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**Review Article**

# The Effect of Massage Therapy on Pain Intensity in Fracture Patients : A Systematic Review

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**Abstract**

**Aims**: Pain disorders are common in patients with fracture disease. Massage therapy is considered effective for reducing the pain intensity of fracture patients. The Purpose of the Systematic review is to investigate the effect of massage therapy on pain intensity in patients with fractures.
**Methods:** The English full-text research publications from 2012 to 2023 that were found using the Google Scholar, Pubmed, and Science Direct databases were published in China (4 articles) and Iran (2 articles). Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) techniques, articles were chosen. Quality assessment was conducted using the Joanna Briggs Institute (JBI) Critical Appraisal Skills Programme. Six articles examined pain intensity with the usual Visual Analogue Scale (VAS).
**Results:** The outcomes achieved were Six articles. It has also been demonstrated to lessen fracture patients' pain. Numerous massage therapy techniques, such as foot massage, reflexology massage, auricular acupressure, and elbow massage therapy, were employed in the studies that made up the evaluation. In the intervention and control groups, the mean pain intensity scores before and after the intervention were 5.72 + 0.97 and 5.66 + 0.92, respectively. The three measures of pain intensity in the intervention group showed a significant difference, according to the Friedman test.
**Conclusion:** The analysis concludes that massage therapy is a highly effective means of reducing pain in those who have suffered fractures. More investigation is need to confirm these results and assess different forms of massage therapy, though.

**Keywords:**
**Fracture, Massage Therapy, Pain, Randomized Controlled Trial, Visual Analog Scale**

## INTRODUCTION

Pain is a common phenomenon after all surgeries. After surgery, there is often acute discomfort that needs to be relieved while the body heals. Tissue gets injured during surgery. Sensitization of peripheral and central pain pathways as well as emotions of dread, anxiety, and frustration are some of the responses that are triggered by surgical injury in the pain matrix (1). About 70% of patients report having excruciating pain during the first 24 hours following surgery. Excessive pain following surgery raises the risk of drug abuse, impairs lung function, can induce pneumonia or tachycardia, raises blood pressure, slows healing, and lengthens hospital stay (2). Even though prescription drugs are the most often used pain relief technique, up to

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80% of cases still report having postoperative pain (3). Non-pharmacological pain treatment methods have come to the attention of nursing systems due to side effects of medications and other issues such as inadequate or non-accessible anodynes (4).

Pharmacological and non-pharmacological methods are the two therapies or approaches available to nurses for managing pain. A nurse can adopt an autonomous strategy by using a non-pharmacological technique. On the other hand, chronic pain is treated with several of these non-pharmacological methods. Non-pharmacological remedies need to be developed more and more in a number of areas, including acute postoperative pain, due to concerns about the adverse effects of pharmaceutical treatment (1).

A complementary and alternative intervention approach could be a successful method for improving adherence and managing pain (5). Complementary medicine is among the non-pharmacological methods. Traditional treatments can be used with complementary therapies such body and mind therapy, massage, acupuncture, and relaxation therapy to lessen postoperative discomfort (6). Massage therapy (MT), one of the most well-liked non-drug therapies, is the therapeutic manipulation of the body with the hands or mechanical equipment to keep it supple (7). Massage treatment is one of the approved and successful complementary and alternative therapies. Osteoarthritis sufferers find that massage therapy helps them relax and have a better quality of life (8). Additionally, using massage as a relaxation method could enhance sleep quality (5).

A randomised clinical trial was carried out by (9), investigating the impact of foot massage on pain intensity and anxiety in patients who have undergone surgery for a tibial shaft fracture. The outcomes showed that patients who had tibial shaft fracture surgery experienced less anxiety and pain. As a result, massage is advised in orthopaedic surgery as a noninvasive and appropriate intervention, particularly following tibial shaft fracture procedures. Furthermore, the study "Effect of Foot Reflexology on Postoperative Pain in Patients Having Tibia Plating Surgery: A Randomised Clinical Trial" shows that In patients having tibia plating surgery, foot reflexology treatment lowers postoperative discomfort. So, patients undergoing orthopaedic surgery can benefit from this technique by feeling less pain and anxiety (2). A reviews that prove the benefits of massage therapy for pain level in fracture patients. Based on these descriptions, the authors are interested in analyzing the effect of massage therapy for pain level in fracture patients using a systematic review method of various relevant research results. The results of current research on the effectiveness of massage therapy for reducing pain levels in fracture patients would be compiled in our review.

