≥6 mm
Color	Variable or translucent	Red
Form	Discrete	Amorphous
Relation to stigma	Is the stigma	Covers up stigma
Rebleeding rate[b]	About 50%	About 35%

[a]Size refers to diameter and height above ulcer base.
[b]Rebleeding rate is on medical therapy (histamine two receptor antagonist drugs or proton pump inhibitors, transfusions, and correction of coagulopathies).

Jensen DM.Gastroenterology 2002

28

"adherent clots" saptanan hastalarda rekürren ülser hemorajisini önlemede medikal veya endoskopik tedavi ?

Table 3. Outcomes After Randomization by Treatment Group

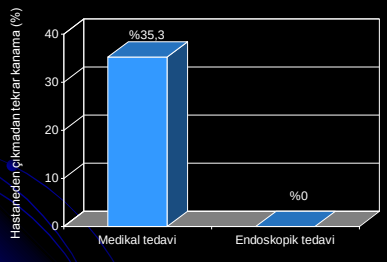
	Medical treatment	Endoscopic treatment	*P* value
Patients	17	15	
Rebleeding before discharge	6 (35.3%)	0	0.011
Further endoscopic treatment	4 (23.5%)	0	0.045
Units RBCs transfused[a]	2.3 ± 0.9	1.0 ± 1.0	0.35
Hospital days, median	4	4	0.33
ICU days, median	1	1	0.44
Ulcer surgery, 30 days	2 (11.8%)	1 (6.7%)	0.62
Mortality, 30 days	1 (5.9%)	1 (6.7%)	0.93

[a]Expressed as mean ± SEM.

Jensen DM.Gastroenterology 2002

29

"adherent clots" saptanan hastalarda rekürren ülser hemorajisini önlemede medikal veya endoskopik tedavi ?



Jensen DM.Gastroenterology 2002

30

Sonuç

- PPİ'leri H_2RA'lerinden daha etkili
- P.ülser + "without major stigmata of recent haemorrhage" sözkonusu ise oral PPİ yeterli
- P.ülser + "with major stigmata of recent haemorrhage" sözkonusu ise yüksek doz oral PPİ veya İV PPİ tedavileri uygun
- H.pilori eradikasyonu
- NSAİD alanlarda PPİ'leri ile "co-therapy"

31