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Quality of life and cost-effectiveness of combined therapy for reflux esophagitis*

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Abstract: Objective: To evaluate clinical, Quality of Life (QoL) and medical cost outcomes in patients with symptomatic reflux esophagitis (RE) receiving different "triple combination therapy". Methods: A multicenter medical effectiveness trial conducted in 10 hospitals of 5 regions in Zhejiang Province. 248 patient-volunteers were assigned to 8 weeks of "triple combination therapy" with Lansoprazole plus Cisapride and Sucralfate or Ranitidine plus Cisapride and Sucralfate. Main outcomes assessment included symptoms scale scores, RE severity, QoL at baseline and 8 weeks. Medical cost data were collected with cost analysis questionnaire. Results: (1)More Lansoprazole group patients noted RE symptoms resolution than Ranitidine group(92.3% vs 78.4%, $P<0.01$). There was no striking difference between two groups in RE healing rate (90.8% vs 82.9%, $P>0.05$). (2)RE significantly impaired QoL of patients($P<0.001$). Compared with Ranitidine group, QoL in Lansoprazole group had significant improvement (rate of "good" QoL 64.5% vs 45.6%, $P<0.01$). (3)There was close correlation between symptomic effectiveness and QoL rating scale in both the Lansoprazole and Ranitidine group($P<0.01$, $r=0.235$ and 0.353 respectively). There were no statistical difference of medical cost between the two groups ($P>0.05$). Conclusion: RE significantly impaired QoL of patients. "Triple combination therapies" can significantly improve RE symptoms and QoL. Lansoprazole combination therapy was more cost-effective than Ranitidine combination group.

Key words: Reflux esophagitis(RE), Quality of life, Cost-effectiveness
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INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most common chronic disorders that results from abnormal reflux of gastric contents into the esophagus, affecting 10% of the population in the United States (Hawden *et al.*, 1995). Forty percent of patients with sympotomatic GERD develop erosive reflux esophagitis (RE) and face potentially morbid consequences including impaired QoL, esophageal ulceration and hemorrhage, and increased risk for Barrett's esophagus (Hawden *et al.*, 1995; Devault *et al.*, 1995). The incidence of GERD is increasing in the developing countries. An epidemiologic study in China showed prevelances for GERD and RE were 5.77% and 1.92% respectively (PAN *et al.*, 1999). Once diagnosed with RE, patients require lifelong therapy (McDougall *et al.*, 1996). In the USA about 20% GERD patients consume more than 1 billion dollars of over-the-counter medicine each year for reliving symptoms (Hawden *et al.*, 1995). Ideally, medical therapy should heal esophagitis, relieve reflux symptoms, prevent relapses, and improve QoL with low medical costs. In short, treatment strategies for RE should improve patient outcome at reasonable cost. Treatment consists of lifestyle modifications, pharmacologic therapies including acid suppression H_2 receptor anatagonists or proton pump inhibitors (H_2RA or PPIs), prokinectic and sulcrafate, or surgery. However, the optimal treatment strategy remains controversial.

We applied two "triple combination therapies" to patients with RE. Our aim was to evaluate their effective elimination or ameliorating

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symptoms, the healing proportion of RE, and to determine the cost-effectiveness and QoL with different combined therapy.

MATERIALS AND METHODS

Patients were recruited from May 2000 through May 2001 in 10 hospitals of 5 regions in Zhejiang Province. Three hundred and twenty-seven adult patients satified the eligibility criteria which included esophageal erosions under endoscopy and having one or more of three symptoms: heartburn, sour regurgitation and chest pain. The main criteria for exclusion were the presence of peptic ulcer, cancer or systemic diseases (severe renal, cardiac or hepatic disease, etc), use H_2RA, PPIs, or prokinectic drugs in the past 2 weeks. Finally 248 RE patients voluntarily received the following "triple combination therapy" for 8 weeks: (1) group A: lansoprazole (30 mg once daily) plus cisapride (10 mg three times a day) and sulcralfate(1.0 g three times a day); (2) group B: ranitidine (150 mg twice daily) plus cisapride (10 mg three times daily) and sulcralfate (1.0 g three times daily). Patients were asked to complete three questionnaires including symptoms rating scale, QoL and medical cost at baseline and after 8 weeks. Endoscopy was repeated after 8 weeks.

