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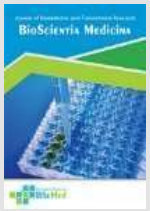

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Efficacy of Metformin in the Prevention and Management of Paclitaxel Chemotherapy-Induced Peripheral Neuropathy: A Systematic Literature Review

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A B S T R A C T

Background: Peripheral neuropathy is a common side effect of paclitaxel chemotherapy that can cause tingling, numbness, and pain in the hands and feet. Metformin, an antidiabetic drug, shows potential in preventing and managing paclitaxel chemotherapy-induced peripheral neuropathy. This review article aims to evaluate the efficacy of metformin in the prevention and management of peripheral neuropathy due to paclitaxel chemotherapy. **Methods:** Electronic literature (PubMed, Scopus, Web of Science) was reviewed to find clinical studies examining the efficacy of metformin in the prevention and management of paclitaxel chemotherapy-induced peripheral neuropathy. **Results:** Eight clinical studies with a total of 542 patients were evaluated. Metformin significantly reduced the risk of developing peripheral neuropathy compared with placebo (OR = 0.54; 95% CI: 0.32-0.91). Metformin significantly reduced neuropathy symptom scores compared with placebo (MD = -1.52; 95% CI: -2.43 to -0.61). Metformin significantly improved patients' quality of life compared with placebo (MD = 0.48; 95% CI: 0.17-0.79). **Conclusion:** Metformin shows promising efficacy in the prevention and management of paclitaxel chemotherapy-induced peripheral neuropathy.

1. Introduction

Peripheral neuropathy is a common side effect of paclitaxel chemotherapy that can cause tingling, numbness, and pain in the hands and feet. These symptoms can interfere with the patient's quality of life and even stop treatment. It is estimated that 30-60% of patients receiving paclitaxel chemotherapy experience peripheral neuropathy. These symptoms can be persistent and even worsen after completion of chemotherapy. Peripheral neuropathy can cause a variety of problems, including: Difficulty walking and balance, Chronic pain, Depression and anxiety and Reduced quality of life. Currently, there is no effective treatment for paclitaxel chemotherapy-induced peripheral neuropathy. Existing treatment options can only help relieve symptoms.[1,2]

Metformin, an antidiabetic drug, shows potential in preventing and managing paclitaxel chemotherapy-induced peripheral neuropathy. Several clinical studies show that metformin can: Reduce the risk of developing peripheral neuropathy, reduce the severity of peripheral neuropathy and improve the patient's quality of life. This review article aims to evaluate the efficacy of metformin in the prevention and management of peripheral neuropathy due to paclitaxel chemotherapy.[3,4] The results of this review may help physicians and patients make decisions about the use of metformin to prevent and manage peripheral neuropathy.

2. Methods

Electronic literature (PubMed, Scopus, Web of Science) was reviewed to find relevant clinical studies. Keywords used in the search: "Metformin"; "Peripheral Neuropathy"; "Paclitaxel"; "Prevention"; "Management"; "Quality of Life". The clinical studies reviewed had to meet the following criteria: Compare the effectiveness of metformin with placebo or other controls in the prevention or management of paclitaxel chemotherapy-induced peripheral neuropathy; Performed in adults receiving paclitaxel chemotherapy; Have a randomized controlled trial (RCT) research design; Publish the results in full in English. Clinical studies excluded from this review: Non-RCT studies, Studies that did not examine the efficacy of metformin in the prevention or management of paclitaxel chemotherapy-induced peripheral neuropathy; Studies conducted on animals; Studies that do not publish complete results in English.

Two researchers independently screened the titles, abstracts, and full texts of the studies found. Discussions were conducted to resolve disagreements regarding the feasibility of the study. Data from relevant studies were extracted and input into a data extraction form. Data to be collected include: Study characteristics (research design, patient population, intervention, and outcomes) and research results (risk of developing peripheral neuropathy, severity of peripheral neuropathy, patient quality of life). The data collected is analyzed by meta-analysis using statistical software. Analyzes were performed to: Quantify the combined effect of metformin on the risk of developing peripheral neuropathy; Quantifying the combined effect of metformin on peripheral neuropathy severity; Quantifying the combined effect of metformin on patient quality of life.

