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Effects of Melatonin on Preventing Postoperative Intraperitoneal Adhesion Formation in Rats

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Abstract : This study was performed in rats to find the minimum dose of melatonin that can effectively prevent the formation of postoperative intraperitoneal adhesions. Forty-two Sprague Dawley male rats were divided into six groups consisting of 7 rats, respectively. After celiotomy, five abrasions of 0.5×1 cm area were made on the antimesenteric serosal surface of the colon with a scalpel blade. The abdominal cavity was filled with 1 ml of solution containing 1 mg/kg (Mel 1), 3 mg/kg (Mel 3), 10 mg/kg (Mel 10), 30 mg/kg (Mel 30) and 5% ethanol solution (sham) through the catheter, using a sterile syringe before abdominal closure. Control group was given no adjuvant. The locations and values of adhesion were assessed through the second operation on the 14th day after the first operation. The adhesions were located on serosa to mesentery (54 of 210, 25.7%), serosa to serosa (44 of 210, 21%), serosa to omentum (12 of 210, 5.7%) and serosa to parietal peritoneum (0 of 210, 0%). The incidences of adhesion in Control, Sham, Mel 1, Mel 3, Mel 10 and Mel 30 were 68.6%, 91.4%, 57.1%, 60.1%, 17.1% and 20%, respectively. The values of adhesion separation in Mel 10 and Mel 30 group were lower than those in other groups. However, there was no significant ($p<0.05$) between Mel 10 and Mel 30 group. This study showed that 10 mg/kg of melatonin were effective in reducing the intraperitoneal adhesion.

Key words : melatonin, rats, reducing the intraperitoneal adhesion.

Introduction

Postoperative adhesion formation is a common complication of virtually every intraperitoneal surgery and occurs when fibrous strands of internal scar tissue left by the operation bind anatomical structures to one another. During normal healing process after postsurgical peritoneal injury, fibrin deposition and fibrinolysis are in equilibrium but if this balance is tilted towards deposition by factors suppressing fibrinolytic activity and leading to excessive fibrin deposition (10). Various methods and agents have been tried to prevent postoperative adhesions. The microsurgical technique and gently handling have somewhat reduced the occurrence of adhesions but have not been able to prevent them entirely. Various adjuvants have been tried to prevent postoperative adhesions, these are as follow: anti-inflammatory agents (NSAIDs, corticosteroids, hydroxyprogesterone, caproat), antibiotics, rubricate (fluid) agents (normal saline, chlorhexidine, sodium carboxymethyl-celloulose, hyaluronic acid, dextran 70, chitosan), fibrinolytic agents (pro-CPU inhibitor), antioxidative agents (vitamin E), physical barrier (oxidized regenerated cellulose, poly vinyl alcohol membranes) (3,7,10,13,15,21,22,33,34). Despite their widespread use and advances in medicine, benefit derived from them remains unclear and the problem of peritoneal adhesions still remain unsolved. The purpose of adhesion prevention is to reduce or completely prevent the occurrence, severity, extent and area of adhesions without disturbing the normal healing process. In many ways adhesion formation resembles an inflammatory process. Mediators of inflammation have been implicated in adhesion formation. Abdominal postsurgical adhesions develop following trauma to the mesothelium, which is damaged often by surgical handling and instrument contact, foreign materials, desiccation and overheating and that time, free radical is released from the impaired sites.

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone produced in the pineal gland. It is best known as being produced in the pineal gland, but there is document for its formation in retina, ovary, lens and gastrointestinal tract. Some cells and body fluids contain exceptionally high levels of melatonin, For example, bone marrow cells (5) have melatonin concentration orders of magnitude greater than those in the serum; Also, melatonin levels in bile and cerebrospinal fluid (29) are very much higher than in blood. Recent studies have found that melatonin is a very potent free radical scavenger as well as electron donor. It is twice as potent as vitamin E in inactivation of peroxyl radicals (27,32). Free radicals are molecules that have an unpair valence electron; this makes these molecules highly reactive and they often damage neigh-

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boring molecules by abstracting an electron from them. The function of antioxidants is to minimize the molecular destruction due to free radicals and reactive intermediates. Locally generated free radicals such as superoxides, peroxides, and hydroxyl radicals are potential oxidizers of polyunsaturated fatty acids, therefore could induce adhesions by damaging cellular membranes (18,25,26).

