



# The Effect of Pre-emptive Oral Melatonin versus Placebo on Post-operative Analgesia in Infants after Thoracotomy for Closed Cardiac Surgeries: A Randomized Controlled Study

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## Abstract

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**BACKGROUND:** Thoracotomy pain is one of the severest types of pain that should be managed properly, especially in children. Opioids are the most widely prescribed analgesics for post-operative pain, but they can have a number of undesirable side effects. Melatonin could be employed as an adjuvant analgesic therapy during procedural discomfort as it had no known major side effects.

**STUDY DESIGN:** This was a double-blinded, controlled randomized study.

**METHODS:** Fifty patients divided randomly into two equal groups. One hour before surgery, children in M group (n = 25) were given 0.5 mg/kg orally of melatonin 3 mg tablets) and patients in Group P (n = 25) received a placebo (5 ml of water by syringe 5 ml) orally. Post-operative pethidine consumption over the 1<sup>st</sup> 24 h (mg) was recorded, the intraoperative fentanyl consumption (HR and ABP) at baseline, 1 min after induction, at skin incision, and every 30 min till the end of the surgery were recorded. Neonatal Infant Pain Score (NIPS) at 4 h, 6 h, 8 h, 12 h, 18 h, and 24 h postoperatively was recorded. Other reported data include demographic data, extubation time, days of ICU stay, and complications.

**RESULTS:** Total post-operative pethidine consumption (mg) over 24 h was significantly lower in M group than P group (3.48 ± 2.23 vs. 7.68 ± 4.52 p = 0.01). Intraoperative fentanyl consumption (ug) was significantly lower in M group than P group (10.28 ± 4.98 vs. 17.08 ± 7.39 p < 0.001). As regards NIPS, it was statistically lower in M group than P group in all times except at 8 h and 24 h with significant difference.

**CONCLUSION:** Oral melatonin is an effective and safe pre-emptive drug as it reduces the total post-operative pethidine consumption over the first 24 h and decreased post-operative pain scores without any unpleasant effects in pediatrics undergoing closed heart surgery.

## Introduction

One of the most severe types of pain is thoracotomy incision, and it should be treated as such, especially in children [1]. Inadequate post-operative pain treatment can jeopardize respiratory function, cause surgical extubation to be delayed, raise costs, and cause hospital discharge to be delayed [2].

Opioids are the most widely prescribed analgesics for post-operative pain, but they can have a number of unfavorable side effects, such as nausea, vomiting, itching, and respiratory depression [3].

Melatonin is an indoleamine produced naturally by the pineal gland. It has a variety of physiological roles, including circadian rhythm regulation, season change modulation, antioxidant, oncostatic, anti-inflammatory, and anticonvulsant properties [4]. Melatonin's analgesic action can be attributed to Gi-coupled melatonin receptors, Gi-coupled opioid-I-receptors, or

GABA receptors, resulting in a decrease in anxiety and pain [5]. Gitto *et al.* [6] theorized that melatonin may be effective as an analgesic in premature neonates who are undergoing unpleasant procedures such as endotracheal intubation and mechanical ventilation with no adverse effects found.

Melatonin could be employed as an adjuvant analgesic therapy during procedural discomfort, as the usual sedatives and analgesics group had higher pro-inflammatory and anti-inflammatory cytokines linked with pain than the melatonin-treated neonates [6]. As a result, melatonin may be a valuable perioperative medication because it has no known major side effects [7], [8], [9].

The aims were to investigate the effects of premedication with oral melatonin on NIPS scores, post-operative pethidine consumption, extubation time, and post-operative ICU stay.

Primary outcome was post-operative total pethidine consumption over 24 hours.

## Patients and Methods

The taken approval was granted by our Institutional Ethical Committee Cairo University, (N-101-2021) and clinical trial registration approval no. NCT05141344 (clinical trials.gov), a randomized, double-blinded study, patients ASA I, II, III, less than 18 months, and acyanotic and cyanotic patients were scheduled for thoracotomy undergoing closed heart surgery at Cairo University Hospital's pediatric cardiac surgery theater. Patients with airway abnormalities, heart failure, endocrine disorders, renal or hepatic diseases, any coagulation disorders, neuromuscular diseases, a history of fever, infection at the blockage site, also Patients having hypersensitivity to any drug, beta blockers, any analgesics received within 24h of surgery or any psychotropic drugs were removed from the trial. Patients having hypersensitivity to any drug, beta-blockers, any analgesics received within 24 h of surgery or any psychotropic drugs were removed from the trial. Fifty patients were enrolled to research groups based on a computer-generated random list, and they were sealed in consequently numbered opaque envelopes. To achieve the double-blinded design, the tablets were administered by a physician who was not one of the researchers. The anesthetist met the guardians, took informed consent, confirming fasting hours 2 h for clear fluids and 6 hrs for solid, examined the children undergoing surgery, and checked routine investigations.

