Article

Discovery Medicine 2023; 35(177): 632–641
https://doi.org/10.24976/Discov.Med.202335177.62

Animal Feasibility Study of a Novel Spinal Cord Stimulation Multicolumn Lead (Heron Lead)

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Published: 1 August 2023

Background: Currently available spinal cord stimulation paddle leads require a laminectomy, limiting the types of clinicians who can implant and increasing the risk of complications. Recently, WISE S.r.l. designed a prototype multicolumn lead named the Heron® lead that can be implanted percutaneously. The purpose of the study was to examine the efficiency of placing a paddle lead percutaneously.

Methods: Ten sheep were assigned to either the Heron lead group (n = 7) or the control group (n = 3). The sheep were observed for 13 weeks after implantation. Neurological and clinical examinations were conducted prior to surgery and then during the follow-up period. The implantation sites were evaluated through macroscopic observations during the article explantation and the lead migration was evaluated by comparing the article positioning at the surgery, four weeks after the surgery and at the explantation day through fluoroscope images. A qualitative comparison was made between the results collected with the test article and the control article.

Results: Observations at the surgical sites indicate that test animals appeared to have less swelling around the surgical wound than control ones in the first 14 days, but no impact on wound healing was noticed. Additionally, no clear difference was observed in pain scores between the two groups, with observations tending to show that the maximum pain was occurring later in the test group with respect to the control group. General clinical observations showed no major difference between the two groups, and determined clinical abnormalities were not directly related to the procedure. Lastly, neurological deficits frequency decreased from the first to last animal operated, regardless of their test or control status.

Conclusions: Our study concluded that the Heron lead is safe to implant, with a safety profile similar to the control article. Additionally, we conclude that the Heron lead is effective in reducing lead migration events.

Keywords: spinal cord stimulation; paddle lead; feasibility study; neuromodulation; lead migration

Introduction

Spinal cord stimulation (SCS) is a non-opioid therapy that can be used for the treatment of chronic neuropathic pain [1]. Specific pain conditions that can be managed by SCS include painful diabetic neuropathy, complex regional pain syndrome, and failed back surgery syndrome [2,3]. The indications for SCS are progressively broadening with recent evidence supporting its use in the treatment of several headache conditions and chemotherapy-induced neuropathy [4,5].

As the indications for SCS grow, SCS continues to receive increased research attention in efforts to improve safety and efficiency, while minimizing side effects and burden to the patient. Today, there are two main categories of leads used in SCS systems: percutaneous and paddle leads [6]. Both lead designs have similar outcomes about pain reduction, long-term healthcare costs and with regards to reoperation necessity. Neurological complications are exceptional with both types of leads [7–9]. The percutaneous lead is the easiest to implant and the least invasive [6]. Yet, the use of paddle leads is widespread since they are less prone to migration, and they require significantly lower energy thus prolonging the life of SCS battery. Percutaneous implantation can be done by chronic pain physicians, while paddles can only be implanted through a small laminectomy thus requiring a neurosurgeon.

Recently, efforts have been made to design a new paddle lead that can be implanted percutaneously without the requirement of a laminectomy. The goal is to provide the advantages of a paddle lead with the surgical advantage of placing it percutaneously without the need to perform

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a laminectomy. Here, we evaluate a prototype multicolumn lead made to conform to the *dura mater* that can be implanted percutaneously. The purpose of this preliminary feasibility non-human *in vivo* clinical animal study was to macroscopically evaluate the local tissue effects of the lead following its implantation in the sheep epidural space and to verify its functionality in terms of migration.

Materials and Methods

Lead Patterns

This study examines the prototype multicolumn called Heron® lead (WISE S.r.l., Cologno Monzese (MI), Italy). The Heron lead is intended to be implanted in the epidural space in the spinal canal. The cranial portion of the lead (i.e., paddle) contains two columns of electrodes made of a thin film conductor made of precious metals supported on a thin silicone sheet enclosing a nitinol spring that determines the cranial lead shape. When deployed (implanted) at the target location conform to the *dura mater* within the epidural space in the spinal canal (Fig. 1). The caudal portion of the lead displays ring electrodes for connection to the implantable pulse generator or to the lead extension (not used in this study).

