Efficacy of Melatonin in Children With Postconcussive Symptoms: A Randomized Clinical Trial

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abstract

BACKGROUND: Approximately 25% of children with concussion have persistent postconcussive symptoms (PPCS) with resultant significant impacts on quality of life. Melatonin has significant neuroprotective properties, and promising preclinical data suggest its potential to improve outcomes after traumatic brain injury. We hypothesized that treatment with melatonin would result in a greater decrease in PPCS symptoms when compared with a placebo.

METHODS: We conducted a randomized, double-blind trial of 3 or 10 mg of melatonin compared with a placebo (NCT01874847). We included youth (ages 8–18 years) with PPCS at 4 to 6 weeks after mild traumatic brain injury. Those with significant medical or psychiatric histories or a previous concussion within the last 3 months were excluded. The primary outcome was change in the total youth self-reported Post-Concussion Symptom Inventory score measured after 28 days of treatment. Secondary outcomes included change in health-related quality of life, cognition, and sleep.

RESULTS: Ninety-nine children (mean age: 13.8 years; SD = 2.6 years; 58% girls) were randomly assigned. Symptoms improved over time with a median Post-Concussion Symptom Inventory change score of −21 (95% confidence interval [CI]: −16 to −27). There was no significant effect of melatonin when compared with a placebo in the intention-to-treat analysis (3 mg melatonin, −2 [95% CI: −13 to 6]; 10 mg melatonin, 4 [95% CI: −7 to 14]). No significant group differences in secondary outcomes were observed. Side effects were mild and similar to the placebo.

CONCLUSIONS: Children with PPCS had significant impairment in their quality of life. Seventy-eight percent demonstrated significant recovery between 1 and 3 months postinjury. This clinical trial does not support the use of melatonin for the treatment of pediatric PPCS.

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WHAT'S KNOWN ON THIS SUBJECT: Approximately 25% of children have persistent postconcussive problems after a mild traumatic brain injury with significant impairment in their quality of life. Evidence-based approaches for their management are limited. Melatonin is a promising neuroprotective agent that is commonly used in clinical practice.

WHAT THIS STUDY ADDS: The evidence from this randomized trial does not support the use of melatonin for the treatment of persistent postconcussive symptoms at 4 weeks postinjury in typically developing children even in the context of sleep disturbance.

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Persistent postconcussive symptoms (PPCS) are a common and significant problem among children after mild traumatic brain injury (mTBI), yet few evidence-based treatments are available.[1,2] mTBI and concussion account for 90% of all traumatic brain injuries (TBIs), affecting as many as 1 in 10 children and adolescents before 16 years of age.[3,4] Although the majority of children recover quickly, a significant proportion (11% to 30%) have PPCS one month later.[1,5,6] PPCS have a significant and detrimental effect on children's quality of life, participation in school and recreational activities, and family functioning.[7,8]

More evidence-based treatments are needed after mTBI. Early management is directed by sport-related concussion guidelines, which recommend an initial limited period of rest followed by gradual reintegration into school and activities.[9,10] For children with persistent symptoms, the evidence for treatment is more limited.[9,11,12] Small studies suggest that specialized therapies, graded-exercise programs, and multimodal collaborative care may be helpful.[2,13–15] However, these treatments are often expensive and not readily available in most communities.

Melatonin is a promising, well-tolerated, neuroprotective agent in TBI. It has antioxidant and antiinflammatory properties[16,17] and is associated with improved behavioral and pathologic outcomes in animal TBI models.[17] It also has therapeutic potential in relieving symptoms that are common in PPCS[11,18–20] and is often recommended as a part of the management plan.[21] Although it is often considered a nutritional supplement, rigorous evaluation of such nutraceuticals is nevertheless important to ensure best evidence-based practices.[22] Our aim was to determine if treatment with melatonin improves PPCS after mTBI and concussion in youth. We hypothesized that treatment with melatonin (3 or 10 mg) for 28 days would result in a greater decrease in PPCS when compared with a placebo, with the null hypothesis being that melatonin and a placebo are equally effective or ineffective. Furthermore, we investigated whether the effect of melatonin was independent of its effects on sleep.

METHODS

Study Design

We conducted a single-center, randomized, double-blind, placebo-controlled trial at Alberta Children's Hospital. The rationale for the trial, design, and analysis plan have been published previously.[23] This study was approved by the university research ethics board. Enrollment occurred between February 2014 and April 2017. Changes to inclusion criteria (ie, lower age limit decreased from 13 to 8 years and time since last concussion decreased from 12 to 3 months) were made in December 2014 to improve recruitment. The trial was conducted in accordance with the standards of Good Clinical Practice. Potential participants were children seen in the emergency department with a medically diagnosed concussion and/or mTBI who consented to telephone follow-up. Concussion and/or mTBI was defined by using the American Academy of Neurology criteria.[24] Outcome assessments were performed just before treatment commenced, weekly during treatment, at the end of treatment (posttreatment), and again at 4 and 6 months postinjury. Follow-up was completed in October 2017.

