A Preliminary Study of Melatonin in Irritable Bowel Syndrome

Lekha Saha, MD, DM, Samir Malhotra, MD, DM,* Surinder Rana, MD, DM,† Deepak Bhasin, MD, DM,† and Promila Pandhi, MD, DM**

Background and Aims: Melatonin is involved in the regulation of gut motility and sensation. We aimed to determine if melatonin was effective in improving bowel symptoms, extracolonic symptoms, and quality of life (QOL) in irritable bowel syndrome (IBS) patients.

Methods: Eighteen patients (aged 18 to 65 y; 6 females) were randomly assigned to receive either melatonin 3 mg (n = 9) or matching placebo (n = 9) at bed time for 8 weeks. The overall IBS scores, extracolonic IBS scores, QOL scores were assessed at 2, 4, 6, and 8 weeks during treatment and at 16, 24, and 48 weeks during follow up.

Results: Compared with placebo, melatonin taken for 8 weeks significantly improved overall IBS score (45% vs. 16.66%, $P < 0.05$). The posttreatment overall extracolonic IBS score was significantly lower (49.16% to 13.88%, $P < 0.05$) when compared with placebo group. The overall improvement in QOL score was 43.63% in melatonin group and 14.64% in placebo group that is statistically significant.

Conclusions: The result of this study showed that melatonin has some beneficial role in IBS. Further studies using large number of patients may provide a definite answer.

Key Words: irritable bowel syndrome, melatonin, placebo, clinical trial

(*J Clin Gastroenterol* 2007;41:29–32)

Irritable bowel syndrome (IBS) is a gastrointestinal (GI) disorder characterized by altered bowel habits and abdominal pain in the absence of detectable structural abnormalities. In addition, patients commonly complain of a variety of extracolonic symptoms that include nausea, lethargy, backache, and urinary symptoms.[1] It is one of the most common conditions encountered in clinical practice but one of the least well understood. With the availability of better techniques to study colonic and GI motility and visceral sensory function, along with the development of newer concepts on the importance of the brain in regulating gut function, significant progress has been made toward a better understanding of the pathogenesis of IBS. This common condition is estimated to affect 15% to 20% of the general population at any one time.[2] In some patients, symptoms can be so severe and intrusive that they interfere with a person's quality of life (QOL) and ability to cope with work, which can result in much time off work.[3,4] Such patients are often refractory to current conventional treatment and undergone repeated investigations and to have been referred to other specialities to seek a cause for their problem and some may have undergone surgery without symptomatic relief.[5] Thus, IBS patients not only continue to suffer from their symptoms but can also be a significant drain on health care resources.[6]

The pathophysiology of IBS is not fully understood. A multicomponent conceptual model of IBS has been postulated involving physiologic, affective, cognitive, and behavioral factors.[7] IBS is associated with visceral hypersensitivity and with a high cooccurrence of psychiatric symptoms, in particular affective dysregulation.[8–10]

Melatonin (5-methoxy-*N*-acetyltryptamine), a close derivative of serotonin (5-HT), is a pineal gland neurohormone that is implicated in the control of the sleep-wake cycle. Apart from the pineal gland, the GI tract is another large source of endogenous melatonin. Many reports have shown that melatonin is involved in the regulation of GI motility. It exerts both excitatory and inhibitory effects on the gut.[11–13] The precise mechanism through which melatonin regulates GI motility is not clear, although some studies suggest that this may be related to blockade of nicotonic channels by melatonin[14] and/or the interaction between melatonin and Ca^{2+} activated K^+ channels.[15]

Melatonin may also be involved in mediating gut visceral sensation because patients with functional abdominal pain are reported to have lower urinary excretion of 6-sulphatoxy melatonin and to exhibit a circadian rhythm of lower amplitude compared with healthy controls.[16]

Received for publication January 25, 2006; accepted July 13, 2006.
From the Departments of *Pharmacology; and †Gastroenterology, Post Graduate Institute of Medical, Education and Research (PGIMER), Chandigarh, India.
Conflict of Interest: None declared.
Ethics approval: The study protocol was approved by the institutional ethics committee of the Postgraduate Institute of Medical Education and Research, Chandigarh, India where the study was conducted. The informed consent was obtained from all the patients before included in the study.
Reprints: Lekha Saha, MD, DM, H NO 1223, Sector –32B, Chandigarh 160032, India (e-mail: lekhasaha@rediffmail.com).

