



## Use of Melatonin as a Pre-anesthetic Agent

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### Abstract

**B**ackground: Surgeons need to prolong the duration of anesthesia and analgesia, in addition to preventing the release of pro-inflammatory factors in anticipation of post-operative disorders (POD). **Objectives:** To achieve the surgeons' goals mentioned above, melatonin was chosen as a pre-anesthetic agent. **Methods:** To test the ability of melatonin to prolong the duration of anesthesia, 24 adult rats were separated into (A (control), B, C and D). Group (A) was treated with distilled water (D.W.) (5 ml / kg, orally), while groups (B, C and D) were treated with melatonin (20 mg/kg, orally) and after (0, 15, 30, and 45) minutes, all groups were injected with (ketamine and xylazine). Formalin induced paw licking test was used to detect analgesic and anti-inflammatory effects of melatonin, animals in groups (A and B) (five/group) were injected with formalin into plantar surfaces of the rat's paw 45 minutes after treatment with either distilled water (A) or melatonin (B). **Results:** Group (D) showed a significant prolongation of the duration of anesthesia compared to other groups (A, B, C). On the other hand, the formalin induced paw licking test revealed that melatonin has analgesic and anti-inflammatory effects represented in the significant delay in onset of paw licking accompanied by a significant decline in number of rats' attempts to lick their paws, both in the 1<sup>st</sup> phase (analgesia) and the 2<sup>nd</sup> phase (anti-inflammatory) compared to the control group. **Conclusion:** We conclude from our current study the possibility of using melatonin as a pre-anesthetic agent.

**Keywords:** Melatonin, Pre-anesthetic agents, Analgesic, Anti-inflammatory, Formalin.

### Introduction

Melatonin is a tryptophan-derived hormone produced largely by the pineal gland in brain [1]. It has important biological effects on the body through its effect on the circadian rhythm [2]. Melatonin is synthesized from a pathway containing tryptophan and serotonin [3] and regulates its effects through two chief pathways. The first pathway is receptor binding (membrane, cellular and nuclear receptors), membrane receptors include both M1 and M2. Binding of melatonin to the M1 receptor leads to inhibition of adenylylcyclase activity in target cells. Whereas, melatonin binding to the M2 receptor stimulates the hydrolysis of phosphoinositides. But the M3 receptor is a cytosolic receptor binding of melatonin to the M3 receptor will influence calcium signaling through interactions with target enzymes and structural proteins. In particular, the binding of melatonin to orphan receptors ( $\alpha$  and  $\beta$ ) has recently been determined, which are nuclear receptors. The second pathway is not receptor dependent, by

eliminating toxic free radicals [4]. In fact, melatonin receptors are found in many organs for example the brain, retina, bone marrow, intestines, bile, lymphocytes, platelets, skin, ovaries, and testis and mainly in the suprachiasmatic nucleus [5-8].

In major surgeries, it is necessary to prolong the duration of anesthesia. Therefore, in our current research, the ability of melatonin to cause this prolongation was tested with the anesthesia mixture (ketamine and xylazine), which is the most used in the field of veterinary surgeries [9].

Among the problems that occur after surgery are what is called postoperative disorders (POD), which are caused by the release of pro-inflammatory cytokines (PIC) during anesthesia [10], which is supported by what researchers have reached [11-13] about that peripheral surgery may stimulate the discharge of (PIC) for example IL6\_type as this cytokines cross central nervous system, inducing neuroinflammatory responses and brain harm.

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Melatonin suppresses the release of the cytokine [14-16]. This positivity that melatonin possesses is added to the reasons that prompt us to choose it in our current study.

The formalin test is used to detect both analgesic effects through the first phase (immediate pain) of the test resulting from direct stimulation of nociceptors and anti-inflammatory effects through the second phase (late-onset pain) [17-19].

Another thing that attracted us to choose melatonin in our current study as a pre-anesthetic agent is that it has a unique role in the central nervous system, where surgeons care to maintain its safety during anesthesia, including a neuroprotective, free-radical scavenger, anti-apoptotic agent [20-22], thus, the surgeons' goals for the success of the surgical operation are achieved.

