Comparison of the Impacts of Auriculotherapy with Electrical Stimulation and Vaccaria Seeds on Colposcopy Pain: A Randomized Clinical Trial

Samaneh Jouya, Nahid Golmakani, Seyed Reza Mazloum, Hamid Abdi, Zohreh Yosefi

The online version of this article can be found at http://ebcj.mums.ac.ir/article_10012.html
Comparison of the Impacts of Auriculotherapy with Electrical Stimulation and Vaccaria Seeds on Colposcopy Pain: A Randomized Clinical Trial

Samaneh Jouya¹, Nahid Golmakani²*, Seyed Reza Mazloum³, Hamid Abdi⁴, Zohreh Yosefi⁵

Received: 16/11/2017
Accepted: 25/12/2017

Abstract
Background: Colposcopy is an invasive medical procedure, which involves pain and discomfort. Auriculotherapy is a medical technique that can facilitate the reduction of pain.
Aim: The aim of this study was to compare the impacts of auriculotherapy with electrical stimulation and Vaccaria seeds on colposcopy pain.
Method: This controlled randomized, clinical trial was conducted on 93 females undergoing colposcopy in Ghaem Hospital, Mashhad, Iran, in 2017. The study population was selected through convenience sampling technique, and then randomly assigned into three groups, namely transcutaneous auricular stimulation (TAS), Vaccaria seeds, and placebo. The TAS group was subjected to electrical stimulation at four auricular acupuncture points 40 min before colposcopy, using a Pointer Excel stimulator (2 Hz). In the Vaccaria seed group, the seeds were fixed on the same acupoints three days prior to colposcopy. The participants were asked to press each point for 1 min, three times a day. The placebo group were provided with three adhesive patches without any seeds. After colposcopy, pain intensity was monitored using the visual analog scale. Data analysis was performed using Kruskal-Wallis and exact Chi-square tests in SPSS software, version 22.
Results: The three groups were comparable in terms of the demographic data (P>0.05). The mean pain intensities in the TAS, seed, and placebo groups were 49.0±24.2, 49.5±26.0, and 65.1±26.6, respectively. A significant difference was observed among the three groups regarding the pain intensity (P=0.02). There were also significant differences between the TAS and placebo groups (P=0.01) and between seed and placebo groups in this respect (P=0.02). However, the TAS and seed groups showed no significant difference in this regard (P=0.94).
Implications for Practice: The use of auriculotherapy with TAS and seeds could effectively reduce the patient’s pain during colposcopy.

Keywords: Auriculotherapy, Colposcopic Biopsies, Colposcopy, Electrical Stimulation, Pain

¹. MSc Student of Midwifery, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran
². Assistant Professor, Department of Midwifery, Evidence-based Health Care Research Center, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran
³. Instructure, Evidence-based Caring Research Center, Department of Medical Surgical Nursing, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran
⁴. Assistant Professor, Department of Chinese Traditional Medicine, School of Complementary and Persian Traditional Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
⁵. Professor, Department of Obstetrics and Gynecology, Women's Health Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

* Corresponding author, Email: golmakanin@mums.ac.ir
Introduction
Cervical cancer is one of the most prevalent gynecologic cancers in developing nations. The prevalence of cervical cancer is gradually decreasing in the world. However, this disease is still the second most common cancer in women throughout the world, affecting about 500,000 new cases each year, 80% of which occurs in the developing countries (1). The abnormal cervical cells can be detected on a cervical smear prior to the development of cervical cancer.

The usual practice performed after obtaining abnormal cervical screening test result is colposcopy. Colposcopy involves the visualization of the cervix using a stereoscopic binocular microscope of low magnification. This medical procedure facilitates the implementation of a diagnostic biopsy or treatment in form of large loop excision of the transformation zone. Colposcopy is an integral part of cervical screening program that aims to prevent cancer in women by detecting precursor lesions, which can lead to the development of cancer if left untreated (2).