This study, therefore, was designed to find the minimum dose of melatonin that can effectively prevent the formation of postoperative intraperitoneal adhesions in rats.

Materials and Methods

Experimental animals

Forty-two Sprague Dawley male rats, weighing between 200 and 210 g were housed in a climate-controlled animal-care facility (relative humidity 40% and temperature 24-26°C), with a 12-hour light/dark cycle. The animals had standard rodent chow and water *ad libitum*. Animals were randomly divided into six groups, each consisting of 7 rats for this experimental study. Four groups were treated intraperitoneally with 1 ml solution containing 1 mg/kg (Mel 1), 3 mg/kg (Mel 3), 10 mg/kg (Mel 10) and 30 mg/kg (Mel 30) of melatonin before abdominal closure, respectively. One group was treated intraperitoneally with 1 ml of 5% ethanol (IP Sham) and the other group was given no adjuvant (Control).

Preparation of materials

Melatonin was obtained as a dry powder (Sigma Co. Seoul, Korea) dissolved in 99% ethanol and then diluted in distilled and autoclaved water and the final ethanol concentration was 5%. Melatonin concentrations were 0.2 mg(1 mg/kg), 0.6 mg (3 mg/kg), 2 mg (10 mg/kg) and 6 mg (30 mg/kg) per 1 ml experimental solution, respectively.

Surgical procedures

Anesthesia and preparation for surgery were similar in all groups. Each rat was anesthetized with 6 mg/kg of xylazine and 75 mg/kg of ketamine intramuscularly. Sterile surgical protocols were maintained throughout. A 1~2 cm long midline abdominal incision was made, the cecum was retracted upwards, and ascending colon exposed. The anti-mesenteric serosa defects of the ascending colon right after the cecum were created by light scraping about 0.5 × 1 cm area with a sterile scalpel blade to promote petechia, and allowed to air dry for 5 minutes. Total five distinct surgical defects were made in order to induce adhesions. Control group had no adjuvant solution into abdominal cavity, and then the intestine was replaced in normal position. The sham group was infused 1 ml of 5% ethanol solution through the catheter, using a sterile syringe a entire abdominal cavity, before closure. In other experimental groups, the abdominal cavity was infused with 1ml solution (respectively, solution containing 1, 3, 10 and 30 mg of melatonin per kilogram) through the catheter using a sterile syringe before closure. The catheter was then removed, and abdomen was closed using 3-0 nylon (BLUE NYLON Ailee Co. LTD, Korea) in simple interrupted suture pattern.

Postoperative evaluations

Two weeks later, the animals were killed and the intra-abdominal cavity was inspected through a U-shaped incision. Adhesions were identified, counted and evaluated with separation strength by two independent investigators, who were unknown for this experiment. The separation strength of the adhesion sites was evaluated with Manual Direct Drive Test Stand(MOD, MECMESIN Ltd. UK). For microscopic evaluation, tissue samples were collected from 3 rats in all groups. Collected tissues included adhesions, serosal scars and grossly normal part. Each was fixed in 10% formalin, and multiple segments containing injured area from each group were routinely processed for histological examination.

Statistical analysis

The significance of differences in the separation strength of the each group was assessed by one-way ANOVA test. The multiple comparisons on parameters were performed using DUNCAN test. Probabilities of less than 0.05 were accepted as significant.

Results

The second laparotomy was performed in all experimental groups at 2 weeks after surgery. The results of the adhesion assessments, separation strength values and histological examinations were tabulated.

Locations and incidences of the adhesions

Two weeks after induction of peritoneal adhesions, the peritoneum was inspected for the locations (Table 1), incidences (Fig 1) and degrees (Table 2) of adhesions. All of the animals were admitted for occurrences of adhesions. Adhesions were identified in total sites; serosa to mesentery (54 of 210, 25.7%), serosa to serosa (44 of 210, 21%), serosa to omentum (12 of 210, 5.7%).

