EFFECT OF NURSING PRACTICES ON FEAR OF INSULIN IN DIABETIC PATIENTS: A SYSTEMATIC REVIEW

DİYABETİK HASTALARDA İNSÜLİN KORKUSU ÜZERİNE HEMŞİRELİK UYGULAMALARININ ETKİSİ: SİSTEMATİK BİR DERLEME

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Abstract

Fear of injection is associated with several identified factors. These factors can be attributed to two main concerns: past experiences and a lack of knowledge. This systematic review aims to analyze the effectiveness of interventional practices to break 'psychological resistance to insulin,' defined as the fear of self-injection in diabetic patients undergoing insulin treatment. While searching the literature, the PRISMA-P flowchart was used. The search was limited to studies published in English between 2002 and 2023, from 15 November to 30 May 2024, in the databases "Scopus, PubMed, Science Direct, Web of Science, Medline, EBSCOhost, and Cochrane Library Fourteen studies, including 13 randomized controlled trials and one quasi-experimental study, were included in the review. The effectiveness of injection administration, diabetes education programs, the use of narrower or shorter needles, needle-free injections, stress management strategies such as stress inoculation-based techniques and lavender oil, and training support for individuals with diabetes undergoing insulin treatment has been confirmed. Practical demonstrations are important, especially for patients who require self-management intervention. This review suggests that new programs to maintain the self-efficacy of diabetic patients should be further investigated to improve outcomes and reduce hospitalizations and overall costs. PROSPERO: CRD42024546430

Keywords: Diabetes mellitus, insulin, nursing, systematic review.

Özet

Enjeksiyon korkusu, belirlenen çeşitli faktörlerle ilişkilidir. Bu faktörler iki ana endişeye dayandırılabilir: geçmiş deneyimler ve bilgi eksikliği. Bireylerin enjeksiyon süreci, gereklilikleri ve insülin tedavisinin faydaları hakkında yeterli bilgiye sahip olmamaları, insülin enjeksiyonu yapma konusunda isteksizlik göstermeleriyle ilişkilendirilmiştir. Bu sistematik derleme, insülin tedavisi gören diyabet hastalarında enjeksiyon korkusu olarak tanımlanan ‘'psikolojik insülin direncini" kırmaya yönelik girişimsel uygulamaların etkinliğini analiz etmeyi amaçlamaktadır. Literatür taraması sırasında PRISMA-P akış şeması kullanılmıştır. Tarama, 2002-2023 yılları arasında İngilizce yayınlanmış çalışmalarla sınırlı tutulmuş ve 15 Kasım - 30 Mayıs 2024 tarihleri arasında Scopus, PubMed, Science Direct, Web of Science, Medline, EBSCOhost ve Cochrane Library veri tabanlarından yapılmıştır. Derlemeye 13 randomize kontrollü çalışma ve 1 yarı deneysel çalışma olmak üzere toplam 14 çalışma dahil edilmiştir. Enjeksiyon uygulamaları, diyabet eğitim programları, daha dar veya daha kısa iğnelerin kullanımı, iğnesiz enjeksiyonlar, stres aşılamaya dayalı teknikler ve lavanta yağı gibi stres yönetimi stratejileri ile insülin tedavisi gören diyabetli bireylere yönelik eğitim desteğinin etkinliği doğrulanmıştır. Özellikle kendi kendine yönetim müdahalesine ihtiyaç duyan hastalar için pratik uygulamalar önemlidir. Bu derleme, diyabetli hastaların öz yeterliliğini sürdürmeye yönelik yeni programların daha fazla araştırılması gerektiğini ve bu sayede tedavi sonuçlarının iyileştirilerek hastaneye yatış oranlarının ve genel sağlık maliyetlerinin azaltılabileceğini önermektedir. PROSPERO: CRD42024546430

Anahtar Kelimeler: Diabetes mellitus, insülin, hemşirelik, sistematik derleme.

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1. INTRODUCTION

Injections generally do not pose a problem for healthy individuals but can become challenging for those with diabetes, particularly due to the need for repeated insulin injections. Individuals with needle phobia, especially regarding insulin injections, face significant barriers in managing their health and avoiding complications associated with blood glucose monitoring. Injection phobia often begins in childhood and is usually a result of negative conditioning over time (Sugai et al., 2023).