Pre-medication was given to all patients. One hour before surgery, children in M group (n=25) were given 0.5 mg/kg orally of melatonin (NATROL melatonin 3 mg tablets manufactured by NATROL LLC Chatsworth, CA91311, USA, contain Vitamin B6 10 mg to support the body natural product of melatonin and calcium carbonate 63 mg), (the tablet was divided according to the dose needed, it was dissolved in 5 ml of water, to be given by syringe 5 ml) and patients in group P (n =25) received a placebo (5ml of water by syringe 5 ml), orally too in the pre-operative room.

The patients were taken to the OR and placed on a warming mattress, pulse oximetry, electrocardiography (ECG), and non-invasive blood pressure were attached, and the baseline heart rate (HR) and blood pressure (BP) were reported.

Induction was done by 3 percent sevoflurane, then peripheral cannula was inserted and fentanyl 2-3 µg/kg and atracurium 0.5mg/kg were given to facilitate intubation and pressure control ventilation was adjusted to keep end tidal CO<sub>2</sub> between 30 and 35 mmHg. The maintenance was done by sevoflurane 0.3–1.5% in 1:1 ratio, an oxygen-air mixture and atracurium infusion (0.5 mg/kg/hr) to maintain muscle relaxation. On the non-dependent side, a large line was inserted in external jugular vein, and on the dependent side, an arterial line was put. Following induction, the HR and

invasive arterial blood pressure (ABP) were reported. A temperature probe (nasopharyngeal) was put, as well as a urinary Foley catheter to assess urine output.

Intercostal block was done to all patients under aseptic conditions by tilting the patients on their left side (lateral position) and 0.5 mg/kg bupivacaine 0.25% diluted with isotonic saline (total volume 15 ml, 5 ml in each level), at T4 to T6 was injected.

Intraoperatively, intravenous nitroglycerine was given if the systolic pressure was greater than 85 mmHg in infants or above 95 mmHg in children. As well if the HR more than the baseline values by 20%, an additional dose of fentanyl (1–2 µg/kg) was given intravenously for analgesia.

After completion of the surgery and proper hemostasis, the closure was done in layers after ensuring expansion of the collapsed lung. Then, all anesthetics were stopped and morphine 0.1 mg/kg IV was administered at closure. Then, the patient was taken to the pediatric intensive care unit.

The severity of pain was measured by the Neonatal Infant Pain Score (NIPS) by a nurse who was unaware to the study [10], [11], and IV pethidine (0.5 mg/kg) was given as rescue analgesia to keep the NIPS less than 4.

Our primary goal was post-operative pethidine consumption over the first 24 hours and the secondary outcomes were NIPS post-operative, the intraoperative opioid consumption (HR and ABP) at baseline, 1 min after induction, at skin incision, and every 30 min till the surgery was completed. Other reported data include demographic data, extubation time, days of ICU stay, and complications (vomiting, diarrhea, irritability, seizures, and blood pressure changes).

### Sample size

Sample size calculation was calculated using MedCalc® Version 14.10.2 (MedCalc software bvba). In a pilot study on five infants undergoing cardiothoracic surgery with thoracotomy incision, the mean 24 hour post-operative pethidine consumption in the usual care group was 0.12±0.03 mg/kg. A total number of 44 cases achieve 80% power to detect a 20% reduction in pethidine consumption at a 0.05 significance level. Assuming 15% dropouts, the number of the envelopes will be increased to 50 envelopes (25 in each group).

### Power analysis

The Statistical Package for the Social Sciences (SPSS) version 26 was used to code and enter the data (IBM Corp., Armonk, NY, USA). For normally distributed quantitative data, mean and standard deviation were

used; for non-normally distributed quantitative variables, median and interquartile range were used; and for categorical variables, frequencies (number of cases) and relative frequencies (percentages) were used. For regularly distributed quantitative variables, the unpaired t-test was employed, whereas for non-normally distributed quantitative variables, the non-parametric Mann–Whitney U-test was utilized. The Chi-square (2) test was used to compare categorical data. When the anticipated frequency is < 5, the exact test was utilized instead. The Kaplan–Meier method was used to plot survival curves, and the log-rank test was used to compare them.  $p < 0.05$  was considered significant.

