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MRI Guidance Technology Development in a Large Animal Model for Hyperlocal Analgesics Delivery to the Epidural Space and Dorsal Root Ganglion

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Abstract

Background: Development of new analgesic drugs or gene therapy vectors for spinal delivery will be facilitated by “hyperlocal” targeting of small therapeutic injectate volumes if spine imaging technology can be used that is ready for future clinical translation.

New Method: This study provides methods for MRI-guided drug delivery to the periganglionic epidural space and the dorsal root ganglion (DRG) in the Yucatan swine.

Results: Phantom studies showed artifact-corrected needle localization with frequency encoding parallel to the needle shaft, while maximizing bandwidth (125 KHz) minimized needle artifact. A custom constructed 8-12 element surface coil (phased array) wrapped over the spine in conjunction with lateral recumbent positioning achieved diagnostic quality signal to noise ratio at the depth of the DRG and afforded transforaminal access via anterolateral or posterolateral vectors, as well as interlaminar access. Swine epidural anatomy was homologous with human anatomy. Injectate containing 2% gadolinium allowed imaging of injectate volumes in increments as small as 10 microliters and discrimination of epidural flow from intraparenchymal injectate delivery into a DRG. All technical and technological elements of the procedure appear clinically translatable.

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Comparison with Existing Methods: Computed tomographic or fluoroscopic guidance cannot directly visualize drug delivery into the DRG due to contrast medium toxicity, nor reliably identify epidural injection volumes of < 50 microliters.

Conclusions: MRI-guided hyperlocal delivery in swine provides a translatable and faithful model of future human spinal novel drug- or gene therapy vector delivery.

Keywords

MRI-guidance; epidural; Intraganglionic; spinal injection; animal model

1. INTRODUCTION

Interventional pain physicians perform over 2 million epidural injections annually (Food and Drug Administration, 2014). Over the past half century, transforaminal approaches and advances in fluoroscopic and computed tomography (CT) guidance have improved the anatomic targeting of the epidural space, allowing for safe delivery of currently available therapeutic agents, local anesthetics and corticosteroids (El-Yahchouchi et al., 2016, and Lee et al., 2018). Off-target toxicity of these drugs is minimal or reversible and therefore unwanted or undetected spread to anatomical structures adjacent to the targeted site, usually a single spinal nerve, is well tolerated by patients. Furthermore, current clinical practice calls for administration of therapeutic drugs in a volume of 2-3 mL following pre-injection of 0.5-1 mL of contrast media to exclude vascular distribution and assure coverage of the targeted spinal nerve. Such injectate volumes can be imaged reliably with the currently available technologies (fluoroscopy or CT).

Advances in neurobiology have identified numerous potential molecular targets (ion channels, cytokines, neurotransmitters) for interruption of the nociceptive pathway in the peripheral nervous system (Pleticha et al., 2016). These molecular targets can be accessed via the primary sensory neurons, anatomically located in the dorsal root ganglion (DRG). Developing drugs to target these analgesic mechanisms is limited by anatomical off-target effects, which may not be overcome by improved molecular designs. Rather, a drug that has a solely beneficial effect when acting on a disease-affected nociceptive nerve root may cause deleterious side effects when acting on other parts of the nervous system such as autonomic or cranial nerves. For instance, the TRPV1 receptor agonist resiniferatoxin (RTX) is a potent neurotoxin (Unger et al., 2019) that may lead to unwanted loss of heat sensation, which may not be acceptable beyond the specific spinal nerve underlying a pain syndrome. Another example are adeno associated viral (AAV) vectors that required to be directly delivered to the dorsal root ganglion (DRG) to achieve transduction of primary sensory neurons (Pleticha 2016). Thus, the development of new classes of molecularly specific analgesic agents directed to these nociceptive targets is constrained by the challenge of highly selective (hyperlocal) spinal nerve targeting. To develop hyperlocal spinal drug delivery a new generation of spinal image guidance is required, along with corresponding large animal models to test the efficacy of anatomically specific delivery to the periganglionic epidural space and/or the DRG in a faithful model of future human spinal novel drug- or gene therapy vector delivery.

