The Effect of Earplugs and Eye Masks Usage in the Intensive Care Unit on Sleep Quality: Systematic Review

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Abstract

Introduction: Patients in the intensive care unit (ICU) have severe and complex disease characteristics and their sleep problems should not be ignored. Poor-quality sleep is associated with impaired immune function and associated susceptibility to disease and infection, decreased energy levels, delirium, delays in recovery. This study is conducted to examine the results of studies examining sleep quality using earplugs and eye masks in the ICU. Methods: PubMed, Science Direct, Google Scholar, and Medline databases were scanned using “Earplugs, Eye masks, Sleep quality, Intensive care units” as keywords. For the search strategy, a query in a patient-intervention-compare-result (PICO) format was used. P: Patients in intensive care; I: Earplugs and eye mask; C: Noise, Light, and Sleep Quality; O: Using earplugs and eye masks improves sleep quality. Results: We included the 17 most eligible studies meeting defined inclusion/exclusion criteria involving 1,372 participants. Randomized controlled trial was used mostly as study design. The interventions within the scope of the studies were earplugs, eye masks, relaxing music, and quiet time protocol. Richard Campbell Sleep Questionnaire and Verran and Snyder Halpern Sleep Scale were the most used scale. Most of the studies reviewed found that the use of non-pharmacological interventions showed a significant improvement in sleep quality. Earplugs and eye masks were found to have potential positive effects on sleep quality and delirium incidence in ICU patients. Conclusion: The use of earplugs and eye masks is a noninvasive, economical, and effective way to improve sleep quality in adult ICU patients.

Introduction

As a special group, patients in the intensive care unit (ICU) have severe and complex disease characteristics and their sleep problems should not be ignored. Poor-quality sleep is associated with impaired immune function and associated susceptibility to disease and infection, decreased energy levels, delirium, delays in recovery, and impaired cognitive, respiratory, cardiac, and endocrine functions. Therefore, quality sleep is important in critical illnesses. It was reported that the prevalence of sleep dis-
orders in critically ill patients is more than 50%, and that sleep disorders in ICU patients are closely related to mortality, infection rate, and complications [1].

Patients with critical illnesses admitted to the ICU are exposed to an interrupted day/night routine, high levels of noise (e.g., staff conversations and alarms) and light levels throughout the night, invasive and painful procedures, harmful odors, numerous physical restraints (monitor tips, catheters and oxygen masks, or mechanical ventilation) and disease-related stress [2]. Studies reported that patients applying to the ICU regularly experience low sleep quality and duration, with frequent awakenings and loss of circadian rhythm [1, 3]. In the literature, it is reported that the mean ICU noise level is 53–65 dB, and it rises above 80 dB in a 24-h period. The World Health Organization states that the optimum standard noise levels in the ICU during the day and night should be 35 and 30 dB, respectively, and that higher noise levels can cause adverse effects such as sleep disturbances, low arterial O₂ saturation, hypertension, delayed recovery, and increased risk of rehospitalization in patients [4].

Another important environmental factor that causes sleep disturbance in the ICU is exposure to light. The regular light and dark cycles used to regulate the body’s biological clock play a major role in the sleep and wake cycle. Exposure to light affects the circadian rhythm and inhibits melatonin secretion at night [5]. Melatonin has neuroendocrine functions and plays a role in the regulation of the sleep-wake cycle. The light level used during night patient care and visits in ICUs is 200 lx and this level suppresses melatonin secretion [6].

In the ICU, it is important for the treatment and care team to evaluate the patients’ sleep. Subjective and objective criteria are used to evaluate sleep quality. Polysomnography (PSG) and actigraphy (ACT), which are among the objective techniques, allow the measurement of brain activity. Although PSG is the gold procedure for qualitative and quantitative sleep assessment in ICU, its limitations such as electrodes and recording devices can create potential disturbances in the examination environment.

The biggest advantage of these methods is that both the quantity and the quality of sleep can be evaluated. Especially Richard Campbell Sleep Questionnaire (RCSQ) and Verran and Snyder Halpern Sleep Scale (VSH) are preferred to determine sleep quality and sleep disorders [1, 7, 8].

