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SYSTEMATIC REVIEW: ANALYSIS OF THE CORRELATION BETWEEN NEUROPATHIC PAIN AND VEGF LEVEL

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ABSTRACT

Neuropathic pain is caused by a lesion or disease of the somatosensory system, including peripheral fibres (Aβ, Aδ and C fibres) and central neurons, and affects 7–10% of the general population. Multiple causes of neuropathic pain have been described and its incidence is likely to increase owing to the ageing global population, increased incidence of diabetes mellitus and improved survival from cancer after chemotherapy. Literature search through database PUBMED using the keyword “neuropathic pain” combined with several terminologies such as: 'vascular endothelial growth factor', and 'VEGF'. We take only randomized control trial with English language. We excluded studies that specifically examined another induceable factor which can also cause neuropathic pain. Twenty four hundred and two hundred sixty seven kinds of literature were found, 53 of which were related to neuropathic pain and VEGF, only 6 included the study criteria. The occurrence of neuropathic pain is closely related to increased levels of VEGF-A bound to its receptor, namely VEGFRs. Increased VEGF-A can occur in both the central and peripheral nervous systems which is influenced by various conditions such as hypoxia, inflammation, leukocyte accumulation, increased blood sugar levels in diabetes mellitus, and malignancy. Stem cell therapy with VEGFA has been developed and can be a therapeutic option in neuropathic pain.

Keywords: Neuropathic pain, vascular endothelial growth factor

1. INTRODUCTION

Neuropathic pain is the kind of pain caused by lesions or diseases of the somatosensory system, including peripheral fibers (Aβ, Aδ and C fibers) and central neurons, and affects 7-10% of the general population. Various causes of neuropathic pain have been described and its incidence is likely to increase due to an aging global population, increased incidence of diabetes mellitus and improved survival from cancer after chemotherapy.[1]

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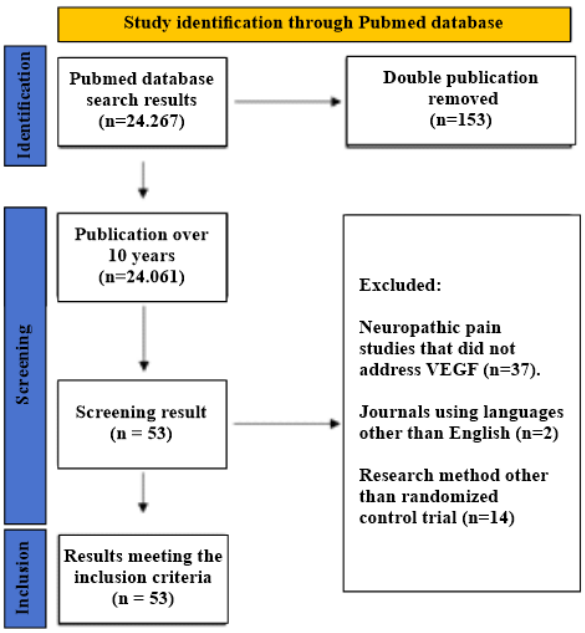
Epidemiological studies have shown that their prevalence in the general population may be as high as 7 to 8%, accounting for 20 to 25% of individuals with chronic pain. Clinically, neuropathic pain syndromes are characterized by a combination of positive and negative phenomena. Positive phenomena include various pain symptoms, paresthesias and/or dysesthesias, which by definition are abnormal painless sensations (e.g., tingling, numbness, tingling). Negative phenomena usually include neurological sensory deficits in the painful area, along with other deficits (motor, cognitive etc), depending on the location of the lesion.[2]

2. METHOD

2.1 Searching method and Inclusion Criteria

A search was conducted through an online database (PUBMED) with publication dates prior to the last 10 years for all studies related to 'neuropathic pain' and 'vascular endothelial growth factor'. Medical Subject The title or keyword we used in our search was "neuropathic pain" combined with some terminology such as: 'vascular endothelial growth factor' OR 'VEGF'. We only included English language studies, randomized control trials. We excluded studies that specifically examined other biomolecular factors that may induce the occurrence of neuropathic pain.