### Results

A total of 50 patients who were scheduled for thoracotomy undergoing closed heart surgery in the pediatric cardiothoracic surgery theater of Abu El-Reesh Hospital were enrolled in the study. These patients were randomly allocated into two equal groups using the closed envelope method.

There were no statistically significant differences in the demographic data of the patients (Table 1).

Intraoperative heart rates, systolic blood pressure, and diastolic blood pressure were comparable between the two groups (Figures 1-3).

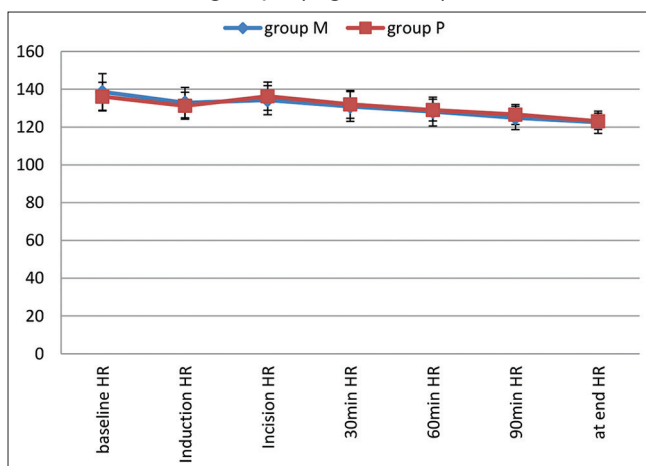


Figure 1: Intraoperative heart rates

As regards intraoperative fentanyl consumption, it was statistically lower in M group than P group with statistical significance (Table 2).

There were no statistically significant differences regarding time of extubation and ICU stay (Table 2).

The time to first request of rescue analgesia was statistically significantly longer in M group than P group as shown in the Kaplan–Meier graph (Figure 4).

As regards NIPS, it was statistically lower in M

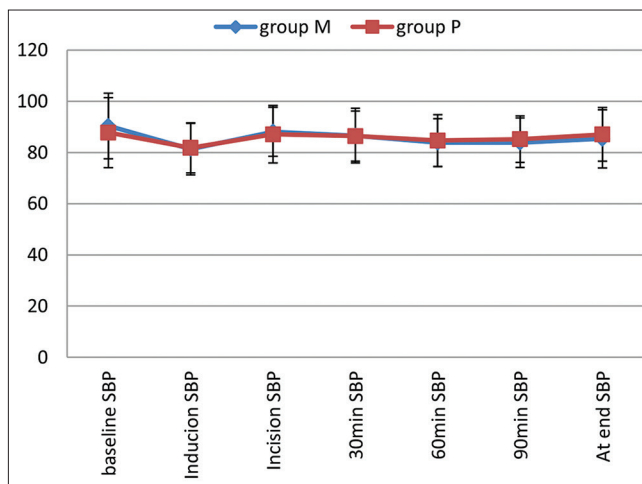


Figure 2: Intraoperative systolic blood pressure

group than P group in all times except at 8 h and 24 h with significant difference (Figure 5).

Total post-operative pethidine consumption was significantly lower in M group than P group with significant difference (Table 3).

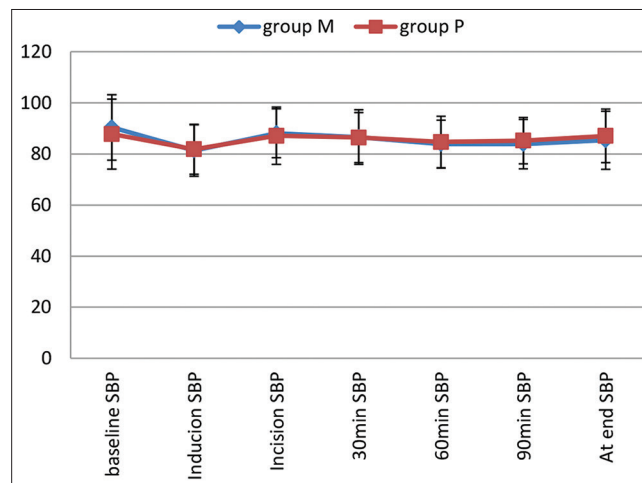


Figure 3: Intraoperative diastolic blood pressure

No any complications were observed in the patients in the both study groups (Figure 6).

