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The online version of this article can be found at http://ebcj.mums.ac.ir/article_11102.html

Evidence Based Care Journal 2018 08:07 originally published online 01 October 2018
DOI: 10.22038/ebcj.2018.31495.1783

Online ISSN: 2008-370X

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Received: 05/05/2018
Accepted: 26/06/2018

Abstract

Background: The cycle of pain, fear, and anxiety may lead to prolonged labor and cesarean section. Acupressure is one of the methods for pain relief.

Aim: Therefore, this study aimed to compare the effect of acupressure on bladder-GV20 and gallbladder-GV20 points on the labor pain in primiparous women.

Method: This randomized clinical trial was conducted on 158 primiparous women, who referred to the Um Al-Benin Specialized Women Hospital, Mashhad, Iran in 2017. The first stage of labor included five and four pressure cycles on acupressure points in bladder and gallbladder in the intervention groups 1 and 2, respectively. In the second stage of labor one pressure cycle on the same points were completed. The control group only received the routine cares. The duration of uterine contractions was assessed by touching the uterus apex. Moreover, the pain intensity was evaluated by the visual analog scale. All the data were analyzed by the SPSS version 25

Results: The mean pain intensity in both stages of the intervention groups was significantly different from the control group and was significantly lower in the gallbladder group (P<0.001). The mean duration of contractions in the first stage was significantly different between the three groups (P<0.001).

Implications for Practice: According to the findings of this study, pressure on bladder-GV20 and gallbladder-GV20 points can attenuate pain intensity in the first and second stages of labor. Moreover, this technique prolongs the duration of contractions in the first stage of labor. Consequently, this method can be recommended as a complementary approach in labor.

Keywords: Acupressure, GV20 point, Labor pain intensity, Primiparous
Introduction

Labor is one of the most painful events during the life of women (1). Labor pain intensity is affected by the physical (age, parity, and fetal position), psychological (personality types, fear, and anxiety), economic, social, and cultural factors (2, 3). Labor pain is mild in 15%, moderate in 35%, severe in 30%, and very severe and intolerable in 20% of the cases (4).

The labor pain causes changes in the levels of catecholamines, beta-endorphins, blood pressure, pulse, and oxygen consumption of mother. Increased oxygen consumption leads in diminished arterial pressure and ultimate bradycardia. In addition, increase in catecholamines causes reduction in blood supply to uterus, abnormal labor progress, and decreased Apgar score (5).

Moreover, the defective cycle of pain, fear, and anxiety is associated with an increase in pain intensity, prolonged labor and increased frequency of cesarean section (4). Therefore, one of the main goals in midwifery care is labor pain management (6).

Pharmaceutical and non-pharmaceutical approaches can help to relieve the labor pain. Medications often have an appropriate effect on alleviating the labor pain, but their application is accompanied by some limitations and complications (7, 8). In recent years, the non-pharmacological methods of pain relief have been the subject of interest, including acupressure. The acupressure as a branch of acupuncture is a non-invasive, relatively inexpensive, and non-complicated procedure (9, 10).

According to the traditional Chinese medicine, all the elements in nature consist of yin and yang. These two forces are in contradiction with each other and they need to be in balance for human health (11). Acupressure can balance the Chi energy, as well as the two yin and yang forces. The pressure on the nerve fibers and their stimulation prevents pain transmission from the spinal cord to the brain. On the other hand, this method can relieve the pain by augmenting the secretion of endogenous endorphins (12, 13).

In order to relieve the labor pain, multiple points are suggested on the surface of the ear, organs, trunk, and scalp (1, 7, 14-19). Stimulating these points triggers and enhances the uterine contraction and Chi balance resulting in improved labor pain (20). Some of these points are found on the surface of the bladder canals, gallbladder, and meridian Du. In some articles regarding acupressure and acupuncture, bladder points of 31, 32, and 67, gallbladder point of 21 and Du 20 have been considered as effective points in attenuating labor pain (2, 13, 15, 16, 21).

The aforementioned channels also have a number of points on the scalp surface. The areas on the scalp surface are in direct contact with the central nervous and endocrine systems. Consequently, they can directly affect the cortical, cerebellar, thalamocortical, thalamic, hypothalamic, and pineal body (22). Furthermore, the points on scalp surface can regulate Yin-Yang, Chi-blood, and Zang-Fu organs. Several reports are published about the treatment through stimulation of scalp points for disorders, such as sense disorder, mental illness, and various types of acute and chronic pains (23).

