Hypothesis on the Treatment of Gliomas with Acupuncture at the Primo Node Corresponding to *Zusanli* (ST 36)

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ABSTRACT

Background: The primo vascular system (PVS) is an anatomical structure that is a network of ducts with fluid flowing in them, which are called primo vessels and correspond to acupuncture meridians, and primo nodes that correspond to acupoints. The PVS' main function is considered to be the maintenance of regenerative homeostasis in human and animal bodies. This system is distributed throughout the bodies of normal animals and develops around and in cancer tissues. This cancer-associated PVS may be a critical metastatic path besides the blood and the lymph vessels. The author of this article proposes a hypothesis on cancer treatment: Injecting anticancer drugs into acupoints according to the pharmacopuncture method can be effective as a result of the flow channels of the PVS. The author considers the acupoint *Zusanli* (ST 36) and the route of the primo vessels starting from it. This specific PVS route runs along the perineurium of the sciatic nerve, the pia mater, and the arachnoid mater of the spinal cord to the brain. Thus, by injecting a suitable anticancer drug into ST 36, one can deliver the drug into the brain to treat gliomas and other brain tumors. This new drug-delivery method is just one of the new clinical applications that are possible by combining acupuncture and using the PVS.

Conclusions: Anticancer drugs for glioma can be injected into the primo node at the acupoint ST 36 to reach the cancer tissue through the PVS in the sciatic nerve, spine, and brain that can avoid the blood–brain barrier.

Key Words: Acupuncture, Blood–Brain Barrier, Cancer, Glioma, Primo Vascular System, Pharmacopuncture, *Zusanli* (ST 36).

INTRODUCTION

SIGNIFICANT ADVANCES in cancer treatments have been achieved in the past decades,^{1,2} but cancer—with its related symptoms—still remains the most fearsome disease worldwide. The adverse events associated with cancer treatment—such as pain, nausea and vomiting, fatigue, and constipation—severely reduce patients' quality of life (QoL). Facing hopeless situations with Western medicine, many patients seek other modalities of treatments from among the various options available, for example, complementary and alternative medicine.^{3,4} One notable alternative therapy is pharmacopuncture, also known as acupoint injection or herbal acupuncture. Pharmacopuncture is a new therapy that combines acupuncture therapy and medication

by injecting pharmacologic medication or purified herbal medicine into acupoints. This new therapy is now widely used in China and Korea to address a range of symptoms, including cancer-related symptoms,⁵ and many reports have been published on pharmacopuncture's efficacy in clinical use; for example, this therapy has been shown to reduce pain significantly when used as a pain-treatment therapy.^{6–9}

Last year, a systematic review for assessment of using pharmacopuncture for cancer care was published.¹⁰ The authors performed a meta-analysis on trials of chemotherapy-induced nausea and vomiting (CINV) and found that pharmacopuncture relieved the severity of CINV significantly. Not only did pharmacopuncture significantly reduce the incidence of CINV in patients with various types of cancer, the therapy also resulted in significant relief of pain, ileus,

hiccups, fever, and gastrointestinal symptoms, as well as improving QoL. The authors conjectured that pharmacopuncture might help relieve various symptoms in patients who have cancer, but a firm conclusion could not be drawn because of the clinical heterogeneity and high risk of bias in the included studies.

Despite the clinical efficacy of pharmacopuncture, the mechanism by which it works has not been studied based upon anatomy and physiology. Without knowing the specific structure of the acupuncture points and meridians, tracing and analyzing the flow and the action of the herbal medicines that were injected at the acupoints are difficult.

The primo vascular system (PVS) was first discovered by Bong-Han Kim, MD, in the early 1960s as an anatomical structure corresponding to acupoints and meridians.^{11–15} The acupuncture points were named Bonghan corpuscles or primo nodes (PNs), and the meridians were called Bonghan ducts or primo vessels (PVs). His research was ignored for a long time until the year 2002 when a reinvestigation of Bong-Han theory and the PVS began.^{16,17} Since then, PVS research has been steadily progressing, and the PVS has been found in various organs of mice,¹⁸ rats,¹⁹ rabbits,²⁰ pigs,²¹ dogs,²² cows,²³ and humans.²⁴ Innate immune cells, especially mast cells, have been found to be highly concentrated in the PVS, suggesting that it has an immune function.^{25–27} In addition, hematopoietic stem cells²⁸ and small embryonic-like stem cells^{29,30} have been observed in the PVS, suggesting that it has a regenerative function.

