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Full Length Research Paper

Subdermal injection of gadolinium with ASIS device in normal humans' glabella

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Our previous study which monitored human muscular contractions with an accelerometer found out that the human muscles ran away from the electrical stimuli of an electromagnetic (EMG) needle. Thus, where the needle tip must likely end up every time is just outside of the fascia, or right in the subdermal bloodless space. The current study further explored the above hypothesis by using MRI to monitor the location of gadolinium injections. Using the initial prototype of the ASIS (Automatic Subdermal Injection System) device, gadolinium was successfully injected into the subdermal bloodless space in three out of three normal subjects' glabellas. This innovation may have a major impact on the healthcare industry because bloodless injections imply longer-lasting medication, which will benefit most, if not all, injectable products.

Key words: Subdermal bloodless space, subdermal injection, injectable EMG needle, electrical stimulation, MRI with gadolinium, muscular contractions.

INTRODUCTION

Our previous study which monitored human muscular contractions with an accelerometer found out that the muscles always responded on first stimulation with an electromagnetic (EMG) needle but never with subsequent stimulations. This implies that the muscles ran away from electrical stimuli, just like balloons away from a firecracker. The physiological explanation for this has to do with the neuromuscular junction, which is the portion of the muscle that first contacts the path of the stimulating current (Witzemann, 2006). This muscle must also contract and shorten first, thus forcing the muscles to run away (Figure 1). Of course, if the muscle does not cross the path of the stimulating current, then contraction cannot happen.

ASIS Corporation has developed and patented the only automatic subdermal injection system (ASIS) for delivery of injectable products to the optimum spot, just outside of the fascia, which exists subdermally (between the skin and muscle) or interfascially (between the deeper muscles). ASIS device creates bloodless space, preventing unnecessary distant spread and adverse reactions. This space remains bloodless as long as the skin is lifted up or filled with an injectable product.

The muscles in question for the majority of injectable products are just beneath the skin, so only the subdermal bloodless space is involved in all practicality. The subdermal bloodless space is the optimum injection spot because many injectable fillers act on nerve endings and nerve endings exist only on the fascia, not inside the muscle, where fillers like BOTOX is typically injected (Allergan, BOTOX).

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Figure 1. The portion of the muscle contacting the path of the stimulating current, which must also contract and shorten first, forcing the muscles to run away.

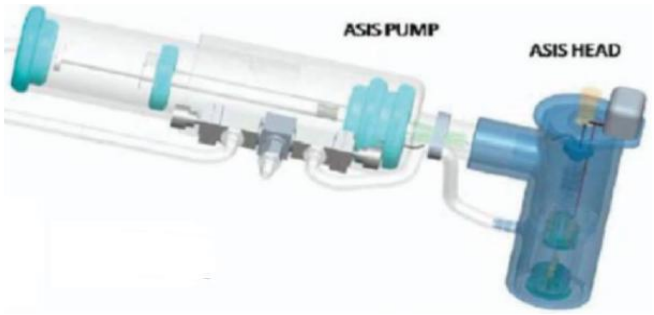

Figure 2. ASIS device concept.

MATERIALS AND METHODS

This study attempted to use the ASIS device to confirm that subdermal bloodless space existed by injecting gadolinium into three human subjects' glabella. The sample size is small because a particular disease population was sought in order to determine the relative prolongation of gadolinium. Subjects with Cervical Dystonia, Chronic Migraine, or Upper Limb Spasticity were recruited.

Our study was conducted in compliance with the Good Laboratory Practice (GLP), and all procedures were approved by the Institutional Review Board. The essential mechanism of stimulation and injection is just what the injectable EMG needle was made for (EMGneedles.com). Further, injectable monopolar EMG needles and gadolinium have been used for years, so using them together in a human does not require extra precautions. In addition, gadolinium has been injected all over the human body, including the human wrist, so using injecting subdermally does not present extra risks (Hinshaw, 1977). Although gadolinium has not been injected into the subdermal bloodless space on purpose, we do know that gadolinium has been inside such bloodless space, uneventfully, since abscesses or hematomas always light up on MRI with gadolinium, which arise from and are contained within bloodless spaces (both subdermal as well as interfascial). Given that bloodless spaces do not exist until and unless they are occupied by a product, no special precautious are needed to be taken; once injected, the injectable product takes over control and responsibility.