According to a study by Skilnand et al. (2002), the labor pain intensity was less in the acupuncture group (GV20, BL34, BL32, BL67, BL60, LI4, LU7, HT7, ST30, ST29, GB34, ST36, SP8, KI3, LR3, and GB21), compared to the control group (24). Bo et al. (2006) showed that the labor pain intensity in the scalp acupuncture group was significantly lower than the control group (P<0.01) (25). In a study performed by Durga et al. (2012), the pressure on eight scalp points (BL5, BL8, and BL9 for bladder points, GB8, GB16, GB17, and GB18 for gallbladder points, in addition to GV20 point) caused a decrease in pain during the active phase of labor (P<0.001) (26).

There are limited reports concerning the effect of acupressure on the scalp points on the labor pain relief. Moreover, the literature regarding acupuncture and acupressure suggests that reduction in the number of pressure points decreases the individual discomforts caused by manipulation while maintains the effectiveness (27). With this background in mind, the present study aimed to compare the pressure on the three points of bladder (i.e., BL5, BL8, and BL9), four points of gallbladder (i.e., GB8, GB16, GB17, and GB18), and GV20 on the pain intensity among the primiparous women.

Methods

This single-blind randomized clinical trial was conducted in the Um Al-Benin Specialized Women’s Hospital, Mashhad, Iran. The data were collected during 22 May 2017-21 November 2017. The
statistical population of this study included all the women who referred to this hospital for delivery during the study period. In order to determine the sample size in the first stage of labor, the study performed by Ziaei (28) and the formula for comparing the means in two independent groups were used. In addition, the pilot study on 10 participants was applied for sample size calculation for the second stage of labor. Finally, the sample size was calculated as 55 for each group (total of 165 people) regarding the test power of 80%, the confidence coefficient of 95%, and drop-out of 10%.

The inclusion criteria entailed 1) being primiparous, 2) gestational age ≥ 37 weeks, 3) age of 18-35 years, 4) singleton fetus with vertex presentation, 5) fetal weight of 2500-4000 g, 6) spontaneous vaginal delivery (4-5 cm cervical dilatation with at least two contractions of 20 sec and more within 10 min), 7) healthy skin in the pressure areas, 8) no history of medical and obstetric problems, and 9) pain intensity ≥ 50 mm based on visual analog scale (VAS) on admission.

The exclusion criteria included 1) using any analgesics, 2) fast delivery, 3) emergency cesarean section, 4) abnormal fetal heartbeat, 5) lack of progress, and 6) unwillingness of the mother to continue participating in the study. The research instruments were a demographic profile form, a form about the first and second stage of labor, and the VAS for pain assessment.

The validity of the demographic profile and labor data forms were evaluated using the content validity method. The reliability of the labor data form was confirmed by equivalent method and r=0.917. The VAS was a 100-mm tape, indicating zero as no pain and 100 as maximum pain. The validity of this tool has been verified in various studies and the reliability was in accordance with a study by Kordi et al. (r=0.91) (14). The validity of VAS was confirmed in the present study by content validity method. Moreover, the reliability of the latter tool was assessed by the equivalent method with r=0.982. Furthermore, to validate the correctness of the points and the method of applying pressure, the researcher passed a five-session training course with an acupuncturist and received the approval.

In this study, the participants were selected by the convenience sampling method and were then divided into three groups through random allocation. The intervention group 1 receives acupressure on bladder points of BL5, BL8, BL9, and GV20. The intervention group 2 had pressure on gallbladder points of GB8, GB16, GB17, GB18, and GV20. The control group just received the routine cares (Figure 1).

For random allocation, on the first day of referring to the hospital, the letters A, B, and C were written on three papers and placed inside an envelope for the bladder, gallbladder, and control groups, respectively. The first three participants were asked to take the papers randomly. Afterwards, the
order of first three people was repeated for the rest of the participants. For blinding the study, the same pressure was applied in all the participants of the intervention groups by one of the researchers and a researcher assistant who was unaware of the intervention type in the groups completed the measurements.