The Lamitrode S-8 Lead (Abbott, Abbott Neuromodulation, Austin, TX, USA) was used as the control. This lead is intended to be used with Abbott neurostimulation systems by connecting to a compatible pulse generator, either directly or with a compatible lead extension. Abbott neurostimulation systems are indicated for SCS in the treatment of chronic pain of the trunk and limbs, either as the sole mitigating agent or as an adjunct to other modes of therapy used in a multidisciplinary approach. The Lamitrode S-8 lead is composed of platinum-iridium electrodes and terminal end contacts, silicon paddle, and polycarbonate polyurethane insulation.

Animals

Investigation of the novel lead was completed *in vivo* on Blanche du Massif Central sheep (age: 2–4 years, weight >50 kg). Animal source was Bergerie de la Combe aux Loups, France. This study was approved by NAMSA Ethical Committee. The project authorization number associated with this study for NAMSA is APAFIS#22914-2019091916114859 v10 (100%). The study was conducted in the NAMSA facility in Chasse-sur-Rhône, France. NAMSA is an Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International accredited facility and is registered with the French Department of Agriculture for animal housing, care, and investigations. The sheep model has been selected due to the similar properties of the sheep and human spine with regard to anatomy and biomechanics [10–12]. Six sheep each received an implantation of a Heron Lead (i.e., test article) in the epidural space at lumbar level under fluoroscopic guidance. Three sheep each received an implantation of a control article in the epidural space at lumbar level under fluoroscopic guidance. In all surgeries, a small laminectomy was necessary to access the epidural space. The cranial part of each lead (i.e., paddle) was positioned within the epidural space in the spinal canal at lumbar level (for the test article only: the lead was also substantially deployed when implanted) and the caudal part (i.e., cable) was implanted in the surrounding subcutaneous tissue. The duration of the current study was 13 weeks long. Indeed, 13 weeks was considered a sufficiently extended period to confirm the test article works safely, by mimicking the human clinical settings.

Animal Management

Housing conditions conformed to the European requirements (Directive EU/2010/63). The animals were housed in-group with other animals from an unrelated study at arrival and during the acclimation period. The animals were kept under laboratory conditions. The animals' housing room temperature and relative humidity were recorded daily. The recommended temperature range for the room was 15–24 °C. The light cycle was controlled using an automatic timer (12 hours of light, 12 hours of dark).

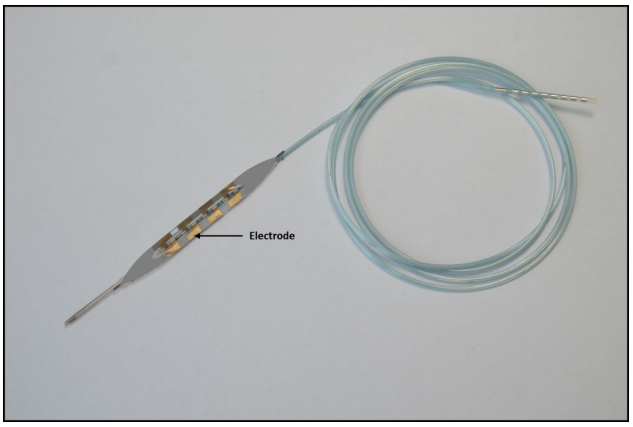

Fig. 1. Heron lead design.

Standard hay was provided *ad libitum* and supplemented with a commercially available pelleted sheep feed (Special Diet Services, Argenteuil, France). Minerals were provided *ad libitum* (Sodimouton, Salins Agriculture, Clichy, France). Potable water was delivered *ad libitum* through species appropriate containers or delivered through an automatic watering system. No contaminants present in the feed or water were expected to adversely impact the results of this study.

It was predetermined that in the event the animal was injured, ill or moribund, care would have been conducted in accordance with current veterinary medical practices. If warranted for humane reasons, euthanasia would have been conducted following veterinary advice.

Pre-Operative Procedure

Prior to the surgery, a neurological examination was conducted. Each animal was weighed (body weight range: 63 to 80 kg; age: 2.8 and 3.75 years, skeletally mature) one day prior to the surgery. Antibiotic treatments (ac. clavulanic amoxicillin, Synulox® suspension, Zoetis France, Malakoff, France) were administered using the intramuscular (IM) route the day before the surgery as a prophylactic and preventive measure. The sheep were also fasted before implantation.