Swine are a useful large animal model for spinal drug delivery due to their structural homology with the human spine, tolerance of anesthesia, and potential for behavioral outcomes based on gait / stance analysis (Karriker et al., 2013; Pairis-Garcia et al., 2015; Pleticha et al., 2014). The use of swine as a model for intrathecal, epidural, and intraganglionic drug delivery under CT guidance has been described by us and others (Brown et al., 2015; Pleticha et al., 2014, 2013). However, in CT guided drug delivery injectate volumes of 0.3 mL or more are typically required for visualization; detection and localization of smaller drug volumes is likely not reliable. Even more challenging is the selective injectate delivery into the DRG, i.e., intraganglionic, because neither the target, the DRG, nor the necessarily small volume injectate, 50 μ L, can be imaged directly. Rather, the CT-based approach relies on demarcating the periganglionic space with a relatively large volume of contrast media (250-500 μ L) followed by injection of the active agent in a radiolucent preparation into the (presumed site of the) DRG. Iodinated contrast media cannot be injected into the DRG because it is inherently neurotoxic. Moreover, imaging an injection volume that is as small as 10 to 50 μ L is below the sensitivity of even the best current CT scanners.

MRI has significantly greater contrast resolution than CT, providing the ability to differentiate soft tissues and to detect paramagnetic contrast agents. MRI guidance has been reported in clinical spine pain management injection procedures for imaging of epidural delivery and delivery to spinal articulations, but reported injectate volumes were large, in the range of 500 to 3000 μ L, reflecting the current clinical practice for local anesthetic-plus-corticosteroid therapy (Fritz et al., 2009, 2008; Jonczyk et al., 2014; Maurer et al., 2014). Furthermore, intraganglionic delivery with MRI guidance has not been reported.

Here we describe the development of MRI guidance equipment and techniques for small volume drug- or gene vector delivery to the periganglionic epidural (ED) space and for direct intraganglionic (IG) delivery. Employing swine as a model that closely approximates human spine anatomy, we developed a custom MRI coil, a series of MRI sequences optimized for speed or target resolution, improved guide and injection needles, and an anterolateral transforaminal needle trajectory, to demonstrate imaging characterization of injectate distribution with volumes of 50 μ L.

2. METHODS

2.1 Animals

Yucatan minipigs (Exemplar Genetics, Sioux Center, IA) weighing between 30 and 40 kg were used. All procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of the Mayo Clinic. The animals were sedated by intramuscular injection of Telazol (tiletamine and zolazepam, 5 mg/kg; Fort Dodge Animal Health), xylazine (2 mg/kg; AnaSed, Akorn), and glycopyrrolate (0.01 mg/kg; Baxter Healthcare). The pigs were then intubated, and general anesthesia was maintained by 1.5%–2% isoflurane (Terrell, Piramal Healthcare) during injection procedures.

2.2 Mislocalization artifact correction

Needle localization accuracy studies were carried out with commercially available MRI compatible needles (22 gauge, 10 cm length [Philips Invivo, Gainesville, FL] or 15cm length [ITP, Molecular Synthetics, Santa Monica, CA]) fixed to a plastic grid, with the needle tip located at the intersection of grid lines. The grid was then packed with ground beef as a phantom tissue environment as animal muscle tissue is in common use as a tissue substitute in MRI phantom studies (Dong et al., 2015). These studies used a standard head coil in a 3 Tesla closed bore clinical MRI imager (GE Medical Systems, Waukesha, WI). The localization of the needle tip and the size of the needle artifact were measured as a function of frequency encoding orientation and bandwidth.

2.3 Construction of custom MRI coils and design optimization

MRI examinations of the swine spine were carried out on a 3 Tesla, 70 cm closed bore clinical imager (GE Medical Systems, Waukesha, WI). Animals were imaged both prone and side lying to assess conspicuity and freedom from artifact of the DRG and its environs in the neural foramina. Signal to noise ratio (SNR) at the tissue depth of the DRG (10 cm) was measured with existing surface coils of single loop design and multichannel overlapping loops. The need for improved image quality provided the motivation for fabrication of a custom phased array coil optimized for swine spinal anatomy.

