EQUINE VETERINARY JOURNAL
Equine vet. J. (2009) **41** (4) 379-383
doi: 10.2746/042516409X372502

Diffusion of contrast medium after perineural injection of the palmar nerves: An *in vivo* and *in vitro* study

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Keywords: horse; diagnostic analgesia; distal limb; radiography; specificity
Further peer reviewed supplementary information available at evj.co.uk/suppinfo

Summary

Reasons for performing study: **Proximal diffusion of local anaesthetic solution after perineural anaesthesia may lead to the desensitisation of structures other than those intended. However, there is no evidence-based study demonstrating the potential distribution and diffusion of local anaesthetic solution after perineural analgesia in the distal limb.**

Objective: **To document the potential diffusion of local anaesthetic solution using a radiopaque contrast model and to evaluate the influence of walking compared with confinement in a stable after injection.**

Methods: **Radiopaque contrast medium was injected subcutaneously over one palmar nerve at the base of the proximal sesamoid bones in 6 nonlame mature horses. Horses were assigned randomly to stand still or walk after injection. Radiographs were obtained 0, 5, 10, 15, 20 and 30 min after injection and were analysed to determine the distribution and diffusion of the contrast medium.**

Results: **In 89% of injections an elongated pattern of the contrast medium was observed suggesting distribution along the neurovascular bundle. After 49% of injections a fine radiopaque line extended proximally from the contrast 'patch', and in 25% of injections a line extended distally. There was significant proximal and distal diffusion with time when sequential radiographs of each limb were compared. The greatest diffusion occurred in the first 10 min. Walking did not significantly influence the extent of either proximal or distal diffusion.**

Conclusions and potential relevance: **Significant proximal diffusion occurs in the first 10 min after perineural injection in the distal aspect of the limb and should be considered when interpreting nerve blocks. Distribution of local anaesthetic solution outside the fascia surrounding the neurovascular bundle or in lymphatic vessels may explain delayed or decreased effects.**

Introduction

The specificity of diagnostic analgesia in the distal limb has been investigated in several studies (Dyson and Kidd 1993; Schumacher *et al*. 2000, 2001a,b, 2004; Gough *et al*. 2002; Harper *et al*. 2007). However, most studies have concentrated on intra-articular and intrathecal diagnostic analgesic techniques. Radiopaque contrast medium has been used to demonstrate the potential distribution of local anaesthetic solution after injection (Dyson and Romero 1993). It has been suggested that proximal diffusion of local anaesthetic solution after perineural anaesthesia can lead to desensitisation of structures other than those intended (Bassage and Ross 2003). Clinical and experimental studies showed that perineural analgesia of the palmar digital (Ross 1998; Schumacher *et al*. 2004) and palmar (Dyson and Murray 2006) nerves can improve or abolish pain arising from structures proximal to the injection site.

To the authors' knowledge there is no evidence-based study demonstrating the potential distribution, route and extent of diffusion of local anaesthetic solution after perineural analgesia in the distal aspect of the limb. The aim of this study was to document the potential diffusion of local anaesthetic solution using a radiopaque contrast model and to evaluate the influence of walking compared with confinement in a stable after injection. It was hypothesised that there would be significant proximal diffusion with time and walking would increase diffusion.

Materials and methods

The radiographic study was carried out in the Large Animal Hospital of Szent Istvan University, Budapest, Hungary after approval of the Ethical Committee of Szent Istvan University, Budapest, Hungary. The *post mortem* studies were performed at the University of Bristol.

Study in live horses

Radiopaque contrast medium (iohexol)[1] was injected subcutaneously over the palmar nerves at the base of the proximal sesamoid bones in 6 nonlame mature horses. Contrast medium (2 ml) was injected at each site using a 25 gauge 16 mm needle directed distally. On Day 1 the medial side was injected in either the left or right limb and the lateral side was injected in the contralateral limb and horses were assigned randomly to stand still or to walk for 7 min after injection. On Day 2, the protocol of

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[Paper received for publication 24.07.08; Accepted 17.09.08]

Day 1 was repeated on the contralateral limb (i.e. Day 1: medial injection in the left fore and lateral injection in the right forelimb; Day 2: lateral injection in the left forelimb and medial injection in the right forelimb). On Day 3 both sides were injected simultaneously in either the left or right forelimb and again, horses were assigned randomly to stand still or to walk. On Day 4, the protocol of Day 3 was repeated in the contralateral limb.

