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The success of IRAP treatment in degenerative joint disease in Swedish racehorses

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List of abbreviations

IRAP	Interleukin-1 Receptor Antagonist Protein
iv	Intravenous
ia	Intraarticular
im	Intramuscular
OA	Osteoarthritis
IL-1	Interleukin 1

Contents

1. Introduction

During my studies in Veterinary Medicine at Szent István University my interest in sporthorse-medicine has been growing. My initial interest in sporthorses came from my earlier education in the horse industry while I became a professional trainer.
My studies have revealed to me the real background of good performance and the importance of equine anatomy and physiology. While the horseracing sector got smaller in some countries it has become a major industry in countries such as Sweden, Norway and France, here in Europe.
Horses that perform well earn vast amounts of money, and as a result, the role of the veterinarian has become more important in these fields.

Lameness is one of the most common reasons why horses are not able to work or fulfil their potential (Pool and Meager, 1990; Rossdale *et al* 1985; Jeffcott *et al*. 1982 and Stover, 2003). The harder and more intense the workload of a horse, the more strain is put onto their bodies and limbs and therefore the more likely that malfunctions will occur.

"No Hoof, No Horse" they say and the same could be said of joints in racehorses.
More than half of all equine lameness is due to joint diseases and injury (James Casey, DVM, MS, The Horse. " Joint Disease and Lameness" July 23 2007, Article # 10062).
Joint injury, joint disease secondary to trauma or injury, and osteoarthritis (OA) are major causes of attrition and loss of function in horses .(Stacey Oke, DVM, MSc ,Fact sheet from " The Horse": " Medicating Horses")

Throughout the year, various types of athletic horses are gearing up for their peak competition season. Intra-articular medications are widely employed in equine practice and there are a lot of therapies and treatments to help with joint disease. These therapies are designed to decrease inflammation and protect the cartilage for long-term benefit.
One quite new treatment gaining popularity, which is being used to support conventional joint treatment is the use of IRAP.

IRAP (Interleukine-1-Receptor Antagonist Protein) is different from other products as it treats the one of the causes of joint disease. The mode of action is to restore joint and the cartilage function. It is an anti-inflammatory therapy that blocks interleukin-1 (IL-1). Interleukin-1 is one of the major inflammatory substances that the body releases in the event of injury, resulting in inflammation. The process of IRAP-production is a natural occurence in the horse. The antagonist protein competes with IL-1 by binding to the IL-1-receptor without causing inflammation.

The antagonist protein in IRAP is manufactured in white bloodcells, thus the preliminary step in the therapy is blood collection. The collected blood is incubated in the presence of specially designed glass beads. Theses glass beads are amplifiing the production of the antagonist protein.

When the IRAP has reached the desired level, the veterinarian can inject the substance into the injured joint.

The use of this therapy is supported by several studies. One of them was performed at the Colorado State University. The study showed that IRAP treated horses have reduced lameness, improved joint histology (cellular make up) and a tendency for cartilage preservation.

2. Literature survey

2.1 General Anatomy of Joints

Before one can understand the role IRAP, there must be a basic understanding of joint construction and function.

First, there are three broad categories of joints:

1) Fibrous

2) Cartilaginous

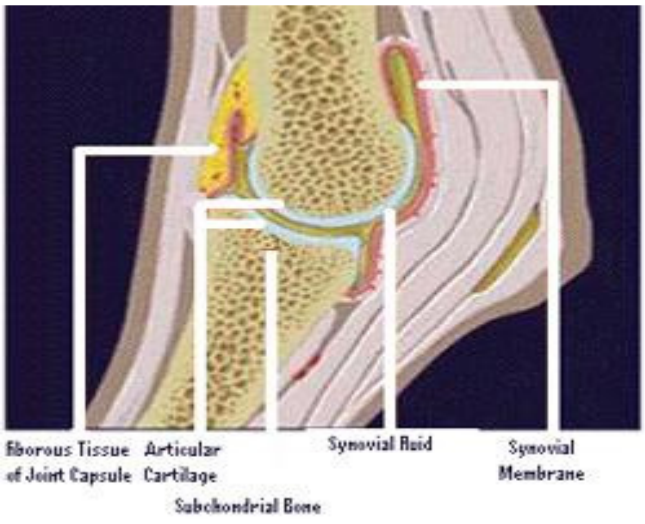
3) Synovial

Only one of the three is at risk for injury and disease as the result of ongoing activity.