Figure 1. Reference selection



2.2 Screening and Data Extraction

Screening and data extraction were performed independently by the authors. All studies retrieved from the literature search were screened for relevance based on title and abstract according to the above inclusion criteria. Where relevance could not be determined based on the abstract and title, the full text was reviewed. Risk factors such as tumor, diabetes militus, neurological injury were extracted from all studies that met the inclusion criteria.

2.3 Risk of Bias Assesment

Newcastle-ottawa quality assessment scale was used to evaluate the risk of bias in this study. The criteria assessed were listed in several questionnaire questions with a total of 3 criteria. The risk of bias assessment was completed independently by the authors. The risk of bias assessment is shown in Table 1.

3. RESULT

From the search results there were 24,267 references, then there were 53 sources related to neuropathic pain but only 6 studies were included in this paper because 47 others did not meet the inclusion criteria. The 6 studies all used a randomized control trial research design. Figure 1 shows the flowchart of searching and collecting references.

4. DISCUSSION

4.1 Neuropathic pain

Neuropathic pain is caused by lesions or diseases of the somatosensory system, including peripheral fibers (Aβ, Aδ and C fibers) and central neurons, and affects 7-10% of the general population. Various causes of neuropathic pain have been described and its incidence is likely to increase due to an aging global population, increased incidence of diabetes mellitus and improved survival from cancer after chemotherapy.[1] There is no gold standard or set of methods or biological markers that can be related to neuropathic pain. Certain neuropathic pain conditions such as postherpetic neuralgia, diabetic neuropathic pain and central post-stroke pain may pose diagnostic problems, but the underlying cause is clear. For certain mixed conditions, it may be even more difficult to delineate the boundaries of neuropathic and non-neuropathic pain[3].

4.2 Role of VEGF in neuropathic pain

Vascular endothelial growth factor A (VEGF-A) is an anti parallel homodimeric "cys loop" protein. VEGF-A has isoforms VEGF-Axxxa and VEGF-Axxxb. The XXX variation is an amino acid (145, 165, 189, 206) genetically determined 'vegfa'[4]. VGEF-A as a whole has capabilities in neurobiology, neurotrophic, neuroprotective, and pro angiogenic factor[5]. In humans, recombinant human VEGFA165a (Rh-VEGF-A165a)

has a nociceptic effect in the form of pain sensitization, while Rh-VEGF-A165b has the opposite effect[6]. VEGFA receptors consist of two types including VEGFR-1 and VEGFR-2. VEGF-A165a has full agonist binding to VEGFR-1/2, while VEGF-A165b has partial VEGFR2 agonist/inhibitor binding properties to VEGF-A165a[4]. VEGF-A binding to VEGFR-1 occurs due to pathological processes such as inflammation or tumor associated angiogenesis while binding to VEGFR-2 in physiological processes of angiogenesis and neuroprotective mediation[7].

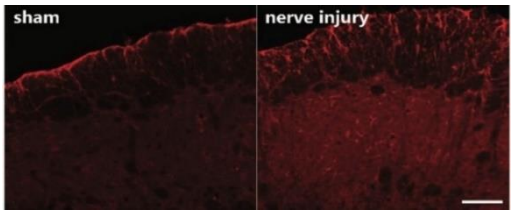


Figure 2. Comparison of VGEF-A changes in the medullary dorsal horn in the sham group (without dental implants) and with dental implant-fitted rats

