Institutional report - Cardiac general

Effect of melatonin in the prevention of postoperative pericardial adhesion formation

Mahmood Saeidia, Roohollah Sobhania, *, Minoo Movahedib, Samira Alsaeidic, Reza Eshraghi Samanid

aDepartment of Surgery, Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
bDepartment of Obstetrics and Gynecology, Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
cDepartment of Internal Medicine, Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran

Received 8 February 2009; received in revised form 1 April 2009; accepted 2 April 2009

Abstract

To evaluate the efficacy of melatonin in preventing postoperative pericardial adhesions, 12 single breed dogs were randomized equally into experimental (melatonin) and control groups. After ketamine anesthesia, a vertical midsternal incision was done and the parietal pericardium of the inferior site of the heart was opened vertically. To promote adhesion formation, abrasions were created on both parietal and visceral pericardial surfaces in an area of 2 cm^2 with two vertically reciprocal movements of dry gauze. In the melatonin group, 5% ethanol plus 10 mg/kg melatonin in 10 ml NaCl and, in control group, 10 ml NaCl dilution vehicle containing 5% ethanol was instilled intrapericardium on to the abrasion sites. After a 6-week recovery period, the animals were evaluated for grading of adhesion formation by an examiner blinded to the groups. The extent of adhesions was graded from 0 (no adhesion) to 3 (total involvement of the traumatized area). The results showed that adhesion scores were significantly lower in melatonin group (1.00±0.63) compared with controls (2.66±0.51); P=0.001. We conclude that melatonin administration effectively reduced postoperative pericardial adhesions in dogs. The use of melatonin in the prevention of pericardial adhesion formation in human subjects warrants further investigations.

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Keywords: Adhesion; Cardiac surgery; Pericardial; Prevention; Melatonin

1. Introduction

Adhesion formation after pericardiotomy is a significant cause of morbidity and mortality in congenital or adult cardiac surgery especially at the time of re-operation. Over the past decades, continued researches have been done to resolve the problem of postoperative pericardial adhesions using different types of pericardial substitutes or pharmacological agents. Despite these attempts, however, there is still no ideal method to prevent postoperative pericardial adhesion formation [1].

Although the mechanism of adhesion formation is not fully understood, inflammatory responses are involved in its pathogenesis. Increasing of reactive oxygen species (ROS), occurring during open surgery, can play a role in postoperative adhesion formation. Evidence showed that ROS scavengers could prevent adhesion formation in animal models [2].

Melatonin (N-acetyl-5-methoxy-tryptamine), a pineal secretory product, has many roles in regulating biological activities such as sleep, reproduction, tumor growth, and ageing. A recently documented function of melatonin is free radical scavenger activity. Besides this ability, it stimulates several antioxidative enzymes which increase its efficacy as a powerful antioxidant. Melatonin has been widely used as a protective agent against various processes that damage tissues via free radical mechanisms [3]. A few previous experimental studies have showed that melatonin could prevent postoperative intraabdominal adhesion formation [4–7]. To the best of our knowledge, there is no report on the efficacy of melatonin in preventing postoperative pericardial adhesions. The aim of this study was to evaluate whether melatonin administration would prevent adhesion formation in an experimental pericardial adhesion model in dogs.

2. Material and methods

2.1. Animal preparation

A total of 12 single breed dogs with the mean weight of 23 kg (20–25) were randomized equally into melatonin and control groups. The study protocol was approved by Isfahan University of Medical Sciences, Ethics Committee for Animal Researches. Procedures were carried out at Dr Torabinejad Clinical and Experimental Research Center. Animal care was in compliance with the ‘Guide for the Care and Use of Laboratory Animals; 1996’ [8].
2.2. Surgical procedure

The surgical procedure was for a single surgeon to operate on dogs in each of the two groups in turn. Acepromazine (0.1 mg/kg IM) was administered for sedation. An intravenous line and electrocardiographic monitoring were established. Prophylactic antibiotics (cefaclor sodium 40 mg/kg) were given intravenously just before the operation. Anesthesia was induced with sodium thiopental 3 mg/kg IM immediately followed by endotracheal intubation. Before incision, the chest wall was shaved and prepared with povidone iodine. Under sterile conditions, the thorax cavity was opened via a vertical midsternal incision. Then, the parietal pericardium of the inferior site of the heart (near the apex) was opened vertically. To promote adhesion formation, abrasions were created with two vertically reciprocal movements of a dry gauze in an area of 2 cm² on both visceral and parietal pericardium at the inferior site of the heart. In melatonin group, 5% ethanol plus 10 mg/kg melatonin in 10 ml saline and, in control group, 10 ml saline dilution vehicle containing 5% ethanol was instilled intra-pericardium on to the abrasion sites. Melatonin was obtained as a dry powder (Sigma, St Louis, MO, USA), dissolved in 99% ethanol and then diluted in saline just before injection. The final ethanol concentration was 5% and the amount of melatonin was 200–250 mg/mouse per 10 ml injectable solution.