The injectable contrast medium for MRI, Magnevist is provided as a sterile, clear, and colorless to slightly yellow aqueous solution for intravenous injection (Bayer, Corporation 2014). Gadolinium is typically given intravenously; however, the initial ASIS concept device subdermally administered Magnevist®, the N-methylglucamine salt of the gadolinium complex of diethylenetriamine pentaacetic acid. While a local injection of 1 mL of gadolinium diluted with 9 mL of NS was not expected to cause unexpected adverse reactions, subjects did obtain pre-gadolinium Bun/Creatinine blood tests, which were all within normal limits (Formica and Silvestri, 2004).

In order to standardize our procedure to provide consistency between subjects, we stabilized the skin surface as reference from which the muscles would run away. At the same time, this would allow the subdermal bloodless space room to expand and hold the gadolinium being injected. Thus, a suction cup was fashioned to the EMG needle so that the skin could be lifted up as much as possible. The initial ASIS concept/working model is shown in Figure 2.

In two out of three normal subjects' glabella, gadolinium was injected intramuscularly and subcutaneously (Figure 3), with MRI taken promptly after for comparison at the Magnolia Imaging Center in Westminster, California. A recording of the injection process using the ASIS prototype is available at http://www.mediafire.com/?prjv2i9dmtncpox. A GE closed 1.5 Tesla MRI was used with the following parameters:

T1, TE: 115/Ef, TR: 4350, Fl: p+	T2, TE: 12.8/Ef, TR: 467, Fl: p+
EC: 1/1 41.7 kHz	EC: 1/1 25 kHz

Figure 3. Gadolinium injected intramuscularly. Scan on the left is before injection took place and scan on the right is after injection took place.

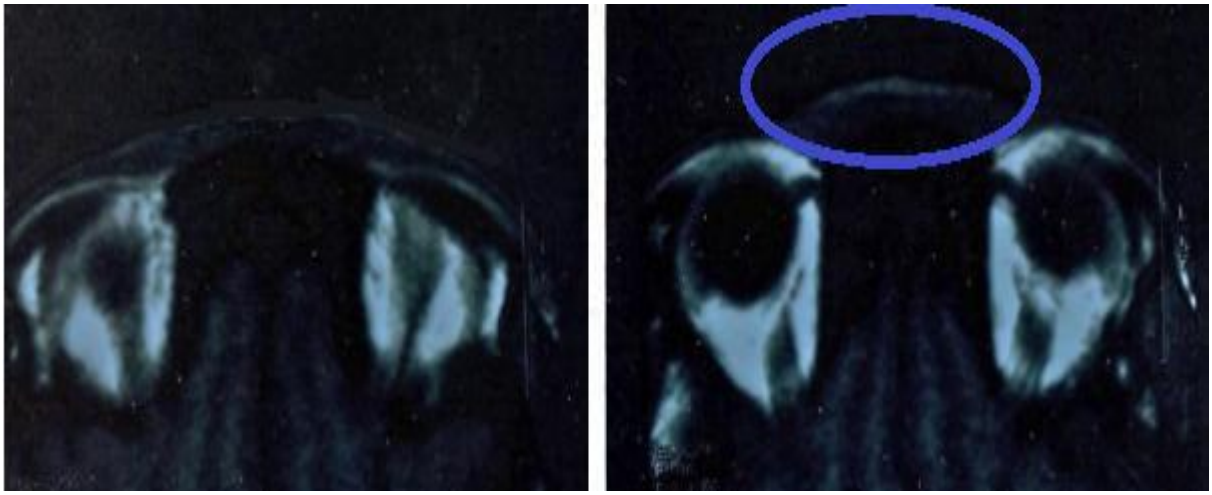

Figure 4. Gadolinium injected subcutaneously. Scan on the left is before injection took place and scan on the right is after injection took place.

RESULTS AND DISCUSSION

The ASIS device prototype consistently delivered gadolinium into the subdermal bloodless space for three out of three normal subjects' glabella. MRIs were taken promptly after gadolinium injection (Figures 4 to 7). MRI and gadolinium imaging documentation and scans can be viewed at http://www.mediafire.com/?fir6o4yd0vnragg.