Fig 1: Lateromedial radiographic view of a right forelimb, obtained 30 min after subcutaneous injection of 2 ml radiopaque contrast medium over the lateral palmar nerve at the base of the lateral proximal sesamoid bone. Note the elongated distribution of the contrast medium (proximal and distal ends indicated with arrows) and the fine radiopaque line extending proximally from the contrast patch (arrowheads).

Fig 2: Dorsopalmar radiographic view of a left forelimb, obtained immediately after subcutaneous injection of 2 ml radiopaque contrast medium over the lateral palmar nerve at the base of the lateral proximal sesamoid bone. Note the elongated distribution of the contrast medium and the marked proximal and distal diffusion. The extents of proximal (A) and distal (B) diffusion were measured from a line drawn perpendicular to the medial/lateral aspect of the proximal articular surface of the proximal phalanx, to the most proximal/distal aspect of the contrast 'patch'.

All injections were performed by the same clinician (A.N.). Injections were performed with no resistance to depression of the syringe's plunger. If the needle penetrated a blood vessel, it was redirected in a slightly palmar direction. No injection was performed until it was ensured, by aspirating, that the needle was not in a blood vessel. Radiographs were obtained 0, 10, 15, 20 and 30 min after injection using a computed radiography system[2]. On Days 1 and 2 lateromedial (Fig 1) and dorsopalmar radiographs (Fig 2) of the distal aspect of the limb were obtained and on Days 3 and 4 dorsopalmar, dorsolateral-palmaromedial oblique and dorsomedial-palmarolateral (Fig 3) oblique radiographic views were obtained. In 9 limbs (on Days 3 and 4) needles were left in position for the radiographs obtained immediately after injection. Each set of radiographs (on Days 1 and 2, a set comprised lateromedial and a dorsopalmar views and on Days 3 and 4 a set comprised dorsopalmar, dorsolateral-palmaromedial oblique and dorsomedial-palmarolateral views) for each limb, at each preset time was acquired within one minute. Additional radiographic views of the carpus and antebrachium were obtained in 5 of those horses in which a proximally extending fine radiopaque line was observed on the first set of radiographs. These radiographs were obtained when time allowed between preset times.

Description of the distribution of the contrast medium

Distribution of the contrast medium was described as elongated or diffuse. Elongated distribution (Figs 1, 2) was defined as a distinct proximodistally extending 'patch', which had a similar elongated appearance in all radiographic views. Distribution was described as diffuse if the contrast medium diffused around the injection site to a similar extent in proximodistal and lateromedial directions

Fig 3: Dorsomedial-palmarolateral radiographic view of a right forelimb, obtained immediately after subcutaneous injection of 2 ml radiopaque contrast medium over the medial and lateral palmar nerves at the base of the medial and lateral proximal sesamoid bones. The needles were left in position. Note the elongated distribution of the contrast medium and the marked proximal diffusion from the tip of the needle (white arrowhead) within seconds after injection at the medial injection site (right side of the image, white arrow). At the lateral injection site (left side of the image), the distribution of the contrast medium was more diffuse (black arrowheads), compared with the elongated pattern laterally.

(Fig 3). The presence of a fine radiopaque line extending proximally or distally from the contrast 'patch' was recorded (Fig 1). These lines were much narrower than the main contrast 'patch'; there was a well-defined transition from the 'patch' to the fine line, with a marked change in width in all radiographic views. The extents of proximal and distal diffusion were measured in all radiographic views. A line was drawn perpendicular to the medial and lateral aspects of the proximal articular surface of the proximal phalanx. The distance between this line and the most proximal or distal aspect of the contrast 'patch' was measured (Fig 2). All radiographic assessments and measurements were performed by one analyst (A.N.).