At the end of the procedure, the pericardium remained open. Before closing the sternum, a tube was entered into the thorax through the 5th or 6th intercostal spaces for air exchange. The sternum was closed with steel wire and muscles and subcutaneous layer with 2-0 monofilament absorbable suture in two layers, continuously. Skin was then closed with 2-0 Nylon suture in continuous fashion. The lungs were hyperventilated and thereafter, the tube was removed and skin at the entering site was pursed with silk immediately. All dogs were housed at a constant room temperature (22 ± 2 °C) with 12-h light and dark cycles, and were provided standard food and water ad libitum.

2.3. Evaluation of adhesions

After completion of the 6-week recovery period, the animals underwent a secondary surgery and were evaluated for grading of adhesions by macroscopic findings (Table 1). The investigator who participated in scoring the adhesions had no prior knowledge as to which group the dogs belonged. The extent of adhesions in the operation site was evaluated using an established scoring system [9]. According to this system the extent of adhesions was evaluated as follows: zero, no adhesion; one, 25% of traumatized area; two, 50% of traumatized area; and three, total involvement.

2.4. Statistics

The statistical comparison of adhesion scores between the two groups was made using Mann–Whitney test. A P < 0.05 was considered to be significant for the test.

3. Result

All animals tolerated the procedure with no apparent postoperative complications. The survival rate was 100% in both groups. There were one grade 0, four grade 1, and one grade 2 adhesions in melatonin group and two grade 2 and four grade 3 adhesions in controls; Fig. 1. Adhesion scores were found to be significantly lower in melatonin group (1.00 ± 0.63) compared with controls (2.66 ± 0.51); P = 0.001.

4. Discussion

Postoperative pericardial adhesion formation is a significant cause of morbidity and mortality in cardiac surgery with still no ideal preventive method. Some works focused primarily on substitutes (autogenous, heterogenous, and synthetic) providing a barrier between epicardium and pericardium or overlying sternum while others have evaluated the ability of a variety of pharmacological agents to reduce or prevent adhesion formation after cardiac operation [1]. The efficacy of synthetic and xenogeneic membranes is recognized [10]. However, these membranes have been reported to be associated with epicardial reaction, capsule formation, and calcification, and have not demonstrated consistent effectiveness. Furthermore, these forms of membrane are not transparent and may interfere with visualization of the cardiac architecture during the operation [11]. On the other hand, systemic anti-inflammatory drugs and topical application of fibrinolytic agents have also been shown to reduce adhesion formation. However, both modalities have some side effects like bruising, bleeding, and impairment of wound healing [12].
Inflammatory responses are important in the pathogenesis of adhesion formation. Reduction in tissue oxygenation due to ischemia is known to be involved in adhesion formation. Free radicals, significantly produced after endothelial tissue damage, are able to react rapidly with oxygen and so exacerbate the oxygen deficit [2]. Moreover, free radicals such as superoxides, peroxides, and hydroxyl radicals are potential oxidizers of polyunsaturated fatty acids resulting in peroxidation of cellular membrane lipids and increased vascular permeability [13]. This leads to the formation of serosanguineous exuda, which in turn initiates adhesion formation. These adhesions are generally lysed within 72 h after formation by the endogenous fibrinolytic activity [14]. However, in a state of an imbalance between fibrin deposition and dissolution, deposited fibrin may persist and fibrinous adhesions may develop [2].

Antioxidant and scavenging activities of melatonin and its efficacy in preventing postoperative adhesion formation have been found recently. The antioxidant effects of melatonin were examined using different organ ischemia-reperfusion models [15] and its preventive role was investigated in postoperative intraabdominal adhesion formation [4–7]. In an experimental study by Demirbag et al., both melatonin and hyaluronate/carboxymethylcellulose membrane were effective in prevention of adhesion formation in a rat uterine horn model with no significant difference between the two methods in adhesion scores [5]. The effects of different routes (intraperitoneal or subcutaneous) and treatment schedules (10 mg/kg; single dose or 5 days) of melatonin on postoperative adhesion formation was investigated by Ozcelik et al. in a rat uterine horn model [4]. They found a significant reduction in postoperative adhesion formation in rats treated with melatonin, regardless of application procedure and duration of the agent. Even a single dose of melatonin therapy was effective in the prevention of postoperative intraperitoneal adhesion formation [4].

In the present study, which is the first on the prevention of postoperative pericardial adhesion formation by melatonin, we found that melatonin significantly reduced adhesion formation in an experimental pericardial adhesion model in dogs. Although melatonin significantly reduced pericardial adhesions in our study, just one animal was free from any adhesions in melatonin group. Therefore, the most appropriate dose or delivery method for clinical application needs to be determined. According to the time of re-operation in current cardiac surgery, the follow-up period of six weeks in our study is short and further experiments with longer observation periods are necessary to elucidate the efficacy of melatonin.

5. Conclusion

The use of melatonin effectively reduced postoperative pericardial adhesions in the described dog model. Further studies are necessary with melatonin on human subjects and comparative studies with other preventive agents that have been found effective in the prevention of pericardial adhesion formation.

Acknowledgment

The authors would like to appreciate the kind assistance and financial support provided by the Research Chancellor of Isfahan University of Medical Sciences, as well as the colleagues, especially Dr Shahriar Adibi, DVM (Dr Torabinejad Clinical and Experimental Research Center), who helped us in conducting this study. Also, we are thankful to Dr Ali Gholamrezaei, MD (Isfahan University of Medical Sciences) who helped us in preparing this report.

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