TABLE 1. Baseline Characteristics of Study Individuals

	Placebo (n = 9)	Melatonin (n = 9)	*P*
Male	6	6	
Female	3	3	
Age (y) median (interquartile ranges)	22 (19-68)	27 (27-60)	> 0.5
Duration of disease (y) Median (interquartile ranges)	6 (2-10)	2 (2-10 y)	> 0.5
IBS Symptoms [Median (interquartile ranges)]			
Pain severity	50 (10-100)	50 (40-80)	> 0.5
Pain frequency	70 (5-100)	50 (30-90)	> 0.1
Bloating	70 (20-100)	70 (10-100)	> 0.1
Bowel habit dissatisfaction	50 (10-90)	60 (10-85)	> 0.5
Life interference	50 (10-90)	70 (40-100)	> 0.1
Overall IBS score	240 (160-450)	300 (250-365)	> 0.5
Extracolonic features [median (interquartile ranges)]			
Nausea/vomiting	30 (3-50)	40 (5-80)	> 0.1
Headaches	50 (10-90)	40 (10-70)	> 0.5
Thigh pain	50 (20-80)	50 (10-80)	> 0.5
Body aches	40 (10-80)	30 (10-60)	> 0.1
Backaches	60 (10-100)	30 (10-70)	> 0.05
Early satiety	20 (10-90)	30 (10-60)	> 0.5
Excess wind	50 (10-90)	30 (10-100)	> 0.05
Heart burn	20 (10-50)	50 (10-90)	> 0.1
Urinary symptoms	20 (10-50)	30 (10-90)	> 0.1
Lethargy	70 (50-90)	70 (25-100)	> 0.5
Overall extracolonic scores	180 (90-302)	235 (94-300)	> 0.05
QOL scores [median (interquartile ranges)]			
Psychic well-being	30 (10-75)	45 (20-70)	> 0.05
Physical well-being	40 (10-70)	40 (20-55)	> 0.5
Mood	20 (10-70)	30 (20-50)	> 0.1
Social relationship	50 (10-80)	50 (45-70)	> 0.05
Locus of control	20 (10-52)	40 (10-60)	> 0.1
Coping with work	50 (20-60)	60 (40-63)	> 0.1
Overall QOL score	200 (100-362)	260 (190-325)	> 0.1

A randomized, double blind, placebo controlled study have also demonstrated that administration of melatonin at bedtime for 2 weeks significantly attenuated abdominal pain and reduced rectal pain sensitivity.[17] Therefore, the present study was conducted to demonstrate the role of melatonin in IBS patients.

SUBJECTS AND METHODS

Subjects

Eighteen patients with IBS aged 18 to 65 years and refractory to conventional treatment were enrolled in this randomized double blind placebo control trial. IBS was diagnosed according to Rome II criteria for the diagnosis of IBS.[18]

Rome II Criteria for the Diagnosis of IBS

At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has 2 of the following 3 features:
1. Relieved by defecation.
2. Onset associated with changes in stool frequency.
3. Onset associated with changes in stool form.

Design

This was a randomized, double blind, placebo controlled study. Patients who met the inclusion and exclusion criteria were recruited and randomized into 2 groups to receive either melatonin 3 mg or an identically appearing placebo at a bed time for 8 weeks.

Inclusion Criteria

1. Patients of both the sexes with an age of 18 to 65 years.
2. Patients with established IBS and symptoms must have been present for more than 3 months.
3. Patients willing to give informed consent.