Table 1. Postoprative locations of adhesions in rats on day 14 after operation

	Location*			
	Total	S-S	S-M	S-O
Control	24	11	11	2
IP sham	32	12	16	4
Mel 1	20	8	11	1
Mel 3	21	7	9	5
Mel 10	6	3	3	0
Mel 30	7	3	4	0

Locations of adhesions: S-S=serosa-serosa; S-M=serosa-mesentery; S-O=serosa-omentum.

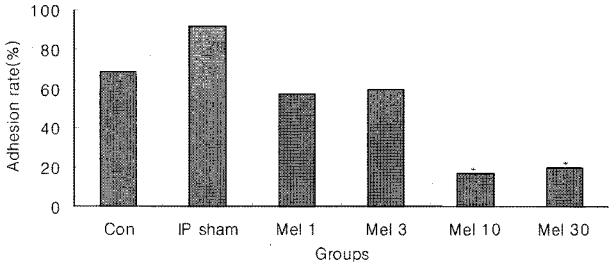

Fig 1. Adhesion incidences in rats on day 14 after operation.
Con: The control group treated with no adjuvant.
IP sham: The group treated with 1 ml of 5% ethanol before abdominal closure.
Mel 1, Mel 3, Mel 10 and Mel 30: The groups treated with 1 ml solution containing 1, 3, 10 and 30 mg/kg of melatonin, respectively, before abdominal closure.
*: $p<0.05$ compare with the control group.

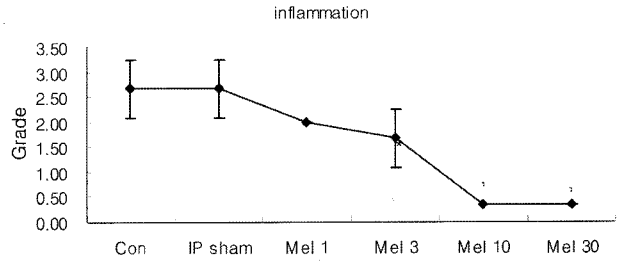

Fig 2. Inflammation grade of adhesion area in experimental groups. : $p< 0.05$ compare with the control group.

Separation strength values (gram force, gf) of the adhesions

1) Control Group : severe adhesions were developed in 24 of 35 (68.6%) induced peritoneal adhesion sites, and adhesion separation strength value is 264.7 ± 140.2 gf.

2) IP sham Group : severe adhesions were developed in 32 of 35 (91.4%) induced peritoneal adhesion sites, and adhesion separation strength value is 378.8 ± 153.2 gf.

3) Mel 1 Group : moderate to severe adhesions were developed in 20 of 35 (57.1%) induced peritoneal adhesion sites, and adhesion separation strength value is 201.5 ± 118.9 gf. There were insignificant reductions in adhesions in comparison with Control and IP sham Group ($p>0.05$).

4) Mel 3 Group : moderate to severe adhesions were developed in 21 of 35 (60%) induced peritoneal adhesion sites, and adhesion separation strength value is 116.1 ± 94 gf. Compared to Control and IP shame Group, no statistical significant reduction of adhesion formation was found in this ($p>0.05$).

5) Mel 10 Group : moderate adhesions were developed in 6 of 35 (17.1%) induced peritoneal adhesion sites, and adhesion separation strength value is 29.4± 30.3 gf. Extents and values of adhesion formation in this Group were statistically significant reduction in comparison with those in Control and IP sham Group ($p<0.05$).

6) Mel 30 Group : moderate adhesions were developed in 7 of 35 (20%) induced peritoneal adhesion sites, and adhesion separation strength value is 45.1 ± 44 gf. There were significant reductions in adhesions compared with those in Control and IP sham Group ($p<0.05$), but no significant reduction in comparison with that in Mel 10 Group ($p>0.05$).

