

Relationship between Proprioception and Risk of Falling in Patients with Chemotherapy-Induced Peripheral Neuropathy

ISRAA S. ABDELHAMEED, M.Sc.*; NAHED A. SALEM, Ph.D.*; MOHAMED A. HASSAN, M.D.** and RANIA M. TAWFIQ, Ph.D.*

The Department of Physical Therapy for Neurology and Neurosurgery, Faculty of Physical Therapy, Cairo University and Department of Clinical Oncology**, Faculty of Medicine, Cairo University*

Abstract

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is an adverse effect of cancer treatment that results in sensory impairment and, in severe cases, can also result in further motor manifestations, including cramping, weakness, and/or wasting of the muscles. Proprioception is essential for maintaining joint stability during movement. Thus, proprioceptive impairment may be a predisposing factor for postural instabilities and a higher likelihood of falling.

Aim of Study: To investigate the relationship between proprioception impairment and the risk of falling in CIPN patients.

Subjects and Methods: Seventy-five patients with pathologic diagnoses of cancer and CIPN from both sexes with ages varying between 40 and 60 years old were included in this study. Patients were diagnosed based on careful clinical evaluation by the neurologist and nerve conduction study (NCS) and recruited from the Centre of Clinical Oncology and Nuclear Medicine, Kasr Al-Aini Hospital. Proprioception was measured by a joint position reproduction (JPR) test using a digital inclinometer at 10° dorsiflexion (DF), 11° and 25° plantarflexion (PF) in eye open position (EOP) and eye closed position (ECP), and the risk of falling was measured by the Timed Up and Go (TUG) test and Functional Reach Test (FRT).

Results: There were non-significant correlations between risk of falling (TUG, FRT tests) and joint position error (JPE) at all angles in EOP and ECP except a weak positive significant correlation between TUG and JPE (at 10° DF of the right side in ECP and at 25° PF of the left side in ECP) and a weak negative significant correlation between FRT and JPE (at 10° DF of the right side in EOP and at 25° PF of the left side in EOP and ECP respectively).

Conclusion: There is a weak relationship between proprioception impairment and the risk of falling in patients with chemotherapy induced peripheral neuropathy.

Correspondence to: Dr. Israa S. Abdelhameed,
The Department of Physical Therapy for Neurology and Neurosurgery, Faculty of Physical Therapy, Cairo University

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Introduction

CHEMOTHERAPY-INDUCED peripheral neuropathy (CIPN) is a prevalent, quite severe, and dose-limiting adverse effect of cancer treatment. Tingling, numbness, burning, and pain are among the sensory symptoms that make up the clinical picture of CIPN. In cases of greater severity, there may also be motor manifestations, including cramping, weakening, and wasting of the muscles [1].

Individuals who have neuropathy at baseline, are older, have diabetes, or are smokers have clinical risk factors that set them up for polyneuropathy. Thirty percent of patients with polyneuropathy continue to have symptoms six months or more after finishing treatment. Polyneuropathy may persist for weeks to months following the initial course of treatment [2].

Chemotherapeutic agents cause neurotoxic consequences on sensory cellular bodies in the dorsal root ganglia (neuronopathy), the myelin sheath (myelinopathy), and the axonal components (axonopathy), which include the mitochondria, ion channels, microtubules, and related capillaries. Typical degenerative pathways are then set off, which may cause the loss of epidermal fibers by causing the generation of pro-inflammatory cytokines, activating apoptotic signaling cascades, and changing neuronal excitability. Since the peripheral nervous system (PNS) is not as well protected from neurotoxic harm as the central nervous system (CNS), its dorsal root ganglia are susceptible to damage. This could help to explain why people with CIPN tend to have more sensory involvement [3].

Proprioception is essential for maintaining joint stability during movement. So, proprioceptive im-

pairment may be a risk indicator for clinical pain development [4]. A distorted kinaesthesia (both throughout the joint and within its neuromuscular control) impairs normal joint function. It may cause an imbalance in the production of muscle force, hence increasing the risk of joint injuries [5].

The symptoms of CIPN can include muscular weakness, loss of ankle reflexes, and deficits with equilibrium, coordination, and gait control. These issues greatly raise the possibility of falling and its subsequent related injuries [6].

So, this study aimed to explore the relationship between proprioception impairment and the risk of falling in patients with CIPN.