Colposcopy is an invasive medical procedure associated with a degree of pain and discomfort, which results in patients' unwillingness to return for follow-up (3). An unsuccessful pain relief evokes irritating memories and physiological reactions (e.g., increased heart rate and vascular spasm) (4). Colposcopy is followed by heightened anxiety due to its associated pain (5). Pain assessment and documentation are the primary stages of health care providers (6). Various interventions have been used to reduce pain during colposcopy. Accordingly, the use of local anesthetics (1% lidocaine injection) (7), music (3), and video colposcopy (8) have been reported to be effective in the improvement of patients' pain during colposcopy (2).

In a randomized clinical trial, Church et al. (2001) compared the analgesic effects of ibuprofen and benzocaine gel on the reduction of pain induced by colposcopy. They demonstrated that ibuprofen and topical benzocaine gel, alone or together, provided no advantage over placebo in decreasing the colposcopy pain (9). One of the most common strategies for pain management is the use of analgesics. However, these medications are associated with a variety of adverse side effects (e.g., drowsiness, constipation, dry mouth, gastrointestinal bleeding, and addiction).

Pharmaceutical options are currently the first and best choice for acute pains. Complementary and alternative medicine therapies, especially auriculotherapy, offer additional options for pain management (10). Auriculotherapy is a healthcare modality in which the external surface of the ear, or auricle, is stimulated to alleviate pathological conditions in other parts of the body (11). This technique tends to be more cost-effective, less invasive, and of lower risk than the second- and third-line conventional treatments of strong narcotics.

Auriculotherapy, facilitating the reduction of medication doses, can mitigate the severity of pain (10). The practice of auricular therapy is based on the philosophy of balance and unity among the universe, living beings, and energy flow. The main idea of auriculotherapy is the recovery of the harmonized and balanced state of the body. There are various techniques for acupoint stimulation, including manual (e.g., use of a needle, Vaccaria, or magnetic seeds), electrical, laser, and transcutaneous electrical methods. Although the optimal method of stimulation has not been determined yet, the non-invasive methods are preferred because they are easier, painless, and better tolerated (12).

Auricular acupressure involves the stimulation of acupoints and meridians without using needles. The stimulation of an acupoint with acupressure can activate small myelinated nerve fibers sending impulses into the spinal cord, midbrain, pituitary, and hypothalamus (13). This medical intervention is a noninvasive procedure, which requires less technical expertise and is acceptable to the patients (14).

Acupressure eliminates imbalance in vital energy, removes pain, reduces muscle tension, improves blood circulation and vital activities, and decreases anxiety symptoms (15). Acupressure involves the use of special small balls that are made of steel or plant seeds stabilized by small patches on the external ears. These seeds can remain on the ears for 3-6 days and not injure the ears (16). The use of acupressure with seeds has been investigated in several studies. For instance, Yeh et al. (2012) in a one-group, repeated measures design study showed that the application of Vaccaria seeds for seven days resulted in the reduction of chronic low back pain (17).

However, Kwan et al. (2011) reported that acupressure with seeds had no significant effect on perineal pain in women during the first 48 h post-delivery (18). Chang et al. (2012) used auricular
acupressure to manage postoperative pain and knee motion in patients with total knee replacement. Although the pain scores gradually decreased over time, the intergroup differences was not statistically significant in either of the pain scores (14).

According to the recent studies, the application of transcutaneous electrical nerve stimulation (TENS) on acupuncture points is effective in producing analgesic effects (19). In transcutaneous auricular stimulation (TAS) method, the therapist stimulates each ear point with an electrical probe. The opioid peptides enkephalin and dynorphin are two subfractions of the larger polypeptide molecule, known as beta-endorphin, which are activated by different frequencies of electrical stimulation. The analgesia produced by low-frequency electroacupuncture (2 Hz) has been reported to be selectively attenuated by enkephalin antibodies (11).

Recently, several small trials have demonstrated the efficiency of TAS in relieving pain and reducing analgesic requirements following hysterectomy and inguinal surgery (20). Similarly, Tsang et al. (2011) revealed the effectiveness of auricular TENS in the alleviation of post-hysterectomy pain by observing lower level of pain in true TENS group than that in sham group after the intervention (19).