Participants

Participants were enrolled by using a 2-step process: first by telephone at 2 to 4 weeks and then in person 2 weeks later. We enrolled children ages 8 to 18 years if they had PPCS and a ≥10-point increase in their total symptom score on the Post-Concussion Symptom Inventory (PCSI) postinjury when compared with their preinjury score (assessed at enrollment).[25] Children were ineligible if they had a significant medical or psychiatric history, a previous concussion within the last 3 months, persistent symptoms after a previous concussion, or a more severe TBI previously. Other exclusions included lactose intolerance, use of neuroactive drugs, and inability to complete questionnaires. All participants and their guardians provided written consent. At the time of enrollment, a standardized interview and medical examination were performed. Figure 1 outlines the trial details. An independent trial monitoring board periodically reviewed safety data. No interim analyses of efficacy were performed.

Randomization and Masking

After enrollment, participants were randomly assigned by using a random-block-size design (block sizes 3, 6, and 9) to 3 parallel treatment groups with a 1:1:1 allocation: placebo, melatonin 3 mg, and melatonin 10 mg. The computer-generated randomization list was created and held by an external statistician. An independent pharmacist created sequentially numbered, identical treatment packages. Melatonin and placebo tablets were identical in appearance and flavor. All investigators, outcome assessors, parents, and children were blinded to treatment groups.

Intervention

The study drug was taken sublingually one hour before sleep time at night for 28 days and was continued even if symptom resolution occurred. No restrictions were placed on the use of other medications. Participants were advised to avoid analgesia overuse, abstain from contact sports, perform light exercise,

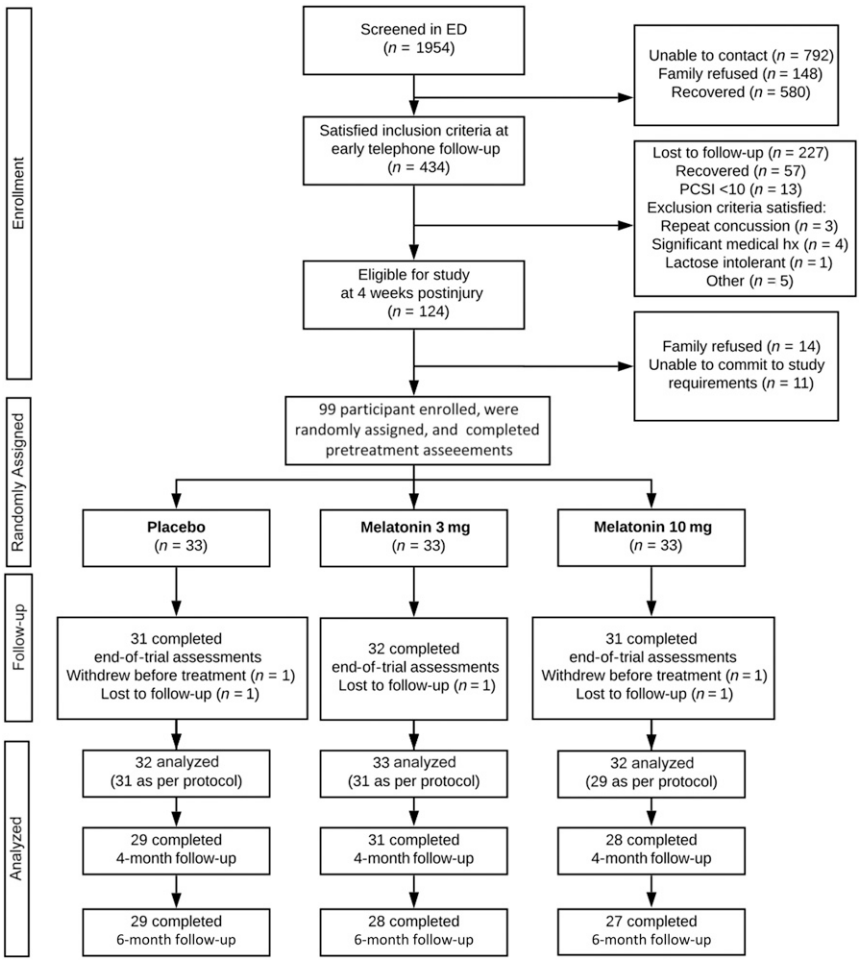

FIGURE 1

Consolidated Standards of Reporting Trials diagram demonstrating the enrollment, interventions, and follow-up of study participants. ED, emergency department; hx, history.

and gradually return to school. Compliance and adverse events were monitored weekly.

Outcomes

The primary outcome was the change in Post-Concussion Symptom Inventory–Youth (PSCI-Y) total score for youth self-report at the end of 28 days of treatment, which was calculated as pretreatment score minus end-of-treatment score. This standardized, 26-item questionnaire provides an overall rating of PPCS (total score range: 0–156). The PCSI-Y has 4 specific domains derived from factor analysis (physical, cognitive, emotional, and fatigue) and a high level of internal consistency and reliability (α = .92).[26,27]

Secondary outcomes were behavioral, cognitive, and sleep problems and functional impairment, which are common complaints among PPCS. The Post-Concussion Symptom Inventory–Parent (PCSI-P), a parent-proxy questionnaire, was completed (total score range: 0–104).[26] Health-related quality of life was assessed by using the Child Health Questionnaire (Parent Form 50 [parent]; child form 87 [child]).[28] Behavioral adjustment and everyday executive functioning were assessed by using the parent-report versions of the Behavior Assessment System for Children, Second Edition and the Behavior Rating Inventory of Executive Function, respectively. Scores for the Behavior Assessment System for Children, Second Edition and the Behavior Rating Inventory of Executive Function are age- and sex-adjusted T-scores (mean = 50; SD = 10). Neurocognitive ability was assessed by using a computerized assessment battery (CNS Vital Signs). The Neurocognition Index was used as a global score of neurocognition. The validity of test performance was assessed by using the Test of Memory Malingering (TOMM).[29] These measures have demonstrated validity in TBI and concussion.[30–33]

Sleep was assessed by using a wrist-worn accelerometer (Actiwatch[2]) on the nondominant wrist for 5 to 7 days before and after treatment.[34] Actigraphy was used to measure sleep-activity patterns, including total sleep time, onset latency, efficiency, and wake after sleep onset (WASO) (amount of time). Epochs were set at 15 seconds.