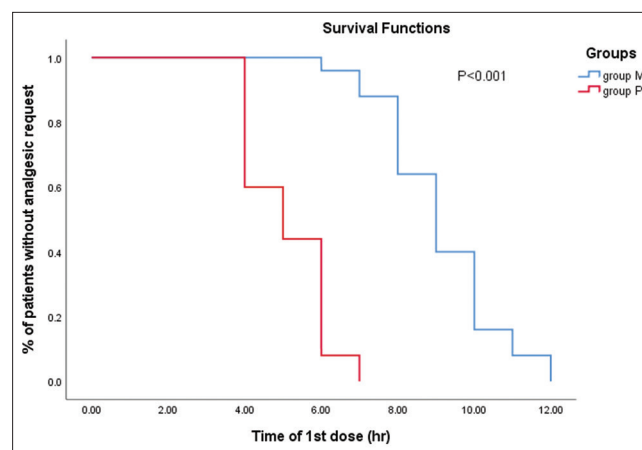


Figure 4: Kaplan–Meier graph

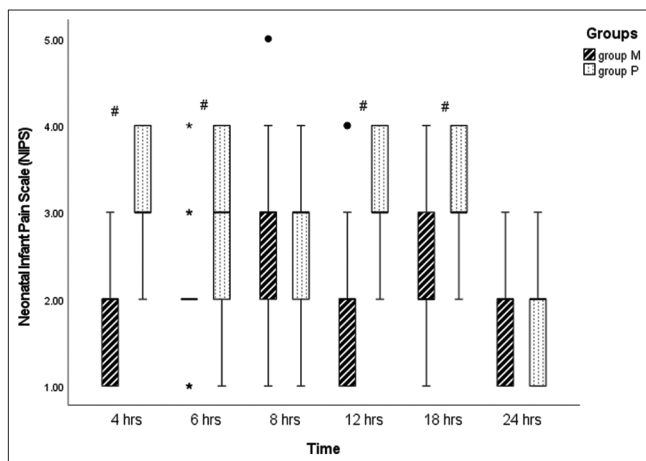


Figure 5: NIPS Data expressed as median and interquartile range(IQR)

Discussion

Every patient, especially children, has a fundamental right to adequate pain control. Pain is more sensitive in neonates than in older infants and adults, and painful operations have both short- and long-term implications. Pain management may also help to improve clinical outcomes by lowering the risk of surgical sequelae such as tachycardia and dysrhythmia, as well as impaired wound healing and atelectasis [1].

Pre-emptive analgesia is achieved by administering opioids, regional blocks, and other analgesic modalities before surgery to reduce the severity and length of post-operative pain [3].