In a clinical trial, Sabine et al. (2003) observed a significant reduction in the pain scores of the electrical acupuncture group and concluded that the electrical stimulation of auricular acupuncture points by P-STIM™ was more effective in lowering chronic cervical pain than the conventional manual auricular acupuncture (21). On the other hand, Richard et al. (1999), investigating the effect of TENS on low back pain, reported no significant difference between the TENS and placebo groups in this regard (22).

The lack of correlation between the clinical benefits and the evidence of auriculotherapy protocol implies the need to further explore this intervention that may have its clinical value (23). There are doubts about the effectiveness of complementary medicine. One of the main challenges for introducing this therapeutic approach to nursing practice is the need for a rigorous research support for the rapid entry of nursing interventions into this category and the determination of effectiveness of complementary therapies (24).

Auriculotherapy is performed in a variety of ways. However, there are limited studies that compare these methods. Acupressure with ear seeds is the most common auriculotherapy method since it is an effective, economic, and simple approach (25). Nonetheless, as this procedure often takes several days and weeks, the seeds may be removed or displaced. Moreover, this technique requires frequent referral to clinics.

On the other hand, the electrical stimulation of the ear is a newer method efficiently facilitating the generation of natural frequencies in the nerves under treatment (26). This technique entails only one session and can reduce the patients’ pain; moreover, it does not require home patient cooperation.

Cervical cancer is the most frequent cause of mortality among the gynecologic cancers worldwide. This disease is also the second most common cancer among the Iranian females (1). There are contradictory results regarding the effectiveness of auriculotherapy on pain.

The comprehensive literature review and experiences of the research team in colposcopy wards highlighted the need for finding safe, simple, cost-effective, and available techniques for relieving the pain caused by this medical procedure. With this background in mind, the present study was conducted to compare the effects of electrical stimulation and Vaccariae seeds on pain intensity during colposcopy.

**Methods**

This controlled randomized, clinical trial was conducted on 93 women undergoing colposcopic biopsies at Ghaem Hospital, Mashhad, Iran, within May-September, 2017 using a post-intervention design. The study population was selected through convenience sampling method. The participants who met the inclusion criteria were randomly assigned into three groups, namely TAS, seeds, and placebo groups based on random numbers in SPSS software.

The minimum sample size was calculated to compare the means of two populations. A pilot study was performed on 30 women (10 cases from each group) in order to evaluate the mean and standard deviation of pain intensity (48.1±13.3 in the control group and 37.8±12.2 in the TAS group). Finally, the sample size was calculated to be 25 cases for each group at 95% confidence interval and 80%
power, which was enlarged to 35 cases to avoid baseline imbalance.
A total of 12 subjects were excluded from the study due to the removal of seeds for more than 24 h (3 cases in seeds group) and unwillingness to participate in the study (9 cases in the TAS and placebo groups). Therefore, the study was continued with 93 women (32, 30, and 31 cases in the TAS, seeds, and placebo groups, respectively).
The inclusion criteria were: 1) age of ≥ 18 years, 2) first experience of colposcopy, 3) nonpregnancy and nonlactation, 4) absence of lesion or rash on the ears, 5) lack of addiction to drugs and alcohol, 6) lack of psychological and severe diseases, 7) no history of auricular treatment in the past 6 months, and 8) normality of vital signs. On the other hand, the exclusion criteria included: 1) unwillingness to continue participating in the study, 2) unusual sensitivity to ear touching, 3) consumption of certain drugs, 4) incidence of inflammation, infection, or itching, and 5) removal of the seeds for more than 24 h in the seed group.
Data collection tools included the sociodemographic and colposcopy (SDC) questionnaire, visual analog scale (VAS), and a checklist for the seed group. The SDC questionnaire was filled out three days before colposcopy. The content validity of this questionnaire was approved by seven faculty members of School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran. Furthermore, the reliability of this instrument was confirmed by a test-retest reliability method performed with an interval of three days (r=0.90).
The VAS was used to assess the pain intensity after colposcopy. The VAS adopted in this study was comprised of horizontal lines with 0 representing one pain extreme (e.g., “no pain”) and 100 signifying the other pain (27, 28). The validity and reliability of this scale were confirmed by the previous studies. For instance, Bijur et al. (2001) reported the intraclass correlation coefficients of 0.97 for the measurement of acute pain (29).
In the present study, the inter-rater reliability of the scale was established during the pilot study. To this end, pain intensity was estimated in 10 women by two observers (i.e., the researcher and his supervisor). Then, the correlation between the two assessments was calculated through Pearson’s correlation coefficient (r=0.87). In the next step, the researcher showed the scale to the participants 5 min after colposcopy and asked them to choose the number that accurately showed their level of pain.
The auricular therapy was delivered by the researcher, who was a professional midwife accredited for practicing auriculotherapy. Prior to the study, the researcher participated in the auriculotherapy workshop for three days and also acquired the practical skills by the aid of a traditional medicine specialist for two weeks.
After sterilizing the acupoints with 70% alcohol, the TAS group was subjected to transcutaneous auricular stimulation at four acupoints (i.e., Shenmen, Relaxation, Tranquilizer, and Endocrine) using the Pointer Excel II stimulator at the frequency of 2 Hz for 30 sec on each acupoint (Figure 1). This intervention was conducted on the two ears 40 min before colposcopy.