Studies on melatonin secretion in patients hospitalized in the ICU show that patients experience acute sleep deprivation because of low melatonin secretion at night. Considering all factors affecting sleep quality, there are effective interventions to improve sleep quality, about the fact that noise and inappropriate light are directly related to sleep deprivation and the harmful effects of this deficiency on ICU patients. Light and noise control can control anxiety and improve patients’ sleep. One of the ways to control light and noise is through earplugs and eye masks, which are noninvasive and cost-effective and considered convenient to use. Studies showed that the usage of tools such as earplugs and eye masks positively affect sleep, is low-cost, useful, and that qualified and longer sleep time is obtained [9–11]. We reviewed the published literature systematically on the impact of using earplugs and eye masks on patient sleep quality in ICUs. So, in this systematic review, it was aimed to answer 3 key questions:
1 Which techniques are used to evaluate sleep quality?
2 Are earplugs and eye masks effective on sleep quality?
3 What are the other factors affecting sleep in the ICU?

The aim of this review was to systematically examine the studies investigating the effect of earplugs and eye masks on sleep quality in the ICU.

Materials and Methods

This systematic review was conducted to investigate the results of studies examining sleep quality using earplugs and eye masks in the ICU. For this purpose, PubMed, Science Direct, Google Scholar, and Medline databases were scanned using “Earplugs, Eye masks, Sleep quality, Intensive care units” as keywords. For the search strategy, a query in a patient-intervention-compare-result (PICO) format was used. P: Patients in ICU; I: Earplugs and eye mask; C: Sleep Quality; O: Using earplugs and eye masks improves sleep quality. Original studies published between January 2010 and October 2020 were evaluated.

Inclusion Criteria

Peer-reviewed prospective and retrospective cohort studies, randomized, and nonrandomized controlled trials were evaluated for inclusion. Studies that have been published (in press or online) or have been accepted for publication have been accepted for inclusion.

Exclusion Criteria

Abstracts, study protocols, letters to the editor, non-peer-reviewed publications, non-English studies, case series, case reports, and non-controlled studies were excluded from the study. Studies were reviewed based on systematic review (PRISMA) guidelines. As a result of the screening, 1,708 studies were obtained, and 20 studies in accordance with the inclusion/exclusion criteria were included in the study, 17 studies were examined because the full text of 3 studies could not be reached (Fig. 1).

The information flow was summarized in Figure 1. In total, 1,708 studies were found in the first literature search, which seemed to be potentially relevant to the study subject. Using abstract and title, 1,616 studies were excluded. Of the studies, 40
studies were not suitable for research questions and 32 studies were duplicate studies. So, they were eliminated. Of these, 20 studies were found to be potentially relevant. Full text could not be reached were eliminated in 3 articles. The remaining articles \((n = 17)\) obtained in full text and assessed in depth. Studies included in the review were ranked according to their level of scientific evidence as specified by the Agency of Healthcare Research and Quality [12].

**Study Selection and Data Extraction**

Titles and abstracts of potentially relevant articles were screened independently by two reviewers (E.P. and K.S.), full-text articles were assessed for eligibility by two reviewers (E.P., K.S.), and any discrepancies were resolved by a third reviewer (I.C.).

**Results**

Seventeen research articles were examined in this study. The characteristics of the studies are given in Table 1 under the headings of “author/authors (year), intervention, study design and evidence levels, sample size, evaluation method, results, and conclusion.”

The publication date of the reviewed studies was between 2012 and 2020. The interventions within the scope of the studies were earplugs and eye masks in eight studies; earplugs in three studies; eye masks in three studies; earplugs, eye masks, and relaxing music in two studies; and earplugs, eye masks, and quiet time protocol in one study. Interventions were conducted individually or in combination as three studies (often without intervention vs. control group). The patients included 17–300 patients in tertiary ICUs (general or private). The total number of patients was 1,372.

Studies were conducted in different countries of the world (Iran, China, Thailand, Austria, France, India, Egypt, Australia, Britain, Turkey, Belgium, and the USA). As a study design, it was observed that eight of the studies were randomized controlled, three were quasi-experimental pretest/posttest, two were controlled clinical studies, one was prospective randomized controlled, one was two-group two-stage crossover, one was randomized open label, and one was observational pre/posttest.