Exclusion Criteria

1. Pregnant or breast-feeding females.
2. Organic GI, anal, hepatic, or other systemic disorder.
3. Previous history of GI surgery.
4. History of cerebral disease.

The primary end point was improvement in overall IBS and extracolonic IBS score at the end of 8 weeks treatment. The secondary end point was assessment of QOL score at the end of 8 weeks treatment. A validated IBS questionnaires were used for rating IBS symptoms, extracolonic features, and QOL measures.[16] Compliance to therapy was evaluated. Patients were allowed to continue all the regular medications and adverse drug reactions were monitored by both close and open methods.

TABLE 2. Pretreatment and Posttreatment Scores for IBS Symptoms of Patient in Both the Placebo and Melatonin Group

	Melatonin (n = 9)			Placebo (n = 9)		
	Before	After	*P*	Before	After	*P*
IBS Symptoms						
Pain severity	50 (40-80)	35*† (10-50)	* < 0.001 † < 0.05	60 (10-100)	60 (0-100)	> 0.05
Pain frequency	50 (30-90)	35*† (10-50)	* < 0.001 † < 0.01	70 (5-100)	80 (0-100)	> 0.05
Bloating	70 (10-100)	30* (10-50)	* < 0.001	70 (20-100)	60 (10-100)	> 0.05
Bowel habit dissatisfaction	60 (10-85)	30* (0-50)	* < 0.01	50 (10-90)	45 (0-100)	> 0.05
Life interference	70 (40-100)	40* (10-50)†	* < 0.001 † < 0.05	60 (10-90)	50 (0-80)	> 0.05
Overall IBS score	300 (250-365)	170*† (75-200)	* < 0.001 † < 0.05	240 (160-450)	200 (100-400)	> 0.05
Improvement in overall IBS score	45% (39-71.15)†			16.66% (− 16-47.3)		† < 0.05

Results are expressed as medians (interquartile range).
*$P < 0.05$ when compared with baseline values.
†$P < 0.05$ when compared between groups.

Statistical Analysis

Median values (with interquartile ranges) were used for symptom scores. Intraindividual pretherapy and posttherapy scores were compared using the Wilcoxon Signed test. Comparison between independent groups was carried out using the Mann-Whitney *U* Test. *P* value less than 0.05 was considered statistically significant.

RESULTS

The baseline characteristics of the 18 patients enrolled in the study are given in Table 1. There is no significant difference in age, duration of disease, IBS symptoms, extracolonic features, and QOL score between 2 groups.

Scores for individual IBS symptoms, and overall IBS scores are shown in Table 2. Melatonin significantly decreased the individual and overall IBS symptoms scores (*P* values ranges from $P < 0.05$ to $P < 0.001$) (Table 2). In the placebo group, both the individual symptom score and overall IBS symptom score were not significantly decreased after treatment (Table 2).

Table 3 shows the changes in the extracolonic IBS scores in both the groups. The posttreatment overall extracolonic IBS score was significantly lower in the melatonin group ($P < 0.001$) when compared with pretreatment value and was also significantly lower ($P < 0.05$) when compared with placebo group (Table 3). Whereas in the placebo group though there was decrease in the overall extracolonic IBS score at the end of

TABLE 3. Pretreatment and Posttreatment Scores for Extracolonic Feature of Patients in Both the Placebo and Melatonin Group