## **Material and Methods**

### **Animals**

In this research, male white Albino rats were used, which were raised in the laboratory animal house of the University of Mosul/ College of Veterinary Medicine, and their weights were between (250-300 gr). Bearing in mind that the weights of male rats are close in each experiment. In terms of lighting, the experimental animals underwent a 24-hour adaptation process, half of which was light and the other half dark. Regarding the temperature of the laboratory in which the breeding was carried out was (25±2°C) humidity 50% ±10%. The time of conducting the experiments was set between 9.00 a.m. and 3.00p.m.

### **Drugs and chemicals**

Melatonin (Vitane Pharmaceuticals, USA) at 20 mg were dissolved in (5 ml) D.W. to obtain required dose which given orally. The dose of melatonin (20 mg/kg, orally) used in the current study was determined based on [23]. ketamine 10%. xylazine HCL 2%(Alfas An company Holland) diluted in D.W. to obtain the desired dose for each drug (ketamine 50mg/kg and xylazine 5mg/kg) to be injected at 2 ml/kg, intraperitoneally separately.

### **Experiments**

#### **1- Effect of pre-treatment of adult male rats with melatonin on the induction and duration of anesthesia with ketamine and xylazine.**

The experimental animals were separated into four groups, with a rate of 6 for each group :

A-The first group was given distilled water (5 ml/kg, orally ) and then immediately intraperitoneal injections of ketamine (50 mg/kg ) and xylazine (5 mg/kg) .

B-The second group was given melatonin (20 mg/kg, orally ) and then after 15 minutes intraperitoneal injections of ketamine (50 mg/kg ) and xylazine (5 mg/kg) .

C-The third group was given melatonin (20 mg/kg, orally ) and then after 30 minutes intraperitoneal injections of ketamine (50 mg/kg ) and xylazine (5 mg/kg) .

D-The fourth group was given melatonin (20 mg/kg, orally ) and then after 45 minutes intraperitoneal injections of ketamine (50 mg/kg ) and xylazine (5 mg/kg) .

Note: After completing the injection of the ketamine and xylazine mixture in each animal, the induction and duration of anesthesia were calculated.

**A-Onset of anesthesia**= time of injection-time of loss righting reflex

**B-Duration of anesthesia**=time of loss righting reflex-time of regain of righting reflex

#### **2-Detection of the analgesic and anti-inflammatory effects of melatonin using formalin induced paw licking test**

To conduct this experiment, two groups of rats (A (control), B) (5/group) were subjected to the formalin induced paw licking test, where initially the two groups (A, B) were treated with either DW (5 ml/kg, orally) or melatonin (20 mg/kg, orally) respectively and after 45 minutes 20 µL of (2.5 % formalin) was injected into plantar surfaces of the rat's paw in both groups.

The Onset time of paw licking and the number of rats' attempts to lick their paws were calculated, both in the first phase (immediate pain) 0-5 minutes, which represents (analgesia phase), and the second phase (late-onset pain) 10-45 minutes, which represents (anti-inflammatory effects stage) (23).

### **Statistical Analysis**

All data were analyzed by *Analysis of Variance* (ANOVA), and are expressed as mean ± standard error of the mean. Significant differences between the control and treatment groups were determined by least significant difference (LSD). All statistical analyses were performed using SPSS. Statistical significance was determined based on values of  $p < 0.05$ .

### **Results**

#### **Effect of pre-treatment of adult male rats with melatonin on the induction and duration of anesthesia with ketamine and xylazine.**

Intraperitoneal injection of ketamine (50 mg/kg) and xylazine (5 mg/kg) into groups (A (control), B, C

and D) after (0, 15, 30 and 45) minutes of treating rats with melatonin (20 mg/kg, orally), respectively, resulted in a prolongation of the duration of anesthesia in a manner dependent on the time of pre-treatment with melatonin, it was represented by a significant increase in the duration of anesthesia in

group (D), which reached to (170 ± 13.56) minutes compared to the values of the duration of anesthesia in the groups (A (control), B and C) which reached to (72±5.68, 92.66 ± 16.45, 90.50±13.28) minutes according to the succession of groups (Table 1).