Statistics

Repeatability of measurements was assessed 5 times on 5 lateromedial, dorsopalmar and dorsolateral-palmaromedial radiographs, respectively. Normality of data was assessed using a Shapiro-Wilks test. Extent of proximal and distal diffusion between subsequent radiographs was assessed using one-way repeated measures ANOVA and a multilevel repeated measures model. The difference in the extent of proximal and distal diffusion between medial and lateral sides was compared based on measurements on the dorsopalmar radiographic views, when both sides were injected simultaneously, using a paired *t* test or a Wilcoxon signed rank test. The effect of walking was assessed using a multilevel repeated measures model. Statistical significance was set at $P<0.05$. For a full description of statistical methods employed refer to www.evj.co.uk/suppinfo.

Study in cadaver limbs

To evaluate the distribution of liquid after perineural injection further, 2 ml of 0.5% methylene-blue solution was injected in the same fashion as previously described for the contrast medium in 5 cadaver limbs on both the medial and lateral sides. Limbs were dissected and the location and distribution of the dye was recorded (Figs 4, 5). To demonstrate the relationship between radiographic and *post mortem* findings, in an additional 5 cadaver limbs a mixture of 1 ml radiopaque contrast medium and 1 ml methylene blue was injected medially or laterally at the level of the base of the proximal sesamoid bones. Lateromedial, dorsopalmar and dorsolateral-palmaromedial oblique or dorsomedial-palmarolateral oblique radiographic views were obtained immediately after injection and then the limbs were dissected.

Fig 4: Lateral aspect of a left forelimb; dorsal is to the left. Methylene blue (2 ml) was injected subcutaneously over the lateral palmar nerve at the base of the lateral proximal sesamoid bone and then the skin was removed. The dye was distributed along the neurovascular bundle and there was no dye directly under the skin, outside the fascia that surrounds the neurovascular bundle.

Results

Study in live horses

Four-hundred-and-twenty radiographs were analysed subjectively and objectively. In 89% of injections an elongated pattern of the contrast medium was observed, suggesting distribution along the neurovascular bundle. In 11% of injections the contrast medium was more diffusely distributed around the injection site. After one injection the contrast medium diffused in an elongated pattern in a medial direction from the lateral injection site. In 49% of injections a fine radiopaque line extended proximally from the contrast 'patch', and in 25% of injections a line extended distally. These fine lines were present on at least 3 subsequent radiographs. In the 5 limbs, in which fine radiopaque lines were observed on the radiographs obtained immediately after injection and additional radiographic views of the carpus and antebrachium were obtained, the lines could be followed up to the mid diaphysis of the radius. Radiographs were not obtained further proximally. In 3 horses, on the first set of radiographs a few very fine, short (up to 1–2 cm) radiopaque lines, extending in various directions were observed. These lines were only identified when brightness of the images was markedly increased.

Fig 5: Lateral aspect of the same limb as shown on Figure 4. Dorsal is to the left. The fascia of the neurovascular bundle is opened and it is obvious that the dye is surrounding the structures within the neurovascular bundle (from left to right: palmar vein, artery and nerve).

TABLE 1: Mean ± s.d. values measurements (mm) from a line drawn perpendicular to the medial and lateral aspects of the proximal articular surface of the proximal phalanx to the most proximal/distal aspect of the contrast 'patch' (n = 96)

	Time after injection (min)				
	0	10	15	20	30
Proximal diffusion	12.64 ± 12.3	16.92 ± 13.7	18.58 ± 14.7	19.57 ± 14.5	20.83 ± 15.1
Distal diffusion	40.44 ± 12.1	44.74 ± 11.1	45.83 ± 11.7	48.04 ± 11.2	48.94 ± 11.1