Patients and Methods

This is a cross-sectional observational study was performed at the Centre of Clinical Oncology and Nuclear Medicine, Kasr Al-Aini Hospital in the period from January 2023 to June 2023. All patients were evaluated and assessed as one group by the digital inclinometer for proprioception impairment and by the timed Up and Go and functional reach tests for the risk of falling. The Faculty of Physical Therapy's Ethical Committee, at Cairo University has authorized the current research (No: P.T.REC/012/003605).

Participants:

Seventy-five patients with pathologic diagnoses of cancer and CIPN were included in this study. Patients were diagnosed based on careful clinical evaluation by the neurologist and nerve conduction study (NCS). Participants were considered suitable for this study based on the subsequent criteria for eligibility. (1) Age ranged from 40 to 60 years old; (2) Both sexes; (3) The duration of treatment with chemotherapeutic agents was from the beginning of treatment up to 6 months; (4) They were medically stable; (5) Independently ambulant patients; (6) The body mass index ranged from 18.5 to 30kg/m²; and (7) The performance status ranged from 0 to 2, according to the World Health Organization.

Patients who met any of the following criteria were not allowed to take part in the study: (1) A history of other neuropathies (such as genetic peripheral neuropathy linked to nutritional agents or neuropathy related to paraneoplastic syndrome); (2) Any illnesses that could aggravate peripheral neural damage, which includes diabetes, impaired kidney function, alcoholism, deficiencies in vitamin B12, HIV, vasculitis, cerebral or spinal cord tumors; (3) Balance-related orthopedic problems, vestibular system disorders, or visual impairment; (4) Motor impairment such as muscle weakness caused by motor peripheral neuropathy or any other neurological or musculoskeletal disease; (5) Orthostatic hypotension; (6) Moderate to severe fatigue according to the Fatigue Severity Scale (FSS).

Procedures:

Study objectives and procedures were explained to each participant before starting the study, and a consent form was signed by each participant. Also, they were informed that the data collected would be used for publication. All participants' characteristics regarding age, height, weight, and BMI were collected.

Determination of body mass index (BMI):

The following formula was used for estimating BMI: BMI = Weight (kg) / height (m)².

Orthostatic hypotension assessment:

This involved taking blood pressure readings while sitting and standing. Orthostatic hypotension is indicated by a drop of 20 millimeters of mercury (mm Hg) in the systolic blood pressure, and/or a drop of 10mm Hg in the diastolic blood pressure within 2 to 5 minutes of standing.

Evaluation of ankle proprioception using the digital inclinometer:

The measurement of ankle proprioception was performed individually for the right and left feet using a digital inclinometer. Ankle proprioception was assessed at angles of 10° DF, 11° PF and 25° PF in EOP and ECP positions, utilizing the active reproduction test [7].

Repeated positioning, whether actively or passively, is known as joint position sense. Initially, the extremity that was attached to the inclinometer was positioned at the desired angle, and a minimum of 10 seconds elapsed to allow the subject to memorize this position. Subsequently, the extremity was moved to its initial position. The participant was instructed to actively return the extremity to the desired position. The measurement of the angular error, which represents the deviation from the target angle, was recorded. Active positioning refers to the capability of actively returning the extremity to its intended posture. This measurement assesses the functioning of muscle and capsular receptors. Following a preliminary examination, the participants were instructed to adjust their ankles to specific angles. The optimal measurement, which indicated the closest distance to the desired angle, was documented throughout the three trials. The evaluation procedures were conducted bilaterally, on both the left and right sides [7].

Evaluation of risk of falling using Timed Up and Go (TUG) Test:

The TUG is a valid and reliable dynamic balancing measure that can be utilized to track clinical changes over time. When using a modified cut-off score of 10.7 seconds, the TUG has been demonstrated to have a high diagnostic accuracy of 88.9%, a sensitivity of 90%, and a specificity of 88.5% [8].

• *Test steps and procedures:*

- a- The patient needs to take a seat in a standard arm-chair with his or her arms resting on the chair's arms and their back against it. Any walking assistance device should be close by.
- b- Conventional walking aids and shoes ought to be worn.
- c- Patients need to be told to walk at a speed that is both safe and comfortable.
- d- Time the test using a stopwatch, recording the results in seconds.
- e- Determine the length of a 3-meter (9.8-foot) walkway and label it.
- f- At the start of the walkway, set up a chair with a standard height (seat height 46cm, arm height 67cm).
- g- Tell the patient to sit on the chair, relax his or her arms on the chair, and support back against the chair.
- h- When using an assistance device for walking, the upper extremities should be close by but not on it.
- i- Guide the patient through the test.
- j- Say "Go" once the patient is ready. As soon as you press the start button, the stopwatch should begin, and it should stop when the patient's buttocks touch the chair seat.