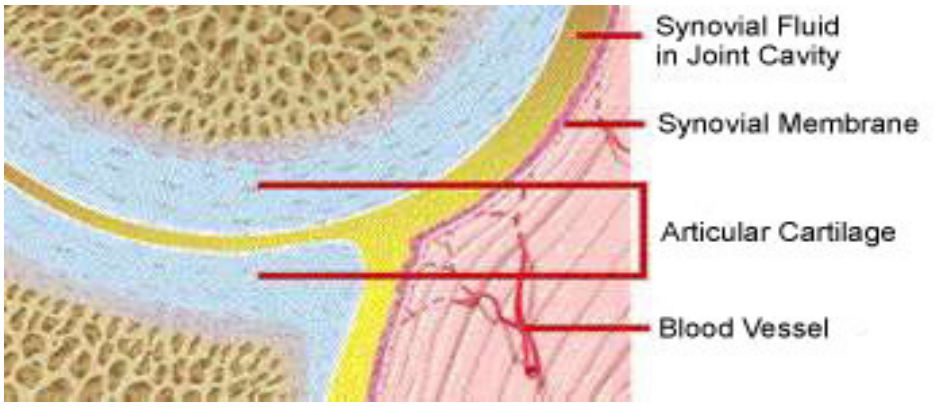
Fibrous joints are the least likely to be afflicted with disease because they are basically immovable. They include joints in the skull and those between the shafts of some long bones.

The second category -the cartilaginous joints- is in much the same position as far as their potential for disease is concerned because they also have limited movement. These cartilages are primarily joints of the pelvis and vertebral bodies.

The synovial joints are at greatest risk in a horse's body due to their increased capacity for moment,. A synovial joint consists of two or more bony ends covered by articular cartilage. The cartilage is smooth and resilient. If it is properly lubricated, a joint will allow frictionless movement.



Joint structure overview (source: holistic-horse-health) fig. 2/1



Joint structure in Detail (source: holistic-horse-health) fig. 2/2

The structure of a synovial joint is designed to absorb concussion and permit movement. The ends of the bones are encased in a fibrous capsule.. The outer part of the joint capsule is the fibrous layer and the inner part consists of synovial membranes that line the sides of the joint capsule. The synovial membrane secretes fluid that lubricates the joint. Additionally to being a lubricant, the synovial fluid also supplies nutrients and removes waste products from hyaline articular cartilage, thus it is essential for the cartilage-metabolism.

An important component of synovial fluid is hyaluronic acid, also known as sodium hyaluronate or hyaluron (Funktionelle Histologie, Liebig, 2003).

Articular cartilage is made up of chondrocytes embedded within an extensive "extracellular matrix". This matrix contains collagen (type 2), proteoglycans, and a large amount of water. In healthy joints this matrix is continuously "turned over," or replenished, to stay healthy and capable of resisting forces during motion.

The role of the cartilage is to act as the cushion between the bones of a joint. The articular cartilage is the weight-bearing component of the synovial joint. It is avascular, aneural and alymphatic (Dijkgraaf *et al*., 1995; Saw *et al*, 2007, Frisbie, 2006; Aigner *et al*., 2006).
It is the only area of the joint that cannot be repaired following damage.
Therefore it is essential that the surrounding synovial fluids and connective tissues that protect and nurish the cartilage are kept in top condition.

2.2 Pathogenesis

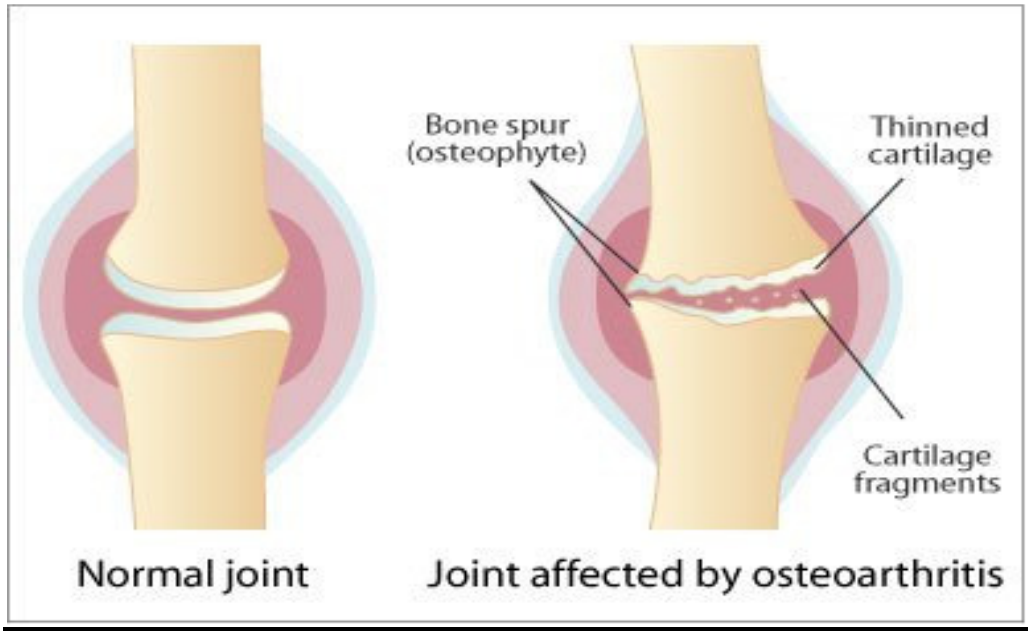
"Arthritis" is a general term that refers to an inflammation in a joint
(Ted S. Stashak, Cherry Hill. Practical Guide to Lameness in Horses 1995, 146-147).
Signs of inflammation are heat, pain, swelling and loss of function. Although an arthritic horse may show some or none of these signs, in most cases mild to moderate lameness, stiffness, joint-effussion and poor performance in competition are seen.