**TABLE 1. Effect of pre-treatment with melatonin on the induction and duration of anesthesia with ketamine and xylazine in adult male rats.**

Time of melatonin administration	Time of induction of anaesthesia (minute)	Time of duration of anaesthesia (minute)
(A):Control(D.W),then immediately give the anesthetic mixture	10.83±2.19	72±5.68
(B):15 minutes before giving anesthetic mixture	11.33±3.84	92.66±16.45
(C): 30 minutes before giving anesthetic mixture	10.50±1.87	90.50±13.28
(D):45 minutes before giving anesthetic mixture	8.83±2.44	170±13.56 <sup>*ab</sup>

The values represent the mean ± standard error of (6 rats/group)

\*- The value contrasts significantly comparison to the values of the control group at the level of significance  $P < 0.05$

a -The value contrasted significantly comparison to the values of the group treated with a melatonin 15 minutes before anesthesia at a significant level  $P < 0.05$

b -The value contrasted significantly comparison to the values of the group treated with a melatonin 30 minutes before anesthesia at a significant level  $P < 0.05$

**-Detection of the analgesic and anti-inflammatory effects of melatonin (20 mg/kg, orally) using formalin induced paw licking test.**

Our current study found that melatonin was given (45) minute before to the formalin injection into plantar surfaces of the rat's paw lead to a significant prolongation in the onset of paw licking which reached (220.20± 52.28) seconds compared to the control group (35.00±14.11 seconds) (Fig. 1).

In addition, the formalin induced paw licking test revealed that melatonin has analgesic effects (first phase (0-5)minutes) represented by recording a

significant reduction in the number of rats' attempts to lick their paw from (29.0±8.86) times in the control group to (11.0±5.53) times in the group treated with melatonin 45 minutes prior exposure to the formalin test as well as melatonin also has anti-inflammatory effects (second phase (10-45)minutes), represented by a significant decline in the number of rats attempts to lick their paw from (647.00 ± 79.134) times in the control group to (185.20±53.177) times in the group treated with melatonin 45 minutes prior exposure to the formalin test (Table 2).

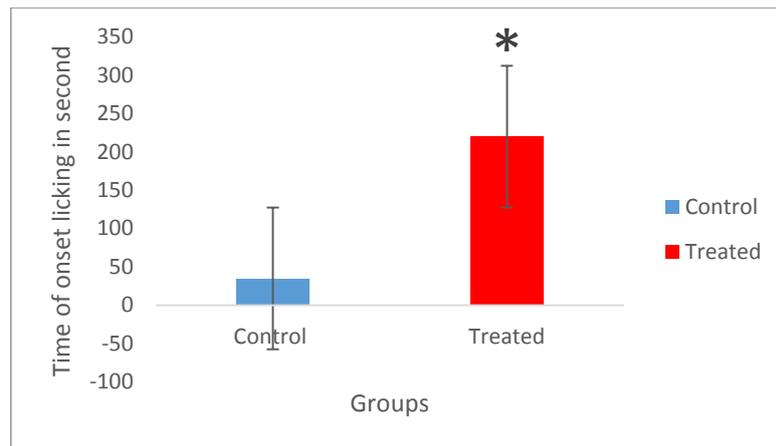
**TABLE 2. Detection of analgesic and anti-inflammatory effects of melatonin using formalin-induced paw licking test in rats**

Groups	The number of rats' attempts to lick their paws	
	1 <sup>st</sup> phase	2 <sup>nd</sup> phase
	(0-5) minutes analgesic	(10-45) minutes anti-inflammatory
A- Control group(Distal water)	29.0±8.86	647.00±79.134
B-Treated group (melatonin)	11.0±5.53*	185.20±53.177*

The values characterize the mean ± standard error of 5 rats/group.