4.2.1 Role of VEGF-A in neuropathic pain in the central nervous system

In previous studies, VEGF-A is known as a modulator of endothelial cell mitogenesis, vasculogenesis, and vascular permeability, angiogenesis, and lymphanogenesis. VEGF-A also has a role in neurobiological activities, namely neurotrophic and neuroprotective in the peripheral and central nervous system involving microglia, astrocytes, and schwann cells. In the experiment, the injection of VEGF-A inhibitor has an inhibitory effect on tactile allodynia when with partial sciatic nerve ligation, it is known that VEGF-A can modulate pain after trauma to the peripheral nervous system. Experiments in two groups of rats with teeth removed and replaced by implants and another group without implants to determine the role of VEGF-A in the central nervous system were carried out by changing the expression of VEGF-A in the medullary dorsal horn, because the medullary dorsal horn (trigeminal subnucleus caudalis) receives nociceptive information from the orofacial by evaluating changes in tactile allodynia and blood-brain barrier permeability through blockade of VEGF-A receptors (VEGF R-1/2)[5]. It was found that the implanted group of rats experienced upregulation of astrocytic VEGF-A in the medullary dorsal horn and mechanical allodynia. Inhibition occurs at VEGFR-1/2 receptors where specifically, inhibition of VEGFR-1 causes decreased blood brain barrier permeability; inhibition also occurs at VEGFR-2 significantly causing anti-allodynia. The downregulation of VEGF-A for mechanical allodynia was also evaluated with VEGF-A164 Si RNA and found to be significant in prolonging the effect of tactile allodynia[5]. Comparison of changes in VGEF-A levels in the groups without dental implants and with implants as shown in Figure 2.

In the results of this study, it is stated that the mechanism of neuropathic pain, especially the tactile allodynia effect, results from increased VEGF-A expression through two different mechanisms, first through VEGF-A R1 binding which will increase blood barrier permeability and have an effect on chronic neuropathic pain & VEGF-A R2 induces an increase in astrocytus cells in the central nervous system[5].

4.2.2 Role of VEGF-A in neuropathic pain in the peripheral nervous system

Neuropathic pain can be acute or chronic. In studies that emphasize the mechanism of chronic neuropathic pain conducted in rats with interventions in the form of partial sciatic ligation (PSL). PSL will induce the mechanism of injury and hypoxia, it will stimulate VEGF-A to bind to its receptors, namely VEGFRs. The injury activates the cytokine-chemocine complex, namely CXC-chemocine receptor 4 (CXCR4), then activates M1 & M2 macrophages mediated by macrophage inflamatory proteins (MIPs) along with monocyte chemoattractant-1 (MCP-1) to produce an inflammatory response. Inflammation and leukocyte accumulation cause chronic neuropathic pain[8]. Comparison of VGEF-A expression in bone marrow with fluorescent green as shown in Figure 3.

This study clarifies that the occurrence of neuropathic pain (tactile allodynia) occurs due to peripheral nerve injury that induces an increase in VEGF-A through the reaction of inflammation-associated leukocytes. Increased binding of VEGF-A R1 leads to excess accumulation of macrophages and VEGF-A R2 which affects endothelial cell proliferation to perform pathological angiogenesis, the effects of these two receptors later cause a neuroinflammatory state thus increasing peripheral nerve sensitization in neuropathic pain.

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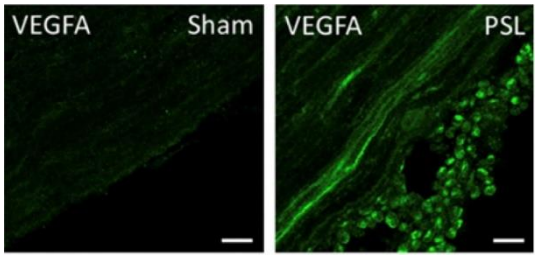

Figure 3. Comparison of localized VGEF-A expression in bone marrow with green fluorescent protein in the sham group (sciatic nerve) and with rats with partial sciatic nerve ligation**.**

4.2.3 Role of VEGF-A in neuropathic pain of diabetes millitus

In a study with mouse experiments, β-pancreas cells were ablated, causing type 1 diabetes millitus. This study is to determine chronic pain that often occurs in patients with diabetes. Pain sensitization was measured using von Frey filaments for mechanical stimulation and the Hargreaves test for heat stimulation and then evaluated the spinal cord using immunoblot. Pan-VEGF-A was not significantly decreased but VEGF-A165b was decreased. This increases the binding to VEGFR-2 increases, thus inducing vascular breakdown.[1,2,6]

In the study obtained in diabetes CD31 and IB4 decreased in endothelial cells so that vascular integrity decreases. Decreased levels of VEGFA165b as an anti-nociceptive cause pain stimulation in diabetes to increase followed by vascularization breakdown. Administration of Rh-VEGFA165b can reverse the neuropathic pain phenotype and prevent apoptosis[9]. Representation of epidermal/dermal nerve innervation and Langerhans cells with PGP9 staining as shown in Figure 4.