One of the most common and important type of arthritis is osteoarthritis (OA).

"Osteoarthritis is a specific form of arthritis that involves a progressive destruction of articular cartilage." (Caron and Genovese, 2003) It is also the most common cause of lameness in horses. Recent studies show that approximately 60% of lameness in horses is related to osteoarthritis (Caron and Genovese, 2003).

In arthritic joints the balance between the breakdown of the old cartilage and the production of the new, healthy cartilage tips toward the destructive phase. The result is that the cartilage physically degenerates over time.

The pathogenesis of the development of osteoarthritis is variable. 'Primary osteoarthritis' refers to healthy joints that got damaged by abnormal forces.
Alternatively Osteoarthritis can develop secondary to reasons such as trauma (for example a chip fracture) or as a result of poor conformation.



Evolution of Osteoarthritis (source: ABCHealth-and-Wellbeing) Fig.2/3

2.3 Diagnosis

Considering how common Equine Osteoarthritis is, it is surprisingly hard to diagnose.
The diagnosis of lameness will be made with an orthopedic lameness examination.

This includes :

a) Anamnesis

b) Visual examination

c) Examination on the standing horse

d) Examination at exercise

e) Manipulation and flexion test

f) Further Examination such as nerve- or joint blocking, radiography, ultrasound and so on.

Anamnesis

A medical history should be taken on every horse. Records should include information regarding duration, intensity of lameness, clinical signs and previous treatments.

The owner should be asked easily understandable questions like:

How long has the horse been lame?

What sort of work is it expected to perfom?

Has the horse been involved in any accidents that you know of?

How does the lameness change while working, if at all (worsens or improves, or no change)?

Is the horse intermittently or repeatedly lame?

When was the horse shod last?

Has the horse been treated by another veterinarian or the owner for the same complaint? If so, what did this involve and when?

Visual Examination and Palpation

A visual Examination is carefully made when the horse stands at rest on a flat surface. It should be seen from a distance to evaluate the body type, condition and conformation as well as posture and weight bearing/shifting. The next step is a closer observation where each limb and muscle group is examined for swelling or asymmetry, abnormal use, atrophy, hypertrophy, wounds or cracks.

The horse will get palpated to find warmth, pain or hardening of the muscles. Each abnormality should be assessed as a possible reason for lameness.

Palpation of a front leg fig. 2/4

Examination at Exercise

The characteristics of gait should be observed from a little distance. It should be observed from behind, from front and the side, in both walk and trot, to arrive at a conclusion. This allows the observer to accurately decide which legs are involved and to what degree of lameness.

It is also helpful to observe the horse tacked-up and lunged or on a treadmill. Generally it can be said that forelimb lameness is best viewed from front and side while hindlimb lameness is best observed from side and back.

Lameness produces visible clues such as nodding of the head or asymmetry of the gait, alterations of foot flight and placement, length of stride or the degree of fetlock extension, action of the shoulder and symmetry in gluteal rise.

Manipulation and Flexion Test

Lameness provocation is performed to exacerbate the baseline lameness or to provoke a hidden gait abnormality and to localize the source of hidden pain (Ted S. Stashak, Ora Robert Adams, Adams' Lameness in Horses (1987) 146-147)
Ideally the flexion test should be performed first on the contralateral side to the suspected lame leg. The ideal duration of flexion is one minute up to one and a half minutes (Ted S. Stashak, Ora Robert Adams, Adams' Lameness in Horses (1987) 146-147). The force during flexion varies but is recommended as hundred to hundred-fifty N as a moderate force. It should be taken into consideration that the amount of force depends also on size of the horse and the joint being flexed.

Proper evaluation of the results of a flexion test requires that the horse can be observed while trotting on a straight line on a firm, non-slippery surface. The horse should be trotted immediately after the limb is placed to the ground. If possible the horse should be trotted away from the examiner for a minimum of fifteen to twenty meters.

A positive flexion test is defined as obvious lameness that is observed for more than three to five strides while the horse trots in a straight line immediately after flexion (REF). A mild response, even in sound horses, is often seen in the first few strides. But a sound horse will ‘warm out’ of this response quickly i.e. this apparent lameness will disappear quickly.

Flexion test of the front leg fig. 2/5

Further Examination

If we perform a lameness examination, we often will use nerve blocks to try and determine the location of the problem. The way it works is that the areas we inject in are "blocked" so that they become painless.