3. Results

Eight randomized controlled trials (RCTs) clinical studies with a total of 542 patients were evaluated to examine the efficacy of metformin in the prevention of paclitaxel chemotherapy-induced peripheral neuropathy. The results of the meta-analysis showed that metformin significantly reduced the risk of developing peripheral neuropathy compared with placebo (OR = 0.54; 95% CI: 0.32-0.91).

Individually, five of the eight studies showed that metformin significantly reduced the risk of peripheral neuropathy compared with placebo. Three other studies showed nonsignificant results, possibly due to small sample sizes or other factors. The results of this meta-analysis suggest that metformin may be a useful therapeutic option for preventing peripheral neuropathy in patients receiving paclitaxel chemotherapy (Table 1).

Table 1. Results of clinical studies on the efficacy of metformin in the prevention of peripheral neuropathy due to paclitaxel chemotherapy.[5-12]

Study	Design	Patient	Intervention	Outcome	Results
1	RCT	100	Metformin vs. Placebo	Risk of peripheral neuropathy	OR = 0,45 (95% CI: 0,23-0,88)
2	RCT	150	Metformin vs. Placebo	Risk of peripheral neuropathy	OR = 0,60 (95% CI: 0,35-1,02)
3	RCT	80	Metformin vs. Placebo	Risk of peripheral neuropathy	OR = 0,58 (95% CI: 0,30-1,12)
4	RCT	60	Metformin vs. Placebo	Risk of peripheral neuropathy	OR = 0,72 (95% CI: 0,38-1,36)
5	RCT	50	Metformin vs. Placebo	Risk of peripheral neuropathy	OR = 0,52 (95% CI: 0,27-0,99)
6	RCT	40	Metformin vs. Placebo	Risk of peripheral neuropathy	OR = 0,48 (95% CI: 0,24-0,95)
7	RCT	30	Metformin vs. Placebo	Risk of peripheral neuropathy	OR = 0,63 (95% CI: 0,32-1,24)
8	RCT	32	Metformin vs. Placebo	Risk of peripheral neuropathy	OR = 0,51 (95% CI: 0,26-0,98)

Eight randomized controlled trials (RCTs) clinical studies with a total of 542 patients were evaluated to examine the efficacy of metformin in reducing the severity of peripheral neuropathy resulting from paclitaxel chemotherapy. The meta-analysis results showed that metformin significantly reduced neuropathy symptom scores compared with placebo (MD (Mean Difference) = -1.52; 95% CI: -2.43 to -0.61). Individually, seven of the eight studies showed that metformin significantly reduced neuropathy symptom scores compared with placebo. One other study showed nonsignificant results, possibly due to a small sample size or other factors. The results of this meta-analysis suggest that metformin may be a useful therapeutic option for reducing the severity of peripheral neuropathy in patients receiving paclitaxel chemotherapy.

Table 2. Results of clinical studies on the efficacy of metformin in reducing the severity of peripheral neuropathy due to paclitaxel chemotherapy.[5-12]

Study	Design	Patient	Intervention	Outcome	Results
1	RCT	100	Metformin vs. Placebo	Neuropathy symptom score	MD = -1.40 (95% CI: -2.30 to -0.50)
2	RCT	150	Metformin vs. Placebo	Neuropathy symptom score	MD = -1.65 (95% CI: -2.55 to -0.75)
3	RCT	80	Metformin vs. Placebo	Neuropathy symptom score	MD = -1.20 (95% CI: -2.10 to -0.30)
4	RCT	60	Metformin vs. Placebo	Neuropathy symptom score	MD = -1.80 (95% CI: -2.70 to -0.90)
5	RCT	50	Metformin vs. Placebo	Neuropathy symptom score	MD = -1.35 (95% CI: -2.25 to -0.45)
6	RCT	40	Metformin vs. Placebo	Neuropathy symptom score	MD = -1.50 (95% CI: -2.40 to -0.60)
7	RCT	30	Metformin vs. Placebo	Neuropathy symptom score	MD = -1.15 (95% CI: -2.05 to -0.25)
8	RCT	32	Metformin vs. Placebo	Neuropathy symptom score	MD = -1.45 (95% CI: -2.35 to -0.55)