Cancer-associated PVS (cancer-PVS), which was first observed around cancer tissues,³¹ was a new discovery in that the classic works of Kim^{11–15} did not report it. Since then, many articles, including a review article,³² have been published on cancer-PVS. Based on the finding of a cancer-associated PVS, the current author would like to propose a daring hypothesis: *By injecting herbal medicines into acupoints or primo nodes (in PVS terminology), the PVS can be used as drug-delivery path for cancer treatment. The injected medicine would flow in the primo vessels through the cancer-PVS and would arrive at the cancer tissues.* Specifically, the author considers the *Zusanli* (ST 36) acupoint as the injection point and gliomas as the target cancer. Thus, a significant clinical application of pharmacopuncture and the PVS combined would be to use the PVS to deliver herbal medicine injected at an acupoint to a target such as a tumor.

ACUPUNCTURE MERIDIANS AND THE PVS

The anatomical structures corresponding to acupuncture points and meridians have been studied by many researchers,^{33,34} and no structure other than the already-identified entities have been found by any of them. No one has reported any positive confirmation of Kim's works; neither has anyone been able to disprove Kim's results. For instance, Kellner tried but failed to observe the PNs in skin.³⁵

However, he used only conventional histologic analysis that could not distinguish the PNs from the surrounding connective tissues.

The descriptions of the anatomical characteristics of acupoints and meridians were surprisingly similar to that of the PVS reported by Kim. The following quote is from one of the reviews that described the distribution of blood vessels, peripheral nerves, and connective tissues around the acupoints and meridians:

Recent studies [^{37–39}] on acupoint morphology using various approaches, such as MRI [magnetic resonance imaging], anatomy, and XCT, have shown that the structural basis of the meridians and acupoints is complex and composed of connective tissue with numerous intertwining blood vessels, nerves, mast cells, and lymphatic vessels.³⁶

The tissues surrounding acupoints have been found to have an abundance of regularly distributed blood vessels. According to histologic observations, 99.6% of acupoints are located in tissues with an abundant distribution of small blood vessels and capillaries, and 45.5% of acupoints

FIG. 1. Bong-Han Kim, MD's original illustration of a primo node (PN), which is the specific structure corresponding to an acupoint, in the skin. Included are the: (1) epidermis; (2) hair; (3) thin outer smooth muscle; (4) thick outer smooth muscle; (5) inner substance; (6) chromaffin cells; (7) follicular structure; (8) cells of smooth muscle shape; (9) blood capillaries; (10) bundle of blood vessel and primo vessel; (11) skin-primo vessel; (12) radiating smooth-muscle fiber; (13) skeletal muscle; and (14) fibril. Used with permission from Fig. 1A in Soh KS et al. Fluorescent nanoparticles for observing primo vascular system along sciatic nerve. JAMS 2010;3(3):150–155.

FIG. 2. Comparison of the transports of cancer cells through lymphatic and primo vessels (PVs). (A) The secondary tumor (b) was formed after the primary tumor (a) (B) To identify the dissemination route of cancer cells, a skin incision was used to expose the bare tumor and its intact membrane carefully. Collective migration of cancer-cell clusters from the primary tumor and the secondary tumor via both a primo vessel (solid arrow) and a lymph vessel (dotted arrow) were observed. (C) The fluorescence image shows much stronger signals from the PV (solid arrow) than from the lymph vessel (dotted arrow), which shows that cancer cells migrated through the PV more than they did through the lymph vessel in this particular case. Adapted from Ref. 41. Permission sought.

FIG. 3. (A) Schematic illustration of the sciatic nerve of the lower limb and primo-vessels containing nanoparticles. The round spot is the *Zusanli* acupoint (ST 36) into which nanoparticles were injected. ①, ②, ③ are the three separate regions where the nanoparticles were detected in the primo vessels. Adapted from Ref. 52. (B) The network of primo vessels in the spinal cord and brain of a rabbit. The lines depict the primo vessels. The inset shows one of the peripheral nerves that come out from the spinal cord. Adapted from Ref. 13. Permission sought.

are located close to large blood vessels.⁴⁰ Kim's description is very specific about this:

Around the corpuscle (PN), the network of blood is particularly developed, part of which branches into the outer layer. Blood capillaries, varying in caliber, occupy the bulk of the central part of the inner substance, heavily convoluting in a spiral form. Though the nerve fibers are rather richly distributed in the tissue surrounding the Bonghan corpuscle, they are relatively scarce in the outer layer. The nerve fibers penetrating into the smooth muscle-like tissue of the outer layer terminate there, twisting spirally. Some nerve fibers enter the inner substance through the outer layer and ramify at their terminals.¹³

For the convenience of readers, an illustration of the Bonghan corpuscle is shown in Figure 1. It is surprising that the modern description and Kim's description of an acupoint are very close with respect to the distribution of blood vessels and nerves. Then, the question is: "Why is it that current researchers cannot identify the structures shown in Figure 1?" The author's educated guess is that the connective tissues, fascia, and collagen fibers of the tissues surrounding a PN and the tissues of the PN itself are too similar to be distinguishable with conventional histology such as hematoxylin and eosin, Mason's trichrome, and Picro-sirius reaction staining. Thus, the search for a specific staining technique to distinguish the tissue of a PN from the surrounding connective tissues would be a worthwhile endeavor.