• *Scoring [9]:*

- a- 10sec. or less: this is normal.
- b- 11-20sec: within the normal ranges for older people.
- c- 20-30 seconds: Poor mobility or might be due to poor mentality.
- d- 30 seconds or more: The patient is prone to falling or losing balance.

Evaluation of risk of falling using functional reach Test (FRT):

The longest distance that can be reached in a forward direction is measured by the FRT. It was demonstrated that for both younger and older persons, the FRT had high accurate validity, test-retest reliability, and interobserver reliability [10]. Every patient completed one practice trial and three test trials following the examiner's explanation and demonstration of the FRT. A tape measure that was fixed to the wall at the patient's acromion height was used to measure the distance in the FRT. An examiner took the starting and final reach positions while standing four feet away from the tape measure to determine the patient's reaching distance. Patients made a loose fist, stood with their feet comfortably spaced around shoulder-width apart, and positioned their arms parallel to the tape measure without contacting the wall (starting position). Next, the patients reached forward as far as they could without balance loss (end position). At both the starting and

ending positions of the tape measure, the third metacarpal joint's position was recorded. Patients were permitted to balance on their toes; however, the trial was deemed invalid if they touched the wall, stepped forward while reaching, or gripped their clothes with one hand. During the test, every patient was under observation. The functional reach was determined by taking the mean of the three test trials' initial and final positions [11].

Interpretation: extremely high fall risk: unreachable; Less than 6" (15,2cm) is a high risk of falling; between 6" and 10" (15,2 to 25,4cm) is a moderate risk of falling; and more than 10" (25,4cm) is a low risk of falling.

Sample size:

Sample size calculation was selected based on the previous study of Blackwood & Rybicki [12]. A sample size of 63 would achieve 80% power and Correlation Coefficient (r) = 0.346 and Coefficient of Determination (r^2): 0.12 with a significance level (α) of 0.05 using a two-tail exact correlation bivariate normal model. Assuming a 20% loss to follow-up, at least 75 patients were needed to conduct this study. Sample size calculation was done using G Power and Sample Size Calculations software, version 3.0.11 for MS Windows.

Data analysis:

The demographic information and data gathered about the subjects were presented using descriptive statistics. To find out how TUG, FRT, and ankle JPE are correlated, the Spearman rank correlation coefficient was used. $p < 0.05$ was established as the significance level for statistical tests. Version 25 of the Statistical Package for Social Sciences (SPSS) for Windows was used to conduct all statistical analyses.

Results

Subject characteristics:

In this study, 75 patients with CIPN took part. Their ages ranged from 40 to 60 years old, with a mean \pm SD of 50 \pm 6.31 years. Table (1) summarizes the characteristics of the participants.

Table (1): Participant characteristics.

	Mean \pm SD	Maximum	Minimum
Age (years)	50 \pm 6.31	60	41
Weight (kg)	61.60 \pm 8.21	79	45
Height (cm)	167.07 \pm 6.60	180	153
BMI (kg/m ²)	21.97 \pm 1.69	24.9	19.2
	N	%	
<i>Sex distribution, n (%):</i>			
Females	49	65	
Males	26	35	

SD: Standard deviation.

- TUG, FRT and ankle JPE of study group:

The mean value \pm SD of TUG in the study group was 10.54 ± 0.83 , with 8.11sec as a minimum value and 12.1sec as a maximum value. The mean value \pm SD of FRT was 28.42 ± 4.82 cm, with 20cm as a minimum value and 37cm as a maximum value. (Table 2).

Table (2): Descriptive statistics of TUG, FRI and ankle JPE.

