Randomised Controlled Trial

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The impact of oral melatonin on pain and anxiety reduction during venipuncture in pediatric patients: a double-blind randomized clinical trial

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Background: Pain resulting from therapeutic procedures and injections is a prevalent source of stress for children. Immediate side effects of pain in infants include syncope, irritability, sleep disturbances, and nutritional issues. This study aimed to investigate the effects of oral melatonin on alleviating pain and anxiety in pediatric patients undergoing venipuncture.

Methods: This double-blind, randomized controlled trial was conducted in the pediatric emergency ward. Patients were randomly assigned to one of two groups; the intervention group received 0.5 mg/kg of oral melatonin (maximum 5 mg) 30 min before venipuncture, while the placebo group received an equivalent amount of a placebo 30 min before the procedure. Using the Face, Legs, Activity, Cry, Consolability (FLACC) scale, postcanulation fear, pain severity, compliance, and potential side effects were evaluated.

Results: In total, 202 patients (113 male and 89 female) in the intervention and control groups were included in the analysis. The mean pain score during venipuncture was 1.52 ± 3.04 in the intervention group and 2.04 ± 6.57 in the control group ($P < 0.001$). In the intervention group, only 19 (18.8%) patients reported pain during venipuncture, whereas 79 (78.2%) patients in the control group reported pain ($P < 0.001$). Less than half (44.6%) of the patients in the intervention group experienced anxiety during venipuncture, while the majority (94.1%) of the patients in the control group exhibited anxiety ($P < 0.001$). The venipuncture success rate was 60.4% in the intervention group and 51.5% in the control group ($P = 0.257$).

Conclusion: Administering 0.5 mg/kg of oral Melatonin 30 min before venipuncture reduces procedure-related pain and anxiety in pediatric patients and may be associated with higher venipuncture success rates.

Keywords: anxiety, FLACC, melatonin, pain, pediatric patients, venipuncture

Introduction

Pain experienced during therapeutic procedures and injections is one of the most prevalent and distressing experiences for children[1,2]. The fear of painful injections can vary based on various factors, including age, sex, mood, physiological or mental characteristics, and prior experiences[3]. Immediate side effects of pain in infants may include syncope, irritability, sleep disorders, and nutritional problems[4]. Moreover, short-term complications such as delays in wound healing and mental pathologies are expected[5]. In the long term, biochemical and endocrine dysregulations may become evident, including increased blood glucose levels, sweating, and mood and behavioral changes[6,7].

Both inpatient and outpatient pediatric cases are subjected to a wide array of painful procedures, ranging from blood sampling and intravenous catheterization to bone marrow aspiration and biopsy[8]. Intravenous catheterization stands out as one of the most common invasive and painful nursing procedures, with children frequently describing it as one of the most distressing aspects of their illness, hospitalization, or even routine inpatient visits[9]. Parents and guardians often lose trust in the healthcare system and may experience feelings of depression and guilt due to their inability to alleviate their children's suffering when they experience pain[10].

Various strategies have been tested for pain management during venipuncture in pediatric patients, including distraction

HIGHLIGHTS

- Pain resulting from therapeutic procedures and injections is a prevalent source of stress for children.
- Immediate side effects of pain in infants include syncope, irritability, sleep disturbances, and nutritional issues.
- Administering 0.5 mg/kg of oral Melatonin 30 min prior to venipuncture reduces procedure-related pain and anxiety in pediatric patients and may be associated with higher venipuncture success rates.

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techniques like Kaleidoscope and distraction cards, local analgesics, and the Valsalva maneuver[11]. Studies have investigated the local analgesic effects of vapocoolants, needle-free powder lidocaine, amethocaine, and liposomal lidocaine in pediatric venipuncture[12], yielding varied and inconclusive results[13].