**Techniques Used to Evaluate Sleep Quality**

When the characteristics of the evaluation methods of the studies were examined, the scales related to sleep quality were used in subjective evaluations and ACT, PSG were used in objective evaluations and the hormone levels of the patients were evaluated. When the scales used in subjective evaluations were examined, it was seen that RCSQ was followed by three studies and VSH scales in seven studies. The Pittsburg Sleep Quality Index scale was used in two studies, and the questionnaires created by the researchers in two studies. In one study, RCSQ, PSG, and ACT, in one study the questionnaire formed by researchers and Neelon and Champagne Confusion Scale, in one study the Medical Outcome Study Scale (MOSS), Spiegel Scale (SS), and ACT, in one study RCSQ, melatonin, and cortisol levels and in one study, only PSG was used.

An objective assessment of sleep quality measured by PSG was found in two studies and provided important information about the impact of the intervention on sleep quality. Demoule et al. [19] determined that N3 sleep was 21% in the experimental group and 11% in the control group with PSG. Furthermore, the sleep efficiency of the experimental and control groups was determined as 26% and 27%, respectively. Arttawejkul et al. [22] used PSG in their study and determined the sleep efficiency as 65.2 ± 32.85 in the experimental group and 77.10 ± 9.70 in the control group. These 2 experimental studies confirmed the change in sleep quality with noise exposure by PSG measurements.

Le Guen et al. [14] evaluated the effect of earplugs and eye mask using the ACT device in the postanesthesia care unit. No significant difference was found between the ex-
### Table 1. Characteristics of studies on the effect of earplugs and eye masks on sleep quality of patients hospitalized in intensive care units [5, 13–28]