## METHODS

A systematic review was used in this study design. Secondary data from multiple scientific publications were used as the data sources, and various restrictions, including the year of language, publishing, and study methodology. The author conducted several search processes to obtain relevant articles about Massage Therapy On Pain Intensity In Fracture Patiens. Searching procedure was conducted through Google Scholar, Pubmed, Science Direct databases. In the process of searching for the article, the sample keywords used such as “massage therapy” and “pain” and “fracture” and “rct. The inclusion criteria in this study include accessible full-text, English-language articles, quantitative research types, articles with a maximum publication of the last 10 years (2013-2023), and articles that focus on Massage Therapy On Pain Intensity In Fracture Patiens. While the exclusion criteria are using a language other than English, and articles publication more than 10 years.

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We selected articles using the preferred Reporting Items For Systematic Reviews and Meta-Analyses (PRISMA) techniques (9). the PRISMA Flow Diagram as a guide, this research completed the study selection procedure. In addition, the results of the selection of journals are determined using keywords, and validated against inclusion criteria, exclusion criteria, and titles. The inclusion creteria were based on PICO (Population = fractures patient, intervention = massage therapy, Comparison=between massage therapy and other control techniques, and Outcome =Pain Intensity). Observational studies, study protocols, and review articles were the exclusion criteria. Extraction was done manually by analyzing the title articles, author and year publication, design, intervention, Sample and sampling technique, tools, and outcome (Table 1). content analysis screening was completed by the other authors. The article selection process is carried out by looking at the title, content of the article, and inclusion criteria . So finally, there are six articles according to the conditions carried out a synthesis. The PRISMA diagram below illustrates the process of selecting articles according to the title and research inclusion criteria so that six articles that meet the requirements are obtained. To evaluate the calibre of research publications, we employed the Critical Appraisal Skills Programme JBI in quality appraisal (10). The data was analysed using a theme analysis, which involved the following steps: 1) comprehension of the data, 2) recognition of codes, 3) extraction of themes from the codes, 4) repeating of the themes, and 5) definition of themes (11). The summary of the studies or data extraction is in Table 1.

