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Young mouse model high-frequency ultrasound-guided intrathecal injections: drug delivery that concentrates on the central nervous system

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ABSTRACT

Intrathecal injections are crucial for delivering aesthetic, analgesic, or chemotherapy medications to the central nervous system because they allow them to pass the blood-brain barrier. The inability to see the tiny target zone during injection makes it difficult to administer medications via this route in animal studies. Therefore, knowledge of the indirect assessment of vertebral and spinal cord architecture as well as the acquisition of advanced procedural skills is necessary for successful medication delivery. These problems are further exacerbated in studies modelling paediatric drug administration, where the animal is significantly smaller, and in studies using small animals like mice. New approach we have created a technique that uses high-frequency ultrasound imaging to visualise and target the lumbar intrathecal region for injections in order to solve these problems. The method is demonstrated in mice starting on the day after birth. Gadolinium-based magnetic resonance imaging contrast agent was intrathecal administered to test the approach, and the subsequent brain delivery was later confirmed by MRI. The brain was distributed by the MRI contrast agent after successful intrathecal injections. In this investigation, we managed to target 20 animals with an 80% success rate. Conclusion: The new method is anticipated to be more reliable than unguided approaches and convenient for drug delivery to the central nervous system in rodent research. This is a crucial advancement that will enable intrathecal delivery in paediatric mouse models.

Keywords: Intrathecal; Mouse; Ultrasound; Magnetic resonance imaging; Central nervous system; Drug delivery

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INTRODUCTION

Drug development and CNS treatment have long struggled to deliver therapies to the central nervous system, in large part because of the blood-brain barrier's highly selective regulatory behaviour [1]. While the BBB permits the entry of necessary nutrients, it has limited permeability for many chemicals, including medications that need to be CNS-targeted [2]. The BBB is made up of tightly interwoven endothelial cells that act as a physical barrier along the capillaries that carry blood to the brain [3]. Direct injection into the cerebrospinal fluid that surrounds the brain or spinal cord, where brain diffusion is less constrained, is one way to get over the BBB [4]. The least invasive CNS-targeted injection method is the intrathecal injection route, which targets the subarachnoid CSF region around the spinal cord [5]. In clinics, it is frequently used to provide anaesthetics, analgesics, and chemotherapeutics. Preclinical animal models' overall sizes and vertebral structure can differ greatly from those of humans, which can have an impact on the intrathecal space's targeting precision [6]. In mouse models, intracerebroventricular injections and IT injections either through the cisterna magna or the lumbar area have been used to administer medications directly to the CNS [7]. These operations are easier in rats because of their bigger size, but CNS administration is typically more difficult in mice. We provide a technique that use high-frequency ultrasound imaging to direct IT injections in young mice, enhancing the precision and dependability of IT injection in the mouse. US imaging is a non-invasive imaging technique that creates images by using sound wave interactions with biological tissue [8]. It is a potent instrument that enables the visualisation of anatomical structures and whole-body perfusion with rapid imaging speed and high resolution [9]. To target the CNS in mouse models of juvenile disorders, the IT space in young mice postnatal day 16 can be seen with US-guidance [10]. Using a gadolinium-based MRI contrast agent and post-injection MRI to show distribution to the brain, we show that IT injections are successful. The shaved area was covered with ultrasound gel, and the transducer was lowered until the intrathecal space could be seen. Once the intrathecal space. The needle and syringe were adjusted to lie inside the US plane with a dorsal approach from the platform's left side. Both a needle approach parallel to the spine's axis and one in which the needle point and associated US plane were rotated 20 degrees in the caudal direction were tested.

DISCUSSION

Drugs that ordinarily cannot cross the blood-brain barrier, such as anaesthetics, analgesics, or chemotherapy, can now be delivered to the central nervous system through intrathecal injections. The inability to see the tiny target zone during injection makes it difficult to administer medications via this route in animal studies. Therefore, knowledge of the indirect assessment of vertebral and spinal cord architecture as well as the acquisition of advanced procedural skills are necessary for successful medication delivery. These problems are further exacerbated in studies modelling paediatric drug administration, where the animal is significantly smaller, and in studies using tiny animals like mice (the most used mammalian model). We have created a technique that uses high-frequency ultrasound imaging to visualise and target the lumbar intrathecal region for injections in order to solve these problems. The technique is displayed in mice as soon as 16 days after birth. In order to assess the technique, an intrathecal injection of a gadolinium-based MRI contrast agent was made, and the subsequent brain delivery was later confirmed by MRI. The brain was distributed by the MRI contrast agent after successful intrathecal injections. In this investigation, we managed to target 20 animals with an 80% success rate. We anticipate that the novel strategy will enable intrathecal distribution in paediatric mouse models and will be practical for medication delivery to the central nervous system in rodent studies. It will also give higher dependability than unguided ways. In order to effectively organise the activities of the entire body, the central nervous system, which is made up of the brain, spinal cord, and retina, supervises the acquisition, integration, and processing of peripheral information. Trauma, stroke, brain tumours, and neurodegenerative and neurodevelopmental disorders can significantly impair CNS functions and cause severe, permanent disability. As the population ages, the societal and financial burden of CNS illnesses increases globally, increasing the need for more effective and conclusive therapies. Despite the range of medicinal compounds that are clinically available,

CONCLUSION

Medical treatments for CNS illnesses typically only address symptoms rather than slowing or correcting the course of the disease. This is related to both the complicated biological microenvironment and the underlying illness mechanisms. The CNS is shielded from outside influences by a number of barriers, including the blood-brain barrier and the blood-cerebrospinal fluid barrier. This restricts drug molecules' ability to enter the central nervous system, which helps explain the meagre therapeutic gains. As an alternate and perhaps more successful method of treating CNS illnesses, locoregionally treatments based on the deposition of thermoresponsive hydrogels laden with therapeutic chemicals and cells are gaining a lot of attention. The current state of knowledge and difficulties in creating thermoresponsive hydrogels for CNS therapy are discussed in this paper. are examined. The biological barriers that prevent mass and drug transfer to the CNS are first discussed, with special emphasis placed on each barrier's unique characteristics. Then, a critical presentation of the realisation, characterization, and biomedical use of natural and artificial thermoresponsive hydrogels follows. With the aim of defining general guidelines that could improve the successful translation of thermoresponsive hydrogel-based therapies for the treatment of CNS illnesses, the advantages and drawbacks of each design and application are reviewed. Despite significant technical advancements, the blood brain barrier and the blood cerebrospinal fluid barrier still prevent therapeutic compounds from reaching the central nervous system. The majority of currently used clinically effective methods for treating CNS diseases are based on systemic drug administration. However, the biological targets' effective medication concentrations are only moderate, necessitating repeated administration of high therapeutic dosages with the risk of severe, systemic toxicity. Bypassing the natural biological barriers by using surgical techniques or administering the therapeutic molecules directly into the CNS is a frequent tactic to address the disadvantages of systemic administration. But these methods are intrusive and raise the risk. Consequences, such as localised inflammation and neurological injury. To effectively treat CNS illnesses while avoiding side effects, it is imperative to create minimally invasive and precisely targeted drug delivery techniques.

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