Although most physicians are acquainted with the beneficial effects of melatonin in managing jet lag and insomnia, its analgesic and anxiolytic properties, despite being supported by prior experimental studies[14], are less widely known. Research has demonstrated that melatonin can be as effective as Midazolam in reducing anxiety in pediatric patients undergoing surgery, with fewer psychomotor side effects[15]. However, other studies have not confirmed these observations[16].

Melatonin's role in cardiovascular health has garnered attention, with potential therapeutic applications being explored, though the precise mechanisms remain unclear[17]. While melatonin has been found to decrease peripheral resistance, its effects on isolated arteries are not fully consistent across experiments, suggesting that vasodilation cannot be solely attributed to the activation of second messenger cascades associated with melatonin receptors[18]. Elevated serum melatonin levels observed in certain types of hypertension may represent a compensatory mechanism against sympathetic overstimulation[19]. Given melatonin's favorable effects on various aspects of hypertension, including organ protection and minimal side effects, it could play a significant role in managing this prevalent cardiovascular condition[20]. However, caution is warranted in its use, particularly in patients with coronary artery disease (CAD), as its impact on circadian blood pressure profiles suggests a nuanced approach is necessary[21]. Melatonin's potential competition with medications like nifedipine, a calcium channel blocker commonly used to treat hypertension, raises concerns about its interference with antihypertensive therapies[22]. This underscores the importance of monitoring and careful consideration before incorporating melatonin into treatment regimens for hypertensive patients, as it cannot be regarded merely as a dietary supplement due to its potential interactions with other medications[23].

In light of these considerations, our current study seeks to investigate the effects of oral melatonin on reducing pain and anxiety in pediatric patients during venipuncture through a rigorously controlled clinical trial.

Patients and methods

This double-blind, randomized controlled trial was conducted from September 2022 to March 2023 on pediatric patients attending the emergency ward of Taleghani Pediatric Hospital in Golestan, Iran. The trial protocol was registered with the ethics committee of Golestan University of Medical Sciences, Golestan, Iran. The eligibility of all pediatric patients aged 3–6 years was assessed, and they were included if their guardians signed the informed consent form after receiving sufficient explanations regarding the study.

Patients with loss of consciousness, psychological disorders, autism, ADHD, known allergies to melatonin, emergency conditions, or those under treatment with analgesic or anxiolytic medications were excluded. Patients were selected using a simple random sampling method and were randomly allocated to two groups using the block randomization method. The intervention group received 0.5 mg/kg of oral melatonin (maximum 5 mg) 30 min before venipuncture, while the placebo group received an identical physical amount of a placebo 30 min before venipuncture. The company provided the placebo in the same shape and color as the oral melatonin. To accommodate patients who might have difficulty swallowing pills, both melatonin and placebo pills were dissolved in 5 cc of water and prescribed according to the patient's weight. Assessed and recorded post-canulation fear, pain severity, compliance, and possible side effects using the Face, Legs, Activity, Cry, Consolability (FLACC) scale.

Data were analyzed using SPSS software (version 16, SPSS Inc.). Normal distribution of data was assessed using the Kolmogorov–Smirnov (KS) test. The χ^2 test or Fisher's exact test was used to compare categorical variables between the two groups. Numerical variables were compared using the Mann–Whitney test. A P-value of less than 0.05 was considered statistically significant.

Research Registry UIN: 10006.

Written consent was obtained and the study was approved by the institutional review board under the code of ethics (IR.GOUMS.REC.1401.351).

This clinical trial was carried out in Iran at the center of clinical trial registered with a special registration code: IRCT20220812055665N1.

This manuscript adheres to the applicable CONSORT guidelines (Fig. 1)[24].

Results

A total of 101 patients in the intervention group and 101 patients in the placebo group underwent statistical analysis. Table 1 presents the baseline characteristics of the study participants. The mean age of the participants was 3.96 ± 1.13 years, with 113 (55.9%) being male and 89 (44.1%) female. Fever and cough were the most prevalent reasons for hospital attendance in the intervention group (51.5%) and the control group (49.5%). Furthermore, individuals of Fars ethnicity constituted the majority among both the intervention group (45.5%) and the control group (49.5%) patients.