Overnight urinary 6-sulphatoxymelatonin (aMT6s), the major metabolite of melatonin, was analyzed before treatment, midtreatment, and at the end of treatment by using a solid-phase enzyme-linked immunosorbent assay (Cat#RE54031; IBL International, Hamburg, Germany). Individual levels were converted to a ratio normalized by using urinary creatinine concentration.[35]

Sample Size and Statistical Analysis

Data from a previous epidemiological study[1] were used to calculate a Reliable Change Index.[36] A 10-point change (SD = 14.7) in PCSI score indicated a reliable change for subjects who have PPCS at one month and is similar to previous reports.[37,38] On the basis of medical record review, the relevance of 10-point improvement in PCSI score is a difference of ~30% in overall clinical symptoms. Clinically meaningful examples of this would be a 50% reduction in posttraumatic

TABLE 1 Demographic and Clinical Characteristics of Trial Participants

	Placebo (n = 33)	Melatonin 3 mg (n = 33)	Melatonin 10 mg (n = 33)
Demographic characteristics			
Age, y, mean (SD)	14.37 (2.55)	13.31 (2.53)	13.8 (2.61)
Male sex, *n*	13	14	15
Right-handedness, *n*	28	29	31
BMI (SD)	21.09 (2.93)	21.15 (4.37)	19.76 (5.15)
Family income, Canadian $, median (IQR)	122 409 (111 877–152 941)	112 720 (92 013–150 015)	123 536 (91 170–152 587)
Clinical and educational history			
Previous concussion, *n* (%)	15 (45)	13 (39)	16 (48)
Prolonged recovery (>7 d)	11 (33)	7 (22)	7 (22)
Migraine, *n* (%)	11 (33)	11 (33)	14 (42)
ADHD, *n* (%)	2 (6)	1 (3)	5 (15)
Learning support, *n* (%)	5 (15)	2 (6)	8 (24)
Previously seen by a counselor, *n* (%)	11 (33)	9 (3.6)	9 (3.6)
PCSI-Y total preinjury score, median (95% CI)	6 (4 to 8)	3 (2 to 6)	5 (2 to 10)
Mechanism of injury, *n* (%)			
MVA	4 (12)	1 (3)	2 (6)
Sport	23 (70)	21 (64)	20 (61)
Fall	2 (6)	4 (12)	5 (15)
Witnessed	32 (97)	30 (90)	32 (97)
Acute symptoms, *n* (%)			
Loss of consciousness	7 (22)	9 (27)	5 (15)
Retrograde amnesia	9 (27)	7 (22)	6 (18)
Anterograde amnesia	11 (33)	8 (25)	9 (27)
Confusion or disorientation	23 (70)	24 (73)	21 (64)
Slow to answer questions	12 (36)	15 (45)	36.4
Acute headache	27 (2)	30 (90)	31 (94)
Nausea and/or vomiting	19 (57)	15 (45)	57.6
Double vision	12 (36)	10 (30)	12 (36)
Dizziness	25 (76)	22 (67)	27 (82)
Postconcussive symptoms			
Time postinjury, d, mean (SD)	37.5 (6.7)	38.8 (6.2)	38.0 (5.2)
PCSI-Y postinjury score, median (95% CI)			
Total score	33 (27 to 41)	36 (26 to 47)	36 (27 to 46)
Physical	12 (9.3 to 15.7)	14 (10 to 19)	14 (8.3 to 15.7)
Cognitive	9 (6 to 14)	12 (7 to 14.7)	8 (7 to 12.7)
Emotional	6 (2 to 9)	6 (2 to 7.7)	7 (3 to 8)
Fatigue	5 (3 to 6.7)	4 (3 to 6)	6 (4 to 7.7)
Sleep parameter, median (95% CI)			
Total sleep time, h:min	7:46 (7:10 to 8:15)	7:27 (7:06 to 7:45)	7:58 (7:42 to 8:15)
Onset latency, min	20.46 (14.63 to 29.78)	18.38 (10.96 to 23.31)	16.37 (12.52 to 23.59)
WASO, min	34.4 (25.8 to 43.2)	42.6 (34.9 to 45.2)	42.9 (38.2 to 46.4)
Efficiency, %	82.2 (80.5 to 84.3)	82.6 (81.1 to 85.7)	82.4 (80.4 to 84.9)

ADHD, attention-deficit/hyperactivity disorder; IQR, interquartile range; MVA, motor vehicle accident.

headache burden (ie, daily headaches becoming intermittent and less severe or a 50% decrease in analgesic use), returning to full-time education with modifications, or a significant decrease in fatigue with associated increased participation in activities. The sample size (33 per group) was calculated a priori and powered (80%) to detect a 10-point (SD = 14.7) PCSI-Y score change at a significance level of $\alpha = .05$.[1]