1. Effectiveness analysis

Symptoms elimination and amelioration efficacy: The severity of symptoms were classified as follows: 0, no symptom; 1, mild, no interference with normal activities; 2, frequent, mild interference with activities; 3, severe, without spontaneous remission and marked interference with activities. A total score for three symptoms was obtained. "remission" was defined as symptom disappearance; "improvement" as a score decrement $\geqslant$50% of baseline; "ineffectiveness" as a score decrement < 50% of baseline. RE healing analysis: RE healing was defined as disappearance of RE or RE decreasing more than 2 grades by repeat endoscopy.

2. QoL and cost evaluation

5-item QoL questionnaire included assessing the severity and frequency of symptoms related to eating(1, good appetite; 2, taste disturbance; 3, loss of appetite), daily sleeping disturbance (1, >6h; 2, $\leqslant$6h; 3, <4h), anxiety(1, no; 2, occasional; 3, frequent), family life (1, well; 2, fair; 3, poor) and social activities(1, active; 2, common; 3, poor). QoL level was defined as good(Sc < 1.5), fair(Sc $\geqslant$ 1.5) and poor(Sc $\geqslant$ 2.5) according to the average score (Sc) of 5-item QoL. The 3-item cost questionnaire contained monthly direct medical costs(1, ¥200 – ¥500; 2, < ¥1000; 3, $\geqslant$ ¥1000), indirect costs(1, < ¥500; 2, < ¥2000; 3, > ¥2000) and family income(1, > ¥2000; 2, ¥800 – ¥2000; 3, < ¥800). Each item was expressed on a score of 1 to 3. Cost level was defined as high(Sc < 1.5), moderate(Sc $\geqslant$ 1.5) and low(Sc $\geqslant$ 2.5) according to the average of the total score (Sc).

3. Statistical analysis

All data were put into SPSS 10.0 statistical computer system. Statistical analysis was performed with Chi-Square test frequency tables with more than 4 cells. Kendall or Spearman correlation analysis was used to check the relationship between effectiveness, QoL level and medical cost level. All P values were two-tailed, with statistical significance indicated by a value of $P < 0.05$.

RESULTS

Among the 248 subjects with male to female ratio was 2.4 : 1, reflux symptoms were common, and incidence of heartburn was 83.0%, regurgitation was 79.1% and chest pain was 68.0%. *H. pylori* infection rate was 42.3%; 155 patients received Lansoprazole combination therapy, and 93 patients were given Ranitidine combined treatment. There were no significant difference between the two groups, taking into consideration sex, age, *H. pylori* infection, RE symptoms scales and RE severity. The basic characteristics of RE patients were quite similar, as shown in Table 1.

1. Effectiveness analysis

Symptoms remission and total improvement rate in Lansoprazole combination group was 55.5% and 92.3% respectively. Compared with 36.5% and 78.4% respectively in the ranitidine combination group, there were significant difference between the two groups (both $P <$

0.01). Results are shown in Table 2.

Table 1 Basic characteristics in Group A and Group B

Varieties	Group A (n = 155)	Group B (n = 93)	P
Sex(No)			0.221
Male	113	61	
Female	42	32	
Age(years)	48.95 ±14.45	47.98 ±13.67	0.254
H. pylori(No)			0.611
+ / −	63/92	41/52	
Symptoms(%, No)			
Chest pain	67.4(105)	67.74(63)	0.123
Heartburn	88.39(137)	83.87(78)	0.06
Regurgitation	79.35(123)	80.69(75)	0.117
Esophagitis grade			> 0.05
Grade A	33	25	
Grade B	43	33	
Grade C	62	29	
Grade D	17	6	

1. Endoscopic esophagitis Grades (1994 Los Angles classification). Grade A: 1 or more mucosal breaks not more than 3mm maximum; Grade B: 1 or more mucosal breaks > 3 mm maximum length but not continuous between two mucosal folds; Grade C: mucosal breaks continuous between two or more mucosal folds but not circumferential; Grade D: circumferential mucosal breaks.
2. *H. pylori* infection was confirmed with rapid urease test (RUT) or ^{14}C RUT and biopsy specimens Giema stain.

