Iontophoretic drug delivery system for the treatment of brain tumors

Jaehoon Jeong, Jaehyun Jang, and Kyeonggu Lee

***Abstract*— Glioblastoma (GBM) is the most common type of malignant brain tumor. Conventional drug delivery system for the treatment of GBM is convection-enhanced delivery (CED), which distributes drugs directly driven by a pump through a microcatheter. However, CED has physical limitations such as backflow, air bubbles, and tissue heterogeneity due to the pressure gradient. To solve these limitations, we designed a new drug delivery system for treating GBM using principles of iontophoresis. In this study, image-guided iontophoresis technology was developed for precise application of theranostic ink to brain tumors. The MRI identifies the location and shape of a tumor. Based on the MRI, optimal conditions for iontophoresis are decided, including the location for insertion of electrodes and injection of theranostic ink. The charged drug is dissolved in the electrolyte surrounding the electrode of same charge. Application of monophasic electrical current will repel drug ions with the same charge. A monkey brain tumor model was employed to compare the efficacy of the iontophoretic drug delivery system with that of CED system. As a result, the iontophoretic drug delivery system is more efficient than CED in terms of three indications: time, the diffusion quantity of the theranostic ink to normal tissues, and the distribution area of the theranostic ink within the brain tumor.**

***Index Terms*—brain tumor, iontophoresis, and drug delivery system**

I. Introduction

BRAIN tumors can be classified into various types, depending on the presence or absence of metastases and tissue lesions [1]. Especially, among them, glioblastoma (GBM) is the most common type of tumor generated in the central nervous system (CNS). As the most lethal malignant cancer, GBM has a 5-year survival rate of under 10% despite advances in surgery, radiotherapy, and chemotherapy [2, 3]. In conventional therapy, the primary treatment of GBM is surgical resection if the surgical biopsy proves that it is possible, followed by radiotherapy and chemotherapy [4]. Unfortunately, the recurrence of GBM is almost inevitable and re-resection is not the best option for patients with recurrent GBM (rGBM). In most cases of recurrences, treatment for GBM is performed in combination with drug therapy and radiation therapy [3, 5]. Therefore, it is important to develop and complement other treatments such as chemotherapy and radiotherapy, etc. more effectively.

Many efforts in efficient drug delivery to the brain have appeared in numerous studies. The most challenging part of these efforts is to bypass the blood-brain barrier (BBB), which isolates circulating blood from the fluids in the central nervous system (CNS) [6, 7]. Convection-enhanced delivery (CED) is the invasive drug delivery system inserting a catheter into a brain or tumor, which distributes drugs directly driven by a pump through a microcatheter. However, CED has physical limitations such as backflow, air bubbles, and tissue heterogeneity due to the pressure gradient [6]. To solve these limitations, we designed a new drug delivery system for treating GBM using principles of iontophoresis, which can compensate for the limitations of CED.

Iontophoresis is a drug delivery system that transfers ionized drugs with electric currents generated by two electrodes having opposite charges to each other. The drug is pushed out of the electrode that has the same charge as the ionized drug, and the drug is pulled from the electrode that has the other charge. These physical principles allow drugs to move. Through this principle, the permeability of drugs in tissues was enhanced. The iontophoresis is commonly used in the transdermal drug delivery system, but can be used in the field of ophthalmology, even in certain cardiac and neurological situations [8].

In this study, iontophoresis was used to treat brain tumors. We developed an iontophoretic drug delivery system technology for precise application of brain tumors in theranostic ink. By applying current to accurately apply theranostic ink only to brain tumors based on tumor images obtained by patients, we tried to develop the most efficient brain tumor treatment by 1) treating difficult and atypical brain tumors in a minimally invasive treatment, and 2) minimizing exposure to normal tissues of anticancer drugs.

II. Materials and methods

A. Iontophoretic drug delivery system

In this study, image-guided iontophoresis technology was developed for precise application of theranostic ink to brain tumors. The MRI identifies the location and shape of a tumor. Based on the MRI, optimal conditions for iontophoresis are decided, including the location for insertion of electrodes and injection of theranostic ink. The charged drug is dissolved in the electrolyte surrounding the electrode of same charge. Application of monophasic electrical current will repel drug ions with the same charge (see Figure 1).

Jaehoon Jeong is with Electronic Engineering Department, Hanyang University, Seoul, South Korea (e-mail: ihj9941@hanyang.ac.kr).

Jaehyun Jang is with Electronic Engineering Department, Hanyang University, Seoul, South Korea (e-mail: wogusdlq112@gmail.com).

Kyeonggu Lee is with Electronic Engineering Department, Hanyang University, Seoul, South Korea (e-mail: lkg0324@hanyang.ac.kr).

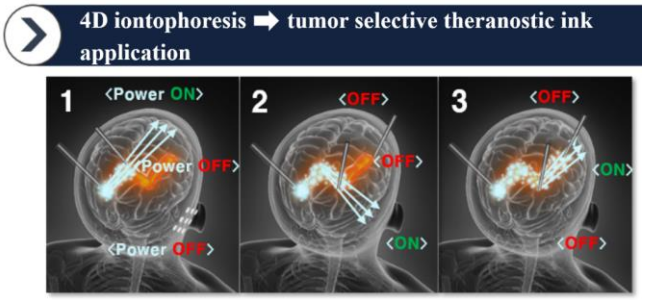


Figure 1. Application of monophasic electrical current will repel drug ions with the same charge through the skin to the tumor.