Masked analysis in the differences in the change in PCSI-Y and PCSI-P scores between groups was performed by using the nonparametric Kruskal-Wallis test (KW) because parametric assumptions were not met. Bias-corrected and accelerated bootstrapped 95% confidence intervals (CIs) (1000 samples) for means and medians were computed.[39] All analyses were performed with an intent-to-treat principle. Time to symptom resolution (as defined by a PCSI-Y total score equal to or less than preinjury) was examined using Kaplan-Meier survival curves. Hierarchical regression was used to predict symptom improvement by entering sleep efficiency (step 1) and treatment group (step 2) to determine how predictive treatment was above and beyond any effects of sleep efficiency. A secondary efficacy per-protocol analysis was performed, excluding participants with protocol violations. The per-protocol analysis included only participants who missed no more than 2 consecutive doses or <5 doses in total (n = 92).

TABLE 2 Median Change in Total PCSI Score and Domain Scores After Treatment

PCSI Change	Placebo (n = 32), Median (95% CI)	Melatonin 3 mg (n = 33), Median (95% CI)	Melatonin 10 mg (n = 32), Median (95% CI)	Melatonin 3 mg to Placebo,[a] Median (95% CI)	Melatonin 10 mg to Placebo,[a] Median (95% CI)	$\chi^{KW2,\ 95}$	P
Total PCSI-Y	16 (13 to 35)	16 (12 to 26)	27 (24 to 34)	−2 (−13 to 6)	4 (−7 to 14)	2.024	.36
Physical	8.0 (4 to 12)	8.0 (5 to 10)	10.0 (6 to 13)	0 (−4 to 4)	2 (−3 to 6)		
Cognitive	6.0 (3 to 11)	4.0 (2 to 8)	7.0 (4 to 8)	1 (−5 to 2)	0 (3 to −3)		
Emotional	2.0 (0 to 5)	2.0 (0 to 5)	5.0 (2 to 6)	0 (−3 to 2)	1 (−3 to 3)		
Fatigue	2.0 (1 to 4)	3.00 (2 to 4)	4.0 (2 to 5)	0 (−2 to 2)	1 (−1 to 3)		
Total PCSI-P	12.50 (7 to 16)	15 (10 to 21)	9.5 (4.5 to 19.0)	3 (−3 to 11)	−2 (−10 to 6)	1.692	.43
Physical	5.0 (2 to 9)	6.0 (2 to 8)	6.5 (4 to 8)	1 (−2 to 4)	0 (−2 to 3)		
Cognitive	2.0 (0 to 6)	3.0 (2 to 4)	2.0 (2 to 6)	1 (−3 to 4)	1 (−1 to 2)		
Emotional	2.0 (0 to 4)	1.0 (0 to 3)	2.5 (0 to 4)	0 (−2 to 1)	0 (−1 to 2)		
Fatigue	2.0 (0 to 4)	3.00 (1 to 5)	2.0 (1 to 4)	0 (−1 to 2)	1 (−1 to 2)		

Positive scores indicate improvement.

[a] Hodges-Lehman median difference between treatment group and placebo; positive score indicates improvement with melatonin 3 mg or melatonin 10mg .

Secondary outcomes were analyzed by using repeated-measures analysis of variance or the KW when assumptions were violated (change in sleep parameters) with significance α set to .01 to allow for multiple comparisons. Frequency and severity of side effects were evaluated by using Fisher's exact test. Subsequent sensitivity analyses using quantile regression were performed to examine any effect of outliers, protocol deviations, and compliance on the primary outcome. All assumptions were checked and sufficed. Statistical analyses were performed by using IBM SPSS version 24 (IBM SPSS Statistics, IBM Corporation) and Stata release 14 (Stata Corp, College Station, TX).

Role of Funding Source

The funding sources had no input in the study design, data analysis, interpretation, report generation, or submission for publication.

RESULTS

Ninety-nine participants (mean age = 13.8 years; SD = 2.6; 58% girls) were enrolled and randomly assigned to the placebo,[33] melatonin 3-mg,[33] or melatonin 10-mg[33] groups. Enrollment details are displayed in Fig 1. Two participants withdrew after random assignment without starting treatment, and 3 were lost to follow-up. Ninety-four participants completed assessments immediately after intervention, and 92 completed the trial according to protocol.

Participant demographics, injury details, and clinical characteristics are summarized in Table 1. The majority of injuries (65%) were sport related, and 95% were witnessed. Treatment started at a mean of 38 days (SD = 6) postinjury. The median PCSI-Y total score before treatment was 36 (range: 6–127); Supplemental Table 5 presents details of symptom complaints.

Primary Outcome (PCSI Change)

There was, on average, a decrease in scores in all groups over time, but there was no significant difference between the groups (Table 2). Participants reported an overall mean decrease in PCSI-Y score of 21 points (95% CI: 16 to 27; $P < .001$) after 28 days of treatment. Parents also reported an overall mean decrease in PCSI-P score of 13 points (95% CI: 10 to 16; $P < .001$). Placebo, melatonin 3-mg, and melatonin 10-mg groups showed a similar median change in PCSI-Y scores (16, 16, and 27, respectively; KW = 2.024; P = .36) and PCSI-P scores (12.5, 15, and 9.5, respectively; KW = 1.692; P = .43; Fig 2).