Anesthesia was induced and maintained by continuous intravenous injection of propofol (Propovet® multidose 10 mg/mL, Zoetis France, Malakoff, France). If necessary, lidocaine was sprayed into the throat to facilitate intubation. Each sheep was intubated, mechanically ventilated, and placed on isoflurane inhalant anesthetic (IsoFlo® 100%, Zoetis France, Malakoff, France) for continued general anesthesia. An intravenous infusion with an electrolyte solution (Ringer lactate, Axience, Pantin, France) was performed during surgery. Pre-operative subcutaneous injection of an anti-inflammatory drug (flunixin; Antalzen® 50 mg/mL solution injectable; Laboratorios calier, Carros, France) was given. Antibiotic treatment (clavulanic acid – amoxicillin; Synulox® suspension, Zoetis, Malakoff, France) was administered.

A neutral ophthalmic ointment (Ocrygel®, TVM, Lempdes, France) was applied to both eyes to protect the corneas from drying.

The surgical area was clipped free of wool, scrubbed with povidone iodine (Vetedine® savon, Vetoquinol, Lure Cedex, France), wiped with 70% isopropyl alcohol (Savetis, Quévert, France), painted with povidone iodine solution (Vetedine® solution, Vetoquinol, Lure Cedex, France), and draped. Each sheep was placed in prone position on a warmed pad. A rectal temperature probe and a rumen tube were placed during surgery. Electrocardiogram, peripheral non-invasive arterial blood pressure and oxygen saturation were monitored. When signs of awakening were observed during the surgery, additional IV injections of propofol (Propovet® multidose 10 mg/mL, Zoetis France, Malakoff, France) were performed. When signs of pain were observed during the surgery, methadone (Comfortan®, Dechra, Northwich, UK) was injected (IV).

Implantation Procedure

Surgery was performed by a neurosurgeon (P.M.) with knowledge and experience using SCS systems using standard aseptic techniques. The implantation was not percutaneous, as in the sheep there is no space between the lamina to pass through to reach the epidural space. So, the test and the control article were positioned over the *dura mater* through a laminectomy. With the animal positioned prone, fluoroscope was used to identify the appropriate level for implant of the articles in the lumbar vertebras. A skin incision was made medially, and myo-laminar dissection was carried down to the lamina bilaterally. The dorsal spinous processes were removed with bone cutting forceps. As the epidural space at the level of the lumbar canal is very narrow in the sheep, without fatty tissue (contrary to human lumbar epidural space), a progressive delicate approach of the epidural space was performed using first a small spherical bur (Stryker 4.0 mm, ref: 5820-110-040, Kalamazoo, MI, USA) then a small spherical diamond bur (Stryker 4.0 mm, ref: 5820-012-040, Kalamazoo, MI, USA) were used to remove the dorsal (outer) cortex, cancellous bone, and a thin portion of the inner cortical layer of the lamina, under constant irrigation with saline solution. When judged necessary by the surgeon, a small spherical diamond bur (Stryker 3.0 mm, ref: 5820-012-030, Kalamazoo, MI, USA) was used to create a hole in the adjacent bone, that was used to fix the article cable with a non-absorbable stitch. Then, using a piezotome equipped with aspherical bur (Stryker 4.0 mm, ref: 5820-110-040, Kalamazoo, MI, USA), under constant irrigation with saline, the thin inner cortical layer was gently penetrated and removed, preserving the *ligamentum flavum*. The *ligamentum flavum* was then removed. Then, the cranial part of each article (i.e., paddle) was positioning in contact with *dura mater*. It was then secured with non-absorbable thread (Prolene 2-0, Ethicon®, Somerville, NJ, USA) to the adjacent soft tissue, and when judged necessary, to the adjacent bone, thanks to the small hole previously created in the adjacent bone. The cable was rolled and placed in a subcutaneous pocket formed by blunt dissection in the surrounding subcutaneous tissue. The cable was secured within the subcutaneous pocket with non-absorbable thread (Prolène 2-0, Ethicon®, Raritan, Somerville, NJ, USA). The stylets could be used for placement of the test article, if necessary, and anchors could be used to secure the cable of the article to subcutaneous tissue, if necessary. The subcutaneous pocket was then closed with absorbable thread (Vicryl 2-0, Ethicon®, Somerville, NJ, USA). For hemostasis during surgery, non-woven compresses or cotton wool were used. Lidocaine (Lurocaïne®, Vetoquinol, Lure Cedex, France) was injected in the subcutaneous tissues to reduce the post-operative pain in six of the sheep (Lidocaine was missing for the four other sheep). The fascia, the subcutaneous tissue and the skin were closed with absorbable surgical thread (PDS II 1, Ethicon® and Vicryl 2-0, Ethicon®, Raritan, Somerville, NJ, USA) using standard surgical technique and disinfected using povidone iodine solution (Vetedine® solution, Vetoquinol, Lure Cedex, France). Lead placement was verified through the fluoroscope. The X-ray image was acquired.