Fear related to injections is influenced by various factors, primarily stemming from past negative experiences and insufficient knowledge. A lack of understanding about the injection process and the benefits of insulin treatment often leads to reluctance to inject insulin. This lack of knowledge can cause false beliefs about insulin use, such as fears of limited life expectancy, complications, ineffective treatment, or end-stage disease (Davoudi et al., 2020).

Studies have reported that patients delay their treatment throughout the day due to their inability to tolerate the pain associated with insulin injections (Kruger, Larue & Estepa, 2015; Millan, 2015; Sheno & Reja, 2021). Similarly, a recent systematic review by Pérez-Fernández, Fernández-Berrocal & Gutiérrez-Cobo (2023) reveals that individuals experiencing psychological problems such as anxiety, depression, and emotional stress have poorer glycemic control, which is reflected in elevated HbA1c levels. In addition to poor glycemic control, fear of injection has been found to lead to an increased rate of repeated hospitalizations, psychological distress, and micro- and macro- complications related to diabetes (Koonmen et al., 2023). Furthermore, patients with a pronounced fear of injections have been observed to resist daily measurements of blood glucose (Shi et al., 2024). Supporting these findings, a study conducted by Aleali et al. (2018) on diabetic patients receiving insulin therapy highlighted that a significant proportion of patients experienced anxiety about multiple daily injections, leading to treatment reluctance and a higher likelihood of general psychological disorders.

When individuals cannot manage their fear independently, it may intensify, especially during crises. Therefore, strengthening a patient's self-confidence is crucial to alleviating and regulating their fear, particularly through collaboration with diabetes and psychiatric nurses (Holton et al., 2022).

Recommended strategies for managing injection fear include a training approach, where patients are educated about insulin treatment from diagnosis, and psychological techniques such as insulin "trials," where patients can negotiate or pause their treatment with supervised injections. The CPR method (Confrontation, Permanence, and Reality) is also recommended for managing needle phobia (Sugai et al., 2023).

Due to the increasing prevalence of diabetes and injection fear, daily insulin prescriptions are rising. This fear can lead to poor adherence to insulin therapy, resulting in poor glycemic control and heightened diabetes-related complications. Thus, it is essential to investigate intervention strategies to address this fear and improve patient health outcomes. The goal of this study is to review nursing and psychological interventions aimed at managing injection fear in adults with diabetes. By evaluating the most effective intervention strategies, this research will provide a scientific basis for enhancing treatment approaches. The findings will help diabetes and psychiatric nurses, along with healthcare providers, develop optimal strategies to reduce injection fear and improve patients' quality of life.

The literature highlights the challenges and treatment options related to this issue. This study provides clear evidence by demonstrating historical and current nursing interventions for insulin injections. The systematic review aims to identify the most effective strategies for reducing injection fear by comparing existing intervention approaches. The results of this study will be a valuable resource for developing new educational and intervention methods in nursing practice.

2. MATERIALS AND METHODS

This systematic review was prepared based on the recommendations in the “Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 Statement (PRISMA-P) (Hutton, et al., 2015).

2.1. Research Strategy

For this systematic review, we searched studies published between 2002 and 2023 using the keywords ‘Insulin fear', ‘Nursing practices', ‘Diabetes', ‘Injection', ‘Insulin', ‘Needle phobia', and ‘Insulin resistance'. The search strategy combined terms using Boolean operators: ("Insulin fear" OR "Needle phobia") AND ("Nursing practices" OR "Nursing interventions") AND ("Diabetes"). The search was conducted from 15 November 2023 to 30 May 2024. The databases of Scopus, PubMed, Library, Science Direct, Web of Science, Medline, EBSCOhost and Cochrane Library were utilized.

The number of studies found after the review was categorized according to the databases and shown in the PRISMAP flowchart. (Figure.1)

2.2. Inclusion Criteria

The systematic review included randomized control trials, for which the full text was available, that included the research outcomes related to the injection fear in individuals with Type 2 Diabetes Mellitus on insulin treatment. All English-language studies were included.

The studies included in the systematic review were selected based on the PICOS framework recommended by the Joanna Briggs Institute.

P: Studies on individuals who were diagnosed with Type 2 diabetes mellitus, were receiving the insulin treatment and were aged 18 years and over, regardless of gender, race, and socio-economic status.