	Mean \pm SD	Maximum	Minimum
TUG (sec)	10.54 ± 0.83	8.11	12.1
FRT (cm)	28.42 ± 4.82	20	37
JPE at 10° DF (degrees)			
<i>Right side:</i>			
EOP	2.31 ± 2.19	0	8
ECP	2.87 ± 2.61	0	7
<i>Left side:</i>			
EOP	2 ± 1.98	0	6
ECP	2.60 ± 2.29	0	7
JPE at 11° PF (degrees)			
<i>Right side:</i>			
EOP	1.91 ± 1.80	0	7
ECP	2.27 ± 1.85	0	7
<i>Left side:</i>			
EOP	2.09 ± 2	0	7
ECP	2.17 ± 1.83	0	6
JPE at 25° PF (degrees)			
<i>Right side:</i>			
EOP	1.48 ± 1.65	0	6
ECP	1.47 ± 1.68	0	7
<i>Left side:</i>			
EOP	1.91 ± 2.02	0	7
ECP	1.69 ± 2.26	0	8

SD: Standard deviation.

The ankle JPE ranged from 0 to 8 degrees. The highest JPE was for the right side in ECP at 10° DF of 2.87 ± 2.61 degrees and for the left side in ECP at 10° DF of 2.60 ± 2.29 degrees. The lowest JPE was for the right side in ECP at 25° PF of 1.47 ± 1.68 degrees and in EOP of 1.47 ± 1.68 degrees. (Table 2).

Correlation between TUG and ankle JPE:

The correlations between TUG and JPE at 10° DF were weak positive non-significant correlations with the right side in EOP ($r = 0.165, p = 0.157$), the left side in EOP ($r = 0.210, p = 0.071$), and the left side in ECP ($r = 0.161, p = 0.167$). The correlation between TUG and JPE at 10° DF of the right side in ECP was a weak positive significant correlation ($r = 0.260, p = 0.024$). (Table 3).

The correlations between TUG and JPE at 11° PF were weak positive non-significant correlations with the right side in EOP ($r = 0.009, p = 0.941$), the right side in ECP ($r = 0.152, p = 0.194$), the left side

in EOP ($r = 0.086, p = 0.461$), and the left side in ECP ($r = 0.019, p = 0.872$). (Table 3).

The correlations between TUG and JPE at 25° PF were weak positive, non-significant correlations with the right side in EOP ($r = 0.058, p = 0.623$), the right side in ECP ($r = 0.035, p = 0.767$), and the left side in EOP ($r = 0.066, p = 0.574$). The correlation between TUG and JPE at 25° PF of the left side in ECP was a weak positive significant correlation ($r = 0.272, p = 0.018$). (Table 3).

Table (3): Correlation between TUG and ankle JPE.

	TUG	
	r-value	p-value
JPE at 10° DF (degrees)		
<i>Right side:</i>		
EOP	0.165	0.157
ECP	0.260	0.024*
<i>Left side:</i>		
EOP	0.210	0.071
ECP	0.161	0.167
JPE at 11° PF (degrees)		
<i>Right side:</i>		
EOP	0.009	0.941
ECP	0.152	0.194
<i>Left side:</i>		
EOP	0.086	0.461
ECP	0.019	0.872
JPE at 25° PF (degrees)		
<i>Right side:</i>		
EOP	0.058	0.623
ECP	0.035	0.767
<i>Left side:</i>		
EOP	0.066	0.574
ECP	0.272	0.018*

r-value: Spearman rank correlation coefficient.

p-value: Probability value.

* Significant at $p < 0.05$.

Correlation between FRT and ankle JPE:

The correlations between FRT and JPE at 10° DF were weak negative significant correlation with JPE at 10° DF of the right side in EOP ($r = -0.281, p = 0.015$), while there were weak negative non-significant correlation with JPE at 10° DF of the right side in ECP ($r = -0.088, p = 0.452$), left side in EOP ($r = -0.128, p = 0.275$), and left side in ECP ($r = -0.059, p = 0.613$). (Table 4).

The correlations between FRT and JPE at 11° PF were weak negative non-significant correlations with the right side in EOP ($r = -0.115, p = 0.326$), the right side in ECP ($r = -0.052, p = 0.658$), the left side in EOP ($r = -0.202, p = 0.082$), and the left side in ECP ($r = -0.106, p = 0.364$). (Table 4).

The correlations between FRT and JPE at 25° PF were weak negative non-significant correlations with the right side in EOP ($r = -0.012, p = 0.915$) and with the right side in ECP ($r = -0.021, p = 0.855$), while there were weak negative significant correlations with the 25° PF of the left side in EOP ($r = -0.241, p = 0.037$) and with the left side in ECP ($r = -0.261, p = 0.024$). (Table 4).