Kaplan-Meier survival curves in Fig 3 illustrate no significant group differences in the probability of symptom survival during treatment or 6-month follow-up. The Cox proportional hazards model showed no significant difference in hazard ratios of symptoms returning to baseline between the placebo and melatonin 3-mg (1.00 [95% CI: 0.49 to 2.06; P = .99]) groups and the melatonin 10-mg group (1.11 [95% CI: 0.54 to 2.29; P = .77]). The proportionality assumption was not violated. Regression revealed no effect of melatonin after any effect of sleep efficiency (pretreatment) was considered (F[1,84] = 0.158; P = .69). Per-protocol analysis did not show any evidence of a favorable effect of melatonin on PCSI-Y change (KW = 2.811; P = .24).

Secondary Outcomes of Sleep, Cognition, and Behavior

Paired sleep actigraphy parameters before and after treatment were available for 66 participants: placebo,[23] melatonin 3 mg,[16] and melatonin 10 mg.[25] Missing data were due to watch unavailability,[16] watch malfunction,[10] and loss of watch.[2] No group differences on actigraphy sleep parameters were apparent after treatment (Table 3).

Cognitive and behavioral outcomes are reported in Table 4. Five participants displayed noncredible effort on the TOMM and were excluded from the analysis of cognitive function. Groups did not differ on changes in cognitive testing,

executive function, or internalizing problems after treatment. Externalizing problems (hyperactivity, conduct, and aggression) were significantly different across groups after treatment (F[2, 84] = 4.928; P = .009). Post hoc paired comparisons demonstrated decreased externalizing problems in the 3-mg melatonin group (P = .008). This had a large effect size (−0.797 [95% CI: −1.327 to −0.266]) compared with the placebo.

Youth and parents in all groups reported improved quality of life at the end of treatment (Supplemental Table 6). Mean parental rating of physical functioning significantly improved from 34.55 to 45.46 (change 95% CI: 8.12 to 13.70; t[86] = 7.77; $P < .001$), and psychosocial functioning increased from 42.07 to 47.50 (change 95% CI: 3.78 to 7.99; t [86] = 5.55; $P < .001$). Changes in quality of life significantly correlated with changes in PCSI-P total scores (Supplemental Fig 4). However, the treatment groups did not differ significantly.

Compliance and Adverse Events

Pretreatment overnight urinary aMT6s levels were not different between groups (mean = 54.59; SD = 33.40; F[2,67] = 0.87; P = .42). Forty-two participants missed at least 1 dose, and 5 participants missed 5 doses or more. Midtreatment urinary aMT6s levels increased in the melatonin groups only: placebo (mean = 36.85; SD = 20.94), melatonin 3 mg (mean = 2595.82; SD = 2891.34), and melatonin 10 mg (mean = 9889.22; SD = 11 372.35; F [2,56] = 9.256; $P < .001$). Sensitivity analyses revealed no effect of compliance or urinary melatonin levels on outcome.

Thirty-two adverse events were reported in 28 participants: placebo (n = 8), melatonin 3 mg (n = 13), and melatonin 10 mg (n = 11). One participant had a serious adverse event (appendicitis) unrelated to the study drug. Eight events involved a known melatonin side effect, and 5 were potentially related (Supplemental Table 7). Ten events were associated with a mild functional impact. The frequency (χ^2 = 1.755; P = .42) and severity (χ^6 = 6.619; P = .36) of adverse events did not differ between groups.

DISCUSSION

In children with PPCS, the administration of melatonin at 4 weeks postinjury for 28 days did not significantly improve postconcussion symptoms compared with a placebo nor was there any effect of melatonin apparent on cognitive or health-related quality of life outcomes. Similarly, most measures of behavior were unchanged. We observed wide CIs in the primary outcome measure, however, suggesting that the sample size was insufficient to definitively conclude an absence of effect. Interestingly, parents reported fewer externalizing problems (mainly decreased hyperactivity) in those participants treated with melatonin, as reported previously in children with neurodevelopmental disability.[40] The mean change of 2.7 T-scores seen in our study, however, is not likely to be clinically significant. Melatonin is often recommended in the management of pediatric PPCS, and both melatonin and a derivative, ramelteon, have been reported to improve sleep complaints in moderate or severe adult TBI.[12,19,21,41–43] Pretreatment sleep actigraphy parameters in our study, however, were not predictive of PPCS improvement with melatonin treatment.