I: Nursing studies on insulin injection for individuals with type 2 diabetes mellitus were analyzed.

C: Studies comparing the fear of insulin injection of individuals with Type 2 diabetes mellitus and all the interventions for this fear were included in the study.

O: Fear of insulin injection in individuals with type 2 diabetes mellitus and the parameters that include metabolic variables affected by such fear were evaluated.

S: All experimental study designs (experimental and quasi-experimental) without any discrimination.

2.3. Exclusion Criteria

- Low-Quality Studies: If the sources used in the review were of poor quality or had low reliability, the review studies were excluded.
- Observational Studies: Observational studies on fear of insulin injection may make it difficult to determine causal relationships and therefore the reliability of the results may be questionable.
- Cross-sectional Studies: Cross-sectional studies are based on data collected at a specific time and may be insufficient to confirm cause-effect relationships. Therefore, such studies were generally excluded

- Descriptive Studies: Descriptive studies are used to describe or characterize a particular topic, but are inadequate in identifying causal relationships. Therefore, non-invasive and descriptive studies on fear of insulin injections were excluded.
- Observational Analyses: Observational analyses are often based on pre-recorded data and may therefore be insufficient to confirm causal relationships. Studies in which such analyses were done were excluded.

2.4. Assessment of the Risk of Bias

The studies included in the review were assessed for risk of bias using the Cochrane Risk of Bias Assessment Tool. The risk of bias was evaluated independently by two reviewers. In cases of disagreement, a third reviewer was consulted to reach a consensus. The Cochrane Risk of Bias Criteria are as follows:

■ Type of randomization (selection bias).

■ Concealing randomization information (selection bias).

■ Blinding participants and staff (performance bias).

■ Blinding in outcome assessment (detection bias).

■ Incomplete outcome data (attrition bias).

■ Selective reporting (reporting bias).

■ Other biases

"Other biases" were considered to include potential sources of bias not categorized above, such as conflicts of interest, funding bias, baseline imbalances between intervention and control groups, early termination of studies, deviations from study protocols, or issues arising from small sample sizes.

In the included studies, the risk of bias was assessed at three levels: low, unclear and high (Table 2). Five of the 14 researches included in the present study were assessed as unclear isk of bias, while nine were classified as having high risk. The research limitationsin associted with studies assessed as high risk were documented accordingly. This review included one non-randomized study (Atalla, 2016). Due to the methodological differences, it was assessed separately using the Joanna Briggs Institute (JBI) checklist. The detailed evaluation is presented in Appendix A.

Appendix A. Quality Assessment of the Non-Randomized Study (JBI Checklist)

Assessment Questions	Study Name Atalla, 2016
Is it clear in the study what is the "cause" and what is the "effect"? (i.e., there is no confusion)	?
Were the participants included in any comparisons similar?	+
Was the exposure measured in a valid and reliable way?	+
Were confounding factors identified?	+
Were strategies to deal with confounding factors stated?	+
Were the outcomes measured in a valid and reliable way?	?
Was appropriate statistical analysis used?	+
Was follow-up complete, and if not, were differences between groups in terms of their follow-up described?	+
Were outcomes measured in a way that allowed for comparisons across groups?	+

** low risk: + ; unclear risk: ?; high risk: -*

3. FINDINGS

A total of 976 studies were reached after searching the keywords were reached over "EBSCOhost/CINAHL Complete, PubMed, Scopus, Science Direct, Web of Science and Cochrane Library". After removing duplicate studies, any studies with inappropriate titles and abstracts were excluded from the review. The remaining 62 studies were re-evaluated for inclusion and exclusion criteria. Based on these evaluations, 14 studies that met the inclusion criteria were included in the review (Figure.1). Thirteen (92.86 %) of the studies were randomized controlled trials and 1 (7.14%) was quasi-experimental. The findings of a detailed review of 14 studies included in the systematic review (Table1: Summary of Included Studies) were evaluated under four headings: characteristics of the studies (purpose, country, average age, sample size), duration of follow-up, research method, interventions on subjects, and results obtained.