The mean pain score during venipuncture was 1.52 ± 3.04 in the intervention group and 2.04 ± 6.57 in the control group patients ($P < 0.001$). Only 19 (18.8%) patients in the intervention group reported pain during venipuncture, while 79 (78.2%) patients in the control group experienced pain ($P < 0.001$). Less than half (44.6%) of the patients in the intervention group reported anxiety during venipuncture; however, the majority (94.1%) of the patients in the control group experienced anxiety ($P < 0.001$).

Furthermore, the venipuncture success rate was 60.4% in the intervention group and 51.5% in the control group ($P = 0.257$). Children in the intervention group exhibited significantly higher cooperation during venipuncture (60.4%) compared to children in the control group (29.7%, $P < 0.001$). Considering the significant difference in sex distribution between the two groups, a two-way analysis of variance (two-way ANOVA) revealed a significant effect of sex on the pain score in FLACC (Fig. 2, $P = 0.005$, $F = 8.16$). No complications were reported in either the intervention or control group patients.

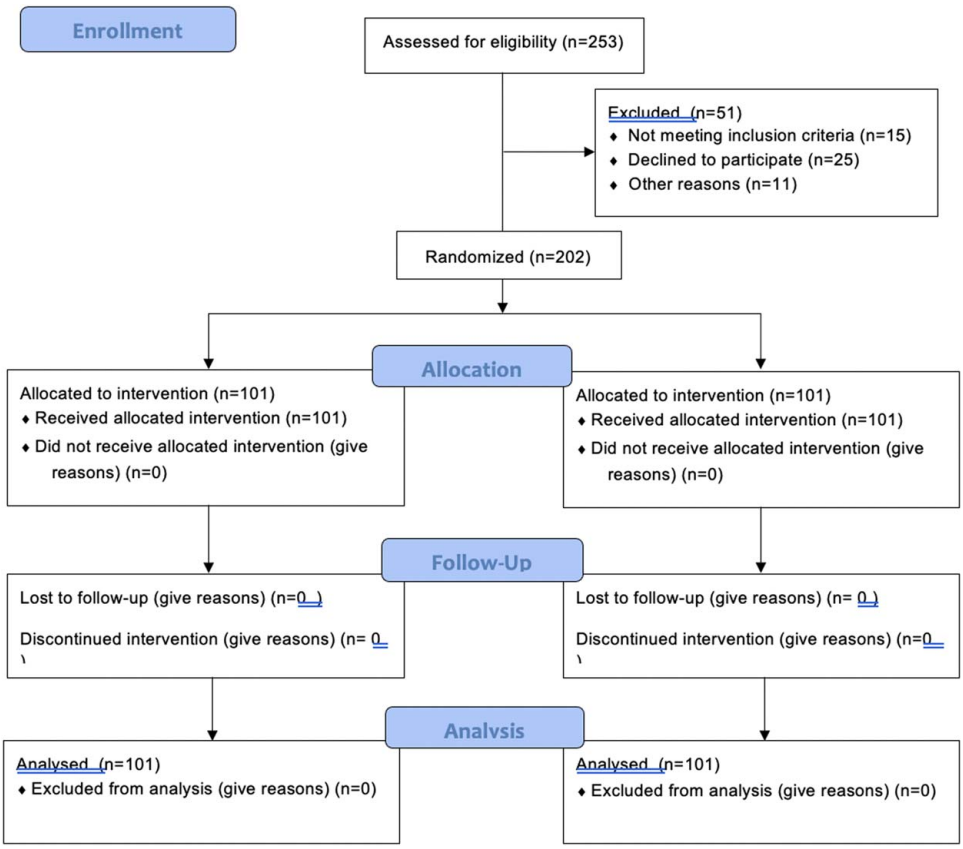

Figure 1. Flowchart and CONSORT criteria.