The ASIS device prototype consistently delivered gadolinium into the subdermal bloodless space for three out of three normal subjects' glabella. The significance of this innovation is not the device itself, but access to the subdermal bloodless space, which will benefit most, if not all, injectable products. The subdermal bloodless space has always been there, but just overlooked (Reilly, 1989); otherwise the ASIS device prototype would not have administered a subdermal injection every time.

If the muscle runs away after electrical stimuli, the EMG needle tip must end up every time just outside of the fascia, or in the subdermal bloodless space. Every water soluble product must eventually diffuse out of that space to reach equilibrium with the rest of the body, but delayed gradual diffusion is preferable for medications that treat chronic illnesses, such as GAMMAGARD for primary immunodeficiency (Baxter Healthcare Corporation, 2014), Immunex Corporation's Enbrel® for plaque psoriasis, and insulin for diabetes. Such diffusion is analogous to crossing a membrane, and it is actually dependent on concentration or a product's osmolality, which can always be modified to achieve the desirable pharmacokinetics for these medications. Thus, injections into the subdermal bloodless space imply longer lasting medicinal effects. In addition, because the bloodless space has the natural ability to expand rapidly and contain abscesses or

Figure 5. Gadolinium injected subdermally in Subject 1. Scan on the left is before injection took place and scan on the right is after injection took place.

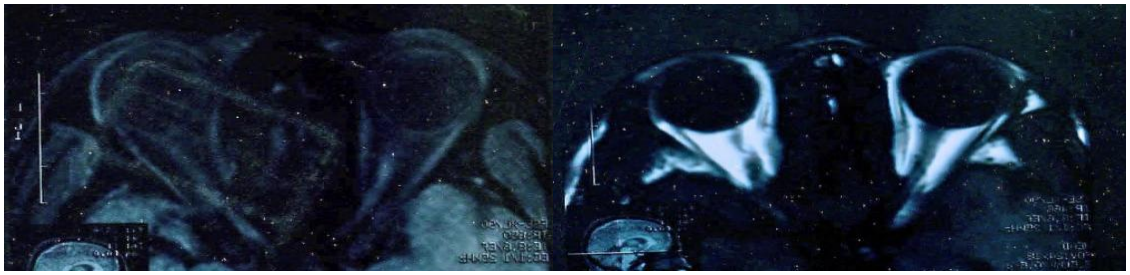

Figure 6. Gadolinium injected subdermally in Subject 2. Scan on the left is before DP3 and scan on the right is after DP4.

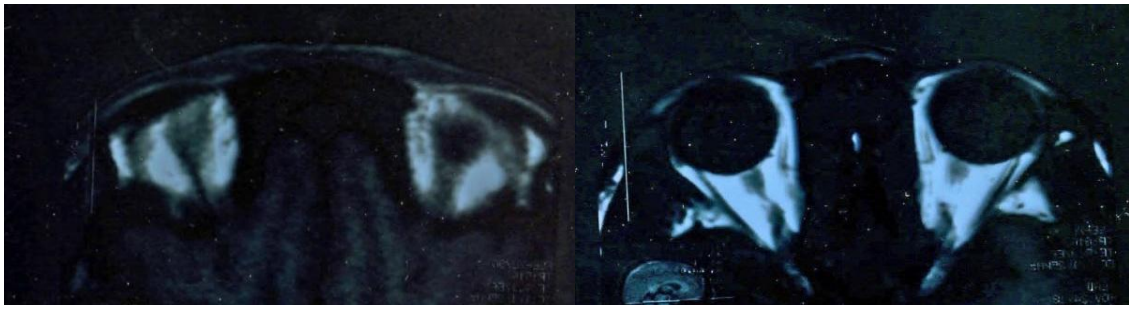

Figure 7. Gadolinium injected subdermally in Subject 3. Scan on the left is before DP5 and scan on the right is after DP6.

hematoma, this will allow rapid, effortless, and painless infusion of injectables (Scott et al., 1998; Gidley and Stiernbery, 1997; Miller et al., 1999; Panoessa and Goldstein, 1976).

Conclusion

Future research should be carried out on gadolinium's retention in the subdermal bloodless space by taking post-injection periodic MRIs. Additional areas for opportunity will be to measure the efficacy of products besides gadolinium that are injected into the subdermal bloodless space.

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