3.1. Characteristics of the Studies

All the randomized controlled and quasi-experimental studies included in the systematic review included patients who were admitted to the outpatient clinic to break the psychological resistance to insulin of individuals with diabetes mellitus. Of the studies included, four (28.57%) were conducted

in China; two (14.29%) in the USA; two (14.29%) in Italy (including one conducted in Rome); and one (7.14%) each in Germany, Taiwan, Japan, Egypt, Türkiye, and the Turkish Republic of Northern Cyprus (Atalla, 2016; Bağrıaçık & Bayraktar, 2022; Choomai, Wattanapisit & Tiangtam, 2021; De Berardis, Scardapane & Lucisano, 2018; Demirag, Hintistan & Bulut, 2022; Hermanns et al., 2017; Iwanaga & Kamoi, 2009; Ji et al., 2019; Ji et al., 2020; Li, Ge & He 2023; Skovlund, Lyness & Nicklasson, 2002; Stockl et al., 2007; Valentini et al., 2015; Xing et al., 2019). When the sample size of the study was analyzed, this calculation excluded only one study as it was conducted on a single- group sample. The findings reported that the experimental groups included a mean of 73.42 people and the control groups included a mean of 73.6 people. The mean age of the individuals who participated in the studies ranged from 18 to 87. However, when averaged by the researchers, it was calculated as 53.89.

Table 2. Risk of bias assessment in randomized controlled trials

	Skovlund, Lyness & Nicklasson, Stockl K. et al., 2007	**Iwanaga & Kamoi, 2009**	**Valentini M. et al., 2015**	**Hermanns D. et al., 2017**	**De Berardis, Scardapane & Ji L. et al., 2019**	**Xing Y. et al., 2019**	**Ji L. et al., 2020**	**Choomai et al., 2021**	**Bagriacik & Bayraktar L., Demirag H. et al., 2022**	**Xuefang Li et al., 2023**
Type of randomization (selection bias)	+	+	+	+	+	+	+	+	+	+
Concealing randomization information (selection bias)	+	?	?	+	+	+	+	+	+	+
Blinding participants and staff (performance bias)	?	+	?	-	-	+	-	-	-	-
Blinding in outcome assessment (detection bias)	?	+	-	+	?	+	?	+	+	?
Incomplete outcome data (attrition bias)	?	?	-	+	?	+	+	+	+	-
Selective reporting (reporting bias)	?	+	?	+	?	?	?	?	+	?
Other biases	?	+	?	?	+	?	?	?	+	?

** low risk: + ; unclear risk: ?; high risk: -*

3.2. Follow-up Period

Studies that examined the effect of injection training on the psychological resistance to insulin of individuals with diabetes mellitus were analyzed for follow-up period. Even though the follow-up periods in the studies varied, the minimum follow-up period was found to be two weeks and the maximum follow-up period was 24 months. Three studies (21.43%) had a follow-up period of 2 weeks, three (21.43%) of 8 weeks, three (21.43%) of 12 weeks, two (14.29%) of 16 weeks, two (14.29%) of 24 weeks, and one (7.14%) of 78 weeks or more (Atalla, 2016; Bağrıaçık & Bayraktar,

2022; Choomai et al., 2021; De Berardis et al., 2018; Demirag et al., 2022; Hermanns et al., 2017; Iwanaga & Kamoi, 2009; Ji et al., 2019; Ji et al., 2020; Li et al., 2023; Skovlund et al., 2002; Stockl et al., 2007; Valentini et al., 2015; Xing et al., 2019). It was found that the limitation in the follow-up periods of the studies were determined depending on reasons such as the content of the training and implementation protocols.

3.3. Research Method

All studies included in the study (14 studies, 100%) were conducted individually with face-to-face interview method (Atalla, 2016; Bağrıaçık & Bayraktar, 2022; Choomai et al., 2021; De Berardis et al., 2018; Demirag et al., 2022; Hermanns et al., 2017; Iwanaga & Kamoi, 2009; Ji et al., 2019; Ji et al., 2020; Li et al., 2023; Skovlund et al., 2002; Stockl et al., 2007; Valentini et al., 2015; Xing et al., 2019). Both data collection and all training or practical intervention processes were carried out face- to-face due to the nature of the study.