	Melatonin (n = 9)			Placebo (n = 9)		
	Before	After	*P*	Before	After	*P*
Nausea/vomiting	40 (5-80)	10 (0-50)*	* < 0.01	30 (3-50)	30 (0-50)*	* < 0.05
Early satiety	30 (0-30)	10 (0-30)*	* < 0.01	20 (10-90)	20 (10-90)*	* < 0.05
Headache	40 (10-70)	20 (10-50)*†	* < 0.01 † < 0.05	50 (10-90)	60 (10-90)	> 0.05
Backache	30 (10-70)	20 (10-45)*†	* < 0.001 † < 0.05	60 (10-100)	60 (20-100)	> 0.05
Excess wind	30 (10-100)	20 (0-50)*	* < 0.001	50 (10-90)	30 (0-90)*	* < 0.02
Heart burn	50 (10-90)	10 (0-50)*	* < 0.001	20 (10-50)	10 (0-50)*	* < 0.05
Body aches	30 (10-60)	10 (0-40)*†	* < 0.001 † < 0.05	40 (10-80)	50 (0-70)	> 0.05
Urinary symptoms	30 (10-90)	10 (0-60)*	* < 0.01	20 (10-50)	10 (0-40)*	* < 0.05
Thigh pain	50 (10-80)	20 (20-50)*†	* < 0.01 † < 0.02	50 (10-80)	40 (10-90)	> 0.05
Lethargy	70 (25-100)	30 (5-50)*†	* < 0.001 † < 0.001	70 (50-90)	60 (30-90)	> 0.05
Overall extracolonic score	235 (94-300)	95 (32-170)*†	* < 0.001 † < 0.05	180 (90-102)	155 (45-295)	> 0.05
Improvement in overall IBS score	45% (39-71.15)†			16.66% (− 16-47.3)		† < 0.05
Improvement in overall extracolonic score	49.16% (35.23-65.51)†			13.88% (− 65.95-50)		† < 0.05

Results are expressed as medians (interquartile ranges).
*$P < 0.05$ when compared with baseline values.
†$P < 0.05$ when compared between groups.

TABLE 4. QOL Measures Before and After Treatment in Both the Groups

	Melatonin (n = 9)			Placebo (n = 9)		
	Before	**After**	***P***	**Before**	**After**	***P***
Psychic well being	45 (20-70)	70 (45-80)*†	* < 0.05 † < 0.05	30 (10-75)	43 (20-90)	> 0.05
Physical well being	40 (20-55)	60 (40-70)*	* < 0.001	40 (10-70)	45 (10-80)*	* < 0.05
Mood	30 (20-50)	50 (50-70)*†	* < 0.001 † < 0.01	20 (10-70)	20 (10-80)	> 0.05
Social relationship	50 (45-70)	70 (50-80)*	* < 0.001 † < 0.01	50 (10-80)	50 (20-80)	> 0.05
Locus of control	40 (10-60)	60 (10-75)*	* < 0.05	20 (10-52)	30 (10-60)*	* < 0.001
Coping with work	60 (40-63)	70 (60-75)*	* < 0.001	50 (20-60)	60 (20-75)*	* < 0.01
Overall improvement in QOL	43.63% (15.38-62)†			14.64% (0-45)		† < 0.05

Data are expressed as Median (interquartile ranges).
*$P < 0.05$ when compared with baseline values.
†$P < 0.05$ when compared between 2 groups.

8 weeks treatment it did not reach the statistically significant level.

The overall improvement in QOL score was [median (interquartile range)] 43.63% (15.38 to 62) in melatonin group and 14.64% (0 to 45) in placebo group (Table 4). The improvement in overall QOL score in melatonin group was statistically significant ($P < 0.05$) when compared with placebo group.

Adverse Drug Reactions: Three patients (16.66%) experienced adverse events. One patient each from both the group experiences drowsiness and 1 patient from the melatonin group reported decreased libido.

DISCUSSION

To our knowledge this may be the second study to explore the role of melatonin in treating IBS patients. The first study done by Song et al.[17] In this first study, administration of melatonin 3 mg at bedtime for 2 weeks significantly attenuated abdominal pain and reduced rectal pain sensitivity. In the present study, use of both melatonin and placebo led to improvement in the overall IBS score and was significantly more in the melatonin group as compared with the placebo group. Similarly, there was improvement in the overall extracolonic symptom score in the melatonin group. The improvement in the overall QOL was also significantly more in IBS patients receiving melatonin. The mechanism of melatonin-induced beneficial effect in IBS patient is not known. The proposed mechanism may be the central nervous system effects (sedative or anxiolytic) of melatonin or its direct effect on the GI tract.