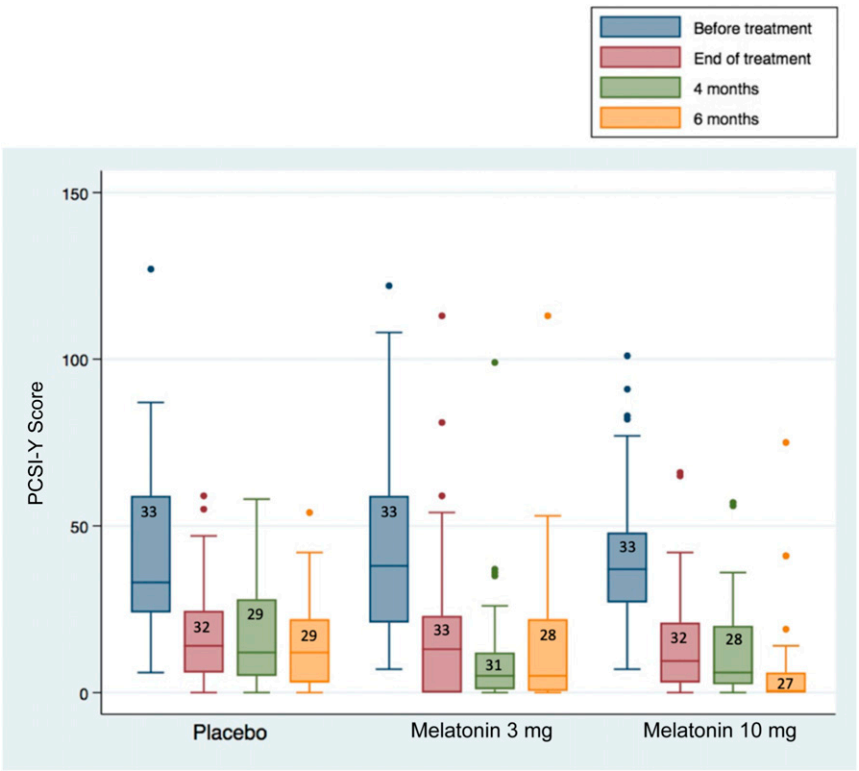

FIGURE 2
Box plots demonstrating the PCSI-Y scores in each group before and immediately after treatment and at 4- and 6-month follow-up time points. There was no effect of melatonin on PCSI-Y change scores immediately after treatment compared with a placebo (χ^2 = 2.024; P = .36).

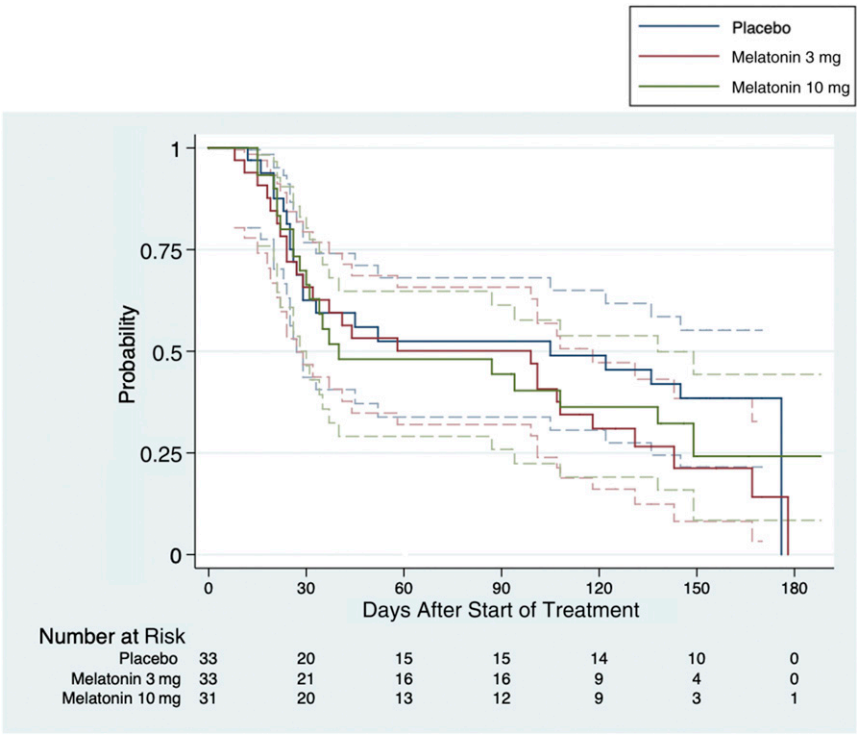

FIGURE 3
Kaplan-Meier curves demonstrating the probability of not returning to preinjury PCSI symptom scores after starting treatment with a placebo, melatonin 3 mg, and melatonin 10 mg for 4 weeks. The dotted lines represent 95% CIs.

This study has several strengths. Although many studies have examined recovery from concussion, few have systematically examined treatments for PPCS. Previous trials have been small, examined a variety of therapies,[2,13–15] and compared interventions to routine care or no treatment and so are susceptible to attribution bias.[44] This is the first randomized placebo-controlled trial of a pharmacologic intervention. It is also one of the largest studies evaluating treatment in children with PPCS. The results are generalizable to typically developing children with mTBI from a variety of etiologies, including sport-related concussion. Children were enrolled and carefully phenotyped at a similar and tight time frame postinjury. As well as recording postconcussive symptoms, we also examined other traditional neurocognitive and behavioral outcomes that may be more robust than symptom ratings and allow for comparisons between treatment groups and other populations.