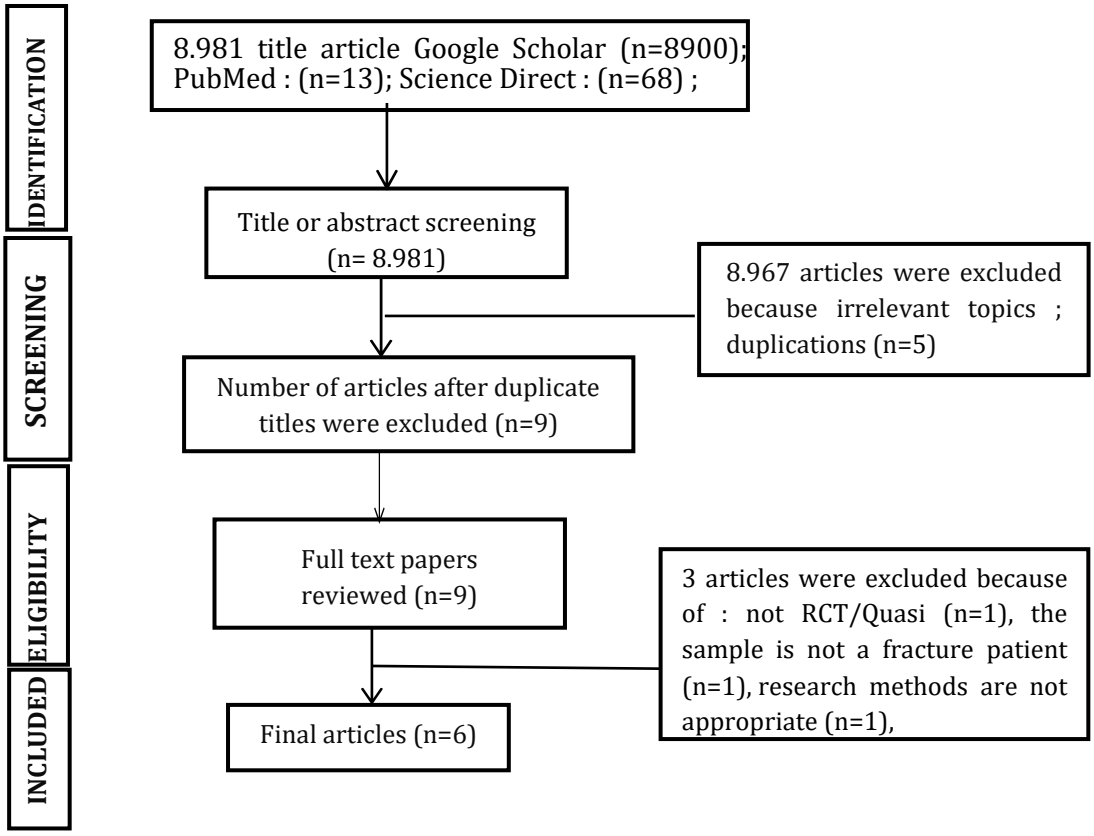


**Figure 1. flowchart of article selection**

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Search Outcome, We found 8.900 articles from Google Scholar, 13 from PubMed, and 68 from Science Direct. Title and abstract screening were firstly done, 8.972 articles were excluded. There were 9 articles for full-text review, 3 of which were excluded. Finally, six articles were included (See Figure 1). Of the six articles, two studies investigated the The Effect of Foot Massage on Pain Intensity, two studies investigated effect of high-quality nursing and comfort nursing on Pain Intensity, one studies investigated the Auricular Acupressure for Managing Postoperative Pain, and one study gave Elbow Pressing Method Combined with Zhongtong Ling Application for reduce Postoperative Pain.

Quality Assessment Results. Out of the six publications, two have moderate validity and four have good validity results due to the fact that neither the participants nor the people not administering the therapy were blind to the assignment of treatment. (See Table 1).

**Table 1. CASP JBI analysis**

| No. | Item | Article Quality Assessment | | | | | |
|---|---|---|---|---|---|---|---|
| | | **1** (12) Chang et al, 2012 | **2** (13) Qiu et al, 2022 | **3** (2) Imani et al, 2020 | **4** (14) Yu et al, 2021 | **5** (15) Zhu et al, 2023 | **6** (16) Pasyar et al, 2018 |
| 1. | *Was truerandomization used for assignment of participants totreatment groups?* | Y | Y | Y | Y | Y | Y |
| 2. | *Was allocation to treatment groups concealed?* | Y | Y | Y | Y | Y | Y |
| 3. | *Were treatment groups similarat the baseline?* | Y | Y | Y | Y | Y | Y |
| 4. | *Were participants blind to treatment assignment?* | N | NA | U | Y | Y | Y |
| 5. | *Were thosedelivering treatment blind to treatment assignment?* | N | Y | N | Y | Y | Y |
| 6. | *Were outcomesassessors blind to treatment assignment?* | Y | N | N | N | Y | U |
| 7. | *Were treatmentgroups treatedidentically other than the intervention ofinterest?* | Y | Y | Y | Y | Y | Y |
| 8. | *Was follow upcomplete and ifnot, were differences between groupsin terms of their follow upadequately described and analyzed?* | N | Y | Y | N | N | Y |
| 9. | *Were participants analyzed in thegroups to whichthey were randomized?* | Y | Y | Y | Y | Y | Y |
| 10. | *Were outcomes measured in the same way for treatment groups?* | Y | Y | Y | Y | N | Y |
| 11. | *Were outcomesmeasured in a reliable way?* | Y | Y | Y | Y | Y | Y |
| 12. | *Was appropriate statistical analysis used?* | Y | Y | Y | Y | Y | Y |
| 13. | *Was the trial's design suitable, and were any departures from the conventional RCT design (parallel groups, individual randomization) taken into consideration during the trial's conduct and analysis?* | Y | Y | Y | Y | Y | Y |
| Prosentase | | 76,9 | 84,6 | 76,9 | 84,6 | 84,6 | 92,3 |
| Result | | *Include* | *Include* | *Include* | *Include* | *Include* | *Include* |