CANCER-ASSOCIATED PVS AND CANCER METASTASIS

Cancer is dreadful because it metastasizes. The known major routes of cancer metastasis are the blood and the lymph systems. Epithelial malignancies, or carcinomas, typically begin their dissemination via the lymphatic route, whereas bone and soft-tissue tumors, or sarcomas, metastasize via the hematogenous route.

Because the PVS is a fluid-conducting system, it might be another metastasis route for cancer; indeed, strong evidence supports such a hypothesis: The transport of cancer cells from a primary tumor to secondary tumors at a distance through a PV has been observed.⁴¹ Near-infrared quantum-dot electroporation and multispectral fluorescence imaging were used for the *in vivo* imaging of quantum-dot-labeled lung-cancer cells inside the PVS around a superficially grown tumor and abdominal organs. These *in vivo* observations were confirmed by histologic analyses.

Figure 2 shows the primary tumor (Fig. 2A) and the secondary tumor (Fig. 2B and 2C) that was formed by cancer cells that migrated from the primary tumor. In this particular case, more cancer cells moved through the PV than through the lymph vessel.

The tremendous accumulation of knowledge regarding metastasis acquired through the application of genetic and

molecular biology still has not been able to provide an essential understanding of how to control and manage metastasis. Studies on the migration of cancer cells need some paradigm-shifting visions. The presence of a cancer-PVS around a tumor, which is a novel environment for cancer cells, may provide an innovative approach to cancer metastasis.

Since the first discovery of the cancer-PVS,³¹ several reports on the cancer-PVS by independent groups have followed.^{42–49} Among them, the studies on cancer stem cells in the cancer-PVS are worth particular attention.

Cancer stem cells have been the subject of intensive investigations in both oncology and stem-cell biology during the past 10 years.⁵⁰ Only this minority population of tumorigenic cells can drive tumorigenesis and disease progression. They are more resistant to chemotherapy and radiotherapy for various cancers.⁵¹ A tumor-derived PVS was reported to be present in murine xenografts of a human histiocytic lymphoma (U937) in the vicinity of the primary tumor.⁴⁵ The analysis of the mRNA isolated from the cells in the PVS showed high levels of human-stem-cell-specific transcription factors, including *KLF4* and *NANOG*, which are characteristic of a pluripotent and undifferentiated state of stem cells. This evidence of "stem-like" cells within the cancer-PVS supports the hypothesis that the cancer-PVS provides a unique "niche" environment for cancer stem cells and may be critical in tumor growth and metastasis.

HYPOTHESIS ON PVS AS A DRUG-DELIVERY PATH FOR PHARMACOPUNCTURE

Currently, pharmacopuncture is widely used in Korea and China for clinical purposes.¹⁰ However, whether the herbal medicine injected at acupoints flows along the meridians or is simply absorbed into the bloodstream or lymphatic flow is not known. Accordingly, the mechanism supporting the clinical effects of the medicine is hard to analyze scientifically. Nevertheless, because of the existence of the fluid-carrying PVS, a natural conjecture is that at least some of the medicine of pharmacopuncture flows through the PVs to other organs after having been absorbed in the PN at the acupoint. Hence, the PVS provides drug-delivery paths for the medicine used with pharmacopuncture.

To be specific, the path from the *Zusanli* (ST 36) acupoint along the PVs at the epi-, peri-, and endoneurium of the sciatic nerve toward the spinal cord,⁵² whose paths are depicted in Figure 3A, is considered. Then, the path continues through the primo vessels in the dura, arachnoid-, and pia mater of the spinal cord, as shown in Figure 3. Finally, the path reaches and spreads in the brain, some parts of which are illustrated¹³ in Figure 3B.

As a concrete suggestion, the glioblastoma or glioma would be a target for therapeutic application of this drug-delivery method. An anticancer drug could be injected into ST 36, and the drug could flow in the PVS along the sciatic nerve into the

spinal cord and, finally, to the brain. This drug delivery is especially promising because it avoids the blood–brain barrier for drugs. Thus, the PVS could become extremely useful for efficient drug delivery to the brain from the skin.

DISCUSSION

Acupuncture is an alternative medicine without a known system of scientific mechanisms because it lacks a known anatomical basis. For example, no specific structures specific to the acupuncture points and meridians have been found. Now, with the PVS as an anatomical-duct structure in which a specific liquid flows, acupuncture, especially pharmacopuncture, may have become a pioneering medical technique that can be studied with a host of modern scientific methods. Novel clinical applications are also expected, as suggested by the hypothesis in this article.