Joint blocks using local anesthetics, such as lidocaine or carbocaine, are important tools during lameness exams to confirm the involved anatomic structures. The horse can be reassessed 15 minutes after nerve block injection to determine if its lameness has changed.
If the horse has improved after blocking and it is more sound, then the anesthetized joint is likely contributing to the lameness.
Another advanced examination to find the reason of lameness is simply doing some x-rays. Classic signs suggestive of equine osteoarthritis on a radiograph are the presence of osteophytes (bony growths at the margins of the joint that form during remodeling of an arthritic joint), sclerosis (seen as increased density of bone), or lysis (the decomposition of the subchondral bone lying directly under the articular cartilage). In some cases we also see a narrowing of the joint space.

2.4 Treatment

The decision of which product or combination of products is the best for the horse will depend on the kind of joint, the horse's function, the degree of lameness and the timing before competition.
We have oral supplements like glycosamin and chondroitin that have been a hot topic in the horse world for some time. These are materials that are not fed to heal the lame or make a chronically unsound horse become sound. They are mainly used with the intention of preventing joint problems from occurring.
Corticosteroids, hyaluronic acid and PSGAG (Adequan®) are the most frequently administered intra-articular medications (Frisbie *et al*., 1997)
We might consider using intravenous (iv) hyaluronic acid or intra-articular (ia)/intramuscular (im) administration of polysulfated glycosaminoglycans (Adequan®) to decrease intraarticular protein concentration and increase hyaluronic acid that will lubricate the joint.
Clinically, Hyaluronacid has been used as a therapeutic treatment for osteoarthritis. In a normal joint, Hyaluronacidis secreted into the synovial fluid by the joint capsules synoviocytes andserves as boundary lubrication. (Schmidt *et al*., 2007)

Interleukine-1-receptor antagonist protein (IRAP) is a novel biological treatment which recently has been used as an aid in the management of lameness caused by inflammation and degeneration within joints. This therapy has become an increasingly popular therapy for horses with osteoarthritis or other inflammatory conditions. (Oke, S. Managing joint health, 2009)
In human medicine IRAP is used for osteoarthritic joints already since 1998.Interleukine-1-receptor antagonist protein (IRAP) has it roots in Europe and has been used comprehensivly in Germany. It is being market in the United States by "Athrex Vet Systems" and recommended for treatment of inflammation of the joint lining and mild to moderate equine osteoarthritis

In 1977 Interleukin-1(IL-1) was originally identified as a regulator of cartilage function. These days IL-1 is recognized for its capacity to produce most, if not all, of the enzymes that are involved in cartilage destruction. Interleukin-1 is an inflammatory cytokine (mediator) that stimulates inflammation after binding to the receptor.

IRAP works like that, that it competes with IL-1. It is binding on the IL-1 Receptor without causing inflammation. The protein is produced by incubating a small volume of horse´s blood with a manufacturer supplied syringe containing glass beads that are coated with a substance designed to promote the production of anti-inflammatory molecules.

3. Materials and Methods

3.1 Place of Examination/ Treatment

This study took place during my summer externship at Hallands Djursjukhus at the horseclinic at Bjertorp/ Sweden.
This clinic has the speciality that it stands on the property of Ake Svanstedt, one of the biggest and succesfullst trotting trainers in Europe.
This has a lot of advantages because first you follow the horse over the whole period of training because all horses will visit the clinic for a short check up once in a while. And second it was very exiting to follow the success of the treatments with every raceperformance.

The whole examination as well as the treatment found place inside the clinic. There is quiet a good system to view and examina the horses at a long enough, flat strip.
The strip was covered with concrete so you also can quiet good even hear if a horse is not clean in his movement.
In some difficult cases we also have been able to drive or lounge the horses for the lameness examination.
Right beside the hall with the walking strip there is a sterile lab where you can work on the IRAP splitting.
The clinic itself bought a special freezer to store all left IRAP doses of its patients. So always a patent returned we had it right on the hand.

The trainer, Ake Svansted came with every new horse he got in training to the clinic to look at maybe existing problems and treating of them before starting to train.
The amount of horses in this study visited the clinic over a period of 1 month. So the caseload of IRAP treatment is quiet high.

All of the horses are in training and performing races in Sweden. Most of the horses are even standing at the same trainer (Ake Svanstedt), who seems to be the biggest trotting trainer in Sweden and on whose ground the clinic is built.

When the horses came to be presented at the clinic we performed a flexion test to find out on which leg and joint the horse is lame and which degree of lameness the horse showed at this time. After treating with IRAP we ask the grooms to come back with the horses 6 days after treatment to figure out whether we have a positive response saying the degree of lameness got better or not.

This study is performed with 12 horses. All of the horses are standardbred trotting horses in the age from 4-6 years of age.