2.4 MRI Sequences for guide needle placement

The needle placement procedure can be divided into three phases: anatomic planning, needle advancement, and documentation of injectate distribution.

2.4.1 Anatomic planning—The known variability in the number of lumbar segments (five or six) in Yucatan swine, and the need to correlate with necropsy findings, obligated spinal enumeration. We adapted human spine imaging sequences to provide spinal enumeration, identification of the DRG, and planning of a safe route to the target.

2.4.2 Needle advancement—Needle advancement was performed freehand in iterative steps. At the start of advancement, this required a rapid imaging sequence sufficient to characterize the needle trajectory and determine needed correction, without the necessity of high resolution. As the needle approached the target, optimal spatial resolution, accurate needle localization, and minimization of needle artifact are paramount for final corrections, requiring unique MRI sequences.

2.4.3 Injectate distribution—Following injectate infusion, it was necessary to exclude intravascular infusion, and document the tissue distribution of the injectate. For this purpose, the injectate contained 2% by volume 0.5 molar gadolinium contrast agent (ProHance [gadoteridol], Bracco, Milan, Italy), allowing documentation with fat-saturated T1 weighted sequences.

2.5 Injection procedures

2.5.1 Epidural injection—Guide needles (22 gauge, 10 cm length [Philips Invivo, Gainesville, FL] or 15cm length [ITP, Molecular Synthetics, Santa Monica, CA]) were

placed under MRI guidance to a point within 1-2mm of the DRG. Periganglionic epidural injections used transforaminal approaches for the L4-5, L5-6 and L6-S1 foramina. An interlaminar or central sacral foramen approach targeted the periganglionic epidural space about the S1 DRG. Epidural injectate was delivered via hand injection directly through the guide needle. Epidural injection volumes varied from 50 to 100 μ L, and contained 2% gadolinium.

2.5.2 Intraganglionic injection—Intraganglionic delivery was performed using a custom manufactured, stepped, convection enhanced delivery (CED) needle (Pleticha et al., 2014). Our previously described CED needle was refined with a new 33-gauge beveled tip; the sharper tip provided easier entry into, without displacement, of the DRG, a phenomenon we directly observed during DRG needle entry in laminectomy procedures (Unger et al., 2017). An injectate containing 2% gadolinium was delivered in 50 μ L volumes via an MRI compatible syringe pump at a maximum flow rate of 8 μ / minute.

3. RESULTS

3.1 Mislocalization artifact correction

The localization of the needle artifact on the MRI image relative to its true location in space was critically affected by the orientation of the needle shaft with respect to the frequency encoding orientation. With frequency encoding perpendicular or oblique to the needle shaft, the representation of the needle was artifactually displaced in the right -left plane from its true location relative to the underlying mounting grid (Fig. 1). Orientation of frequency encoding parallel to the needle shaft eliminated this mislocalization, which was of clinically relevant magnitude relative to the targeted swine DRG, that is 4-5mm in its long axis. The magnitude of the needle artifact was minimized by utilizing maximal bandwidth of 125 KHz. Optimized imaging parameters for these localization studies were found to be a TR/TE of 600/7.7, a Bandwidth (BW) of 125 KHz, slice thickness (ST) of 1mm, matrix of 768 $\times$ 512, 2 NEX, and frequency encoding parallel to the needle.

3.2 MRI coil optimization

Imaging in the prone position as previously described for CT guidance¹⁰ caused respiratory artifacts on MRI. Decubitus positioning mitigated this artifact and provided the additional advantage of allowing an anterolateral approach to the neural foramen. This trajectory provided intraganglionic needle access parallel to the long axis of the DRG. For periganglionic epidural injections, either anterolateral or a typical posterolateral transforaminal approach could be employed.