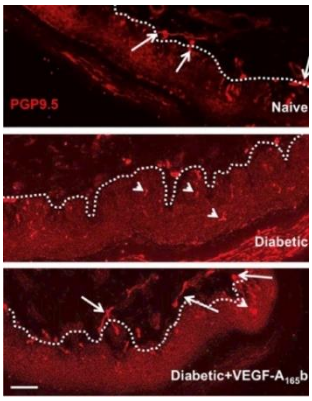

Figure 4. Representative images of epidermal/dermal nerve innervation (dotted lines) (arrows) and Langerhans cells (arrowheads) stained with PGP9.5 in plantar skin from naïve, diabetic, and VEGF-A165b-treated diabetic mice. Nerve cells and Langerhans cells were quantified on the same section.

4.2.4 Role of VEGF-A in tumor neuropathic pain

Anti-cancer chemotherapy causes neurotoxic effects that are often referred to as chemotherapy-induced neuropathy (CIN). Several studies have linked the role of stem cells in reducing the effects of CIN by increasing

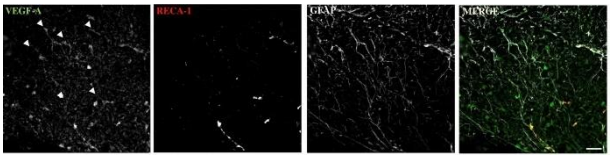

Figure 5. VEGF-A expression in spinal cord endothelial and astrocytic cells. VEGF-A immunoreactivity was analyzed in the dorsal cornu of the spinal cord of naive mice compared to RECA-1 positive endothelial cells and GFAP positive astrocytes; arrows indicate the presence of VEGF-A in astrocytes; scale: 100 m.

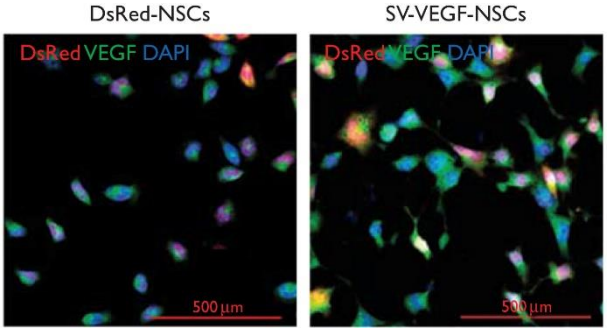

Figure 6. Fluorescence staining with DAPI (blue), VEGF (green), and DsRed (red) of DsRed-NSCs and SV-VEGF-NSCs in vitro. Scale: 500 m.

VEGF levels in mice given oxiplatin continuously. VEGF-A is an anti-parallel homodimeric protein "cys loop" that has a pro-angiogenic effect in forming blood vessels, vascular permeability and endothelial proliferation which in turn provides perfusion to the central nervous system[7]. In the case of tumors VEGFR-1 is more induced resulting in tumor infiltration, activation of tumor-associated macrophages of M2 phenotype, the trial administration of anti-VEGFR-1 mAb (D16F7) significantly and selectively inhibits VEGFR-1.

It was stated that spinal administration of VEGF-A165b resulted in binding with VEGFR-1 more strongly than VEGFR-2, causing a decreased pain threshold and hypersensitivity. This can be seen when immunofloresence astrocytus is more prominent as shown in Figure 5[7].