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# RESULTS

## Analytical Findings

The results of the literature search found 6 articles that met the criteria in Google Scholar, Pubmed, Science direct. Articles come from publications from 2012 to 2023. Research locations in China (4 articles or 67%), Iran (2 articles or 33%). The results of the assessment with the Joanna Briggh Institute (JBI) Critical Appraisal Skills Program (CASP) 2020 found 6 articles of good quality. This review has 648 patients as participants in total. Participants weren't all elderly. Most of them aged more than 40 years, for a number of children's ages 16,37%. The research was carried out in China (66,67%) and Iran (33,37%). There were six studies carried out in a medical facility (2,12–16).

## Type of Massage Therapy

Massage Therapy from six selected literature consists of various therapies. Two of the six articles that are widely used are reflexology massage therapy on the soles of the feet, reflexology massage on the auricular part of the ear, seft therapy, a combination of elbow massage with traditional treatment, and the use of comfortable treatments that include environmental management, psychological management, and pain management, as well as rehabilitation training.

Auricular Acupressure is given with auricular acupressure involving the placement of patches on certain auricular acupressure points performed by a trained acupressure therapist. The patches contain magnetic beads placed on auricular acupressure points on the Segment (TF4) and subcortex (AT4). These patches are maintained for 3 days and given to patients by applying finger pressure and massage on these auricular acupressure points three times a day (at nine in the morning, one in the afternoon, and five in the evening) for three minutes each point (12). Next, the radial side of the forearm is treated three to five times with the Zen one-finger approach, rolling, kneading, and soaking techniques used in traditional elbow massage therapy. Additionally, some acupuncture points receive pressure. (13). The therapy that is widely used in the article is foot massage therapy. This intervention is performed in the form of a foot massage (including the foot, heel, and toes) from the heel to the tip of the toes. The intervention involved massaging the feet for ten minutes (five minutes for each leg), using sweet almond oil, the most often used lubricant in massage therapy.

## Measurement of Pain Levels

Based on multiple experiments, six articles employed the traditional Visual Analogue Scale (VAS) to measure the severity of pain. measured the Foot Reflexology Visual Analogue Scale before and just after the intervention, as well as 2, 4, 6, 12, and 24 hours after the procedure (2). The most popular lubricant used in massage therapy, sweet almond oil, was utilised to provide Foot Reflexology participants a 10-minute foot massage (five minutes per leg) (16). Articles and measures for foot reflexology Measurements using the Visual Analogue Scale were taken both 0.5 and 2 hours before and after the intervention. Using Zhongtong's Visual Analogue Scale (VAS) score in conjunction with the elbow push, the degree of discomfort is measured and compared prior to intervention (T1), one month following intervention (T2), and three months following intervention (T3). Next, pain is tracked at 1, 3, and 7 days following surgery using the Visual Analogue Scale (VAS) scores for both groups. This allows us to evaluate the effect of great nursing care on pain. From the first to the fourteenth day after surgery, comfort nursing care is used in conjunction with rehabilitation education on joint function, discomfort, and Visual Analogue Scale (VAS) score.

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**Table 2. Summary of Included Studies**