Post-Operative Procedure

Each animal was moved to a recovery area and monitored for recovery from the anesthetic until sternal recumbency was achieved. After recovery, each animal was returned to its cage and observed for general health. For sheep that did not receive lidocaine peri-operatively (N

Table 1. Sheep by nomenclature.

Animal number	Article/Group	Implantation date	Termination date
91351	Test	April 28, 2022	June 15, 2022
90216	Test	April 28, 2022	July 28, 2022
91299	Test	April 28, 2022	July 28, 2022
91181	Test	April 28, 2022	May 31, 2022
91107	Test	May 6, 2022	August 05, 2022
91309	Test	May 6, 2022	August 05, 2022
93144	Control	May 19, 2022	August 22, 2022
01157	Control	May 19, 2022	August 22, 2022
92095	Control	May 19, 2022	August 22, 2022
91370	Test	June 17, 2022	September 15, 2022

= 4), two days after surgery, the fentanyl patches (Durogesic®, 75 µg/h, Janssen, Beerse, Belgian) were renewed and maintained for three days. After removal of the patches, the sheep were treated with buprenorphine (Buprecare® multidose 0.3 mg/mL, Axience, Pantin, France) for 4 days, 3 times a day. Sheep that did receive lidocaine peri-operatively (N = 6) were treated with buprenorphine (Buprecare® multidose 0.3 mg/mL, Axience, Pantin, France) for 5 days, 3 times a day. Then, between 2 to 3 times a day during 2 to 5 additional days according to the sheep's clinical status. An antibiotic treatment (clavulanic acid – amoxicillin; Synulox® suspension, Zoetis France, Malakoff, France) was administered IM daily for 14 days after surgery. An anti-inflammatory treatment (flunixin, Antalzen® 50 mg/mL solution injectable, Laboratorios calier, Virbac France, Carros, France) was administered IM daily for 7 days after surgery. The skin incisions were daily disinfected with povidone iodine solution (Vetedine® solution, Vetoquinol, Lure Cedex, France) until staples removal. The surgical staples were removed after complete healing of the incision (2 weeks after surgery).

Clinical Observations

Each animal was observed every day for general health and to detect mortality and morbidity. An individual post-operative follow-up of each animal was conducted daily during the study until complete recovery of each animal (2 or 3 weeks). This post-operative examination included general behavior and appearance, locomotion, posture, gastro-intestinal, urinary, respiratory, cardiovascular system observations, abdominal, cutaneous, subcutaneous, ocular, buccal, nasal, and genital organs, and homeostasis observations, according to guidelines reported by Hampshire and Gilbert in 2019 [13]. A neurological exam was also performed (including posture, trembling limb, muscle weakness, paresis, paralysis, loss of sensibility in the legs, (*etc.*)) daily until complete recovery of the animals (2 or 3 weeks). Pain was assessed daily until 14 days postoperatively for all but one sheep, who was evaluated until Day 21. Pain assessment was based on facial expression, bruxism, muscle tremor, altered posture, and dysphagia. The sum of the five categories created a global pain score.

A detailed clinical examination of the animals was then conducted at least two times a month, including but not limited to general condition, behavior and activity, locomotion, posture, and included a neurological examination. When an animal was injured, ill or moribund, care was conducted in accordance with current veterinary medical practices and study objectives. For group-housed animals, it was not possible to correlate some clinical observations (for example, reduced feces) as it would be with animals housed individually. Therefore, in these instances, general observation for the entire cage was documented. Body weights were recorded to the nearest whole kilogram every four weeks.