Histological examination

The grade of the inflammatory cell infiltration, capillary regrowth and fibrosis on histological samples were evaluated according to the scale respectively as followed: grade 0, absent; grade 1, mild; grade 2, moderate; grade 3, marked. A total score in each group was obtained by sum of individual score to 3 tissue sample per group.

The grade of inflammation was significant decreased in Mel 10 and Mel 30 treatment group ($p<0.05$), but grade of fibrosis and neovascularization did not differ among the groups.

Discussion

Adhesion formation is induced by mechanical injury, ischemia of the mesothelial layer, or the introduction of foreign materials into the peritoneal cavity (4,8,12,14,19,22). Innumerable substances and methods have been used, either locally in the peritoneal cavity or systematically, for an effect to prevent or reduce the occurrence of postoperative peritoneal adhesions. This may either reduce the amount of exudate, prevent its coagulation, reduce contact between surfaces, remove fibrin after its appearance or stop proliferation of fibroblasts (3,10, 18,22,34). An understanding of pathogenic mechanisms of adhesion formation is important for studies aiming at developing strategies for their prevention. The peritoneal surface

Table 2. The strength values for the adhesion separation in each group

Group	No. of animals							Median (mean± SD)
	1	2	3	4	5	6	7	
Control	112	275	251	315	113	527	260	264.7± 140.2
Sham	134	423	405	471	594	398	227	378.9± 153.2
Mel 1	279	276	309	200	58.5	12.5	275.5	201.5± 118.9
Mel 3	26	194	77	105	267.5	143	0	116.1± 94
Mel 10	78	46	0	43	39	0	0	29.4± 30.3*
Mel 30	69	0	0	61	100	86	0	45.1± 44*

*$p< 0.05$ compare with the control group.

consists of a single layer of mesothelial cells with parietal and visceral reflections. Injury to the peritoneum leads to the formation of a fibrinous exudate. Fibrin exudes from peritoneal mesothelial cells, and most of them is lysed and absorbed (9,23). Body defenses most often resolve the fibrinous strands via phagocytosis and enzymatic digestion. However, the defense fails if the injury involves a fairly large area or if there is low concentration of enzymes and leukocytes, and result in performing permanent fibrous adhesions (17). That is, the normal peritoneum has inherent fibrinolytic activity that is derived mainly from the surface mesothelial cells and endothelial cells but, after peritoneal trauma, there is a loss of plasminogen activator activity, and viscous macromolecular solutions can inhibit the removal of plasminogen activator from areas of peritoneal defects, following by serosal fibrinolytic activity was immediately reduced and that this was associated with adhesion formation (31). The postoperative complications resulting from intraperitoneal adhesions include intestinal obstruction, chronic or recurrent pelvic pain, infertility in women, and prolonged operation time (6,11). Despite advancements in surgical technique and prevent agents the clinical consequences of these adhesions are serious. It has been estimated that as many as 30% of all intestinal obstruction are caused by peritoneal adhesion (6).