Table 2 Symptom of remission effectiveness between Group A and Group B

Effectiveness(No, %)	Group A	Group B
†Total effectiveness	143(92.3)	73(78.4)
* Remission	86(55.5)	34(36.5)
Improvement	57(36.8)	39(41.9)
Ineffectiveness	12(7.7)	20(21.6)

Chi-Square test was performed between the two groups, $\chi^2 = 13.236$, $P < 0.01$;
† indicates $\chi^2 = 9.798$, $P < 0.01$; * indicates $\chi^2 = 8.335$, $P < 0.01$.

Endoscopy was repeated on 117 patients after 8-week therapy. Both triple combined therapy groups had high healing rate of RE. The 90.8% (69/76)of esophagitis of the Lansoprazole group was healed. Compared with the 82.9%(34/41) healed in the Ranitidine group, there was no striking difference ($\chi^2 = 1.567$, $P > 0.05$).

2. QoL and QoL-effectiveness analysis

QoL survey questionnaires were answered by 265 patients. QoL was significantly impaired by RE disease, and the rate of "good" QoL was decreased from 62.3% to 19.7% ($P < 0.001$). Compared with the Ranitidine group, QoL in Lansoprazole group showed significant improvement ("good" QoL rate 64.5% vs 45.6% $P < 0.01$), as shown in Table 3.

Table 3 QoL analysis of the RE patients

Group	Good	Fair	Poor	Total
Group 1	165(62.3)	94(35.5)	6(2.2)	265
Group 2*	52(19.7)	186(70.2)	27(10.1)	265
Group 3†**	100(64.5)	54(34.8)	1(0.7)	155
Group 4*‡	41(45.6)	46(51.1)	3(3.3)	90

1. Group 1: patients before RE; Group 2: RE patient; Group 3: Lansoprazole combination; Group 4: ranitidine combination.
2. Compared with Group 1, * $P < 0.001$; Compared with Group 2, † $P < 0.001$, ‡ $P < 0.01$; Compared with Group 4, ** $P < 0.01$.

There was close correlation between symptom remission effectiveness and QoL scale in the Lansoprazole and Ranitidine group($P < 0.01$, $r = 0.235$ and $r = 0.353$ respectively). We also found 41.9% (65/155) of patients in the Lansoprazole group achieved symptom remission and "good" QoL, vs only 24.4% (22/90) in the Ranitidine group. Results are shown in Table 4.

Table 4 Relationship between QoL and symptom remission effectiveness

QoL(no)	Effectiveness			Total
	Remission	Improvement	Ineffective	
Group A	86	57	12	155
Good	65	30	5	100
Fair	20	27	7	54
Poor	1	0	0	1
Group B	31	39	20	90
Good	22	13	6	41
Fair	19	25	12	46
Poor	0	1	2	3

3 by 3 spearman rank correlation tests showed that the coefficient of rank correlation $r = 0.235$, $P < 0.01$ in Group A , and $r = 0.353$, $P < 0.01$ in Group B.

3. Cost-effectiveness analysis

There was no statistical difference of cost between the two groups ($P > 0.05$). The cost-effectiveness relationship coefficient of rank correlation was $r = 0.143$ in Lansoprazole group (P

<0.05), while $r = 0.074$ in ranitidine group ($P > 0.05$), as shown in Table 5.

Table 5 Cost-effectiveness relationship between the two groups

Effectiveness	Cost (Group A)				Cost (Group B)			
	Low	Moderate	High	Total	Low	Moderate	High	Total
Effectiveness	68	55	4	127	34	27	2	63
Ineffectiveness	1	10	1	12	9	7	2	18

Chi-Square test was performed to check the medical cost between group A and group B, $\chi^2 = 4.922$, $P = 0.085$;
Two by Three Kendall rank correlation test was performed to check the cost- effectiveness relationship. The coefficient of rank correlation $r = 0.143$, $P < 0.05$ in Group A; $r = 0.074$, $P > 0.05$ in Group B.

DISCUSSION

Reflux esophagitis(RE) describes the esophageal tissue injury by reflux of gastric and duodenal contents. The primary symptoms of RE are heartburn and regurgitation, but a wide spectrum of additional complaints may be present. Symptoms of reflux and abdominal dyspepsia severely effected the QoL of patients. The goal of therapy should be relief of symptoms, healing of mucosal lesions, prevention of relapse, and improve QoL at low medical costs. Medical therapy is still the initial treatment for RE. In mild RE (grade A or B) patients were recommended lifestyle change and acid suppression (H_2RA or PPIs) or prokinectic therapy. PPIs maintaince or combination treatment (acid suppression plus prokinectic therapy or sulcrafate) comprise the mainstay in the treatment of moderate-severe symptomatic RE (grade C or D).