B. Electrode fabrication

Platinum(Pt), a highly stable material with minimal reactivity, is employed to prevent electrodes from participating in the reaction in the current field created by the applied current. To reduce tissue damage during insertion, the electrode's diameter and thickness are restricted to 1mm and 0.2mm, respectively, and its distal end is rounded. A plate-shaped electrode is used to create a straight current field, and the rear surface of the electrode is insulated. The insulating material uses a biocompatible substance, Teflon, and a thin film coating to insulate only the appropriate portion.

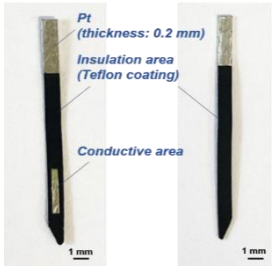


Figure 2. Electrode of iontophoretic drug delivery system

C. Multiple current sources

For 4D iontophoresis, multiple current sources were produced to apply constant current between multiple electrodes. It was built so that, when creating various current sources, 1) four channels are configured, 2) duty cycle can be applied, and 3) remote PC communication is enabled. To this end, the internal circuit of the multiple current source consisted of a current source (REF200), a switch (DG411), and a diode (CGRM4001), and remote connection with the PC was accomplished via the microcontroller (TIF28337) and the Bluetooth module. In addition, a GUI was developed for inputting duty cycle values. In addition, a circuit and a battery are built within the casing to provide for roughly four hours of continuous operation on a buffer basis.

D. Theranostic ink

Theranostic ink is a compound with a conjugated form of contrast agent, anticancer agent, and tumor targeting moiety. It is created as a tiny molecule to travel within a safe current range (0-2 mA) when applied to the brain core.

III. RESULTS

A monkey brain tumor model was employed to compare the efficacy of the iontophoretic drug delivery system with that of CED system. There are three indications of the efficacy in this study: time, the diffusion quantity of the theranostic ink to normal tissues, and the distribution area of the theranostic ink within the brain tumor.

As shown in Figure 3, the iontophoretic drug delivery system is more efficient than CED in terms of the three indications. The iontophoretic drug delivery system distributed the theranostic ink faster than CED over the same volume. In addition, the iontophoretic drug delivery system had less drug diffusion to normal tissues than the CED. For the distribution area of the theranostic ink within the brain tumor, the iontophoretic drug delivery system was wider than CED.

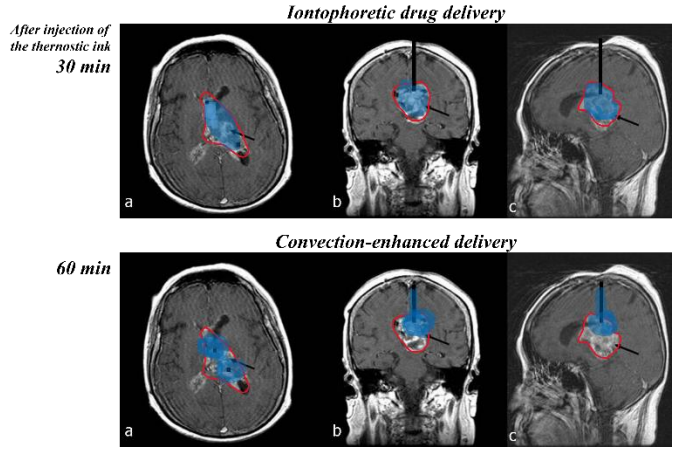


Figure 3. The distribution of the theranostic ink of iontophoretic drug delivery system and CED

IV. CONCLUSION

In this study, we proposed the iontophoretic drug delivery system for the treatment of brain tumors. Based on a monkey brain tumor model, we demonstrated that the efficacy of the iontophoretic drug delivery system was better than the conventional drug delivery system for the treatment of brain tumors in terms of time, the diffusion quantity of the ink to normal tissues, and distribution area of the ink within the brain tumor. In future work, we will conduct the simulation of iontophoretic drug delivery with finite element method-based numerical analysis to optimize electrode position and current.

REFERENCES

[1] ZACHARAKI, E.I., ET AL., CLASSIFICATION OF BRAIN TUMOR TYPE AND GRADE USING MRI TEXTURE AND SHAPE IN A MACHINE LEARNING SCHEME. MAGNETIC RESONANCE IN MEDICINE: AN OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY FOR MAGNETIC RESONANCE IN MEDICINE, 2009. 62(6): P. 1609-1618.

[2] Wang, Y., et al., A risk signature with four autophagy-related genes for predicting survival of glioblastoma multiforme. Journal of Cellular and Molecular Medicine, 2020. 24(7): p. 3807-3821.

[3] Roy, S., et al., Recurrent glioblastoma: where we stand. South Asian journal of cancer, 2015. 4(4): p. 163.

[4] Allard, E., C. Passirani, and J.-P. Benoit, Convection-enhanced delivery of nanocarriers for the treatment of brain tumors. Biomaterials, 2009. 30(12): p. 2302-2318.

[5] van Linde, M.E., et al., Treatment outcome of patients with recurrent glioblastoma multiforme: a retrospective multicenter analysis. Journal of neuro-oncology, 2017. 135(1): p. 183-192.

[6] Mehta, A., A. Sonabend, and J. Bruce, Convection-enhanced delivery. Neurotherapeutics, 2017. 14(2): p. 358-371.

[7] Zhou, Z., R. Singh, and M. M Souweidane, Convection-enhanced delivery for diffuse intrinsic pontine glioma treatment. Current neuropharmacology, 2017. 15(1): p. 116-128.

[8] Semalty, A., et al., Iontophoretic drug delivery system: a review. Technology and Health Care, 2007. 15(4): p. 237-245.