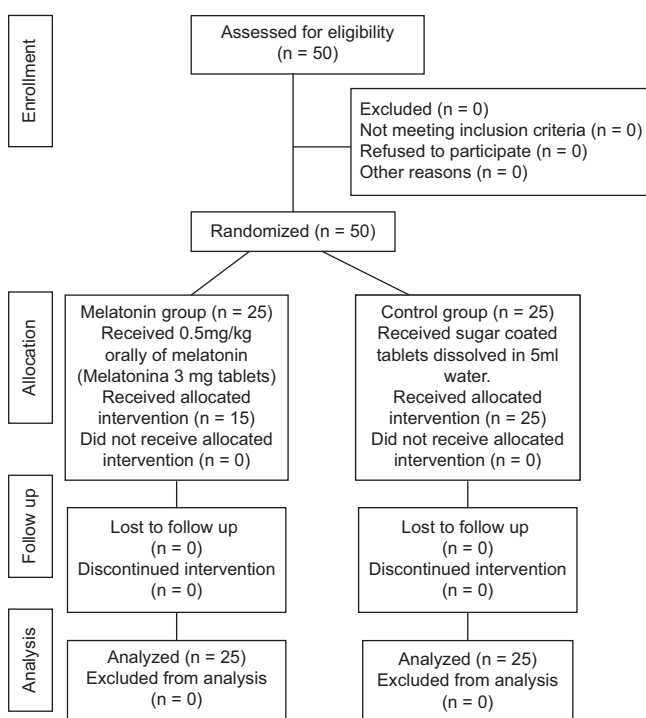


Figure 5: CONSORT Diagram

Table 1: Demographic data and duration of surgery

	Melatonin group (n = 25)		Placebo group (n = 25)	P value
	Mean (SD)	Mean (SD)		
Age (m)	8.44 (4.62)	8.68 (4.61)		0.85
Sex males	12 (48%)	12 (48%)		
Females	13 (52%)	13 (52%)		
Weight (kg)	7.42 (3.16)	7.36 (2.94)		0.94
Duration of surgery (hr)	2.41 (0.33)	2 (0.38)		0.78

For sex, data was represented as count and percentage. For others, Data was expressed as mean and standard deviation. P value < 0.05 is considered significant.

While several research [8], [9], [10] and systematic reviews [7], [11], [12] have proved that melatonin is effective as a pre-medication in adults, its effectiveness in children is less certain. The most widely employed pre-medications. In pediatrics, such as midazolam and alpha2 agonists (clonidine), H1 antihistamines, such as dexmedetomidine [13], are frequently associated with more sedation, a longer recovery time and hospital stay.

Table 2: intraoperative fentanyl consumption, time of extubation and ICU stay

	group M		group P		P value
	Mean	Standard Deviation	Mean	Standard Deviation	
Intraoperative fentanyl consumption (Ug)	10.28	4.98	17.08	7.39	< 0.001
Time of extubation (hr)	2.8	0.71	3.04	0.68	0.69
ICU STAY (Days)	2.96	0.73	3.04	0.73	0.70

Data expressed as mean and SD P value<0.05 is considered significant.

Walking rather than bed transfer to theatre, less post-operative sedation and sleep disturbance, quicker recovery, post-operative analgesia, and prevention of respiratory depression are some of the benefits of melatonin [14], [15]. Furthermore, in contrast to the bitter taste of traditional pre-medications, melatonin can be administered orally, which may be more appealing to children.

The goal of this study was to see how pre-operative melatonin affected post-operative analgesic need in pediatric heart surgery thoracotomy. Melatonin lessened post-operative pain by greatly extending the period of the first rescue request as compared to the placebo group.

The melatonin group had a statistically significant decreased total post-operative pethidine intake throughout the first 24 hours. In most cases, the NIPS was significantly lower in the melatonin group than in the placebo group, except at 8 and 24 hours when the score was less than 4. The total intraoperative fentanyl use in the melatonin group was considerably lower than in the placebo group.

Table 3: total pethidine consumption over 24 hr postoperatively

	group M		group P		P value
	Mean	Standard Deviation	Mean	Standard Deviation	
total pethidine consumption in 24 hrs (mg)	3.48	2.23	7.68	4.52	< 0.01

Data expresses as mean and SD. P VALUE<0.05 is considered significant.

Research done by Palmer et al. [16] found that the use of exogenous melatonin improved the function of the descending pain modulatory system, resulting in a substantial drop in serum brain-derived neurotrophic factor, tropomyosin kinase receptor B and S100B-protein and concluded that the analgesic impact of melatonin

is not related to its effect on sleep quality [17]. Another hypothesis, according to Lee and Curtin [17] and Procaccini *et al.* [18], melatonin's analgesic impact is attributable to its antioxidant and anti-inflammatory properties.

Hemati *et al.* [19], on the other hand, linked melatonin's analgesic function to reversing opioid tolerance.

Kumar *et al.* found that melatonin administration reduced fentanyl usage significantly in the post-operative period following laparoscopic cholecystectomy, which is similar to our findings [20]. Caumo *et al.* also found that after abdominal hysterectomy, total post-operative morphine usage was significantly reduced [10]. Melatonin was also found to have analgesic properties in cataract procedures by Ismail *et al.* [21]. Borazan reported a drop in pain scores and tramadol use after administering melatonin to participants undergoing prostatectomy in his study [22]. Demet Lafl Tunay *et al.* who tested melatonin and Vitamin C versus placebo and observed reduced VAS, morphine intake, and high patient satisfaction scores in Groups M and C compared to Group P, also agree with our findings. Furthermore, the quantity and proportion of patients who needed a diclofenac supplement dose after surgery were considerably lower in the melatonin group compared to the placebo group (10.9 percent and 41.8 percent,  $p = 0.001$ ) [23].