This trial provides useful information about PPCS in children. Participants at enrollment had a high symptom burden and significant impairments in their quality of life. Despite this, neurocognitive, executive, and behavioral function remained well within normal ranges. Participants performed well on symptom validity testing, and only 5% failed to demonstrate credible effort on the TOMM, suggesting that aberrant psychological responses to injury, if present, were not likely to have affected neuropsychological performance.[45,46]

A high proportion of participants displayed significant clinical improvement during the intervention period. This could be due to the natural history of PPCS, comprehensive standardized care, or a placebo effect. Given our previous experience in studies involving similar populations, this preponderance for improvement is unlikely to be due to natural history alone[1,47] but could be artificially inflated by the exclusion of children with a significant psychiatric history.[48] More likely, however, the potential treatment effect is due to the supportive multidisciplinary care model employed in the brain injury clinic and is congruent with outcomes in a collaborative care model for the management of PPCS.[49] Although neither of these factors should affect the results of this trial, the placebo effect could lead to an underestimation of the effect of melatonin.[50,51]

Melatonin doses were chosen to stay within common clinical practice parameters to minimize risks to participants and achieve supraphysiological levels sufficient to target both receptor-mediated and subcellular processes.[52] We

TABLE 3 Changes in Sleep Actigraphy Parameters Before and After Treatment (Posttreatment Minus Pretreatment) by Treatment Group

Change in Sleep Parameter	Placebo (n = 23), Median (95% CI)	Melatonin 3 mg (n = 16), Median (95% CI)	Melatonin 10 mg (n = 25), Median (95% CI)	$\chi^{KW(2)}$	P
Total sleep time, min	−17 (−33.2 to 2.7)	−10 (−40.6 to 5.5)	−8.5 (−29.6 to 22.4)	1.113	.57
Sleep onset latency, min	1.0 (−3.5 to 9.2)	8.4 (−3.9 to 12.2)	1.9 (−7.7 to 12.0)	1.192	.55
WASO, min	1.9 (−1.9 to 10.7)	−0.4 (−3.2 to 3.8)	−0.4 (−3.3 to 0.8)	3.565	.17
Sleep efficiency, %	−0.1 (−3.2 to 2.1)	−4.1 (−10.3 to 1.9)	−3.1 (−6.7 to 4.6)	0.070	.97

TABLE 4 Cognitive and Behavioral Function Before and in the Week After Treatment in Trial Participants

	Pretreatment, Mean (SD)			Posttreatment, Mean (SD)			Change After Treatment, Mean (SD)			F(2, 84)	*P*
	Placebo	Melatonin 3 mg	Melatonin 10 mg	Placebo	Melatonin 3 mg	Melatonin 10 mg	Placebo	Melatonin 3 mg	Melatonin 10 mg		
CNS Vital Signs											
Neurocognitive Index	98.73	93.64	98.04	102.13	99.32	102.14	3.4	5.6	4.11	0.563	.57
	(11.13)	(14.77)	(11.77)	(9.68)	(11.30)	(11.09)	(8.43)	(8.52)	(8.02)		
Composite memory	95.37	93.21	98.45	92.47	93.36	94.86	−2.9	.1	−3.6	—	—
	(15.75)	(24.30)	(17.75)	(16.81)	(20.75)	(20.81)	(16.53)	(16.67)	(18.89)		
Verbal memory	94.84	92.04	98.66	96.06	97.36	94.0	1.2	5.3	−4.7	—	—
	(16.09)	(22.25)	(18.52)	(19.65)	(20.76)	(21.75)	(21.26)	(20.83)	(23.61)		
Visual memory	97.0	96.75	96.75	92.6	92.57	97.41	−4.4	−4.2	−1.6	—	—
	(14.46)	(20.13)	(20.13)	(13.75)	(20.19)	(17.93)	(14.25)	(16.31)	(19.02)		
Psychomotor speed	101.74	95.68	99.9	106.58	102.96	104.24	4.8	6.8	4.3	—	—
	(17.32)	(17.07)	(14.22)	(13.56)	(15.35)	(13.64)	(11.63)	(11.98)	(7.74)		
Reaction time	97.06	95.93	97.55	97.06	97.39	103.34	0.0	1.2	5.9	—	—
	(14.929)	(15.64)	(14.87)	(15.64)	(15.48)	(16.91)	(13.09)	(13.50)	(13.80)		
Complex attention	96.97	88.18	92.32	103.55	97.61	100.43	6.5	9.4	8.1	—	—
	(14.19)	(23.99)	(22.12)	(15.05)	(18.01)	(14.53)	(16.12)	(14.16)	(16.62)		
Cognitive flexibility	103.03	94.79	102.43	110.61	104.89	108.07	−0.1	0.0	−0.1	—	—
	(13.37)	(17.03)	(15.53)	(11.40)	(14.10)	(14.29)	(0.25)	(0.19)	(0.31)		
Processing speed	112.55	110.04	107.11	119.19	117.07	113.43	6.6	6.5	6.1	—	—
	(12.87)	(20.12)	(17.83)	(15.83)	(19.87)	(17.37)	(9.82)	(14.33)	(13.2)		
Executive function	104.13	97.54	104.25	104.13	97.54	104.25	6.9	5.9	6.4	—	—
	(13.08)	(14.79)	(14.63)	(13.08)	(14.79)	(14.63)	(9.26)	(22.46)	(8.51)		
Behavior Assessment System for Children, Second Edition, Parent Report											
Behavioral Symptoms Index	50.93	50.73	48.35	50.93	47.35	48.42	0.0	−3.4	0.1	3.396	.04
	(8.47)	(7.72)	(8.89)	(8.26)	(6.91)	(9.95)	(4.18)	(6.26)	(6.02)		
Internalizing behaviors	55.48	55.73	53.35	54.14	51.81	51.04	−1.3	−3.9	2.3	0.959	.39
	(11.66)	(9.22)	(8.11)	(11.75)	(9.67)	(9.46)	(7.33)	(7.78)	(5.43)		
Externalizing behaviors	47.66	48.85	47.42	48.52	46.15	46.81	0.9	−2.9	−0.4	4.928	.01[a]
	(6.90)	(7.87)	(9.23)	(7.46)	(7.67)	(9.73)	(4.10)	(5.35)	(4.65)		
Behavior Rating Inventory of Executive Function, Parent Report											
Global executive composite	53.03	52.23	50.31	52.17	48.81	50.23	−0.9	−4.1	−0.2	1.003	.37
	(9.23)	(10.12)	(8.92)	(11.26)	(9.76)	(11.35)	(6.93)	(6.84)	(4.78)		
Metacognition	53.79	52.04	51.38	53.14	49.23	51.35	−0.7	−3.3	0.1	2.768	.07
	(8.76)	(9.70)	(8.12)	(1.12)	(9.61)	(11.0)	(6.51)	(6.05)	(4.91)		
Behavioral regulation	51.76	52.12	48.5	50.83	48.54	48.62	−0.9	−4.3	0.4	0.771	.47
	(10.62)	(10.31)	(10.89)	(11.17)	(9.07)	(11.15)	(7.62)	(7.63)	(4.76)		