Patient No 1, 5 years old

Patient No 2, 6 years old

Patent No 3, 6 years old

Patent No 4, 7 years old

Patent No 5, 5 years old

Patent No 6, 4 years old

Patent No 7, 6 years old

Patent No 8, 5 years old

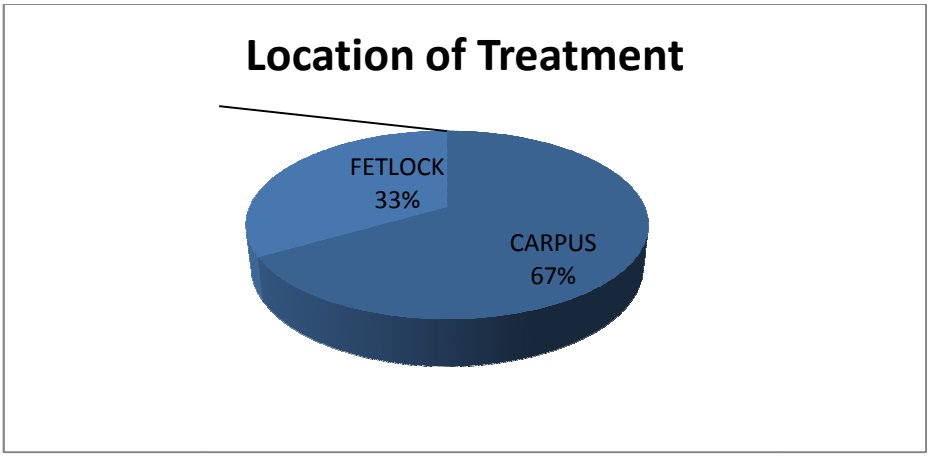
Patent No 9, 8 years old

Patent No 10, 5 years old

Patent No 11, 5 years old

Patent No 12, 6 years old

From this twelve treated horses we injected eight (Patient No. 1, 4, 6, 7, 9, 10, 11, 12) into the carpal joints and four (Patient No.2, 3, 5, 8) into the fetlocks.



Location of treatment fig.3/1

One of the horses (Patient No. 8) showed a half degree of lameness, six of the horses (Patient No.1, 2, 3, 4, 10, 12) showed a lameness degree between one and two, two of the horses (Patient No. 6, 7) showed a lameness degree over two and further three of the horses (Patient No. 5, 9, 11) showed a obvious lameness, degree three or more.

3.2 Treatment

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The fist step of the procedure is taking blood and preparing it for use.

We have a IRAP starter-kit which contains a special 50 ml syringe, a green sealing cap and a butterfly cannula. The syringe is specially prepared with glass beads that stimulate the production of the antagonist protein and an anticoagulant.

IRAP starter kit fig.3/2

For drawing blood we clip the hair at the place of injection and clean it with antiseptic soap. We sweap it of with alcohol to make sure the blood sampling is done under aseptic conditions. We place the butterfly canula on the external jugular vein and gently draw blood with the IRAP syringe and pull the plunger straight that it not may snap off.

If the IRAP syringe is filled with blood we deconnect the syringe from the butterfly cannula and close it with the enclosed green cap. Than we gently invert the blood-filled syringe several times.

The syringe must reach the incubator as soon as possible after the blood has been taken from the horse. If we have to transport the syringe for short period of time a water bath at 37°C gave satisfactory results.

It is important to note that the injections are only suitable to treat the horse from which the original blood was collected, thus a proper identification is required.

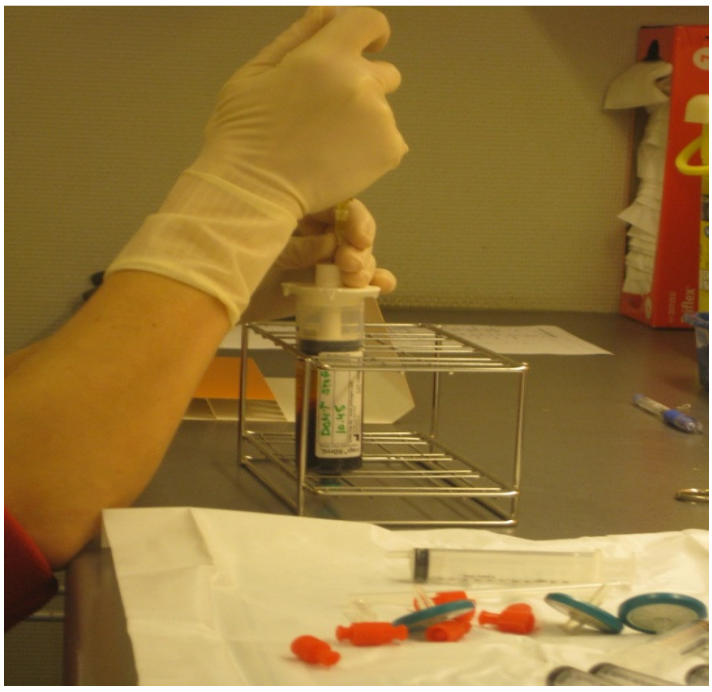
Blood collecting for IRAP in a special syringe fig. 3/3

Not to get in any danger to switch the syringe we directly label it with name of the horse, the date and time. The labeled syringe we incubate the for 24 hours at 37 C.

Melag Incubater for IRAP syringes fig. 3/4

After 24 hours of incubation time we centrifuge the 50 to 60 ml in the syringe for 10 minutes at 3700 rpm. It is very important that the green cap is closed tightly while the centrifugation.