A single loop coil provided guidance for needle placement, but lacked the anatomic coverage needed for anatomic planning and characterization of injectate distribution. An 8-channel overlapping loop phased array surface coil provided both the necessary anatomic coverage and allowed needle placement through the apertures of the individual loops (Supplementary Fig. 1). To optimize signal at the depth of the DRG from the skin surface (~10 cm), the coil was placed underneath the decubitus swine, and wrapped over the posterior aspect of the spine. Further improvement (13%) in SNR at the DRG was obtained

by matching the required superior – inferior anatomic coverage (thoracolumbar junction through the sacrum) necessary in 30-40 kg swine in a custom coil construction.

The custom coil array consisted of 8 to 12, 27.2cm × 10.6cm receive only loop antennas, critically overlapped with adjacent loops to minimize mutual inductive coupling. The overall dimensions of the array were 69.6cm × 10.6cm for the 8-element array and 105.4cm × 10.6cm if the array was extended to 12 elements. There were four 24cm × 5.5cm apertures between adjacent elements to allow for needle access to the subject for posterolateral or anterolateral transforaminal approaches, or an interlaminar or central sacral foramen approach to S1. A flexible silicone grid placed in the coil aperture provided needle skin entry point localization.

3.3 MRI sequences for guide needle placement

3.3.1 Anatomic planning—A sagittal fast spine echo T2 weighted sequence ([1], Supplementary Table 1) of the lumbar region was performed and used to prescribe a T1 weighted coronal sequence ([2], Supplementary Table 1) to allow identification of the most caudal rib, and subsequent designation of the lumbar segments. T1 weighted axial series ([3], Supplementary Table 1) were then prescribed at each segment to be injected from the mid-pedicle to the disc space level.

3.3.2 Needle placement—A rapid (23 seconds) proton density (PD) sequence ([4], Supplementary Table 1) was best used to assess needle trajectory, because it allowed for fast iterative imaging and advancement of the guide needle to the target DRG. As the guide needle approached the DRG, higher resolution imaging that minimized the needle artifact was necessary. The “Final T1 Trajectory” sequence in Supplementary Table 1 [5] provided this by using thinner slices, denser imaging matrix, more repetitions, highest possible bandwidth and by orienting the frequency encoding plane parallel to the needle shaft. This allowed measurement of the distance from the guide needle to the DRG center. The CED needle protrudes beyond the guide needle by 2.6 mm.

3.3.3 Injectate distribution—A fat saturated T1 weighted sequence ([6], Supplementary Table 1) used with the guide needle remaining in place identified injectate localization and could also detect (inadvertent) intravascular injection. A higher resolution sequence with greater longitudinal coverage ([7], Supplementary Table 1) employed after needle removal yielded optimal documentation of the procedure outcome.

3.3.4 Small volume injectate detection and distribution in the epidural space—The imaging method allowed identification of as little as 10 uL of epidural injectate when 50 uL was delivered in 10 uL increments (Fig. 2). Interestingly, we noted that even such a small volume can spread to the supra adjacent foramen, an observation that would not have been possible with C-arm- or CT-fluoroscopy, yet could be documented with the described technique using MRI. As in clinical epidural injections, it is critical to exclude vascular uptake. In this model, intravascular contrast flow could be inferred from the lack of accumulation of gadolinium in the epidural space or DRG after infusion. This may occur if the CED needle penetrates beyond the DRG parenchyma into venous channels. Of note,

partial intravascular flow may go undetected, however, only when there is simultaneous intravascular and tissue uptake.

3.4 Intraganglionic delivery

Intraganglionic CED injections represent the most highly specific hyperlocal targeting goal. MRI guidance allowed, and post-procedure imaging documented, successful intraganglionic gadolinium injectate delivery (Fig. 2).

4. DISCUSSION

Interventional analgesic procedures directed toward spinal nerves are currently constrained by the use of local anesthetics and corticosteroids that have incomplete efficacy, limited durability, endocrine side effects, and rare catastrophic complications. Development of more desirable molecularly specific therapeutic agents will require clinically translatable, anatomically selective delivery of experimental agents in small volumes targeted, if possible, to a single spinal nerve achieving anatomical selectivity either by limiting epidural spread or, ideally, by confined targeting of the new agent to a single DRG. Furthermore, before such new drug and drug delivery strategies can be tested in a phase I clinical trial, demonstration of safety will be required in a large animal model (to support an IND application to the FDA).