Table (4): Correlation between FRT and ankle JPE.

	FRT	
	r-value	p-value
JPE at 10° DF (degrees)		
<i>Right side:</i>		
EOP	-0.281	0.015*
ECP	-0.088	0.452
<i>Left side:</i>		
EOP	-0.128	0.275
ECP	-0.059	0.613
JPE at 11° PF (degrees)		
<i>Right side:</i>		
EOP	-0.115	0.326
ECP	-0.052	0.658
<i>Left side:</i>		
EOP	-0.202	0.082
ECP	-0.106	0.364
JPE at 25° PF (degrees)		
<i>Right side:</i>		
EOP	-0.012	0.915
ECP	-0.021	0.855
<i>Left side:</i>		
EOP	-0.241	0.037*
ECP	-0.261	0.024*

r-value: Spearman rank correlation coefficient.

p-value: Probability value.

* Significant at $p < 0.05$.

Discussion

The purpose of this research was to examine and evaluate the association between proprioception impairment and fall risk in patients with CIPN. There were non-significant correlations between risk of falling (TUG, FRT tests) and joint position error (JPE) at all angles in EOP and ECP except a weak positive significant correlation between TUG and JPE (at 10° DF of the right side in ECP and at 25° PF of the left side in ECP) and a weak negative significant correlation between FRT and JPE (at 10° DF of the right side in EOP and at 25° PF of the left side in EOP and ECP respectively).

The CNS, in accordance with Shumway-Cook and Woollacott [13], incorporates visible, vestibular, and proprioceptive information to generate motor

orders that synchronize the activation patterns of muscles to regulate our sense of equilibrium. According to sensory reweighting theory, which was presented by Pasma et al. [14], the CNS can optimize balance regulation by shifting its reliance on more trustworthy information sources. In order to compensate for other diminished sensory inputs, the CNS combines a particular type of sensory stimulation with balance control [15]. Neuroplastic alterations to the CNS in response to persistent impairments in disorders like PN might delay somatosensory reweighting, or they can occur rapidly, for instance when walking blindfolded or with experimentally diminished somatosensation [16].

According to a case study of a unique patient who lost all large fiber sensory afferents in their body, Horak et al. [17] reported that auditory cues implying perturbation onset may elicit functional postural responses while the direction of perturbation is expected, which supports our study findings. Other studies have also suggested that postural compensation for sensory feedback loss may comprise sensory substitutes and anticipatory mechanisms, with a higher sensitivity to the residual unaffected sensory information [18].

Our findings were also consistent with those of Simmons et al. [19], who discovered that patients with cutaneous sensory deficits use a compensatory motion that is an early switch from an ankle to a hip strategy for maintaining their balance when their sensory input is impaired.

Furthermore, our study's findings agreed with those of Bloem et al. [20], who examined diabetic polyneuropathic (DPN) patients with documented lower limb proprioceptive impairment and found no variations in the patients' and healthy controls' responses to balance correction.

Additionally, DeMott et al. [21], who reported that most patients with PN exhibit fairly normal and stable locomotion behaviors and that most of their falls occur when they have to react rapidly to perturbations like uneven surfaces or unexpected objects, confirm the findings of our study. The justification for that is the ability of the CNS to make a compensatory recovery for the ankle proprioceptive impairment only, which occurred due to the CIPN by the normally functioning other body systems that are required for maintaining our balance (e.g., motor, vestibular, and visual systems).

According to Li et al. [15], proprioception's significance was masked by partial substitution from other sensory subdivisions (such as foot sole cutaneous sensations). Furthermore, Najafi et al. [22] reported that DPN patients may utilize previous experience (e.g., feed forward prediction) and unaffected sensory systems to compensate for the diminished sensory feedback.

The results of the current study are corroborated by Najafi et al. [23], who examined balance control in DPN patients as well as healthy volunteers standing on a soft surface (modifications in somatosensory feedback). They discovered that in DPN patients, the CNS develops an innovative motor compensatory mechanism to anticipate the changes and thereby adapt to the distorting somatosensory input.

However, Kolb et al. [24] found that the sensory manifestations of CIPN are indicators of a higher risk of falling and a higher utilization of healthcare services.