![Figure 1. Acupuncture points on the ear](image)
In the seed group, the researcher attached the Vaccaria seeds on the same acupoints by a piece of opaque adhesive patch. The subjects were asked to press each point for 60 sec three times a day (i.e.,
Evidence Based Care Journal, 7 (4): 55-62

at 10:00, 16:00, and 22:00, respectively). The auriculotherapy was conducted on the external ear on the nondominant side for three days before performing colposcopy until the colposcopy day. The placebo group received opaque adhesive patch without any seeds at four points non-related to pain three days prior to colposcopy.

Research approval was obtained from the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran. Furthermore, informed consent was obtained from all the participants. The subjects were requested to contact the researcher in case of encountering any problems or complications, such as allergy, infection, and pruritus, in order to take an appropriate action. One day before the colposcopy, the researcher phoned the patients and advised them not to use any analgesic drugs, such as ibuprofen, 4 h before going to the hospital.

After collecting and coding the data, they were entered into computer. The data were summarized using the descriptive statistics. The Kolmogorov-Smirnov and Shapiro Wilk tests were used to detect the normality of the quantitative variables. The comparison of the quantitative variables (i.e., age and pain intensity) was accomplished by using one-way ANOVA and Kruskal-Wallis test. Additionally, the exact Chi-square test was run to compare the qualitative variables. Data analysis was performed in SPSS, version 22. P-value less than 0.05 was considered statistically significant.

**Results**

According to the results, the mean ages of the participants in the TAS, seed, and placebo groups, were 39.4±10.5, 42.1±8.2, and 41.6±2.0 years, respectively. The results of the One way ANOVA revealed no significant difference among the three groups in terms of age (P=0.55). Furthermore, there was no significant difference among the three groups regarding the demographic data (P>0.05) (Table 1).

The mean pain intensities in the TAS, seeds, and placebo groups were 49.0±24.2, 49.5±26.0, and 65.1±26.6 (out of 100), respectively. The results of the Kolmogorov-Smirnov and Shapiro-Wilk tests revealed that pain intensity was a non-normally distributed variable (P<0.05).

Furthermore, the Kruskal-Wallis test demonstrated a significant difference among the three study groups considering the mean pain intensity (P<0.02). Additionally, the pairwise comparison of the study groups showed a significant difference between the TAS and placebo groups (P=0.01) as well as between the seed and placebo groups (P=0.02) in terms of the mean pain scores. Nonetheless, no significant difference was observed between the seed and TAS groups in this regard (P=0.96) (Table 2).