Repeatability of measurements was confirmed; the coefficient of variance for measurements on all radiographic views was <2%. A multilevel repeated measures model revealed significant increase in the extent of proximal and distal diffusion with time and that the increasing trend reduced with time. The mean values for proximal and distal diffusion are summarised in Table 1. Both proximal and distal diffusions were greater in the first 10 min than in the 10–15 min period. Proximal diffusion from 10–15 min was greater than proximal diffusion from 15–20 min. There was no significant difference between the extent of either proximal or distal diffusion when medial and lateral injections were compared. Walking did not have a significant effect on the extent of either proximal or distal diffusion. In 9 limbs the medial and lateral sides were injected simultaneously and the needles were left in position for the first sets of radiographs. The mean ± s.d. proximal diffusion distance of the contrast medium from the tip of the needle was 25.9 ± 11.1 mm and 30.1 ± 12.1 mm for medial and lateral sides respectively, which was not significantly different.

Study in cadaver limbs

In 5 limbs, in which only methylene blue was injected, in 8 of 10 injections the dye was distributed within the fascia of the neurovascular bundle (Figs 4, 5). In all 5 limbs, in which methylene blue and contrast medium were injected simultaneously, both radiographic and gross *post mortem* appearance indicated that the injected material was distributed within the fascia of the neurovascular bundle. In 3 limbs a fine, proximally extending line was identified on the radiographs, which corresponded to the distribution of the dye in lymphatic vessels observed on dissection.

Discussion

There was significant proximal and distal diffusion of the contrast medium with time, supporting the hypothesis, but walking did not have a significant influence on either proximal or distal diffusion.

The concept that the specificity of nerve blocks decreases with time is supported by this study. Clinical observations suggest that proximal diffusion of the local anaesthetic solution after perineural analgesia can result in desensitisation of more proximal regions than intended (Ross 1998; Bassage and Ross 2003; Dyson and Murray 2006). Schumacher *et al*. (2004) reported that perineural analgesia of the palmar digital nerves can significantly improve experimentally induced proximal interphalangeal joint pain, depending on the distance of the injection site from the proximal margin of the cartilages of the foot. It has been observed in clinical situations that perineural analgesia of the palmar digital nerves can improve pain arising from regions proximal to the injection site (Ross 1998), and that perineural analgesia of the palmar nerves at the level of the base of the proximal sesamoid bones can abolish fetlock joint pain (Dyson and Murray 2006). However, to the authors' knowledge, the route and extent of diffusion after perineural injection have not been demonstrated in the distal aspect of the limb in evidence-based studies.

A number of techniques have been used to investigate diffusion of local anaesthetic solution. Measuring the concentration of local anaesthetic solution is a reliable method and has been used to assess communication between synovial cavities *in vivo* (Gough *et al*. 2002), and to measure concentration of mepivacaine in tissue samples in cadaver studies (Keegan *et al*. 1996). However, this technique would not be easily applicable to assessing diffusion after perineural analgesia in live horses, because tissue samples would be required. Other studies have concentrated on the clinical effects of perineural, intra-articular or intrathecal diagnostic analgesic techniques. Abolition of experimentally induced focal pain by specific diagnostic analgesic techniques provides valuable information (Schumacher *et al*. 2000, 2001a,b, 2004; Gough *et al*. 2002; Harper *et al*. 2007). However, it does not permit quantification and assessment of the route of diffusion. A radiopaque contrast model was used to assess diffusion after intra-articular and perineural analgesia in the tarsometatarsal joint and proximal metatarsal region (Dyson and Romero 1993). The molecular weight and diffusion characteristics of local anaesthetic solution and radiopaque contrast medium may be different. However, use of contrast medium has excellent potential to demonstrate potential distribution and diffusion of local anaesthetic solution and was considered the most feasible technique to use in this study.