4.2.5 Role of Stem cells & VEGF in neuropathic pain

Neuropathic pain can be caused by mechanical trauma of the peripheral nervous system, tumors and infections. Stem cell transplantation studies have been developed that will improve neuronal function and regeneration in neuropathic pain. Currently developed gene therapy in neuropathic pain uses neural stem cells (NSCs) that express VEGF (SV-VEGF-NSCs)[10]. In an experiment with a sciatic nerve injury model, we compared DsRed-NSCs (stem cells without VEGF) with SV-VEGF-NSCs using fluorescence staining and enzyme-liked immunoabsorbent assay. Comparison of fluorescence in DsRed-NCSs with SV-VEGF-NCSs as shown in Figure 6.

It was confirmed that the remyelination effect of SV-VEGF-NSCs transplantation had a round shape in the myelin sheath and significantly increased myelination axon dansity compared with DsRed-NSCs. This proves that VEGF increases the survival rate of transplanted NSCs, angiogenesis effect in spinal cord injury, and reduces neuropathic pain[10].

5. CONCLUSIONS

The occurrence of neuropathic pain is closely related to increased levels of VEGF-A bound to its receptor, VEGFRs. The effect of VEGFRs on the occurrence of neuropathic pain, namely, VEGFA R1 binding can increase blood brain barrier permeability in central nervous system injuries, increase excess macrophage accumulation in peripheral nervous system injuries and reduce pain thresholds due to binding with VEGFA**165**b patients with chemotherapy; whereas VEGFA R2 binding induces an increase in astrocytus cells in central nervous system injuries, increases endothelial cell proliferation in pathological angiogenesis in peripheral nervous system injuries, increases vascular breakdown due to decreased VEGFA**165**b in diabetes millitus patients, and increases hypersensitivity in patients with chemotherapy. Currently, neural stem cells expressing VEGF have been developed to provide regeneration and remyelination effects in patients with neuropathic pain.

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Table 1. *Selection*

Domain	Geun W Lee et al. (2019)[5]	Madhavi Jere, et al. (2018)[6]	Laura micheli, *et al.* (2021)[7]	Norikazu Kiguchi *et al.* (2014)[8]	Richard *et al.* (2019)[9]	Hye-Lan Lee et al. (2015)[10]
Is the case definition adequate?	yes, with independent validation	yes, with independent validation	yes, with independent validation	yes, with independent validation	yes, with independent validation	yes, with independent validation
Are the cases representative?	sequential or clearly representative set of cases	sequential or clearly representative set of cases	sequential or clearly representative set of cases	sequential or clearly representative set of cases	sequential or clearly representative set of cases	sequential or clearly representative set of cases
Control selection	no description	no description	no description	no description	no description	no description
Definition of control	no source description	no source description	no source description	no source description	no source description	no source description

Table 2. *Comparability*

Domain	Geun W Lee et al. (2019)[5]	Madhavi Jere, et al. (2018)[6]	Laura micheli, *et al.* (2021)[7]	Norikazu Kiguchi *et al.* (2014)[8]	Richard *et al.* (2019)[9]	Hye-Lan Lee et al. (2015)[10]
Comparison of cases and controls by design or analysis	study control for receiving trigeminal subnucleus caudalis nociceptive stimuli	control study to determine the effect of diabetes on neuropathic pain	control study to determine the effect of diabetes on neuropathic pain	control study to determine the effects of inflammation and hypoxia on neuropathic pain	control study to determine the effect of diabetes on neuropathic pain	control study to determine the effect of stem cells on neuropathic pain

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Table 3. *Exposure*

Domain	Geun W Lee et al. (2019)[5]	Madhavi Jere, et al. (2018)[6]	Laura micheli, *et al.* (2021)[7]	Norikazu Kiguchi *et al.* (2014)[8]	Richard *et al.* (2019)[9]	Hye-Lan Lee et al. (2015)[10]
Clarity of exposure	blind case/control	blind case/control	blind case/control	blind case/control	blind case/control	blind case/control
Same case and control method?	Yes	Yes	Yes	Yes	Yes	Yes
Level of non-response	equal ratio for both groups	equal ratio for both groups	equal ratio for both groups	equal ratio for both groups	equal ratio for both groups	equal ratio for both groups