Melatonin or distal water were administered 45 minute prior to the formalin injection into plantar surfaces of the rat's paw

\* The value differs significantly comparison to the values of control group at the level of significance  $P < 0.05$



**Fig. 1. Effect of pretreatment of melatonin on the onset of paw licking induced by formalin injection into plantar surfaces of the rat's paw**

Melatonin or distal water were administered 45 minute prior to the formalin injection into plantar surfaces of the rat's paw

\* The value differs significantly comparison to the values of the control group at the level of significance  $P < 0.05$

### **Discussion**

Preanesthetic agents are very important for the success of surgery, as they help provide surgeons' needs to prolong the anesthesia period, induce analgesia, and prevent post-operative disorders, most of which may result from the release of pro-inflammatory substances during surgery [10-13]. Therefore, the subject of our study was to test melatonin to provide what surgeons need it to prolong the period of anesthesia using a combination of ketamine and xylazine and to detect melatonin's analgesic and anti-inflammatory effects using the formalin induced paw licking test.

Injecting a mixture of ketamine and xylazine into groups (A (control), B, C and D) after (0, 15, 30 and 45) minutes of treating rats with melatonin (20 mg/kg, orally), respectively, resulted in a prolongation of the duration of anesthesia in a manner dependent on the time of pre-treatment with melatonin. The reason for this may be attributed to its pharmacokinetic behavior of melatonin. When it was given 45 minutes before treatment with the anesthesia mixture, may it have reached its peak effect (highest concentration) in the plasma coinciding with administration of anesthesia mixture. Thus, this interpretation is identical to what was reached by [24] about the effectiveness of melatonin in inducing hypnotic effect and its concentration in blood plasma and the mechanism of this hypnotic effect of melatonin is through its association with MT1 receptors and via cAMP dependent signaling pathway [25].

The mechanism of melatonin in prolonging the duration of anesthesia with the mixture of ketamine

and xylazine may be attributed to its ability to inhibit the N-methyl-D-aspartate (NMDA) receptor is a receptor of glutamate, the primary excitatory neurotransmitter in the brain [26] and thus it will enhance the mechanism of action of ketamine, which acts by way of an anesthetic through its inhibitory effect on the same receptor (NMDA) [27], which it led to distinct prolongation in the duration of anesthesia.

The results of our current study represented in the significant prolongation of the duration of anesthesia (ketamine and xylazine) in the group pre\_treated with melatonin confirm what the scientific references indicated about the ability of melatonin to cross the central nervous system and collects in high concentrations in hippocampal cells [28-29]. The rats were treated with melatonin 45 minutes prior to the formalin injection into plantar surfaces of the rat's paw, this time (45 minutes) was chosen based on the results of the first experiment which the group injected with the mixture of ketamine and xylazine, after 45 minutes of giving melatonin, showed a significant prolongation of the anesthesia period compared to other groups.

The formalin induced paw licking test used in our current study revealed that melatonin has analgesic effects against the pain induced in the first phase (0-5) minutes) of the test resulting from direct stimulation of nociceptors [17,18] represented by a clear reduction in number of rats' attempts to lick their paws in the group treated with melatonin (20 mg/kg, orally) 45 minutes before formalin injection from  $(29.0 \pm 8.86)$  times in control group to  $(11.0 \pm 5.53)$  as this decrease was accompanied by a clear

delay in the onset of paw licking from (35.00 ± 14.11) seconds in the control group to (220.20 ± 52.28) seconds. The mechanisms of melatonin-induced analgesia against formalin-induced pain may be attributed to its association with inhibitory G proteins melatonin receptor, inhibitory G proteins - coupled opioid 1-receptors, and  $\gamma$ -aminobutyric acid (GABA) type -B receptors [30-32].

With regard to the pain that occurred in the 2<sup>nd</sup> phase of formalin test (10-45) minutes, resulting from inflammatory mechanisms and central sensitization at the spinal cord level [19,21], the melatonin-treated group (20 mg/kg, orally) 45 minutes before formalin injection a clear reduction was recorded in the number of rats' attempts to lick their paws from (647 ± 79.134) times in the control group to (185.20 ± 53.177) times and this result confirms that melatonin has anti-inflammatory effects and thus will benefit surgeons use melatonin as a pre-anesthetic substance to avoid postoperative disorder (POD) resulting from the release of pro-inflammatory factors during surgery [10-13].