On the other hand, several studies did not show any opioid-sparing impact or decrease in pain scores. In a study done by Naguib and Samarkandi, patients were given 5 mg melatonin orally 100 minutes before laparoscopic gynecologic surgery, and melatonin had no effect on post-operative pain scores at 15, 30, 60, or 90 minutes, or on post-operative analgesia for a 90 min [24]. Acil *et al.* found that a 5 mg melatonin given orally before laparoscopic surgery had no effect on pain levels in patients group of melatonin [25]. In light of the study, the conflicting results could be due to the smaller sample sizes, short post-operative follow-up duration, and various types of surgery used in the other studies. In this study, there was no statistical difference between the two groups in terms of intraoperative heart rates, systolic blood pressure, or diastolic blood pressure that is consistent with Kumar *et al.* [20] and Yildiz *et al.* who found no significant difference in heart rate following oral melatonin treatment. In addition, mean arterial blood pressure did not altered significantly [26].

Frank *et al.*, on the other hand, found that taking 2.5 mg melatonin 1 h before night for 3 weeks reduced systolic and diastolic blood pressure significantly. This could be due to use of melatonin over a longer period of time can decrease the adrenergic outflow and catecholamine levels by interfering with the peripheral and central autonomic systems, however, this is more common in hypertensive patients [27].

Extubation time and ICU stay were both shorter in the melatonin group than in the placebo group, although there was no statistically significant difference.

This goes in line with Soltani *et al.* observed considerably lower morphine intake and mechanical ventilation time in patients with traumatic intracranial hemorrhage who was given melatonin in the surgical ICU [28].

Some studies have been proved the analgesic effect of Vitamin B complex (B1, B6, and B12) in decreasing acute pain either given alone or in combination with acetaminophen or nonsteroidal anti-inflammatory drugs or gabapentin [29], [30], [31].

In the review of literature, there are no available trials investigating if the combination of Vitamin B6 and melatonin potentiates their analgesic effects or not.

Our study was limited in that only less than 18 months with limited number of patients undergoing closed heart surgery through thoracotomy incision only. We did not monitor the sedation effect of melatonin postoperatively. Furthermore, we have no studies demonstrating if adding Vitamin B6 to melatonin preparation potentiates its analgesic effects or not.

Recommendations: Further large studies are recommended in patients of older ages undergoing open heart surgery through sternotomy and recording the sedation score for 24 h also comparing formulas of melatonin containing Vitamin B6 with another one without Vitamin B6 to prove the benefits of addition of Vitamin B6 in pain or not.

The present study concluded that oral melatonin is an effective and safe pre-emptive drug as it reduced the total post-operative pethidine consumption over the first 24 h and decreased post-operative pain scores without any unpleasant effects in pediatrics undergoing closed heart surgery.

## Conclusion

Oral melatonin 3 mg tablets seems to be effective and safe as pre-emptive medication as it reduced the total post-operative pethidine consumption over the first 24 h and decreased post-operative pain scores without any unpleasant effects in pediatrics undergoing closed heart surgery.

## References

1. Wenk M, Schug SA. Perioperative pain management after thoracotomy. *Curr Opin Anaesthesiol.* 2011;24(1):8-12. <https://doi.org/10.1097/ACO.0b013e3283414175> PMID:21084984
2. Gottschalk A, Cohen SP, Yang S, Ochroch EA. Preventing and treating pain after thoracic surgery. *Anesthesiology.* 2006;104(3):594-600. <https://doi.org/10.1097/00000542-200603000-00027>