Discussion

The findings of the current study are expected to contribute significantly to the management of pain and anxiety in pediatric patients undergoing venipuncture, a procedure that is quite common in clinical settings. Furthermore, these findings can potentially enhance pediatric patients' overall hospital experience and increase their compliance with treatment protocols. Moreover, the reduction in anxiety among children is anticipated to have a cascading effect, alleviating parental anxiety, and ultimately leading to higher levels of treatment satisfaction.

Table 1

Baseline characteristics of study individuals

Variable	Intervention ($N=101$)	Control ($N=101$)	*P*
Sex			
Male	49 (48.5%)	64 (63.4%)	0.047
Female	52 (51.5%)	37 (36.6%)	
Ethnicity			
Fars	46 (45.5%)	50 (49.5%)	
Turkmen	27 (26.7%)	27 (26.7%)	0.789
Sistani	28 (27.7%)	24 (23.8%)	
Reason of attendance			
Fever and cough	52 (51.5%)	50 (49.5%)	
Fever and seizure	13 (12.9%)	15 (14.9%)	0.913
Diarrhea	36 (35.6%)	36 (35.6%)	

In the 1980s, Midazolam emerged as the gold standard for managing anxiety in pediatric patients. Presently, oral Midazolam stands out among other benzodiazepines due to its

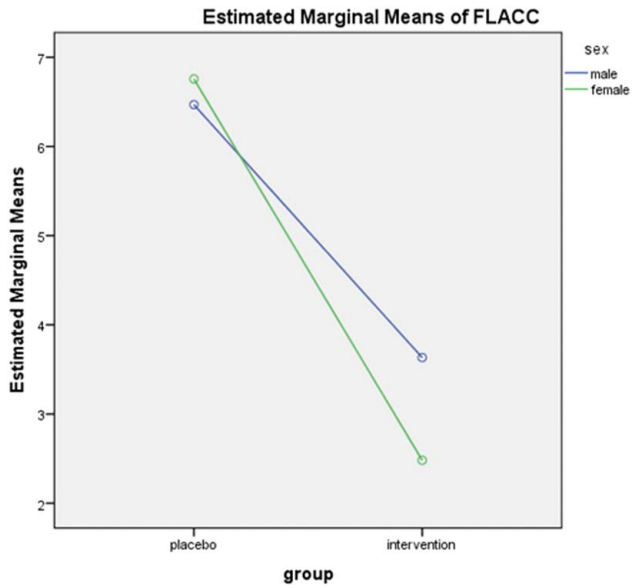

Figure 2. Estimated marginal means of pain in FLACC scale based on group and sex. FLACC, Face, Legs, Activity, Cry, Consolability.

rapid absorption and a lower incidence of induced nausea[25]. However, it is essential to note that Midazolam is associated with potential side effects, including paradoxical reactions, variable bioavailability, excessive sedation, amnesia, and psychomotor disorders[26]. Consequently, in 1999, Naguib proposed melatonin as a viable alternative to Midazolam in preanesthesia scenarios[27].

Samarkandi *et al.*[28] conducted a study demonstrating that doses of 0.25 mg and 0.5 mg of melatonin are equally effective as Midazolam in reducing preoperative anxiety in pediatric patients. Their research also indicated that melatonin is associated with a quicker onset of improvement and a lower incidence of post-treatment excitation. In a similar study, Kurdi and Muthukalai[29] compared the anxiolytic effects of melatonin at two different dosages, 0.5 mg and 0.75 mg, with those of Midazolam. All three patient groups significantly reduced anxiety scores compared to the placebo group. Notably, children receiving melatonin at a dosage of 0.75 mg/kg experienced the most substantial decrease in anxiety and exhibited better tolerance during venipuncture. In a case–control study conducted by Logani and Vaid[30], melatonin demonstrated superior effectiveness in reducing pain and anxiety according to the FLACC scale, aligning with the current study's findings.