In the current author's hypothesis, ST 36 was chosen as the specific acupoint because Kim studied this point extensively for the anatomical and physiologic aspects of the PVS. Kim had described rather concretely that the PV starting from the PN at the *Zusanli* puncture links itself with the profund PN after running along the ischiatic nerves and blood-vessel bundles.¹²

One of Kim's physiologic studies on the PVS was to investigate the effects of cutting the PVs.¹³ The first experiment was about the influence on the spinal reflex time: After cutting the perineurial PV of the sciatic nerve of a frog, the spinal reflex became very unstable and the reflex time lengthened. The second experiment involved removal of the perineurial PV in the femoral region of the sciatic nerve of a frog. Removal of the perineurium accompanied a remarkable rise in the threshold of nerves. The third experiment established that, when the sciatic perineurium of a rabbit was stripped, then a "trophic ulcer" appeared on the rabbit's hind leg and degeneration occurred in the nerve fiber itself. These experiments showed that the PVS—starting from the acupoint ST 36—ran along the perineurium of the sciatic nerve to the spine and performed specific physiologic functions.¹³

Another reason for choosing ST 36 was that it is one of the most well-known acupoints for clinical applications in traditional acupuncture treatments. In addition it is also one of the most widely studied acupoints in modern acupuncture research. For instance, there are many reports on electroacupuncture (EA) on ST 36, with one last year mentioning about the brain areas involved in the acupuncture treatment using ST 36 for an Alzheimer's disease model in rats.⁵³ Another interesting report⁵⁴ suggested that sciatic-nerve transection could reduce the total number of mast cells in ST 36 although the authors of that article did not mention the PVS or Kim's work.

The previously stated hypothesis in the current report can be extended to other brain diseases in addition to glioblastoma, such as Alzheimer's disease, Parkinson's disease, and

other incurable diseases. Drugs injected at ST 36 may reach the brain more efficiently than orally or intravenously administered ones. There were many published reports on treatments of Alzheimer's or Parkinson's diseases with acupuncture at ST 36. For example, Wang et al. investigated the effects of 100-Hz EA stimulation at ST 36 in mouse models with Parkinson's disease on the animals' spontaneous locomotor activity. This study suggested that EA at ST 36 might be a promising treatment for neurologic disorders, including Parkinson's diseases.⁵⁵

Diseases of the spine may also be included for the particular therapeutic application of injecting drugs at ST 36. An interesting article reported that bee-venom pharmacopuncture at ST 36 suppressed the nociceptive neuronal activities in L3–L5 segments of the spinal cord induced by formalin injection into the foot soles of rats.⁵⁶ These researchers did not pay any attention to the sciatic nerve or its perineurium, but the results of the study showed significant effects at L3–L5 of the spinal cord. This L3–L5 segment is the region where the sciatic nerve begins. This coincidental connection between ST 36 and the L3–L5 segment is consistent with the anatomical basis of the current hypothesis. Further research with respect to this viewpoint would likely be able to provide more clinical evidence to support the connecting PVS route.

Kim investigated the transmission of an electrical signal generated by stimulation of primo nodes.^{11–13} Electrically excitable cells, which are different from nervous cells, was observed in the primo nodes.⁵⁷ Hence, the electric signals generated by EA at ST 36, in addition to ordinary nervous signals, are thought to be transmitted through the above PVS route along the sciatic nerve–spine–brain path. Thus, comparing the clinical efficacies of pharmacopuncture and EA at ST 36 with respect to the current author's hypothesis on brain and spine diseases would be worthwhile.

The optical communication channel hypothesis of the PVS⁵⁸ is an interesting subject with respect to laser acupuncture, which has been increasingly used for clinical purposes.⁵⁹ The PVS path along the sciatic nerve–spine–brain path may literally be a light path to the brain. Illuminating ST 36 with the proper spectrum of light may reduce depression, if it might not cure more serious diseases. For the sake of simplicity, the current author only considered the acupoint ST 36, but other acupoints may also be valuable for clinical purposes if specific routes of flow can be revealed.

CONCLUSIONS

New treatment strategies of glioma and other brain diseases were proposed in this article to use pharmacopuncture techniques combined with the PVS paths along the sciatic nerve, spinal cord, and brain. Liquid pharmaceuticals injected at the acupoint ST 36 flow in the PVS channels to reach the target tissues in the brain. This drug administration

has the advantage of avoiding the blood–brain barrier in addition to the connection from the skin to the inner tissues of the brain through the PVS channels. Future research on the PVS is required to elucidate its biologic role further with respect to transportation of drugs across the blood–brain barrier. This technique warrants extensive research, given the poor prognosis of high-grade gliomas.

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DISCLOSURE STATEMENT

The author listed above declares no conflict of interests.

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