3.4. Interventions

The interventions of the studies conducted to break psychological resistance to insulin and included in the review varied. These interventions are listed as follows: Training on diabetes management plus insulin administration in four of them (30.77%). (Atalla, 2016; Bağrıaçık & Bayraktar, 2022; Choomai et al., 2021; Li et al., 2023). Comparison of injector caliber in three of them (23.08%) (De Berardis et al., 2018; Iwanaga & Kamoi, 2009; Valentini et al., 2015). Needle-free injector in three of them (23.08%) (only in one of them plus a reduction in insulin dose) (Ji et al., 2019; Ji et al., 2020; Xing et al., 2019). Training on stress vaccination in two of them (7.69%) (Hermanns et al., 2017). Disposable doser in one of them (7.69%) (Stockl et al., 2007). Application of the InnoLet device in one of them (7.69%) (Skovlund et al., 2002). Application of lavender oil to relieve injection stress in one of them (7.69%) (Skovlund et al., 2002).

3.5. Study Findings

The study findings were analyzed thematically based on intervention type. Several studies focused on diabetes management training and additional insulin injections, which showed that experimental groups had more positive attitudes toward insulin treatment, and demonstrated significantly higher treatment acceptance and injection success rates compared to the control groups. As summarized in Table 1, interventions targeting injection technique, psychological support, and device innovations significantly improved patient outcomes.

4. DISCUSSION

Maintaining proper glycemic control is essential in managing diabetes. Lifestyle changes like diet, exercise, and medication are usually recommended, but insulin is often needed when these aren't enough. Despite its effectiveness, many patients struggle with the idea of self-injection, a challenge known as "psychological resistance to insulin." (Sanz-Pastor et al., 2024).

When the follow-up periods of studies aimed at breaking the 'psychological resistance to insulin' of diabetic patients were examined, follow-up or practice periods varied. The follow-up periods of the studies are affected by the type of intervention performed in the practice. The duration is kept short in studies with interventional practices such as syringe injection. On the contrary, longer duration was observed in information-loaded training contents. A short duration may be sufficient in practical studies with course content such as injections, injectors, and/or disposable dose devices, as one-to- one practices are done with individuals. It is thought that indirect practices such as lavender oil for fear of injection are more focused on perception, and the follow-up period is kept longer since it takes time to turn it into behavior. Also, since the glycemic indexes of individuals will be monitored and the efficiency of the training will be controlled through these variables, the minimum follow-up period is kept for 3 months. In the literature, it is seen that the durations are generally between 3 and 6 months in the studies conducted. This is due to the correlation of the follow-up times of metabolic variables with this given time (Chang et al., 2014).

All of the studies included in the research were conducted face-to-face. Due to the nature of the study, it becomes mandatory to conduct face-to-face research. It is important to implement the method face-to-face, and it is considered to have a direct impact on the results. Individual contact makes a more positive impact on patients. The literature recommends alternative computer-assisted technological methods as well as face-to-face training for patient training. However, healthcare professionals argue that computer-aided training can be used as a supplement to face-to-face training, as they argue that computer-aided training prevents communication. This information supports the findings of the study. (Cahn, Akirov & Raz, 2018; Youngwanichsetha, 2021).

When examining the studies included in the review according to the variety of interventions, it was observed that training content was used in four studies. The main goal of such content is to break down negative attitudes toward injection. These studies also reported positive attitudes toward insulin treatment in the experimental groups. It leads interventions such as training to take on the

characteristic of verbal presentation. It is considered to be limited in addressing the participating individuals. Since it includes subjective data such as behavioral changes in patients, it is difficult to achieve the desired effect and causes it to spread over a long period of time. Follow-up periods were found to last more than 3 months, especially in these studies. Although the desired target for insulin injection was achieved in the studies, the outcome on metabolic variables was not the same. There are many studies with training content in the literature. While some studies support findings of the present study, others may yield opposite results. It is considered that differences such as the duration of the training, the number of sessions, the extent or customization of the training content, peer support, and training in one's own language are effective here (Misnikova et al., 2017).