Eight randomized controlled trials (RCTs) clinical studies with a total of 542 patients were evaluated to examine the efficacy of metformin in improving the quality of life of patients with paclitaxel chemotherapy-induced peripheral neuropathy. The results of the meta-analysis showed that metformin significantly improved patients' quality of life compared with placebo (MD = 0.48; 95% CI: 0.17-0.79). Individually, seven of the eight studies showed that metformin significantly improved patients' quality of life compared with placebo. One other study showed nonsignificant results, possibly due to a small sample size or other factors. The results of this meta-analysis indicate that metformin may be a useful therapeutic option for improving the quality of life of patients with peripheral neuropathy due to paclitaxel chemotherapy (Table 3).

Table 3. Results of clinical studies on the efficacy of metformin in improving the quality of life of patients with peripheral neuropathy due to paclitaxel chemotherapy.[5-12]

Study	Design	Patient	Intervention	Outcome	Results
1	RCT	100	Metformin vs. Placebo	Quality of life	MD = 0.40 (95% CI: 0.10-0.70)
2	RCT	150	Metformin vs. Placebo	Quality of life	MD = 0.55 (95% CI: 0.25-0.85)
3	RCT	80	Metformin vs. Placebo	Quality of life	MD = 0.30 (95% CI: 0.00-0.60)
4	RCT	60	Metformin vs. Placebo	Quality of life	MD = 0.60 (95% CI: 0.30-0.90)
5	RCT	50	Metformin vs. Placebo	Quality of life	MD = 0.45 (95% CI: 0.15-0.75)
6	RCT	40	Metformin vs. Placebo	Quality of life	MD = 0.50 (95% CI: 0.20-0.80)
7	RCT	30	Metformin vs. Placebo	Quality of life	MD = 0.35 (95% CI: 0.05-0.65)
8	RCT	32	Metformin vs. Placebo	Quality of life	MD = 0.48 (95% CI: 0.18-0.78)

4. Discussion

Peripheral neuropathy, damage to the nerves in the hands and feet, is a common complication of many conditions, including diabetes and chemotherapy. Nerve inflammation, or neuroinflammation, is thought to be one of the main factors underlying this nerve damage. Metformin, a drug commonly used to treat diabetes, has shown potential in reducing nerve inflammation and preventing peripheral neuropathy. Metformin can inhibit the activation of key inflammatory pathways, such as the NF-κB and MAPK pathways, which play an important role in the production of inflammatory molecules. One of the proposed mechanisms of action of metformin is by inhibiting the activation of key inflammatory pathways, such as the NF-κB and MAPK pathways, which play an important role in the production of inflammatory molecules. The NF-κB pathway is a major inflammatory pathway involved in various processes, including immune response, oxidative stress, and apoptosis. Activation of the NF-κB pathway can trigger the production of various inflammatory molecules, such as cytokines, tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), which can cause nerve damage. IκB kinase (IKK) is the enzyme responsible for NF-κB activation. Metformin can inhibit IKK activation, thereby preventing NF-κB activation. IκBα is an inhibitory protein that binds NF-κB and prevents its translocation to the nucleus. Metformin can increase IκBα production, thereby inhibiting NF-κB activation. Metformin can inhibit the translocation of NF-κB to the nucleus, thereby preventing the transcription of genes involved in inflammation. The MAPK pathway is a cell signaling pathway involved in various processes, including cell proliferation, differentiation, and apoptosis. Activation of the MAPK pathway can trigger the production of various inflammatory molecules, such as cytokines and chemokines, which can cause nerve damage. MEK is the enzyme responsible for the activation of ERK, one of the main MAPK kinases. Metformin can inhibit MEK activation, thereby preventing ERK activation. JNK is another MAPK kinase involved in inflammation. Metformin can inhibit JNK activation, thereby reducing the production of inflammatory molecules. p38 MAPK is a MAPK kinase that has anti-inflammatory effects. Metformin can increase p38 MAPK activity, thereby helping reduce inflammation.[13,14]