In order to avoid any bias in the results of the study, we needed to equalize the duration of pressure in the two intervention groups. For this purpose, 20 minutes of pressure in the first stage of labor and one pressure cycle in the second stage of labor were performed in each intervention group.

In the intervention group 1, for the first stage of labor, simultaneous with the beginning of uterine contraction the parturient was placed in a semi-sitting position with the head in body alignment. The researcher placed over the head of parturient and applied a fixed pressure with a thumb for 60 sec on each of the BL5, BL8, BL9, and GV20 points. Therefore, the parturient felt the tai chi (heaviness, pressure, hotness, tingling, or numbness) at these points. The pressure was completed within five four-min cycles (i.e., total of 20 min) with intervals of 30 min. After the first stage of labor (10 cm cervical dilatation), a four-minute pressure cycle was resumed on the points at the beginning of the second stage of labor (maternal exiting).

In the intervention group 2, 60 sec of pressure was applied on each of the five GB8, GB16, GB17, GB18, and GV20 points (five-min cycle) with the onset of uterine contraction in the first stage of labor. The pressure was carried out as four five-min cycles with 30-min intervals making a total of 20 min pressure. At the beginning of the second stage of labor, 60 sec of pressure was applied to the points (five-min cycle). For the control group, the researchers in the ward at the Um Al-Benin Hospital took the routine cares.

The labor pain intensity in the intervention groups was measured by the researcher assistant immediately and 30 min post-intervention, followed by assessments every 30 min until the end of the first and second stages of labor. It was also measured in the control group by the assistant immediately after the end of the uterine contractions and then every 30 min until the end of the first and second stages of labor. In addition, the duration of uterine contractions was evaluated according to the procedure of labor partograph by touching the uterus apex from the beginning to end of contractions for ten min by chronometer every 30 min and was recorded in the relevant forms (29).

Finally, out of the 165 participants, two and three individuals were excluded from the bladder-GV20 and gallbladder-GV20 groups, respectively. The drop out in the bladder group were due to the hypertonic contractions and non-progression criteria. The exclusions from the gallbladder group were because of fetal distress and hypertonic contractions. Moreover, one person was excluded from the control group as the result of narcotic intake (flowchart 1).

The present study was approved by the Ethics Committee of Mashhad University of Medical Sciences. A complete explanation of the research objectives was provided to all the participants and written consents were obtained. The individuals were ensured that there was no known acupressure problem. Furthermore, the subjects could leave freely in case they did not want to continue to collaborate at any stage of the research and this would not make any changes to the cares.

All the data were analyzed by Chi-square test, one-way analysis of variance (ANOVA), nonparametric Kruskal-Wallis, Mann-Whitney, and Friedman tests using the SPSS version 25. At first, Kolmogorov-Smirnov test was utilized to determine the normal distribution of the data. According to the results of Kolmogorov-Smirnov test, most of the variables measured in the study did not have a normal distribution. The variables with normal distribution included the mean score of pain at the baseline, 30 min after each intervention cycle, and immediately after the last intervention cycle in the first stage of labor. The non-parametric tests entailed Kruskal-Wallis, Dunn, and Friedman tests. The variables with normal distribution were assessed using one-way ANOVA and Tukey tests (Table 1.4). P<0.05 was considered as significant in all the tests.
Results
According to the findings of Kruskal-Wallis test and one-way ANOVA, the three groups were homogeneous regarding age (P=0.48), body mass index (P=0.45), frequency of shower during labor (P=0.4), and baseline pain score (P=0.23). Moreover, the results of these tests showed a significant difference between the three groups concerning the mean labor pain intensity immediately (P<0.001) and 30 min after each intervention (P<0.001) in the first stage of labor. The significant difference between the three groups was also revealed immediately (P<0.001) and 30 min after the last intervention cycle (P<0.001), as well as in the whole active phase of the first stage (P<0.001).

The pairwise comparison of the groups by Dunn and Tukey with Bonferroni Correction tests demonstrated that the pain score in all measurements of the first labor stage was significantly different in the bladder-GV20 and gallbladder-GV20 groups, compared to the control group (P<0.05).
pain intensity in the gallbladder-GV20 group was found to be significantly lower than the two groups of bladder-GV20 and control at all measurements of pain in the first stage of labor (P<0.05). The intragroup comparisons by the Friedman test showed that the difference in mean pain intensity between the groups of bladder-GV20 (P<0.001), gallbladder-GV20 (P<0.001), and control (P<0.001) was statistically significant (Table 1).