The limitation of the present study is the small sample size. The plasma and tissue levels of melatonin are not studied in the present study. However, its randomized, double-blind design, make this pilot study interesting.

In conclusion, the result of this study showed that melatonin has some beneficial role in IBS. Further studies using large number of patients and measurement of plasma and tissue levels of melatonin may provide a definitive answer.

REFERENCES

1. Whorwell PJ, Mc Callum M, Creed FH, et al. Non-colonic features of irritable bowel syndrome. *Gut*. 1986;27:37–40.
2. Thompson WG. Irritable bowel syndrome: prevention, prognosis and consequences. *CMAJ*. 1986;134:111–113.
3. Drossman DA, Li Z, Andruzzi E, et al. U.S. householder survey of functional gastrointestinal disorders: prevalence, socio-demography and health impact. *Dig Dis Sci*. 1993;38:1569–1580.
4. Holmes KM, Salter RH. Irritable bowel syndrome—a safe diagnosis. *Br Med J*. 1982;285:1533–1534.
5. Talley NJ, Gabriel SE, Harmsen WS, et al. Medical costs in community subjects with irritable bowel syndrome. *Gastroenterology*. 1995;109:1736–1741.
6. Talley NJ, Spiller R. Irritable bowel syndrome: a little understood organic bowel disease? *Lancet*. 2002;360:555–564.
7. Mayer EA, Gebbart GF. Basic and clinical aspects of visceral hyperalgesia. *Gastroenterology*. 1994;107:271–293.
8. Delvaux M. Role of visceral sensitivity in the pathophysiology of irritable bowel syndrome. *Gut*. 2002;51(suppl 1):167–171.
9. Dunlop SP, Jenkins D, Neal KP, et al. Relative importance of enterochromaffin cell hyperplasia, anxiety and depression in postinfections IBS. *Gastroenterology*. 2003;125:1651–1659.
10. Brzezinski A. Melatonin in humans. *N Engl J Med*. 1997;336:186–195.
11. Storr M, Koppitz P, Sibaev A, et al. Melatonin reduces non-adrenergic, non-cholinergic relaxant neurotransmission by inhibition of nitric oxide synthase activity in the gastrointestinal tract of rodents invitro. *J Pineal Res*. 2002;33:101–108.
12. Harlow HJ, Weekley BL. Effects of melatonin on the force of spontaneous contractions of in vitro rat small and large intestine. *J Pineal Res*. 1986;3:277–284.
13. Bubenik GA, Dhanvantari S. Influence of serotonin and melatonin on some parameters of gastrointestinal activity. *J Pineal Res*. 1989;7:333–344.
14. Barajas-Lopez C, Peres AL, Espinosa-Luna R, et al. Melatonin modulates cholinergic transmission by blocking nicotinic channels in the guinea-pig submucous plexus. *Eur J Pharmacol*. 1996;312:319–325.
15. Storr M, Schusdziarra V, Allescher HD. Inhibition of small conductance K^+ channels attenuated melatonin-induced relaxation of serotonin-contracted rat gastric fundus. *Can J Physiol Pharmacol*. 2000;78:799–806.
16. Roberts-Thomson IC, Knights RE, Kennaway DJ, et al. Circadian rhythms in patients with abdominal pain syndromes. *Aust N Z J Med*. 1988;18:569–574.
17. Song GH, Leng PH, Gwee KA, et al. Melatonin improves abdominal pain in irritable bowel syndrome patients who have sleep disturbances: a randomized, double blind, placebo controlled study. *Gut*. 2005;54:1402–1407.
18. Chung O. Irritable bowel syndrome. In: Kasper DL, Braunwald E, Fauci AS, et al, eds. *Harrison's Principles of Internal Medicine*. 16th ed. New York: McGraw Hill; 2005:1789–1793.