<table>
<thead>
<tr>
<th>Variable</th>
<th>TAS (32)</th>
<th>Seed (30)</th>
<th>Placebo (31)</th>
<th>Result of exact Chi-square test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial Education</td>
<td>19 (59.4)</td>
<td>15 (50.0)</td>
<td>20 (64.5)</td>
<td>P=0.81</td>
</tr>
<tr>
<td>Secondary school</td>
<td>9 (28.1)</td>
<td>11 (36.7)</td>
<td>7 (22.6)</td>
<td></td>
</tr>
<tr>
<td>Higher education</td>
<td>4 (12.5)</td>
<td>4 (13.3)</td>
<td>4 (12.9)</td>
<td></td>
</tr>
<tr>
<td>Address</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>City</td>
<td>19 (59.4)</td>
<td>18 (60.0)</td>
<td>23 (74.2)</td>
<td>P=0.25</td>
</tr>
<tr>
<td>Village</td>
<td>11 (34.4)</td>
<td>8 (26.7)</td>
<td>8 (25.8)</td>
<td></td>
</tr>
<tr>
<td>Suburbs</td>
<td>2 (6.2)</td>
<td>4 (13.3)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Job</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>27 (84.4)</td>
<td>28 (93.3)</td>
<td>26 (83.9)</td>
<td>P=0.54</td>
</tr>
<tr>
<td>Employed</td>
<td>5 (15.6)</td>
<td>2 (6.7)</td>
<td>5 (16.1)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (12.5)</td>
<td>6 (20)</td>
<td>3 (9.7)</td>
<td>P=0.48</td>
</tr>
<tr>
<td>No</td>
<td>28 (87.5)</td>
<td>24 (80)</td>
<td>28 (90.3)</td>
<td></td>
</tr>
<tr>
<td>Dyspareunia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13 (41.9)</td>
<td>11 (37.9)</td>
<td>8 (26.7)</td>
<td>P=0.40</td>
</tr>
<tr>
<td>Mild</td>
<td>14 (45.2)</td>
<td>12 (41.4)</td>
<td>11 (36.7)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>3 (9.7)</td>
<td>4 (13.8)</td>
<td>4 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1 (3.2)</td>
<td>2 (6.9)</td>
<td>6 (20.0)</td>
<td></td>
</tr>
</tbody>
</table>

TAS: transcutaneous auricular stimulation

<table>
<thead>
<tr>
<th>Variable</th>
<th>TAS (32)</th>
<th>Seed (30)</th>
<th>Placebo (31)</th>
<th>Result of tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=32</td>
<td>N=30</td>
<td>N=31</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Downloaded from [http://ebcj.mums.ac.ir/](http://ebcj.mums.ac.ir/) at Mashhad University of Medical Sciences on January 01, 2018


**Mean±SD**

<table>
<thead>
<tr>
<th></th>
<th>Mean±SD</th>
<th>Mean±SD</th>
<th>Mean±SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity of pain</td>
<td>49.06±24.2</td>
<td>49.5±26.0</td>
<td>26.6±65.1</td>
<td>P=0.02*</td>
</tr>
<tr>
<td>Comparison of TAS and placebo groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparison of seed and placebo groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparison of TAS and seed groups</td>
<td></td>
<td></td>
<td></td>
<td>P=0.96**</td>
</tr>
</tbody>
</table>

TAS: transcutaneous auricular stimulation
*Kruskal-Wallis test, ** pair-wise test

**Discussion**

This study aimed to compare the effects of auriculotherapy with electrical stimulation and Vaccaria seeds on pain intensity during colposcopy. The results exhibited a statistically significant difference in the mean pain intensity of the three groups. Based on the findings, the TAS and seed groups had a significantly lower level of pain intensity, as compared to the placebo group. The pairwise comparison of the three groups demonstrated a significant difference in the mean pain intensity between the TAS and placebo groups as well as between the seed and placebo groups. However, there was no significant difference between the seed and TAS groups in this respect.