Herein we have presented methods for optimized MRI imaging of the swine lumbar spine and MRI guidance for periganglionic epidural injection and direct CED injection into the DRG. T1 weighted images provided excellent discrimination of the targeted neural elements within the epidural fat of the neural foramen. Rapid PD imaging allowed iterative advancement to the neural foramen, while high resolution T1 imaging with frequency encoding parallel to the needle at high bandwidth provided sufficient guidance for intraganglionic injection. Fat –saturated post injection images allowed exclusion of vascular uptake and documented the distribution of the injectate.

Needle advancement in the current study was performed by the lead author (TPM), who is a sub-specialty boarded neuroradiologist with 20+ years of experience performing clinical interventional pain procedures under fluoroscopic and CT guidance. The goal of the study was to provide an image guidance paradigm comparable to clinical practice, although using MRI rather than CT guidance. The experience of the operator in the procedures described here is a potential confounding effect as less-experienced practitioners may require more extensive training and hands-on instruction to serve as reliable primary operators. Novel analgesic agents, such as gene vectors or neurotoxins, will likely be initially utilized in tertiary care academic environments where image guidance skill sets are available.

4.1 Conclusions

Technologies and techniques of MRI guided DRG targeting described in the present study thereby address barriers towards two goals in the field of chronic pain research. First, the study makes a new large animal available for the preclinical development of a new class of agents for pain treatment, interventional analgesics with long-term effects, especially those agents that may require hyperlocal delivery to a single DRG. Second, the findings create a

path toward the next generation of clinical image-guided pain procedure equipment and techniques that may transform the clinical field of spine intervention in tandem with the development of interventional analgesics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

MRI	magnetic resonance imaging
DRG	dorsal root ganglion
CT	computed tomography
ED	epidural
IG	intraganglionic
SNR	signal to noise ratio
CED	convection enhanced delivery
PD	proton density
IND	investigational new drug

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Fig. 1.

Correction of MRI needle artifacts. (a) Photograph of a 22-gauge needle (arrows) fixed to a plastic grid, with its tip at the intersection of the grid lines (outlined in green). (b) The same 22-gauge needle (arrows) is imaged with the frequency encoding direction oblique to the needle shaft. The true location of the needle mounted on the grid is again outlined in green. The needle appears displaced in the right-left dimension from its true location and it appears larger in diameter; both observations are MRI artifacts. (c) Frequency encoding is parallel to the needle shaft resulting in accurate localization of the needle image; this corrects the localization artifact. Furthermore, the size artifact is much reduced by increasing the bandwidth from 31 KHz to 125 KHz. Bar length = 1 cm.

Fig. 2.

Epidural injectate distribution, intraganglionic injectate targeting, and alternate outcome detection. (a–c) Images with sequence [6], Supplementary Table 1. In a, 10 ul of injectate (arrow) is visible adjacent to the DRG. In b and c, 20 ul and 30 ul have been injected, respectively, layering around the DRG (arrows). (d–f) 50 ul of epidural injectate delivered at the L5-6 foramen (imaged using sequence [7], Supplementary Table 1) length = 1 cm. extends cephalad to the L4-5 foramen (d, arrowhead), about the L5 root sleeve at the L5 pedicle level (e, arrowhead) and the exiting L5 DRG (f, arrowhead). (g) A guide needle is contiguous with the DRG (arrow, imaging sequence [5], Supplementary Table 1). (h) Successful hyperlocal delivery. Contrast accumulation is exclusively in the DRG (arrow). (i and j) Alternate outcome. Fat saturated, post infusion image (j, sequence [6], Supplementary Table 1) shows no gadolinium in the DRG (arrow, imaging sequence [6], Supplementary Table 1) and only minimal dorsal epidural gadolinium (arrowhead) consistent with an intravascular loss of injectate.