| Queue number | Author                     | Intervention                  | Study design and evidence levels | Sample size | Evaluation method                                      | Results                                                                 | Conclusion                                                                 |
|--------------|----------------------------|-------------------------------|---------------------------------|-------------|--------------------------------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------|
| 1            | Van Rompaey et al. [13]    | Earplugs                      | RCT (I)                         | 67 patients | Subjective assessment                                  | The difference between the experimental and control groups was significant ($p = 0.04$). Patients sleeping with earplugs reported that they slept better than the control group ($p = 0.0042$). According to the delirium scale results, the patients in the experimental group showed less cognitive impairment than the control group. | Earplugs can be a useful tool in preventing confusion or delirium. The beneficial effects appear to occur within 48 h after hospital admission. |
| 2            | Le Guen et al. [14]        | Earplugs + eye mask           | RCT (I)                         | 46 patients | Subjective assessment Spiegel versus MOSS Objective assessment ACT | The experimental group had less sleep interruptions evaluated with the MOSS scale ($4 [1–7]$ vs. $7 [3–10]$, $p < 0.05$). There was no significant difference between the groups in terms of ACT parameters. | Earplugs and eye masks applied in the ICU positively affect sleep quality. Such non-invasive and cheap devices can be generalized in ICUs. |
| 3            | Hu et al. [15]             | Earplugs + eye mask + relaxing music | RCT (I)                       | 45 patients | Objective assessment Melatonin and cortisol levels Subjective assessment RCSQ | There was no significant difference in cortisol levels between the groups (mean/SD 82.5±47.3, $p = 0.65$). It was determined that melatonin levels were significantly lower than the night before cardiac surgery ($7.53$, $p = 0.01$), and there were significant differences between the groups in terms of overall sleep quality ($p < 0.05$). | The usage of non-pharmacological interventions reduces the negative effects of noise and is beneficial for inducing patients to sleep. |
| 4            | Babaii et al. [16]         | Eye mask                      | RCT (I)                         | 60 patients | Subjective assessment PSQI                             | The difference in PSQI scores between the experimental and control groups was found to be statistically significant ($p < 0.05$). | Using an eye mask can significantly improve sleep quality in heart patients. Therefore, nurses are recommended to use eye masks in conjunction with current treatments to improve patients’ sleep quality. |
| 5            | Bajwa et al. [17]          | Earplugs + eye mask           | RCT (I)                         | 100 patients | Subjective assessment VSH                              | A significant difference was found between the experimental and control groups in terms of sleep splitting, sleep delay, sleep quality, and sleep duration (mean/SD 10.5±5.2, 2.1±2.2; $p < 0.000$). | It was determined that earplugs and eye masks significantly increased sleep quality in all 3 subscales (discomfort, effectiveness, and support) in critically ill patients. |
| 6            | Litton et al. [18]         | Earplugs                      | RCT (I)                         | 40 patients | Subjective assessment RCSQ                             | There was no significant difference between the experimental and control groups in terms of deep sleep, falling asleep, number of awakenings, wakefulness rate, and sleep quality (mean/SD 10.5±2.52, 2.1±2.2; $p < 0.000$). | It was determined that earplugs in patients admitted to the intensive care unit positively affected patient comfort in terms of noise reduction and ease of usage. |
| 7            | Demoule et al. [19]        | Earplugs + eye mask           | RCT (I)                         | 64 patients | Objective assessment PSG                                | The difference in sleep rate according to PSG parameters between the experimental and control groups was not significant ($p = 0.09$). Sleep time was higher in the experimental group using earplugs all night compared to the control group ($p = 0.039$), and the difference between the groups was significant in the number of long awakenings ($p = 0.02$). | The effect of earplugs and eye masks on the sleep quality of the patients was not significant between the groups. |
| 8            | Menger et al. [20]         | Earplugs                      | Prospective RCT (I)             | 27 patients | Subjective assessment Original questionnaire            | In the experimental group, it was determined that sleep quality was better (median, IQ: 3–4 [1–5] vs. 4, 3–5 [1–5], $p = 0.047$) despite similar similarity of an algesics. | Earplugs improved patient satisfaction as well as improved sleep quality and relieved pain intensity. It can reduce maintenance costs by providing faster recovery. |
| 9            | Mahran et al. [21]         | Eye mask                      | RCT (I)                         | 70 patients | Subjective assessment RCSQ                             | The difference between the groups in mean sleep depth, sleep delay, number of awakenings, sleep efficiency, and sleep quality scores were statistically significant (mean/SD 48.0±9.99, $p = 0.001$). | Using eye masks at night can help improve sleep quality in patients and reduce perceived pain and analgesic requirements. |
| 10           | Arttawejkul et al. [22]    | Earplugs + eye mask           | RCT (I)                         | 70 patients | Subjective assessment PSQI, RCSQ Objective assessment PSG + ACT | There was no significant difference between the experimental and control groups in terms of PSG and ACT parameters. There was no significant difference in subjective sleep quality between the groups according to the RCSQ score ($p = 0.236$). | Earplugs and eye masks significantly reduced the arousal index in patients admitted to the ICU. |
| Queue number | Author Intervention | Study design and evidence levels | Sample size | Evaluation method | Results | Conclusion |
|--------------|---------------------|---------------------------------|-------------|------------------|---------|------------|
| 11 | Daneshmandi et al. [23] Eye mask | Non-randomized, controlled prospective trial (II) | 60 patients | Subjective assessment PSQI | The difference before and after the intervention in the experimental group was significant (mean/SD 1.03±0.66, p < 0.000) | Using an eye mask significantly improves sleep quality |
| 12 | Yazdannik et al. [5] Earplugs + eye mask | Non-randomized, controlled prospective trial (II) | 50 patients | Subjective assessment VSH | The effect of the intervention on sleep efficiency and sleep disturbance was significant between experimental and control groups (mean/SD: 14.54±11.46, p < 0.001). VSH scores were significant between groups (p < 0.001, ER = 47, F = 22.1) | Although wearing earplugs and eye masks is a cost-effective and safe method and can improve perceived sleep quality in ICU patients, more research is needed to demonstrate the effect of this method |
| 13 | Dave et al. [24] Earplugs + eye mask | Crossover design (II) | 50 patients | Subjective assessment RCSQ | In ICU patients, the mean sleep score was 43.06±7.31 in the first night without intervention, and 68.74±6.54 in the second night with intervention (using earplugs and eye masks). The difference between groups was statistically significant (p < 0.05) | It appears that simple interventions such as earplugs and eye masks can be a valuable contribution for patients trying to sleep in ICUs. It can be used as an acceptable sleep intervention for patients and an alternative to sleeping pills |
| 14 | Jones and Dawson [25] Earplugs + eye mask | Comparative studies (III) | 100 patients | Subjective assessment | No significant difference was found between sleep qualities evaluated before and after the intervention. The patients reported that they slept "below average" in the preintervention period | It was determined that simple interventions such as eye masks and earplugs could be used for patients trying to sleep in the critical care unit |
| 15 | Tabas et al. [26] Earplugs + eye mask + QT protocol | Comparative studies (III) | 135 patients | Subjective assessment VSH | While mean scores of sleep disturbances did not differ significantly in the 3 study groups before the intervention (p = 0.95), there was a significant difference between the groups in terms of sleep disturbance after the intervention (p = 0.001). There was no difference between the mean scores of sleep efficiency in the 3 groups before the intervention (mean/SD 127.95±3.93, p = 0.99), but the eye mask groups differed significantly in sleep efficiency after the intervention (Mean/SD 132.28±4.98, p = 0.02) | Using the QT protocol along with eye masks and earplugs improves sleep quality. Therefore, improving sleep quality with such non-drug methods is less costly and has fewer side effects than pharmacological interventions |
| 16 | Koçak and Arslan [27] Earplugs + eye mask + relaxing music | Comparative studies (III) | 64 patients | Subjective assessment RCSQ | In the experimental group, the posttest RCSQ score was (50.21±16.02) and 68.50±17.57 significantly higher than the pretest RCSQ 55.34±16.62 and 49.03±15.53, respectively, for the control group (p < 0.01). It was observed that all vital signs were similar in the experimental and control groups, except for the average daily pulse rate | Earplugs and eye masks can be applied by nurses to patients in the ICU to reduce sleep deprivation and increase sleep quality |
| 17 | Kamdar et al. [28] Earplugs + eye mask + relaxing music | Comparative studies (III) | 300 patients | Subjective assessment RCSQ | The difference between the groups in RCSQ general sleep quality scores was not significant (p = 0.46) | It was determined that the interventions could be applied as a part of care in the ICU and could reduce noise and increase sleep quality |