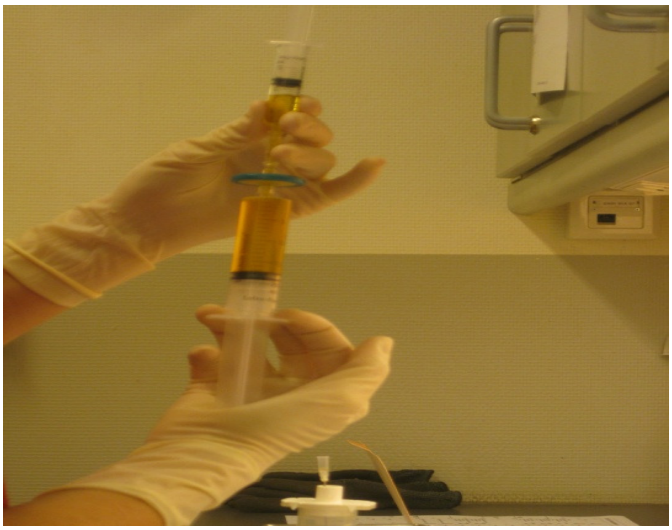
The next step is the serum extraction. To use the syringe in a standing position we are using a disinfected syringe rack on a sterile drape. This procedure will also be done under sterile circumstances. Then a 20 ml syringe with a sterile 100 mm cannula gets connected and we draw out the serum slowly. It is important just to draw the serum and not the erythrocytes.



Collecting Serum after centrifugation fig.3/5

The next procedure is that we filter the serum with a 0.22 µm filter and split it in smaller, better usable doses of 5 ml.

The amount of serum collected from each syringe of blood is usually between 20-25ml. This yields 5-6 doses of IRAP, but the number of doses available for use from each collection is dependent on the specific joint.



Splitting and filtering of the IRAP doses Fig 3/6

Finally we label the 5 ml syringes containing the IRAP serum with the name of the horse and date and time. The doses are rather used freshly or getting stored in a special for this usage bought freezer placed in the clinic. So we always had the IRAP syringes on the hand just in case.

Labeled syringes fig. 3/7

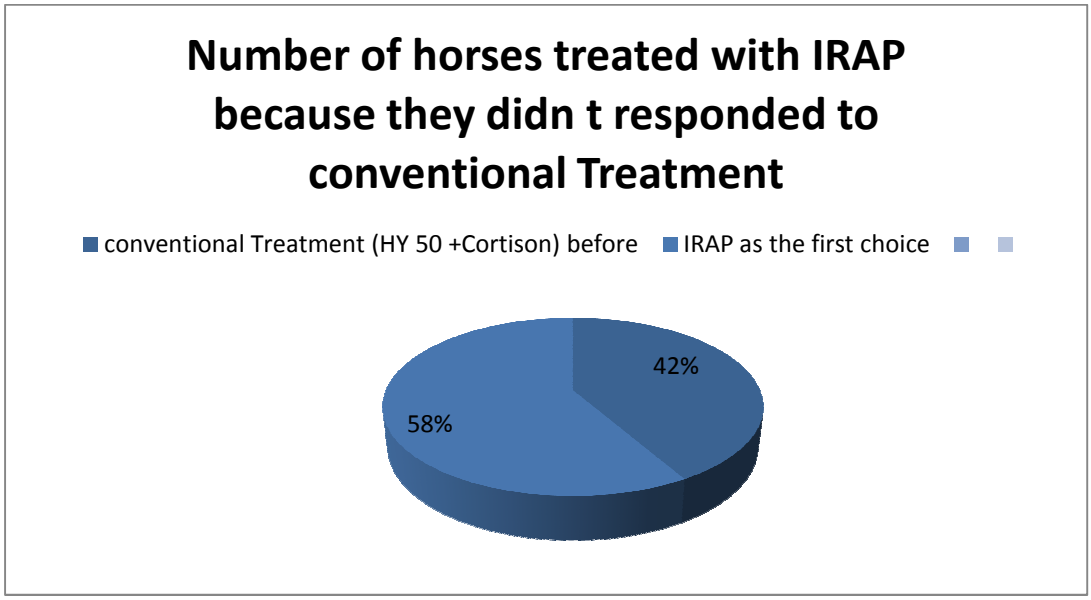
To use the first dose of IRAP directly the hair over the place of injection gets clipped. The skin is cleaned with an antiseptic soap for approximately 10 minutes. The soap is rinsed of with isopyl alcohol. We then inject the IRAP into the joint using a steril needle and syringe while wearing sterile gloves.

IRAP Injection into the Carpus fig. 3/8

After injection, we routinely bandage the joint if possible for 2 days, and the horse should be kept for 1 day on strict stall rest, followed by a day of handwalking only.