In addition, Hanewinckel et al. [25] revealed that participants with confirmed polyneuropathy were more prone to falls and their subsequent injuries.

Furthermore, Reeves et al. [26] found that peripheral neuropathy (PN), which affects up to half of polyneuropathic patients, is linked to peripheral sensory and motor nerve lesions and acts as an independent risk indicator for falling. The exploration of this contrast between the two findings may be due to the variations in the patients participated in both studies as in our study we select patients with CIPN suffering from ankle proprioception impairment only without any problem in any other system affecting balance and postural stability as motor, vestibular and visual systems while in their study they select patients suffering from both sensory and motor dysfunctions.

The present study has some limitations as lack to study the relation between proprioception impairment and risk of falling in CIPN patients treated with different types of chemotherapy drugs to study the neurological complications of each drug separately and more correlations are needed to study this relation among different ages and among each sex separately so further studies are needed to overcome these limitations.

Conclusion:

There is a weak relationship between proprioception impairment and the hazard of falling in patients with CIPN.

Conflict of interest:

The authors declare no conflict of interest.

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العلاقة بين الإحساس العميق وخطر السقوط فى مرضى اعتلال الاعصاب الطرفية الناجم عن العلاج الكيمايى

خلفية: يعد اعتلال الاعصاب الطرفية الناتج عن العلاج الكيمايى أحد الاعراض الجانبية الناتجة عن علاج مرض السرطان والذي ينتج عنه تلف عصبى حسى وفى الحالات المتقدمة قد يتسبب فى بعض الاعراض العصبية العضلية مثل التقلص العضلى والوهن العضلى وضهور العضلات. يعد الاحساس العميق عامل رئيسى لاستقرار المفاصل اثناء الحركة، وعليه فان ضعف الاحساس العميق قد يؤدى لعدم الاستقرار الوضعى وزيادة خطر السقوط.

هدف الدراسة: اجريت هذه الدراسة لتحديد ما إذا كان هناك علاقة بين الاحساس العميق وخطر السقوط فى مرضى اعتلال الاعصاب الطرفية الناتج عن العلاج الكيمايى.

الاشخاص والوسيلة: تم اختيار خمسة وسبعين (٧٥) مريضاً باعتلال الاعصاب الطرفية الناتج عن العلاج الكيمايى من الجنسين كعينة لهذه الدراسة تتراوح اعمارهم ما بين ٤٠ الى ٦٠ عاماً، وتم تشخيص المرضى من قبل اخصائى المخ والاعصاب بواسطة جهاز رسم الاعصاب فى مركز قصر العينى للأورام والطب النووى، وتم قياس الاحساس العميق باختبار استعادة وضعية المفصل باستخدام جهاز مقياس الميل الالكترونى عند الزاوية ١٠° من ثنى مفصل الكاحل والزاويتين ١١° و ٢٥° من المفصل فى حال ابقاء العين مفتوحة ومغمضة، وقياس خطر السقوط باختبار الوقت المحدد للنهوض والتحرك واختبار الوصول الوظيفى.

النتائج: اظهرت النتائج انه لا يوجد علاقة إحصائية واضحة بين ضعف الاحساس العميق (معامل خطأ وضع المفصل فى ثنى وفرد مفصل الكاحل) وخطر السقوط (اختبار الوقت المحدد للنهوض والتحرك واختبار الوصول الوظيفى) فى كل الزوايا فى كل من وضعى ابقاء العين مفتوحة ومغمضة باستثناء علاقة طردية ضعيفة بين اختبار الوقت المحدد للنهوض والتحرك ومعامل خطأ وضع المفصل عند الزاوية ١٠° من ثنى مفصل الكاحل الايمن فى حال ابقاء العين مفتوحة والزاوية ٢٥° من المفصل فى حال ابقاء العين مفتوحة وكذلك علاقة عكسية ضعيفة بين اختبار الوصول الوظيفى ومعامل خطأ وضع المفصل عند كل من الزاوية ١٠° من فرد مفصل الكاحل الايسر فى حال ابقاء العين مفتوحة والزاوية ٢٥° فى حال اغماض العين.

الاستنتاج: من النتائج الاحصائية لهذه الدراسة العملية نستنتج وجود علاقة ضعيفة بين الاحساس العميق وخطر السقوط فى مرضى اعتلال الاعصاب الطرفية الناتج عن العلاج الكيمايى.