RCT, randomized controlled trial; NEECHAM, Neelon and Champagne Confusion Scale; MOSS, Medical Outcome Study Scale; PSQI, Pittsburg Sleep Quality Index; QT, Quiet Time.
performed with the device attached to the nondominant arm of the patient for 12 h (between 20:00 and 8:00) on the first postoperative night. Arttawejkul et al. [22] reported that there was a significant difference between the experimental and control groups evaluated with ACT \( (p < 0.05) \).

Hu et al. [15] analyzed the urine collected at 20:00–08:00 for 2 nights (before and after the intervention) in their randomized controlled study in the surgical ICU. No statistically significant difference was found in the nocturnal secretion levels of melatonin and cortisol in the experimental and control groups.

In seven studies using RCSQ, Dave et al. [24] stated that the difference between groups was significant \( (p < 0.001) \). Kamdar et al. [28] stated that the improvement in subjective sleep quality after interventions was not significant, and Arttawejkul et al. [22] stated that subjective sleep quality was similar between the experimental and control groups according to the RCSQ score \( (p = 0.236) \).

VSH was used in various modifications in 3 studies. Tabas et al. [26], Yazdannik et al. [5], and Bajwa et al. [17] used its 16-item version. The first study confirmed the statistical improvement in subjectively perceived sleep quality in all three subscales (discomfort, efficacy, support) \( (p < 0.05) \). The second study found the difference between efficacy and discomfort subscales of the intervention statistically significant \( (p < 0.001) \), but no significant difference was found in the supplement subscale. The third study confirmed significant improvement in all three subscales (discomfort, efficacy, support) \( (p < 0.001) \).

The Pittsburgh Sleep Quality Index was used in three studies Babaii et al. [16], Daneshmandi et al. [23], and Arttawejkul et al. [22]. The first study determined that the difference was statistically significant \( (p < 0.05) \) in five of the seven areas monitored, while the second study found a significant improvement in sleep quality after the intervention in the total sleep quality score \( (10.46 \pm 4.09/4.86 \pm 1.88, p < 0.001) \). In the third study, it was determined that the intervention did not make a significant difference between experimental and control groups \( (p > 0.05) \). Le Guen et al. [14] determined that the difference was statistically significant after the intervention according to the MOSS and SS evaluations \( (\text{Mean/SD } 20 [4] \pm 15 [5], p = 0.006) \).

Jones and Dawson [25], Van Rompaey et al. [13], and Menger et al. [20] used original questionnaires. Different content-oriented, different numbers of items and, in most cases, subjective assessment was used as a method, but could not be analyzed in detail due to the fact that their characteristics differ from each other and the questionnaires could not be reached completely. In these studies, the effect of interventions on subjective sleep quality was found to be statistically significant.