| Title articles | Authors and year of publication | N | Design | Intervention | Sample and sampling technique | Tool | Outcome |
|---|---|---|---|---|---|---|---|
| Auricular Acupressure for Managing Postoperative Pain and Knee Motion in Patients with Total Knee Replacement: A Randomized Sham Control Study | Ling-hua Chang, Chung-Hua Hsu, Gwo-Ping Jong, Shungtai Ho, Shiow-luan Tsay, and Kuan-Chia Lin (2012) | 62 | Randomized controlled trial. Randomly assigned to the acupressure group and the sham control group (n=31 peer grup) | • Auricular acupressure therapy was used by the therapist. As part of the auricular acupressure process, skin-colored adhesive tape containing magnetic beads was put to the auricular acupoints and remained in place for three days. After that, acupressure was administered three times a day (9 AM, 1 PM, and 5 PM) by repeatedly pressing the acupoints with the fingertips for three minutes each. The last therapy was given at 5:00 PM on the third day after surgery.<br>• In the control group, acupoints were taped with skin-colored adhesive tape in addition to routine care; however, acupressure or massage were not applied. | teknik random sampling | The VAS is a visual analogue scale that ranges from 0 to 100; the SF-MPQ is a Short-Form McGill Pain Questionnaire ; and the Pain PPI is the SF-MPQ's current pain intensity score. | When applied at particular therapeutic locations, auricular acupressure enhances knee mobility and considerably reduces the need for narcotic analgesia in TKR patients (VAS 58.66 ± 20.35). Patients in the acupressure group and the sham control group used analgesic medications at significantly different rates, as indicated by P < 0.05. |
| Application Value of Elbow Pressing Method Combined with | Liyi Qiu, Youren Wang, and Xiaoyu Wang | 82 | clinical study that utilized a randomized controlled trial design | • the intervention group was given the Elbow massage techniques were delivered three to five times on the radial side of the forearm to the intervention group. These | convenience random sampling | VAS: visual analog scale for pain number 0 to 10; | Research indicates that in children with supracondylar humerus fractures, a combination of elbow massage and |

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| Zhongtong Ling Application in Children with Swelling and Pain after Operation of Supracondylar Fracture of the Humerus | (2022) | | with two groups (control & intervention) with pretest-posttest (n=41 peer grup) | techniques comprised rolling, kneading, soaking, and the one-finger Zen method. In addition, certain acupuncture sites are highlighted.<br>• control group, the intervention carried out was traditional treatment without using elbow massage methods. | | | conventional therapy effectively reduces postoperative pain. Before, one month, and three months after the intervention, the patients' level of pain was measured using the Visual Analogue Scale (VAS). With a p-value < 0.001, the research group (n = 41) had a mean VAS score of 5.66±2.12, whereas the control group (n = 41) had a mean VAS score of 7.88±1.61. |
| Effect of Foot Reflexology on Postoperative Pain in Patients Undergoing Tibia Plating Surgery: A Randomized Clinical Trial | Fatemeh Imani, Ebrahim Nasiri , Houshang Akbari , Mohammad Reza Safdari (2020) | 96 | randomized clinical trial with two groups (control & intervention) with pretest-posttest (n =48 peer grup) | • treatment group, participants received An hour prior to shin plate placement surgery, use reflexology massage techniques on the soles of the feet for ten minutes. Pressure is used to the reflex spots on the foot soles in order to perform this technique.<br>• control group, participants only received touch on the feet for one minute without pressure | teknik randomized method sampling | VAS: visual analog scale for pain number 0 to 10; | Baseline pain levels in the treatment group were 8.4±0.9 and 8.1±0.9, respectively, prior to intervention; following intervention, pain scores in this group decreased to 6.9±1.1 and 8.1±1.0, respectively (P<0.001). At various points following surgery, such as 2, 4, 6, 12, and 24 hours, there was also a notable decrease in postoperative pain levels. |
| Analysis of effect of high-quality nursing | Guozhu Yu, Suo Ma, Xiaoli | 78 | prospective randomized controlled | • The intervention group was given the technique with structured education and | technic randomizatio n sampling, | VAS: visual analog scale for pain | The research indicates that the SEFT education |