The Kruskal-Wallis test indicated that the mean labor pain intensity had statistically significant difference immediately (P<0.05), 30 min post-intervention (P<0.05), and during the whole second stage of labor (P<0.05) between the three groups in the second stage of labor. Moreover, the results of Dunn with Bonferroni Correction test revealed that the pain score immediately (P<0.001), 30 min post-intervention (P<0.001), and during the whole second stage of labor (P<0.001) between the gallbladder-GV20 and bladder-GV20 group had significant difference, compared to the control group. In addition, the pain intensity in the gallbladder-GV20 group was significantly lower than the two groups of bladder-GV20 and control at 30 min post-intervention (P<0.001), and during the whole second stage of labor (P<0.05). In the intragroup comparison by Friedman test, the pain intensity was significantly different in each group of bladder-GV20 (P<0.001), gallbladder-GV20 (P<0.001) (Table 1).

According to the results of Kruskal-Wallis test, the three groups were homogeneous in terms of the mean uterine contractions on admission (P=0.54). A significant difference was found between the three groups regarding the mean duration of uterine contractions 30 min after each intervention cycle in the first stage of labor (P<0.001), 30 min after the last intervention cycle in the first stage of labor (P<0.001), and in the whole active phase of the first labor stage (P<0.001).

On the other hand, the difference between the three groups in the duration of uterine contractions 30 min post-intervention in the second stage of labor (P=0.09) and during the whole second stage of labor (P=0.16) was not significant. The Dunn with Bonferroni Correction test demonstrated that the mean uterine contractions contractions 30 min after each intervention cycle in the first stage of labor (P<0.001) were significantly different between the three groups (Table 2).

### Table 1. Comparison of the mean labor pain intensity scores during the first and second stages of labor between the three groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Bladder-GV20 group (Mean ± SD)</th>
<th>Gallbladder-GV20 group (Mean ± SD)</th>
<th>Control group (Mean ± SD)</th>
<th>Test results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First stage of labor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain intensity immediately after each intervention cycle</td>
<td>33.2±7.4</td>
<td>24.2±6.0</td>
<td>83.2±10.1</td>
<td>*P&lt;0.001</td>
</tr>
<tr>
<td>Pain intensity 30 min after each intervention cycle</td>
<td>71.5±8.1</td>
<td>59.5±6.4</td>
<td>87.5±8.7</td>
<td>**P&lt;0.001</td>
</tr>
<tr>
<td>Pain intensity immediately after the last intervention cycle</td>
<td>44.3±10.6</td>
<td>36.7±5.7</td>
<td>91.7±6.5</td>
<td>**P&lt;0.001</td>
</tr>
<tr>
<td>Pain intensity 30 min after the last intervention cycle</td>
<td>76.3±13.7</td>
<td>61.0±24.2</td>
<td>92.5±5.5</td>
<td>*P&lt;0.001</td>
</tr>
<tr>
<td>Pain intensity during whole active phase of the first stage of labor</td>
<td>79.3±7.3</td>
<td>65.5±7.6</td>
<td>93.2±4.7</td>
<td>*P&lt;0.001</td>
</tr>
<tr>
<td>Friedman test result</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Second stage of labor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain intensity immediately after the intervention cycle</td>
<td>35.5±7.9</td>
<td>32.6±14.0</td>
<td>99.7±0.5</td>
<td>*P&lt;0.001</td>
</tr>
<tr>
<td>Pain intensity 30 minutes after the intervention cycle</td>
<td>94.9±3.0</td>
<td>90.4±6.9</td>
<td>99.8±0.3</td>
<td>*P&lt;0.001</td>
</tr>
<tr>
<td>Pain intensity during whole second stage of labor</td>
<td>95.3±2.9</td>
<td>91.3±6.3</td>
<td>99.8±0.4</td>
<td>*P&lt;0.001</td>
</tr>
<tr>
<td>Friedman test result</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P=0.14</td>
<td></td>
</tr>
</tbody>
</table>

* Kruskal-Wallis
** one-way ANOVA
Table 2. Comparison of mean duration of uterine contractions between the three groups