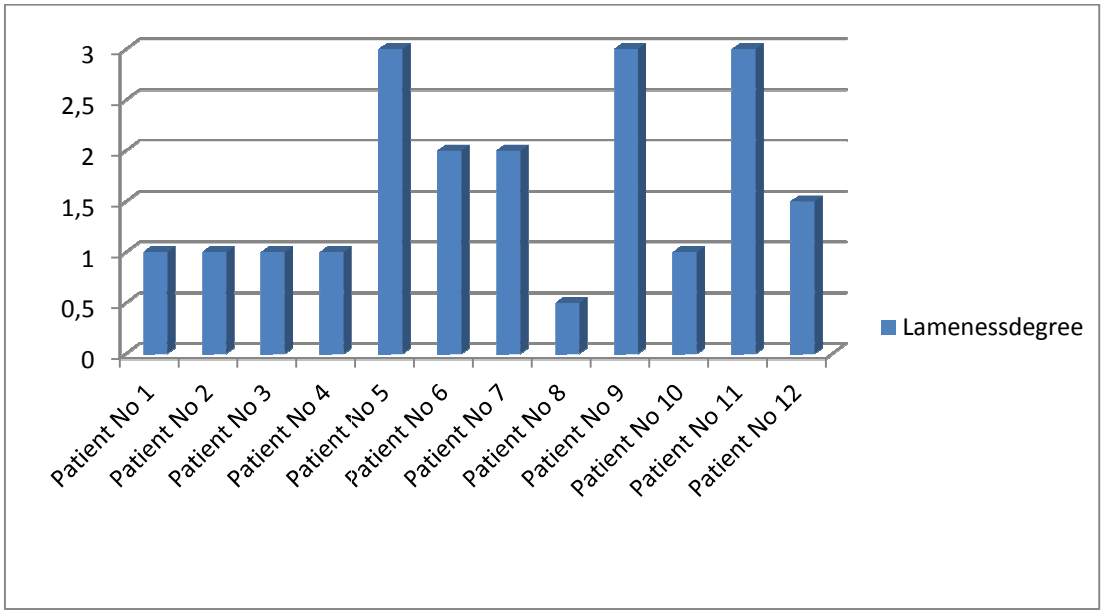
In general 2-3 treatments of the joint are performed, at 8-14 day intervals or whenever the horse returns to getting worse. The volume injected at each treatment is 1-8ml, depending on the kind of joint.

4. Results



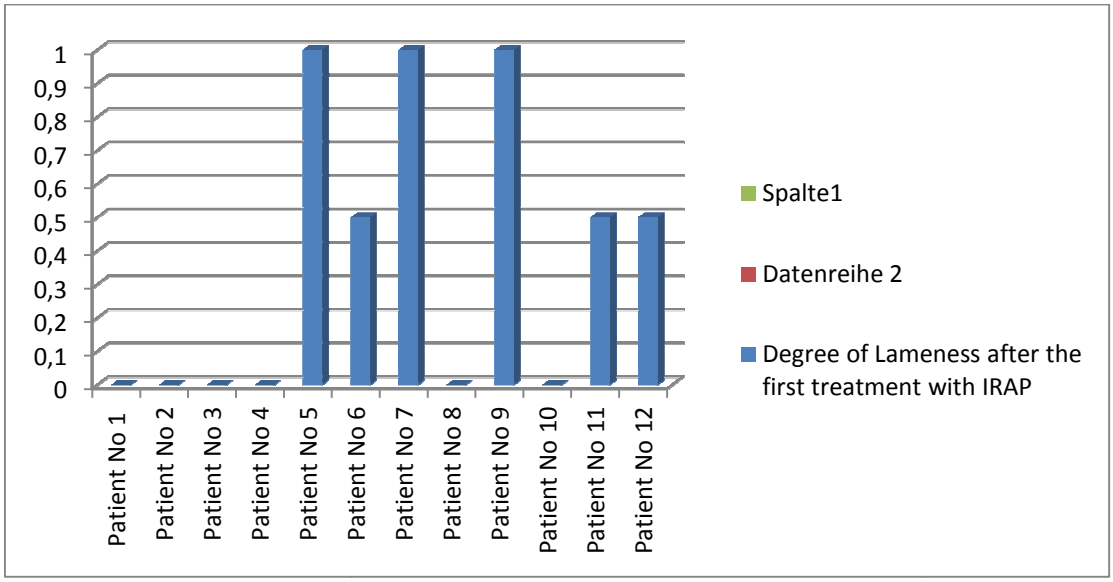
Number of horses treating IRAP as first choice or after no response to conventional treatment