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| on pain of emergency orthopedic trauma patients and related factors affecting postoperative pain | Zhang, Shuangshuang Liu, Lili Zhang, Lingxia Xu (2021) | trial with two groups (control & intervention) with pretest-posttest (n=39) | placing emphasis on the frontal part of the head. This seft technique is to focus so that the pain is reduced. By tapping lightly with your fingers on the frontal part of the head for 5 minutes.<br>• The control group was not given any assistance. | the research group and the control group | number 0 to 10; | approach reduces pain perception. The research group (n=39) had a mean VAS score of 7.31±1.39 before the procedure, and it was 5.84±1.10 one day later. The control group (n = 39) had a mean VAS score of 7.22±1.30 before the procedure and 6.44±1.35 on the first postoperative day. A statistically significant difference between the two groups was shown by a P-value of less than 0.05. |
| Effects of comfort nursing combined with rehabilitation training on joint function, pain level and quality of life in patients with lower extremity fractures | Bo Yang, Yan Wang, Yanying Zhu (2023) | 117 Randomized controlled trial with two groups (control & intervention) with pretest-posttest (n=59) | • Joint mobility rehabilitation approaches, pain management, and psychological support were provided to the intervention group. By diverting the patient's attention from their condition and their discomfort, comfort care attempts to raise the patient's pain threshold and tolerance.<br>• The control group was not given any assistance. | randomly sampling | VAS: visual analog scale for pain number 0 to 10; | The research group (n = 59) had a mean VAS score of 5.72±1.20 on the first post-operative day, while the control group (n = 58) had a mean VAS score of 5.90±1.34 on the same day. Between the two groups, there was no statistically significant difference (P>0.05). 12. No discernible effect of breastfeeding comfort on pain was found. |

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| The Effect of Foot Massage on Pain Intensity and Anxiety in Patients Having Undergone a Tibial Shaft Fracture Surgery: A Randomized Clinical Trial | Nilofar Pasyar, PhD, Masoume Rambod, PhD,and Fateme Rezaee Kahkhaee,(2018) | 66 | Randomized clinical trial with a pre-post design (n=33) | • • The intervention group's feet (including the foot, ankle, heel, and toes) were massaged for five minutes on each foot for a total of ten minutes using sweet almond oil, the most common lubricant used in massage therapy. During the massage, the patient's feet were raised with the use of a pillow. The massage technique was used on both the top and bottom of the feet, with the thumb on the bottom and the toes on the top. After that, the bottom of the foot was given a gentle thumb massage. We repeated this method five or ten times. Approximately twenty hours after the surgery, on the second day, the intervention group received foot massages.<br>• The control group was not given any assistance | teknik randomized method sampling | VAS: visual analog scale for pain number 0 to 10; | Studies show that receiving massage therapy reduces anxiety and discomfort in patients undergoing tibial shaft surgery. Prior to and after the intervention, the average pain intensity scores for the intervention and control groups were 5.72 + 0.97 and 5.66 + 0.92, respectively. The Friedman test revealed a significant difference between the three pain intensity ratings in the intervention group (x2 = 27.63, P < 0.001). |

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## DISCUSSION

Massage therapy is one of the nursing therapies that can be used independently and efficiently to help fracture patients feel less pain (17). based on a study of the literature that comprised six scholarly works that evaluated the effects of massage therapy interventions on fracture pain levels using a randomised control trial methodology. discovered the results showing that massage therapy was successful in reducing discomfort overall. The synthesis of the six publications' characteristics revealed that a randomised control trial was a component of the research design approach. This is due to the fact that it considers the degree of evidence-based research, which includes studies with the following hierarchy of quality: cross-sectional, cohort, case control, quasi-experiment, randomised control trial, clinical trial, systematic review, and meta-analysis. Every study type has unique qualities and benefits; research is better at higher study levels. Furthermore, the choice of sample size has an impact on the article's quality; the higher the sample size, the more precise and superior the research done (18).

This systematic review provides evidence that massage therapy effectively reduces the intensity in postoperative pain. There are six massage therapy techniques found in this systematic review: Two of the six articles that are widely used are reflexology massage therapy on the soles of the feet, reflexology massage on the auricular part of the ear, seft therapy, a combination of elbow massage with traditional treatment, and the one article use of comfortable treatments that include environmental management, psychological management, and pain management, as well as rehabilitation training.

### Type of Massage Therapy

The acupressure method of auricular massage, which uses finger pressure and massage on the auricular acupoints after the treatment, has proven to be easy and safe to use in perioperative healthcare settings. The study protocol was based on professional recommendations regarding acupuncture practice. Even though age, gender, and Body Mass Index were balanced in the groups, indicating good randomization, we tightened the control over BMI in the statistical analysis to improve the validity of our findings because BMI can obscure the need for postoperative analgesics. We minimised potential biases by using a double-blinded study design. Sufficient blinding of patients and data collectors improved the credibility of the primary finding (12).