<table>
<thead>
<tr>
<th>Duration of uterine contractions (sec)</th>
<th>Bladder-GV20 group (Mean ± SD)</th>
<th>Gallbladder-GV20 group, (Mean ± SD)</th>
<th>Control group (Mean ± SD)</th>
<th>Kruskal-Wallis</th>
</tr>
</thead>
<tbody>
<tr>
<td>On admission</td>
<td>37.5±0.0</td>
<td>34.7±0.0</td>
<td>38.6±0.1</td>
<td>P=0.54</td>
</tr>
<tr>
<td>30 min after each intervention cycle in the first stage of labor</td>
<td>54.8±4.9</td>
<td>59.6±5.9</td>
<td>49.8±6.0</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>30 min after the last intervention cycle in the first stage</td>
<td>52.1±1.7</td>
<td>57.9±4.1</td>
<td>43.1±0.3</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Whole active phase of the first stage of labor</td>
<td>66.5±5.8</td>
<td>69.5±3.2</td>
<td>59.7±56.3</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Friedman test</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>30 min post-intervention cycle in the second stage of labor</td>
<td>72.7±2.3</td>
<td>74.4±2.3</td>
<td>70.8±7.5</td>
<td>P=0.09</td>
</tr>
<tr>
<td>Whole second stage of labor</td>
<td>80.3±6.3</td>
<td>82.2±7.2</td>
<td>79.2±2.3</td>
<td>P=0.16</td>
</tr>
</tbody>
</table>

Discussion

According to the findings of present study, the pressure on the scalp points of gallbladder (GB8, GB16, GB17, GB18, and GV20) and bladder (BL5, BL8, BL9, and GV20) reduced the pain intensity in the first and second stages of labor.

The results of Durga et al. (2012) demonstrated that the mean total pain intensity of the first labor stage in the scalp acupressure group was lower than the control group. In the intervention group at the active phase of labor with contraction initiation, the pressure was applied on scalp, bladder (BL5, BL8, and BL9), and gallbladder points (GB8, GB16, GB17, GB18, and GV20). This was continued until the completion of the first labor stage (26). The results of their study are consistent with the findings of the present study.

In the mentioned study, eight points in the scalp area were investigated. We examined each bladder (BL5, BL8, and BL9) and gallbladder (GB8, GB16, GB17, and GB18) points in two groups separately to reduce the number of pressure points. On the other hand, we examined the GV20 point in both study groups because it is known as the most important point in acupuncture books for regulating the body activity and organs. This point is recommended in all the treatments performed by acupuncture techniques.

In the study performed by Durga, the pressure was applied to each of the eight scalp points in consecutive manner for four min with the onset of contraction. Finally, the full duration of the pressure posed on the cranial points was not expressed, while we applied the pressure on each of the points for one min making a total of 20 min in each of the groups. Moreover, in the current study initially the GV20 and then the other points were stimulated in both intervention groups.

Bo et al. (2006) reported that the mean labor pain intensity in the cranial acupuncture group was lower than the control group (25). The results of this study are consistent with the present study. In their study, instead of applying pressure on the cranial points, the points were stimulated by needle, which is different from our study. In the study conducted by Bo et al., unlike to our study, a scalp region was stimulated as the shengzhi region, while we studied a number of points from different regions of the skull.

Seyyedzadeh Aghdam (2012) showed that BL32 and GB21 acupressure had no effect on diminishing the labor pain intensity in the active phase of labor (13). Their study was performed on the same sites of the gallbladder and bladder canals as the present study. However, the findings of the two studies are not consistent. Differences in the design and method of implementation can result in the different findings of the two studies.

In the study completed by Seyyedzadeh Aghdam, placebo p6 point acupressure was carried out in the control group and the mentioned points were stimulated with cupping therapy. We did not consider any placebo points and used thumb pressure to stimulate the points in the intervention groups.

Ziaei et al. (2006) reported that acupuncture on the eight points of GV20, Yangtang, ST36, SP6, LI4, LI3, CV2, and CV3 had no effect on improving the labor pain intensity one hour post-intervention (28). Therefore, the results of mentioned study are inconsistent with the present study. The reason for this difference in results may be attributed to the fact that they used acupuncture to stimulate the points while we used acupressure by fingers. Only the GV20 point was common between the two...
studies and the other points were different between the two researches, which could also cause the variable results of the two studies.