Yeh et al. (2012) conducted a study with the purpose of determining the effects of auricular acupressure on chronic low back pain (17). Although they used the Vaccaria seeds for seven days, their results were consistent with those of our study. It is noteworthy that the reduction of intervention duration to three days can decrease the probability of displacement of the seeds. Moreover, unlike the mentioned study, we had a placebo group, and the level of pain intensity was compared in three groups.

In consistent with our study, Kwan et al. (2011) reported no significant difference in the perineal pain intensity among the women during the first 48 h after delivery following the application of Vaccaria seeds (18). This discrepancy can be ascribed to the difference in the implementation of the intervention. In this regard, in the study of Kwan at al., the points administered with Vaccaria seeds were pressed every 30 sec by the patients, while in our study, each point was pressed for 60 sec. In addition, in the present study, the selection of the points and attachment of labels were performed by a single person (i.e., researcher), whereas in the study of Kwan et al., this was carried out by various midwives. Although all of these midwives were already trained by the researcher, their skill in sticking labels might have varied.

The TENS is used clinically by a variety of health care providers for the reduction of pain. However, the clinical effectiveness of this medical intervention is still a controversial issue (30). In congruence with our study, Tsang et al. (2011) demonstrated that a single session of auricular TENS could significantly reduce post-hysterectomy pain in the TENS group, compared to that in the sham group (19). Similar to our research, the mentioned study implemented one session of stimulation. However, the selected stimulation points, duration of stimulation of each point, and stimulation device were different from those of our study.

Sabine et al. (2003) compared the impacts of electrical stimulation of auricular acupuncture points with P-STIM™ and conventional manual auricular acupuncture. They showed that the electrical stimulation was more effective in reducing the VAS chronic cervical pain score than the conventional manual auricular acupuncture (21). Electroacupuncture can attenuate the release of prostaglandin (19) and may inhibit hyperalgesia.

We postulate that the use of auricular TENS may achieve similar effects, and consequently reduce the pain in our patients. This view may warrant further investigation. Auricular electro acupuncture is also a treatment option for pain; however, it is an invasive procedure that involves the use of auricular acupuncture needles as electrodes. Needling of the acupuncture points on the auricle may lead to complications, such as perichondritis (31).

In consistent with our findings, Richard et al. (1999), investigating the effect of TENS on low back pain, showed that TENS had a comparable effect to that of the placebo at the end of the fourth week on the back pain intensity (22). This discrepancy can be due to the difference between the two studies regarding the type of pain they investigated. In the current study, the TENS was applied for acute pain, while the mentioned study targeted the low back pain, which is a chronic disease. In line with our study, Tsang reported that auricular TENS had a significant mitigating effect on the post-
hysterectomy pain, which lasted for at least 30 min after the stimulation (19). One of the limitations of the present study was the impossibility of using a control group (routine care) due to comparing two different methods of auriculotherapy and having three groups in this study. The current research is among the first studies investigating the colposcopy pain in Iran. It is recommended to conduct further studies on the effect of auriculotherapy on pain reduction by selecting different points and techniques.

**Implications for Practice**

The results of this study indicated that both auriculotherapy techniques used in this study, namely the use of TAS and *Vaccaria* seeds, could effectively lower the intensity of pain during colposcopy. Given the similarity of placebo and intervention groups in all aspects, except for the use of pain management protocol, the difference in patients’ final pain intensity scores could be ascribed to the use of the intervention. As a result, auriculotherapy with TAS and *Vaccaria* seeds could be concluded to be effective in the improvement of pain management during colposcopy.

**Acknowledgments**

We would like to thank all the midwives, nurses, and physicians of Colposcopy Clinic of Ghaem Hospital. Moreover, the authors are grateful to the midwifery instructors of Mashhad University of Medical Sciences. We also appreciate the Research Deputy of Mashhad University of Medical Sciences for funding this study. This paper is part of a master’s thesis approved by Mashhad University of Medical Sciences (code No: IRCT2017043033717N1.)

**Conflicts of Interest**

The authors declare that there is no conflict of interest regarding the publication of this article.

**References**