Fig. 4/1

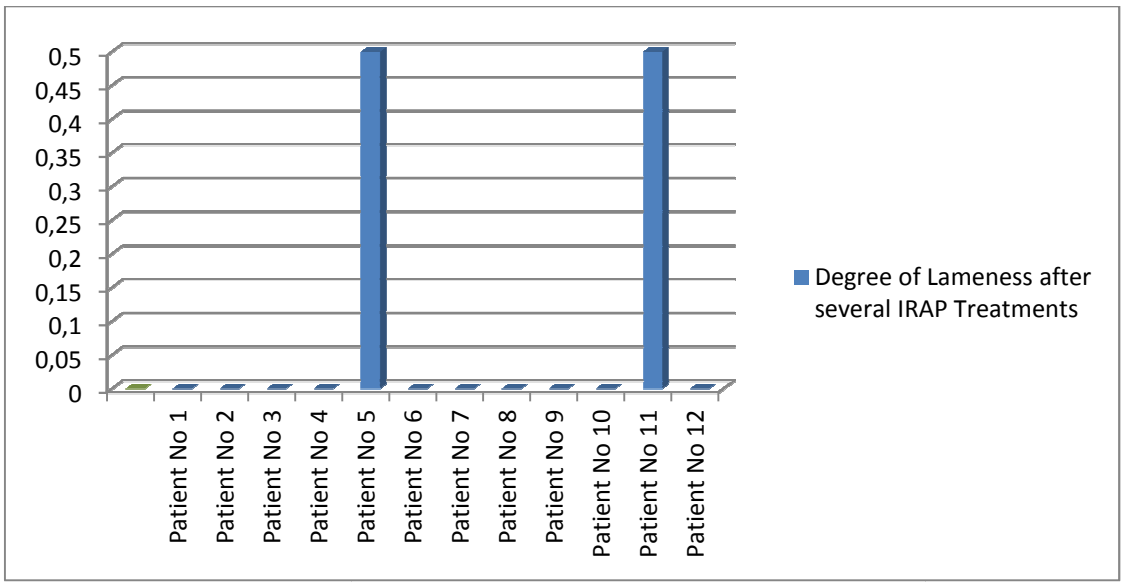


Degrees of lameness before treatment with IRAP Fig.4/2

In seven of the horses (Patient No. 3, 5, 6, 7, 9, 10, 12) we decided to use IRAP because they did not respond to previous treatments with hyaluronic acid and cortison.



Degree of lameness after first treatment with IRAP Fig.4/3



Degree of lameness after two treatments with IRAP in a weekly interval
Fig. 4/4

In all twelve cases the IRAP treatment has been a success. It reduced the degree of lameness in all horses. In two out of twelve horses (Patient No. 5, 11.) there was a lameness with a degree of 0.5 left. The 10 other horses (Patient No. 1, 2, 3, 4, 6, 7, 8, 9, 10, 12) remained sound for the rest of my stay in Sweden (3 month).

5. Discussion

According to other clinics in Sweden they use three joint injections at 7-14 day intervals. According to newly made studies at Colorado State university the most positive effect is seen after the third treatment.

In the study Colorado state university did, they picked the horses out incause of MRI pictures. So they just picked horses already showing changes in the jointcartilage. Also they treated cases of bone cysts or holes below the joint surface that seemed to respond well. Also horses affected with inflammation of the sesamoid bones (sesamoiditis) and inflammation of the covering of the cannon bone (periostitis or bucked shins) responded well to the Iraptreatment.

6. CONCLUSION

This study shows the use of Interleukine-1-receptor antagonist protein (IRAP) for mild to moderate osteoarthiritis especially for joints that we dont want to continually inject with corticosteroids. Clinically, with cortisone injections we often see a sudden respons in the degree of lameness that then gradually wears off over a period. When cortisone injections are repeated we often see a decrease in the interval between treatments. Meaning, that the more cortisone injections a horse has into a particular joint, the shorter the duration of therapeutic effect and the sooner that joint will need to be treated again. The use of IRAP allows us to delay the use of cortisone injections and prolong the athletic life of a horse. In many cases where there has been a very good response to IRAP therapy, cortisone injections can be delayed indefinitely.

It also shows that IRAP might have a very good effect in horses having competitions with drug-testing deadlines related to Fédération Equestre Internationale since its 100 percent body-own material used for treatment and we are not struggling with any withdrawal periods.

Another reasonable use would be in managing medication of joints of obese horses due to concerns of steroids inducing laminitis in certain conditions or for horses that are no longer getting a positive response from hyaluronic acid or corticosteroid injections.

Usually three successive treatments are recommended while the horse stays in training or while gets in rest but according to our present study most of the horses responded after the first treatment already.

Interleukine-1-receptor antagonist protein (IRAP) has uncounted advantages as a new therapy possibility in racehorses. One disadvantage are the costs. Every clinic of course has its own price but in Europe the producing of the IRAP serum plus the first treatment lays approximately arround 750 Euros depending on the country.So with this it is one of the most expensiv joint therapies aswell. But for horses previously affected with sometimes crippling arthritis that can now return to athletic function, IRAP is definitely worth the expense.

In 2002, James Richardson, M.D., a board-certified surgeon and professor of orthopedics at Keele University in England, wrote in the International Cartilage Research Society Newsletter:

"*There is a great cleverness in each cell and learning to work with them, and to trust them to do the right thing in the right place is not new to surgery. We have always depended on the natural biology of tissue healing*."

IRAP is the most recent approach to helping the body heal itself, and even newer types of gene therapies and products on the research horizon will continue this trend.

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