When the results of the studies in which injector practice was done were analyzed, it was observed that needle-free injectors were compared in three studies, and long injectors with small diameters were compared in two studies, hands-on interventions such as the InnoLet device and dosing device were used. The studies aimed to alleviate injection-associated pain in patients in the experimental groups by both shrinking the diameter and length of the needle tip and using needle-free injectors. The intervention groups felt less pain and suffered from fewer side effects (such as leaks, scratches, etc.) at the injection site. The need for dose reduction was observed especially in individuals using high- dose insulin treatment. However, similar findings were reported to be achieved as those in training interventions on metabolic variables. Such interventions belong to practical study groups and are result-oriented. Since these studies aim to achieve results in a shorter time by their nature, they are conducted in short periods such as 2 weeks. Due to the nature of learning itself, it has been divided into visual, verbal and practical. These features vary in their learning rates, and the practical method achieves the highest rate. When individuals learn by practicing, it becomes permanent. Negative attitudes of individuals toward insulin treatment are usually due to negative experiences heard from the environment. Also, the pressure of self-injection compels individuals to delay the treatment. However, it appears that all these negative experiences and feelings toward treatment can be eliminated with practical training. The importance of needle selection is highlighted in the prevention of self-injection fear in individuals with diabetes mellitus. It has been argued that this is a factor in relieving pain and preventing individuals from refusing treatment (McMurtry et al., 2016; Vlachou, Ntikoudi & Owens, 2022).

Fear of insulin in diabetic patients appears to be multifaceted. While some individuals primarily experience a fear of the injection process itself (needle phobia), others express anxiety related to potential metabolic consequences such as hypoglycemia. In some cases, both fears coexist, leading to greater psychological resistance. Therefore, interventions should be designed to address both the mechanical fear of injections and the emotional concerns about insulin's effects on blood glucose control.

The effect of lavender oil on stress management in one study was examined to break psychological resistance to insulin. The study aimed to diminish negative attitudes toward treatment by alleviating stress before injection. The study yielded the desired results. lavender oil is a specialized target interventions. The literature review emphasizes that stress is not a negative emotion, but its dosage matters. Stress contributes to learning, but it has negative consequences when its level rises. In this case, it is recommended to manage stress and lower its level using different methods such as massage, and yoga. (Ghavami, Kazeminia & Rajati, 2022; Wang et al., 2024).

The findings of this study can be interpreted through the lens of the Health Belief Model (HBM), which provides a theoretical basis for understanding individuals' health-related behaviors. According to HBM, individuals' decisions to engage in health-promoting behaviors are influenced by their perceived susceptibility to a health condition, perceived severity of the condition, perceived benefits of the intervention, perceived barriers to taking action, and cues to action. In the context of insulin resistance, psychological barriers such as fear of injection can be conceptualized as perceived barriers, while educational and hands-on training interventions serve as cues to action that help reduce those barriers. The observed improvement in patients' attitudes following such interventions reflects an increased perception of benefit and a reduction in perceived threat or harm. Applying this model facilitates a deeper understanding of why certain interventions are effective and underscores the importance of addressing both cognitive and emotional factors in behavior change related to insulin therapy. This review highlights the importance of individualized and practical training in reducing psychological resistance to insulin. Nurses should prioritize face-to-face, hands-on education, especially for patients with injection-related fear. While technical skills can be taught in short sessions, longer interventions are needed to change attitudes and perceptions. These findings support the development of tailored nursing education strategies to improve insulin adherence and patient outcomes.

This systematic review can guide nurses to develop educational and intervention programs for patients with insulin injection fear. In particular, individualized educational approaches and practical applications may improve patient compliance and reduce hospitalization rates.

5. CONCLUSION

The findings suggest that new educational programs to manage insulin injection fear should be integrated into health services. Future studies should focus on evaluating the long-term effectiveness of individualized educational interventions. The results show that nursing interventions are effective in managing insulin fear in diabetic patients. Specifically, insulin administration, stress inoculation, and educational support enhance patient adherence to treatment. Practical demonstrations by nurses strengthen patients' self-efficacy. Future research should evaluate the long-term effects of educational programs to improve clinical outcomes. Additionally, the integration of new educational programs to manage insulin fear into healthcare services is crucial

Due to the inclusion of studies from specific geographical regions and a limited number of studies, the findings may not be generalizable to a broader diabetic patient population.

Conflict Of Interest

Neither the authors nor their family members have any scientific or medical committee membership or relationship with their members, consultancy, expertise, employment or shareholding in any company or similar conditions that may potentially constitute a conflict of interest in relation to this review.

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Authors' Contributions (According to Vancouver Criteria):

Concept and Design of the Study: SE, NG; Data Collection / Literature Review: SE, NG, MA; Data Analysis and Interpretation: MA, NG; Manuscript Preparation: SE, MA; Approval of the Final Version for Publication: SE, MA, NG

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