The anti-inflammatory effects of melatonin, which was detected by the formalin test in our current study, may be attributed to having melatonin several anti-inflammatory mechanisms, including preventing its production of adhesion molecules important for the process of adhesion of leukocytes to endothelial cells and thus will leukocyte migration and edema decrease, or by preventing molecular damage in all organs, by helping to remove toxic free radicals. With regard to the anti-inflammatory effects of melatonin, it may be related to preventing transmission of factor nuclear factor  $\kappa$ B (NF- $\kappa$ B) to the nucleus and its binding to (DNA), which results in down regulation of pre-inflammatory cytokine factors [27-29]. On the other hand, melatonin's ability to regulate NO, cyclooxygenase-2, and NLRP3 inflammasome gene expression may be responsible for its anti-inflammatory effects [33,34,21].

Based on the results of our current study, melatonin was able to inhibit pain in the first and second phases of the formalin test, while [21] indicated that diclofenac only inhibited the pain caused in the second phase of the formalin test, and with this result, melatonin was superior to diclofenac. what confirms the importance of using melatonin as a pre-anesthetic substance is the results of scientific research [20,21], about melatonin having the following positive effects like a neuroprotective and anti-apoptotic agent, thus, melatonin will reduce the side effects of anesthetic drugs, so that the recovery

from anesthesia will be smoothly and ensures the success of surgery.

### **Conclusion**

We conclude from our current study the possibility of using melatonin as a pre-anesthetic agent due to the prolongation of the anesthesia period induced by the combination of ketamine and xylazine, in addition to its analgesic and anti-inflammatory effects, which were detected using the formalin induced paw licking test.

### **Acknowledgement**

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### **Conflicts of Interest:**

The authors declare there is no conflict of interest.

### **Funding statement**

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## استخدام الميلاتونين كمادة ما قبل التخدير

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فرع الفلسفة والكيمياء الحياتية والادوية - كلية الطب البيطري - جامعة الموصل - الموصل - العراق.

**الخلفية العلمية :** يحتاج الجراحون إلى إطالة مدة التخدير والتسكين، بالإضافة إلى منع إطلاق العوامل المسببة للالتهابات تحسبا لحدوث اضطرابات ما بعد الجراحة. **الهدف :** لتحقيق أهداف الجراحين المذكورة أعلاه، تم اختيار الميلاتونين كمادة ما قبل التخدير.

**طرائق العمل :** لاختبار قابلية الميلاتونين في إطالة مدة التخدير قسمت 24 من الجرذان البالغة إلى (أ) (السيطرة)، (ب، ج، د). عوملت المجموعة (أ) بالماء المقطر (5 مل/كغم، عن طريق الفم)، في حين عوملت المجموعات (ب، ج، د) بالميلاتونين (20 ملغم/كغم، عن طريق الفم) وبعد مرور (45,30,15,0) دقيقة تم حقن جميع المجموعات بمزيج (الكيثامين و الزيلازين). تم استخدام اختبار لعق القدم المستحدث بالفورمالين للكشف عن التأثيرات المسكنة والمضادة للالتهابات للميلاتونين، وتم حقن الحيوانات في المجموعتين (أ و ب) (خمسة / مجموعة) بالفورمالين في سطح اخمص مخلب الجرذان وبعد مرور 45 دقيقة من المعاملة إما بالماء المقطر (أ) أو الميلاتونين (ب). **النتائج:** أظهرت المجموعة (د) إطالة معنوية في مدة التخدير مقارنة بالمجموعات الأخرى (أ، ب، ج). من ناحية أخرى، أظهر اختبار لعق القدم المستحدث بالفورمالين أن الميلاتونين له تأثيرات مسكنة ومضادة للالتهابات تتمثل في التأخير المعنوي في بداية لعق الجرذان لمخالبها مصحوبًا بانخفاض معنوي في عدد محاولات لعق الجرذان لمخالبها، سواء في المرحلة الأولى (التسكين) أو المرحلة الثانية (مضادات الالتهاب) مقارنة بالمجموعة السيطرة. **الاستنتاج:** نستنتج من دراستنا الحالية إمكانية استخدام الميلاتونين كمادة ما قبل التخدير.

**الكلمات المفتاحية:** الميلاتونين، مواد ما قبل التخدير، تسكين، مضاد للالتهاب، فورمالين.