Yazdi *et al.*[31] evaluated the effects of oral Melatonin, dexmedetomidine, and Midazolam on sedation levels in children and anxiety related to separation from parents before elective surgeries. Their study concluded that melatonin-induced sedation was present in more than 31% of the patients. Additionally, in a double-blind, randomized controlled trial, assessed the efficacy of melatonin in alleviating pain and anxiety in children undergoing medical procedures. Consistent with the results of the present study, they found that administering 0.5 mg/kg of Melatonin 30 min before the procedure significantly reduced venipuncture-related anxiety and pain in pediatric patients[12,13].

Dexmedetomidine, along with midazolam, emerges as a preferred choice for pediatric sedation and anesthesia induction, exhibiting better ease of parental separation and acceptance without significant side effects, as indicated by recent studies[32]. The combination of intranasal dexmedetomidine and oral midazolam leads to a shorter onset to satisfactory sedation and higher compliance rates during anesthesia inhalation induction compared to either agent alone. Notably, children premedicated with α2-agonists like clonidine or dexmedetomidine show comparable levels of anxiety and sedation postoperatively to those receiving midazolam[33]. However, they experience less perioperative sympathetic stimulation and postoperative pain, suggesting potential advantages in managing pediatric anesthesia[34]. In preschool-aged children, midazolam exhibits superior anxiolysis with less sedation compared to clonidine and dexmedetomidine premedication. Nonetheless, for cases requiring deeper sedation, dexmedetomidine's ease of administration and rapid onset make it a preferable option over clonidine. These findings underscore the nuanced considerations regarding the choice of sedatives and anesthetics, with dexmedetomidine demonstrating particular promise in certain pediatric populations due to its efficacy and ease of use[35].

Both ketamine-propofol (KP) and propofol-ketamine (PK) combinations are effective for pediatric sedation during upper gastrointestinal endoscopy (UGIE), with PK offering more stable hemodynamics and deeper sedation despite increased side effects[27]. In orthopedic reductions, ketamine-propofol (CoKP) shows advantages over ketamine alone, with faster recoveries, less vomiting, and fewer airway complications[36]. Comparisons with ketamine-midazolam (KM) did not reveal significant differences, indicating both are reasonable options for procedural sedation[37]. KP sedation demonstrates lower adverse events compared to ketamine alone. Both protocols are reliable with minimal side effects, and using ketamine for induction with reduced propofol infusion accelerates postanesthetic recovery[38]. In cardiac catheterization, propofol with low-dose ketamine maintains arterial pressure without affecting recovery[39]. These findings emphasize the importance of considering efficacy, safety, and recovery in selecting sedation regimens for pediatric patients[40,41].

It is essential to acknowledge that the present study had some limitations. Firstly, the absence of alternative active treatments for the control group was primarily due to logistical and financial constraints. Furthermore, it was not feasible to evaluate the effects of different Melatonin dosages within the scope of this study.

Conclusion

In conclusion, the findings of the present study suggest that prescribing 0.5 mg/kg of oral melatonin 30 min before venipuncture reduces procedure-related pain and anxiety in pediatric patients, potentially leading to increased venipuncture success rates. Further research is warranted to evaluate the effectiveness of various dosages of oral melatonin within a larger sample size.

Ethical approval

This study is approved by the Ethics Committee of the Vice Chancellor for Research and Technology of the Golestan University of Medical Sciences (IR.GOUMS.REC.1401.351). All patients and control subjects signed the informed consent. This study was performed in accordance with the ethical standards of the Declaration of Helsinki (2013) and its subsequent amendments.

Consent

Patient consent: Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

S.R. and Dr E.A.: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; Z.A.J.: designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript; S.A.H.: coordinated and supervised data collection and critically reviewed the manuscript for important intellectual content.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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