Melatonin has been found to be a highly potent and versatile antioxidant and free radical scavenger and also immune function and tumor growth inhibition and influences on retinal physiology (1,20,28). The most commonly used and thoroughly experimentally studied antioxidants are the vitamins, ie ascorbic acid, tocopherol and β-carotene. Despite melatonin's discovery over 40 years ago, melatonin was not recognized as a free radical scavenger and antioxidant until the last decade (16). The first evidence that melatonin may promote gluatathion peroxidase (GPx) activity utilized pharmacological doses of the indole. In this study, when melaotinin was given at a dose of 500 μg/kg, neural GPx activity increased 2-fold in the female rat within 30 min. That melatonin, even at physiological levels may enhance GPx activity was suggested by the observations that when the activity of this enzyme was compared in the brain of rats killed during the day and night, nighttime levels were higher. This correlated positively with the nocturnal elevation in circulation melatonin concentrations (2). Melatonin increases the efficiency of oxidative phosphorylation, it could be important in reducing oxidative stress by attenuation the electron leakage and the resultant generation of the O_2. Despite the abundant of information that has accumulated relative to the antioxidative properties of melatonin, there are a number of critical deficiencies in the knowledge as to some of the resulting products that are formed when melatonin scavengers reactive species, the physiological relevance of melatonin as an antioxidant, and its relative importance compared to other better known endogenous and exogenous free radical scavengers. Whereas some antioxidants are produced outside the organism and must be consumed, e.g. the vitamin antioxidants, and others are endogenously synthesized, e.g. glutathion, melatonin derives from both sources. Although previous study of the Bulent *et al* (24) have demonstrated that melatonin was able to prevent adhesion formation while not affecting the normal wound healing, it necessary to find effect of postoperative adhesion prevention with various dose of melatonin. In present study, we performed by using a various dose of melatonin (respectively 1, 3, 10, 30 mg/kg) and found a significant reduction in postoperative adhesion formations in rats treated with melatonin. Administration of the melatonin 10 mg/kg (Mel 10) and melatonin 30 mg/kg (Mel 30) into the abdominal cavity could met with good result ($p<0.05$), but Mel 1 and Mel 3 group have not significant postoperative adhesion reduction. Additionally, no statistically significant difference was detected in the adhesion scores between the Mel 10 and Mel 30 group. On microscopic examination, the grade of inflammation was significant in Mel 10 and Mel 30 group ($p<0.05$), but the grade of fibrosis and neovasculization did not differ among the groups. Some scientists established that melatonin may exert its anti-adhesive effects including diluting fibrin in the original inflammatory exudate and affecting the activity of the inflammatory factors (30). In this study, melatonin have functioning of a anti-inflammation. We could coclude that melatonin was effective on preventing the formation of postoperative adhesion in the rat. Further studied are necessary to elucidate mechanisms about the postoperative adhesion prevention by intraperitoneal administration of melatonin.

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Rat에서 술후 복강 유착방지에 대한 melatonin의 효과

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요 약 : 랫트에서 melatonin(N-acetyl-5 methoxytryptamine)이 복강 내 유착 형성 방지에 미치는 효과를 알아보고자 본 실험을 수행하였다. 총 42마리의 수컷, Sprague Dawley 랫트를 유착 유도 후 무처치 대조군, 5% ethanol 용액을 투여한 sham군, melatonin 1 mg/kg 처치군(Mel 1군), melatonin 3 mg/kg 처치군(Mel 3군), melatonin 10 mg/kg 처치군(Mel 10군), melatonin 30 mg/kg 처치군(Mel 30군) 등 6개 군으로 분류하고 각 군에 7마리씩 배치하였다. 정중개복 후 맹장을 확인하고 맹장에서 0.5 cm 지점의 오름 결장에서 시작하여 3 cm 간격으로, 장간막 반대측 장막 5곳에 0.5×1 cm 크기로 찰과상을 생성하여 유착을 유도하였다. 대조군은 어떤 처치도 없이 복강을 폐쇄하였으며 sham 군은 5% ethanol 1 ml, 나머지 군은 각각의 용량에 맞춰 5% ethanol 에 녹인 melatonin 용액 1 ml를 복강 폐쇄 전 주입하였다. 수술 2주 후에 유착발생빈도 및 정도를 평가하였다. 유착장소는 전군에서 장막-장간막(25.7%), 장막-장막(21%), 장막-대망막(5.7%) 순으로 발생하였다. 유착발생빈도는 Mel 10군이 17.1%로 대조군 68.6%, sham 군 91.4%, Mel 1군 57.1%, Mel 3군 60.1%에 비해 낮았다. 그러나 Mel 30군은 20% 로 유의적인 차이를 보이지 않았다. 유착형성은 대조군, Sham군, Mel 1군, Mel 3군, Mel 10군, Mel 30군에서 각각 264.7±140.2, 378.9±153.2, 116.1±94, 29.4±30.3, 45.1±44로 Mel 10군과 Mel 30군이 유의적인 감소를 보였으나($p<0.05$) 이들 두 군 간의 차이는 나타나지 않았다. 이상의 결과로, 랫트에서 복강수술 후 melatonin 10mg/kg 투여가 복강 내 유착 방지에 효과적이라고 생각된다.

주요어 : 멜라토닌, 랫트, 복강유착 방지.