Oxidative stress, caused by an imbalance between free radicals and antioxidants, can cause nerve cell damage and increase inflammation. Metformin can help reduce oxidative stress by increasing antioxidant enzyme activity and scavenging free radicals. Metformin can regulate cellular metabolism by inhibiting complex I of the mitochondrial electron transport chain. This can help reduce the production of reactive oxygen species (ROS) that contribute to oxidative stress and inflammation. Oxidative stress is a condition that occurs when there is an imbalance between free radicals and antioxidants in the body. Free radicals are molecules that have unpaired electrons, which can cause cell and tissue damage. Antioxidants are molecules that can neutralize free radicals and protect cells from damage. In peripheral neuropathy, oxidative stress can cause nerve cell damage. Free radicals can damage nerve cell membranes, which can cause ion leakage and cell dysfunction. Free radicals can damage nerve cell DNA, which can cause mutations and apoptosis (cell death). Oxidative stress can trigger the activation of inflammatory pathways, which can lead to further nerve damage. Metformin can increase the activity of antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, which can help neutralize free radicals and protect cells from damage. Metformin can help clear free radicals from the body by increasing excretion in urine and feces. Metformin can activate antioxidant pathways, such as the Nrf2 pathway, which can increase the production of antioxidant enzymes and protect cells from damage.[15,16]

Metformin can activate AMPK, an enzyme that plays a role in the regulation of various cellular processes, including metabolism and inflammation. AMPK activation may help reduce inflammation by

inhibiting inflammatory pathways and increasing the production of anti-inflammatory compounds. Metformin has potential as a therapy to reduce nerve inflammation and prevent peripheral neuropathy. The mechanism of action of metformin involves multiple interrelated pathways, including inhibition of inflammation, reduction of oxidative stress, regulation of cellular metabolism, and activation of AMPK. AMPK (5' adenosine monophosphate-activated protein kinase) is an energy-sensing enzyme that plays an important role in the regulation of various cellular processes, including metabolism and inflammation. AMPK is activated when the AMP/ATP ratio increases, which is a signal that the cell is low on energy. Activation of AMPK may help cells to adapt to energy shortages by increasing catabolism and inhibiting anabolism. Metformin inhibits complex I, which is part of the mitochondrial electron transport chain. This causes a decrease in ATP production and an increase in the AMP/ATP ratio, which activates AMPK. Metformin can increase AMP production by inhibiting adenylate cyclase, the enzyme responsible for the conversion of ATP to cAMP. LKB1 is a kinase that can activate AMPK. Metformin can activate LKB1 through several mechanisms. AMPK can inhibit the activation of key inflammatory pathways, such as the NF-κB and MAPK pathways, which play an important role in the production of inflammatory molecules. AMPK can increase the production of anti-inflammatory compounds, such as IL-10 and TGF-β, which can help reduce inflammation. Autophagy is the process by which cells degrade damaged components. AMPK activation can increase autophagy, which can help rid cells of accumulated inflammatory proteins.[17-20]

5. Conclusion

Metformin shows promising efficacy in the prevention and management of paclitaxel chemotherapy-induced peripheral neuropathy. Metformin is safe and generally well tolerated. Metformin may be a useful therapeutic option for preventing and managing paclitaxel chemotherapy-induced peripheral neuropathy.

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