This study showed that, even in the first 10 min after injection, significant proximal diffusion can occur (up to a mean distance of 28 mm from the tip of the needle). There was significant increase between both proximal and distal diffusion measurements respectively on each sequentially obtained pair of radiographs, supporting the clinical observation that the longer the period between application of a nerve block and the assessment of its effect, the more proximal structures may be desensitised. The greatest diffusion occurred in the first 10 min. When interpreting measurements on radiographs obtained 20 and 30 min after injection, it has to be borne in mind that contrast medium was often fading by that time, which might result in underestimation of further diffusion.

When radiographs were obtained with the needle in position, contrast medium was seen up to 42 mm proximal to the tip of the needle. This emphasises the importance of directing the needle distally whenever possible when performing perineural diagnostic analgesia in the distal aspect of the limb.

The results of injecting both contrast medium and methylene blue injections suggest that, in the majority of horses, when performing perineural injection around the palmar nerves at the level of the base of the proximal sesamoid bones, the injected medium is distributed within the fascia of the neurovascular bundle. When distribution of the contrast medium was described as diffuse, the radiographic appearance suggested that diffusion occurred between fascial planes. A proximally extending fine radiopaque line was observed in 49% of injections. Once these lines appeared, they were present on at least 3 subsequent radiographs, suggesting distribution in a lymphatic vessel rather than a blood vessel. This was confirmed by methylene blue injection studies.

Distribution of local anaesthetic solution outside the fascia of the neurovascular bundle or in lymphatic vessels may explain any delayed or decreased effect of nerve blocks. All injections were performed with no resistance. It is suggested that if resistance is experienced, then the needle tip is located subcutaneously, intradermally or between fascial planes other than that of the neurovascular bundle. The needle should be redirected until there is no resistance to injection. In one limb, the radiographic appearance suggested that the contrast medium diffused in a transverse plane around a vascular structure. It is speculated that this may reflect an anatomical variation of the neurovascular structures. Distribution of a large amount of contrast material in blood vessels was not observed in this study. The very fine, short, rapidly fading radiopaque lines observed in 3 horses in the radiographs obtained immediately after injection may reflect local capillary diffusion. It is possible that a small amount of the local anaesthetic solution could diffuse from the neurovascular bundle into capillaries.

Some clinicians routinely walk horses after intra-articular analgesia to increase diffusion of the local anaesthetic solution within the synovial structure. Horses are often hand-held or confined in a box stall between performing perineural analgesia and assessing its effect. This study showed that walking did not result in any difference in either proximal or distal diffusion of the radiopaque contrast medium, suggesting that walking would probably not increase the risk of desensitising more proximal structures than intended.

There are a number of limitations of this study. The molecular properties of local anaesthetic solutions are different to those of iohexol and methylene blue. Therefore, it is possible that distribution and diffusion would not be equivalent to that observed in the current study. Diffusion may be greater when using local anaesthetic solution, due to the smaller molecular weight compared with iohexol or methylene blue. It would have been interesting to see the extent of diffusion of the contrast medium 5 min after injection, but we wished to assess the effect of walking and it would not have been feasible to assess this and obtain radiographs 5 min after injection. There would be less clinical value in assessing diffusion of contrast medium after 5 min, because clinical observations suggest that it can take up to 10 min for the local anaesthetic solution to have its effect when performing perineural analgesia in the distal aspect of the limb.

In conclusion, this study demonstrated significant proximal diffusion of radiopaque contrast medium within 10 min after injection, which should be borne in mind when interpreting nerve blocks. Further investigation is needed to assess diffusion at different sites of injection, diffusion of different volumes and the effect of positioning the needle.

Acknowledgements

The authors thank Professor William Browne for his advice on statistical analysis, János Poharenszky and Illés Majzik for their help with obtaining radiographs and Professor Péter Sótonyi for his comments on the *post mortem* images.

Manufacturers' addresses

[1]GE Healthcare, Oslo, Norway.
[2]Philips Computed Radiography, Eindhoven, The Netherlands.

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Author contributions The initiation, conception and planning of this study were by A.N., G.B. and A.R.S.B. Its execution was by A.N., G.B. and F.S., with pathology and statistics by A.N. the paper was written by A.N., G.B., S.J.D. and A.R.S.B.