Skilnand et al. (2002) indicated that the labor pain score, as well as the need for epidural analgesia and pethidine were lower in the acupuncture group of GV20, BL34, BL32, BL67, BL60, LI4, LU7, HT7, ST30, ST29, GB34, ST36, SP8, KI3, LR3, and GB21, in comparison with the placebo group (24). In the study by Skilnand et al., the acupuncture was used on 16 points, whereas we applied pressure in fewer points (four in the bladder and five in the gallbladder groups). However, their results are in line with our findings.

One reason for the consistent results can be the common channels examined in the two studies (bladder and gallbladder). Furthermore, the findings of present study showed that the pain intensity was lower in the first and second stages of labor in the gallbladder-GV20 group, compared to the bladder-GV20 group.

Among the internal organs of the body, liver is responsible for maintaining the chi free flow, liquefying its movement, regulating the volume of blood flow, and keeping blood in the body. The regulation of the liver through the meridian(s) can be effective in reducing the pain. Among these, the gallbladder channel is linked organically with the liver channel, while the bladder channel is connected to this channel indirectly through the kidney channel. Due to the direct connection between the gallbladder and liver channels, the impacts of this channel in regulating the chi free flow and relieving pain are far more than the bladder channel (11).

One of the factors affecting the pain and duration of labor is uterine contractions. The results of this study showed that the mean duration of uterine contractions 30 min after the last intervention, 30 min after each intervention cycle, and during the whole first stage of labor in the intervention groups was more than the control group. However, the duration of uterine contractions 30 min post-intervention and during the whole second labor stage was not significantly different between the groups. One of the reasons for not having an effect of acupressure in the second stage of labor might be the short duration of intervention (a pressure cycle in intervention groups).

The results of this study revealed that the duration of uterine contractions augmented simultaneously with the reduction of labor pain during labor in the intervention groups. The acupressure not only can increase the intensity and duration of uterine contractions by stimulating oxytocin secretion from the posterior pituitary, but also may relieve the pain by secreting the endogenous endorphins (20).

Chung et al. (2003) reported that applying pressure on the LI4 and BL67 points caused a decrease in pain intensity in the first labor stage, but did not have any effect on the uterine contractions (15). Therefore, the results of their study are in line with the findings of the present study in attenuating the pain during the first stage of labor. However, it is inconsistent in terms of not affecting the uterine contractions.

These mismatching results of the two studies can be attributed to the difference in measuring the uterine contractions. In the study performed by Chung et al., the uterine contractions were measured by a monitoring device and tracing was assessed pre- and post-intervention, whereas we measured the uterine contractions manually.

Kordi et al. (2009) argued that the duration of uterine contractions in the group with pressure on SP6 had no significant difference with the two groups of touch and control (1). The results of the latter study are in disagreement with our findings. The varieties in the study channel and point, study design, and method of pressure can result in the different findings.

There were several limitations in the present study, including the variable viewpoints of the research units toward acupressure, in addition to the individual physiological differences in the threshold of pain tolerance and response rates to acupressure. On the other hand, the physical factors, such as light, noise, and educational status of the hospital could affect the level of pain expressed by the participants. These issues were attempted to get controlled by random allocation of the individuals in the three groups and the labor delivery recovery rooms.

**Implications for Practice**

In general, the results of this study demonstrated that the pressure on the bladder-GV20 and gallbladder-GV20 points relieved the pain intensity in the first and second stages of labor and increased the uterine contractions in the first labor stage. Therefore, these points can be used in the
clinics to relieve the pain of women during labor. On the other hand, the results of the current study suggest that a research should be performed on these points with more pressure cycles in the second stage of labor.

Acknowledgments
The present study is part of a research project from the Master thesis at Mashhad University of Medical Sciences with the ethics code of IR.MUMS.REC.1396.40. The study was registered at the Iranian Registry of Clinical Trials with the code of IRCT20170503033796N2. The authors would like to thank and appreciate all the officials of Mashhad University of Medical Sciences, all midwives, physicians, and residents of the Um Al-Benin Specialized Women's Hospital. Moreover, the authors would extend their gratitude toward the mothers who participated in the current study.

Conflicts of Interest
The authors declare that there is no conflict of interests regarding the publication of this article.

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