Massage therapy based on foot reflexology has been found to have potential health benefits. Reflexology on the feet is a centuries-old therapeutic modality. For ten minutes, various spots on the bottom of the foot must be compressed (19). One more piece of writing The intervention foot massage was performed on the feet (the feet, legs, heels, and toes were included) for five minutes on each leg (total time: ten minutes) using sweet almond oil, the most widely used lubricant used in massage therapy. Each subject's foot was raised with a pillow while they were getting massages. The massage technique was given to both sides of the foot, with the fingers on the dorsal side and the thumbs on the plantar side. The plantar portion of the foot was then touched with one thumb, gradually increasing in power as it progressed higher. The therapist's fingertips landed on the dorsal side of the toe when the patient faced them and applied pressure to the plantar side of the foot. This method was applied to the toes after initially being utilised on the heel. There were five to ten iterations of this procedure (20). Compared to preoperative and postoperative care, massage treatment was found to have a more notable impact on fractures. Massage therapy interventions showed a more notable reduction in postoperative pain. After surgery fractures, massage treatment is a workable and appropriate remedy (21). A quick and easy non-pharmacological treatment that can be

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used in a hospital setting to help fracture patients experience less pain is foot massage therapy. It is easy to use and may be done anytime you like.

The resource function of massage therapy intervention is considerable, as massage techniques are relatively simple and inexpensive. It can be included as part of non-pharmacological treatment to benefit fracture patients. This study therefore has an important impact in further aspects of nursing. Massage treatment essentially works by stimulating the brain's motor neurons through the release of transmitters, such as acetylcholine, which in turn causes cells to activate calcium, which in turn produces protein integrity. Myosin in skeletal muscle is activated when calcium and troponin C are triggered, which helps to preserve function and lessen muscle stress. The process of contraction can result in more smooth muscle in the limbs. Chemical, neuromuscular, and muscular activation can all be enhanced by massage. Actin and myosin filaments in smooth muscles interact chemically. Calcium ions and ATP trigger the contact process, which transforms into ADP to supply energy for limb muscle contraction. (22).

**Measurement Of Pain Levels**

A painful subjective experience brought on by a tissue injury or potential injury is called pain. The most popular method for measuring pain is the visual analogue scale (VAS). The progression of pain levels that a patient may feel is represented graphically by this linear scale. According to this study, individuals who had surgery to treat a tibial shaft fracture experienced less worry and pain. Similar research demonstrated that, in male patients undergoing arthroscopic knee surgery, pain severity decreased following a brief massage of the healthy foot, hands, and upper shoulder (23). A systematic review This intervention may reduce anxiety and pain after surgery, according to a thorough investigation on the effect of massage treatment on anxiety and pain severity after surgery (24). A different report that is comparable to this one suggests that massage reduces acute postoperative pain (25). According to other research, massage treatment lessens discomfort (6). Additionally, studies have shown that massage therapy reduces pain (21).

Massage therapy is effective 3 days after surgery because the pain level begins to decrease and in research conducted (16), foot massage therapy is effective 2 hours after surgery. Because the pain level began to decrease. As for acupressure, it is effective on day 3 after surgery. General advantages are relevance to the topic, detailed explanation of interventions, and systematic evaluation of results.

## CONCLUSION

Patients with fractures may have less severe pain after receiving progressive massage therapy. Progressive muscle relaxation procedures vary depending on the kind of massage therapy, how often it is performed each day, how long it lasts, and when pain is evaluated following fracture surgery. Notwithstanding variations in massage therapy techniques, every study documented noteworthy outcomes regarding the impact of massage therapy on mitigating pain intensity in patients suffering from fractures.

**Conflict Of Interest**
The Author of this article declares that there was No. conflict of interest

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**Ethics Approval**
Not applicable

**Author Contribution**
All stages of this research, including preparation, data collecting, data analysis, preparation, and approval for publishing of this manuscript, are equally contributed to by all authors

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