The main mechanisms of RE include: (1) esophageal mucosa exposure to acid; (2) motility disturbance characterized by lower esophageal sphincter (LES) incompetence delay and gastric emptying; (3) poor esophageal clearance acid and bile reflux. Considering the above factors, we used "triple combination therapy" defined as acid suppression (H_2RA or PPIs) plus prokinectic therapy and sulcrafate. Recent studies showed that combination therapies including acid suppression (H_2RA or PPIs) plus prokinectic therapy or sulcrafate were more effective than single agent. Mckenna *et al*. (1995) reported addition of cisapride 20 mg twice daily to ranitidine 150 mg twice daily improves the 12-week healing rate from 71% to 80%. PPIs combination therapy is more effective than ranitidine combination treatment in symptom relief and RE healing rate (Yang *et al*., 1997; Vigneri *et al*., 1995). We initially reported the results of "triple combination therapy" in a large population. Total symptoms improvement and remission rate was 92.3% and 55.5% respectively in the Lansoprazole combinaton 8-week initial therapy. Compared with 78.4% and 36.5% respectively in the Ranitidine combination group, Lansoprazole combination therapy was more effective ($P < 0.01$). Lansoprazole or Ranitidine combination therapy had a high healing rate under endoscopy (90.8% and 82.9% respectively).

The QoL questionnaire can generally be categorized as a generic and disease-specific RE QoL instrument. Generic questionnaire included SF-36, PGWB (Psychological General Well-Being Index). Specific measurement contained GSRS (Gastrointestinal Symptom Rating Scale), GERD-HRQL (GERD Health Related QoL) and RVAS (Reflux Visual Analogue Scale)(Vic *et al*., 2000). The general QoL is seldom used to measure change as a result of medication intervention because of inadequate focusing on the relationship between severity of symptoms and QoL. "Ad hoc" instrument was defined as a questionnaire developed by groups of researchers to evaluate therapies impacting QoL in GERD patients (Mathias *et al*., 1996). We analyzed different aspects of QoL including physical (eating, sleeping), psychological (stress or cancer anxiety) and social health (family life and social activity) and designed 5-item questionnaire, which was convenient to complete and easily accepted by patients in China.

Cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) are commonly used to evaluate RE therapy outcomes. Due to the lack of comprehensive credit and medical insurance systems in China, it is hard to accurately calculate medical cost. We designated high, moderate

and low grade of cost on a monthly basis of family income, direct medical cost, and decrement income due to RE in Zhejiang Province.

Study showed that RE significantly impaired QoL. Good QoL rate decreased from 62.3% to 19.7% due to RE symptoms. The 8-week triple combination therapy strikingly improved QoL, good QoL was 64.5% and 45.6% respectively in Lansoprazole and ranitidine combination groups. There was close relationship between symptom remission effectiveness and QoL in both groups ($r = 0.235$ and 0.353 respectively). Compared with the ranitidine combination group, medical cost did not increase in the Lansoprazole combination group ($P > 0.05$), which may be due to more patients decreasing indirect costs because of loss of work, sick leave or lower working capacity in the Lansoprazole combination group. Zagari *et al*. (1995) compared three strategies: Lansoprazole 30 mg q.d, cimetidine 800 mg b.i.d and ranitidine 300 mg q.i.d 2 months intermittent therapies. One year result showed the cost of treatment with PPIs and H_2RA were $1192 and $1152, healing rate 80% and 15% respectively. PPIs had lower C/E ratio. Bloom *et al*. (1995) compared omeprazole 20 mg q.d to ranitidine q.d plus metoclo-pramide 10 q.i.d in 184 RE patients. At 8 week, 81.5% of the omeprazole group had healed versus 45.7% of combination group. Omeprazole patients had 19.6 symptom-free days versus 13.5 days in the combination group. PPIs were more cost-effective. These results accorded with our CEA results.

Lansoprazole combination therapy was more effective for symptoms relieving and QoL improvement. Lansoprazole combination therapy was more cost-effective. It should be recommended for RE medical therapy.

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