- PMid:16508407
3. Dahl JB, Møiniche S. Pre-emptive analgesia. *Br Med Bull.* 2004;71:13-27. <https://doi.org/10.1093/bmb/ldh030>  
PMid:15596866
  4. Gitto E, Marseglia L, Manti S, D'Angelo G, Barberi I, Salpietro C, *et al.* Protective role of melatonin in neonatal diseases. *Oxid Med Cell Longev.* 2013;2013:980374. <https://doi.org/10.1155/2013/980374>  
PMid:24349616
  5. Patel S, Naeem S, Kesingland A, Froestl W, Capogna M, Urban L, *et al.* The effects of GABA(B) agonists and gabapentin on mechanical hyperalgesia in models of neuropathic and inflammatory pain in the rat. *Pain.* 2001;90:217-26. [https://doi.org/10.1016/S0304-3959\(00\)00404-8](https://doi.org/10.1016/S0304-3959(00)00404-8)  
PMid:11207393
  6. Gitto E, Aversa S, Salpietro CD, Barberi I, Arrigo T, Trimarchi, G, *et al.* Pain in neonatal intensive care: Role of melatonin as an analgesic antioxidant. *J Pineal Res.* 2012;52:291-5. <https://doi.org/10.1111/j.1600-079X.2011.00941.x>  
PMid:22141591
  7. Yousaf F, Seet E, Venkatraghavan L, Abrishami A, Chung F. Efficacy and safety of melatonin as an anxiolytic and analgesic in the perioperative period: A qualitative systematic review of randomized trials. *Anesthesiology.* 2010;113(4):968-76. <https://doi.org/10.1097/ALN.0b013e3181e7d626>  
PMid:20823763
  8. Pokharel K, Tripathi M, Gupta PK, Bhattarai B, Khatiwada S, Subedi A. Premedication with oral alprazolam and melatonin combination: A comparison with either alone—a randomized controlled factorial trial. *Biomed Res Int.* 2014;2014:356964. <https://doi.org/10.1155/2014/356964>  
PMid:24527443
  9. Khezri MB, Merate H. The effects of melatonin on anxiety and pain scores of patients, intraocular pressure, and operating conditions during cataract surgery under topical anesthesia. *Indian J Ophthalmol.* 2013;61(7):319-24. <https://doi.org/10.4103/0301-4738.99637>  
PMid:23552356
  10. Caumo W, Torres F, Moreira NL Jr., Auzani JA, Monteiro CA, Londero G, *et al.* The clinical impact of preoperative melatonin on postoperative outcomes in patients undergoing abdominal hysterectomy. *Anesth Analg.* 2007;105(5):1263-71. <https://doi.org/10.1213/01.ane.0000282834.78456.90>  
PMid:17959953
  11. Andersen LP, Werner MU, Rosenberg J, Gögenur I. A systematic review of peri-operative melatonin. *Anaesthesia.* 2014;69(10):1163-71. <https://doi.org/10.1111/anae.12717>  
PMid:24835540
  12. Hansen M, Halladin N, Rosenberg J, Gögenur I, Møller A. Melatonin for pre-and postoperative anxiety in adults (Review). *Cochrane Database Syst Rev.* 2015;2015(4):CD009861. <https://doi.org/10.1002/14651858.CD009861.pub2>  
PMid:25856551
  13. National Institute for Health and Care Excellence. BNF: British National Formulary-NICE. United Kingdom: National Institute for Health and Care Excellence; 2019. Available from: <https://www.bnf.nice.org.uk/treatment-summary/premedication-and-peri-operative-drugs> Html [Last accessed on 2019 Jun 25].
  14. Johnson K, Page A, Williams H, Wassemer E, Whitehouse W. The use of melatonin as an alternative to sedation in uncooperative children undergoing an MRI examination. *Clin Radiol.* 2002;57(6):502-6. <https://doi.org/10.1053/crad.2001.0923>  
PMid:12069468
  15. Impellizzeri P, Vinci E, Gugliandolo MC, Cuzzocrea F, Larcan R, Russo T, *et al.* Premedication with melatonin vs midazolam: Efficacy on anxiety and compliance in paediatric surgical patients. *Eur J Pediatr.* 2017;176(7):947-53. <https://doi.org/10.1007/s00431-017-2933-9>  
PMid:28540436
  16. Palmer AC, Souza A, Santos VS, Cavaleiro JA, Schuh F, Zucatto AE, *et al.* The effects of melatonin on the descending pain inhibitory system and neural plasticity markers in breast cancer patients receiving chemotherapy: Randomized, double-blinded, placebo-controlled trial. *Front Pharmacol.* 2019;10:1382. <https://doi.org/10.3389/fphar.2019.01382>  
PMid:31824318
  17. Lee TY, Curtin JP. The effects of melatonin prophylaxis on sensory recovery and postoperative pain following orthognathic surgery: A triple-blind randomized controlled trial and biochemical analysis. *Int J Oral Maxillofac Surg.* 2020;49(4):446-53. <https://doi.org/10.1016/j.ijom.2019.07.006>  
PMid:31420120
  18. Procaccini DE, Lobner K, Anton B, Kudchadkar SR. Melatonin use in hospitalized children for non-anesthetic indications: A systematic review. *Pharmacotherapy.* 2020;40(7):692-703. <https://doi.org/10.1002/phar.2408>  
PMid:32342515
  19. Hemati K, Pourhanifeh MH, Dehdashtian E, Fatemi I, Mehrzadi S, Reiter RJ, *et al.* Melatonin and morphine: Potential beneficial effects of co-use. *Fundam Clin Pharmacol.* <https://doi.org/10.1111/fcp.12566>  
PMid:32415694
  20. Dubey RK, Srivastava S, Gupta PK. Effect of melatonin premedication on postoperative analgesic requirement in laparoscopic cholecystectomy surgery. *IOSR J Pharma.* 2017;7(8):10-5.
  21. Ismail SA, Mowafi HA. Melatonin provides anxiolysis, enhances analgesia, decreases intraocular pressure, and promotes better operating conditions during cataract surgery under topical anaesthesia. *Anesth Analg.* 2009;108(4):1146-51. <https://doi.org/10.1213/ane.0b013e3181907ebe>  
PMid:19299777
  22. Borazan H, Tuncer S, Yalcin N, Erol A, Otelcioglu S. Effects of preoperative oral melatonin medication on postoperative analgesia, sleep quality, and sedation in patients undergoing elective prostatectomy: A randomized clinical trial. *J Anesth.* 2010;24(2):155-60. <https://doi.org/10.1007/s00540-010-0891-8>  
PMid:20186437
  23. Tunay TL, Ilginel MT, Ünlügenç H, Tunay M, Karacaer F, Biricik E. Comparison of the effects of preoperative melatonin or vitamin C administration postoperative analgesia. *Bosn J Basic Med Sci.* 2020;20(1):117-24. <https://doi.org/10.17305/bjbm.2019.4379>  
PMid:31465720
  24. Naguib M, Samarkandi AH. Premedication with melatonin: A double-blind, placebo-controlled comparison with midazolam. *Br J Anaesth.* 1999;82(6):875-80. <https://doi.org/10.1093/bja/82.6.875>  
PMid:10562782
  25. Acil M, Basgul E, Celiker V, Karagöz AH, Demir B, Aypar U, *et al.* Perioperative effects of melatonin and midazolam premedication on sedation, orientation, anxiety scores and psychomotor performance. *Eur J Anaesthesiol.* 2004;21(7):553-7. <https://doi.org/10.1017/s0265021504007094>  
PMid:15318468
  26. Yildiz M, Sahin B, Sahin A. Acute effects of oral melatonin administration on arterial distensibility, as determined by carotid-femoral pulse wave velocity, in healthy young men. *Exp Clin Cardiol.* 2006;11(4):311-3.  
PMid:18651024