Computerized cognition was assessed by using CNS Vital Signs, which provides an overall summary score of cognitive function: the Neurocognitive Index. Parents completed the assessments of behavioral adjustment and executive function. No significant differences between groups were seen in cognitive assessments and executive function before and after treatment. —, not applicable.

[a] Group differences in change in externalizing behaviors were observed, and post hoc pairwise comparisons (Sidak) demonstrated decreased externalizing behaviors in children treated with 3 mg of melatonin (F[2,84] = 4.928; *P* =·01). Positive F values indicate more favorable behavioral change.

achieved this goal, observing excellent tolerability and treatment compliance while demonstrating supraphysiological overnight urinary melatonin levels. The observed melatonin levels and our sensitivity analyses, adjusting for compliance, suggested that treatment failure was unlikely to be due to insufficient melatonin dosing at night.

The lack of an observable effect of melatonin in our study was somewhat surprising, but several possibilities could explain this outcome. Posttraumatic oxidative stress peaks between 3 and 5 days postinjury, although its temporal course and role in chronic mTBI have not been fully elucidated.[53,54] Melatonin may need to be used within the first few days of injury, when oxidative stress is at its highest, to capitalize on its antioxidant properties and reduce the biological consequences of mTBI.[55,56] The excellent tolerability and side-effect profile of melatonin seen in this study provides reassurance that it could be administered early at low risk to the patient. Conversely, the antiinflammatory effects of

melatonin may be more evident with longer treatment durations if persistent neuroinflammation is playing a role in PPCS.[1,5] Future studies are needed to evaluate these hypotheses.

This study has some limitations. The sample size for this study was determined on the basis of 80% power, resulting in the 20% chance that our study was underpowered. The wide CIs found for our primary outcomes indicate that our sample size was too small. Therefore, the results of this study must be interpreted with caution and need to be replicated in a larger sample. Obtaining retrospective reports of preinjury symptoms at enrollment could have introduced a "good-old-days" bias[57,58] that may result in recovery rates being underestimated; however, this should not have affected any response to the intervention. To minimize bias due to attrition, we used an intention-to-treat analysis, imputing missing data using the last observation carried forward approach. Although this technique could introduce bias into the analysis, because the primary outcome data were missing in only 3 participants (1 per treatment group), it is unlikely to have affected our results. A specific pediatric sleep questionnaire would have improved the characterization of sleep disturbances.

CONCLUSIONS

The administration of melatonin at 4 weeks postinjury did not significantly improve postconcussion symptoms in children with PPCS compared with a placebo. Seventy-eight percent of children with PPCS demonstrated significant recovery between 1 and 3 months postinjury. The evidence from this randomized controlled trial does not support the use of melatonin for the treatment of PPCS during this time period postinjury.

ABBREVIATIONS

aMT6s: urinary 6-sulphatoxymelatonin
CI: confidence interval
KW: Kruskal-Wallis test
mTBI: mild traumatic brain injury
PCSI: Post-Concussion Symptom Inventory
PCSI-P: Post-Concussion Symptom Inventory–Parent
PCSI-Y: Post-Concussion Symptom Inventory–Youth
PPCS: persistent postconcussive symptoms
TBI: traumatic brain injury
TOMM: Test of Memory Malingering
WASO: wake after sleep onset

Deidentified participant data (including a data dictionary), the protocol, and the statistical analysis plan that underlie the reported results (text, tables, figures, and appendices) will be available on publication for 5 years. The data (including the clinical data report) will be available to any researchers with a methodologically sound proposal and relevant ethical approvals through the University of Queensland eSpace. Proposals should be directed to k.barlow@uq.edu.au; to gain access, data requestors will need to sign a data access agreement.

Drs Barlow and Dewey were involved in all parts of the study, including study design, obtaining funding, data collection, analysis, and writing of manuscript; Drs Brooks, Kirton, Zemek, MacMaster, Nettel-Aguirre, Yeates, Kirk, Esser, Hill, and Buchhalter, Ms Crawford, and Ms Cameron were involved in the study design, trial operation, analysis, and preparation of the manuscript; Ms Turley and Dr Samuel were involved in data acquisition, data cleaning, and manuscript preparation; Drs Richer, Platt, Boyd, and Hutchison were involved in trial supervision and manuscript preparation; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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