Three of the studies reviewed evaluated the incidence of delirium. Van Rompaey et al. [13] stated that earplugs are beneficial in reducing the incidence of confusion and early delirium during the night. It was noted that there was a significant improvement in subjective sleep quality during the first night of observation \( (p = 0.042) \). Kamdar et al. [28] stated in their study that the usage of earplugs and eye masks provided a statistically significant decrease in daily delirium formation and delirium incidence \( (p = 0.02) \). Le Guen et al. [14] stated a statistically significant decrease in the incidence of postoperative disorientation in the experimental group \( (\text{Control group } \%0, \text{ experimental group } \%0, p = 0.01) \).

**Discussion**

It is understood that different techniques were used to evaluate sleep quality in the studies reviewed. In two studies, the PSG device alone or in combination with other methods was used as an objective assessment method [19, 22]. These studies had some limitations as they were experimentally planned and conducted. Considering the number and duration of REM phases, the ratio of REM and non-REM phases, REM sleep delay, and arousal number, it was determined that the interventions made had a positive effect on sleep quality. Le Guen et al. [14] used a combination of subjective sleep assessment and objective assessment with ACT in their study in postanesthesia care unit, and the quality and amount of sleep monitored with ACT did not differ in the experimental and control groups, but the patients reported subjective improvement.

In the objective assessment of sleep quality, the benefit and suitability of using ACT in intensive care and preoperative care conditions could not be determined. Postoperative conditions of the patients, somatic conditions such as pain, acute critical illness, drugs that alleviate the central nervous system such as analgesia and sedation may cause confusion during the evaluation phase. The levels of melatonin, cortisol, and their metabolites \( (6\text{-SMT in serum/urine}) \) were examined in the evaluation of the interventions investigated.

Various subjective techniques were used frequently to evaluate sleep quality in the studies reviewed. One of the results of this review is to confirm the significant variabil-
ity in the selection of a subjective assessment tool: two studies used an original questionnaire focusing on subjective sleep quality and scales developed in fourteen studies.

Despite the significant variability of subjective assessment tools, it was agreed that the clinically significant effect of the investigated interventions was positive. The number of nights watched in the studies examined ranges from one to five. In the study conducted by Van Rompaey et al. [13], the positive effect of the intervention was confirmed only on the first day of hospitalization for the purpose of critical analysis of the nights observed, other studies did not confirm or evaluate this phenomenon.

Kamdar et al. [28], Le Guen et al. [14], and Van Rompaey et al. [13] stated that the usage of earplugs and eye masks significantly reduced the incidence of delirium. These results are consistent with the results of the observational study conducted by Patel et al. [29] and the meta-analysis results by Litton et al. [18]. In order to prevent delirium that develops due to sleep disorders, the addition of interventions such as noise and light transmission to existing medical treatment made the treatment protocol multi-component. These interventions were rated as comfortable by the participants in most of the studies reviewed.

When evaluating the effect of interventions, 3 studies also evaluated their effects on sleep/analgesic medication. Le Guen et al. [14] and Menger et al. [20] observed that the analgesic need of the intervention group decreased. Yazdannik et al. [5] found no difference between the groups in their study.

**Conclusion**

According to the results of the studies, it was determined that there are scales, technological devices, and laboratory results that evaluate sleep quality as answers to 3 key questions, the use of earplugs and eye masks affects sleep quality positively, and the drugs used as factors affecting sleep in the ICU and the general condition of the patients. The usage of earplugs and eye masks improved the sleep quality of the patients and increased the amount of REM sleep and melatonin release at night. Sleep is a basic need. Ensuring sleep in adequate quality in the ICU is an important factor affecting the quality of care. In ICUs, the sleep quality of all patients and individual and environmental factors that affect sleep should be evaluated primarily. The usage of non-pharmacological sleep-promoting interventions (earplugs, eye masks) has a positive effect on the sleep quality of patients.

**Statement of Ethics**

An ethics statement is not applicable because this study is based exclusively on published literature.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

Each author contributed equally to the paper. E.P. drafted the study and collected the data. E.P., I.C., and K.S. drafted the manuscript. E.P. suggested the topic, supervised study, and reviewed the manuscript. All authors read and approved the final manuscript.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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