27. Scheer FA, van Montfrans GA, van Someren EJ, Mairuhu G, Buijs RM. Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension. *Hypertension*. 2004;43(2):192-7. <https://doi.org/10.1161/01.HYP.0000113293.15186.3b>  
PMid:14732734
28. Soltani F, Salari A, Javaherforooshzadeh F, Nassajjian N, Kalantari F. The effect of melatonin on reduction in the need for sedative agents and duration of mechanical ventilation in traumatic intracranial hemorrhage patients: A randomized controlled trial. *Eur J Trauma Emerg Surg*. 2020;48(1):545-51. <https://doi.org/10.1007/s00068-020-01449-3>  
PMid:32699918
29. Terán F, Medina R, Reyes-Granados V. Synergistic antinociceptive interaction between acetaminophen or metamizol and B vitamins in the formalin test. *Drug Dev Res*. 2006;66(4):286-94. <https://doi.org/10.1002/ddr.20071>
30. Mibielli MA, Geller M, Cohen JC, Goldberg SG, Cohen MT, Nunes CP, *et al.* Diclofenac plus B vitamins versus diclofenac monotherapy in lumbago: The DOLOR study. *Curr Med Res Opin*. 2009;25(11):2589-99. <https://doi.org/10.3111/13696990903246911>  
PMid:19731994
31. Shabayek IA, Abdel-Hamid SM, Elbanna MM. The comparative preemptive analgesic efficacy of addition of Vitamin B complex to gabapentin versus gabapentin alone in orthopedic surgery under spinal anesthesia. *Egypt J Hosp Med*. 2019;74(1):120-5. <https://doi.org/10.21608/EJHM.2019.22640>