Lead placement was verified through the fluoroscope four weeks (Week 4) after the surgery. The X-ray image was acquired.

Terminal Procedures

At termination, the animals were weighed. The animals were euthanized by an IV injection of a lethal solution (pentobarbital: Dolethal®, Vetoquinol or Euthasol® Vet solution injectable, Dechra). The article positioning was verified throughout fluoroscope. The implantation sites (i.e., tissues of the epidural space, spinal cord under the paddle and subcutaneous tissues in contact with the cable) were macroscopically examined by a vet pathologist. Any gross changes in tissues surrounding each article were recorded and any other observations, as appropriate. If visible, the aspect of the articles (location, coloration) was described. The positioning of the articles on the *dura mater* was marked using non-absorbable thread. The article was carefully removed from the implantation sites. The article was subjected to visual inspection. Macroscopic pictures of the areas of interest were taken. Tissues (spinal cord and any areas of interest) were harvested and fixed in 10% neutral buffered formalin (NBF). A macroscopic examination of the spinal cords was performed post-fixation in 10% NBF by a pathologist.

Table 2. Implanted test articles.

Test group	Animal number	Location of subcutaneous pocket	Final location of implant	Observations
	91351*	On the left	Middle of the paddle on L2	When removing the inner cortical layer, movement (nervous reaction) of the sheep, the spinal cord was touched/pressed by surgical instrument. A bleeding of a vein was observed: addition of haemostatic agent (Surgicel®, Ethicon, Raritan, Somerville, NJ, USA) to stop the bleeding. Surgicel® was left in place (localized on the left side of the spinal cord, not in contact with the article).
	90216	On the right	Middle of the paddle on L2	Slight movement of the sheep back at the removal of the inner cortical layer.
	91299	On the left	Middle of the paddle on L2	Slight movement of the sheep back at the removal of the inner cortical layer.
	91181*	On the right	Middle of the paddle on L2	Nothing to report.
	91309	On the left	Middle of the paddle on L2	Slight movement of the sheep at the removal of the inner cortical layer.
	91107	On the right	Middle of the paddle on L3	Nothing to report.
	91370	On the left	Middle of the paddle on L1-L2	Movement of the sheep back when the surgical suction probe touched/pressed the spinal cord.

* Prematurely euthanized.

Results

Study Duration

The reference code per each animal, the implantation and termination day are listed in Table 1. One article per animal was implanted. The article reference and the final location of the test and control articles are listed in Table 2 and Table 3 respectively. Two animals of the test group were prematurely euthanized. One animal (91181) was euthanized on Week 4, due to the discovery of a calcified fetus observed on fluoroscopic imaging. This event was considered incidental. One animal (91351) was euthanized on Week 6 because of persistent paresis of the hind limbs. The paresis was considered surgical procedure-related as a surgical instrument indirectly touched/mechanically pressed the spinal cord after movement of the sheep during the removal of the inner cortical layer. Sheep 91181 was replaced by sheep 91370. A detailed description of the duration of pharmacological treatments for each animal is reported in **Supplementary Table 1**.

Peri-Operative Observations

The critical moment during the laminectomy was the removal of the inner cortical layer which is at the contact with the *dura mater*. Movement of the sheep back (nervous reaction) was observed for 4/7 test animals when the spinal cord was indirectly touched/pressed during the surgical procedure (sheep 90216, 91299, 91309, and 91370, additionally to sheep 91351 euthanized after 6 weeks) (Table 2). Sheep 90216 showed a mild deficit with an improvement at the end of the post-operative follow-up, but still discreetly present until termination, while sheep 91299 showed a delayed slight deficit on Week 10 and 12. For the test sheep 91309 and 91370, neurological signs were present until 5 days and 14 days post-surgery, respectively. For the control group, a slight movement of the sheep back was observed during the positioning of the article in the epidural space of one sheep (92095) (Table 3). This animal showed intermittent neurological signs until Week 6, then had a normal neurological exam after and until termination. For the two test sheep (91181 and 91107) and two control sheep (01157 and 93144) for which no nervous reaction was observed during the surgery, no or slight neurological signs were observed during the first three days post-surgery.

The middle of the test paddle was placed on L2 vertebra level for the five first operated sheep (Fig. 2). For sheep 91107, the middle was positioned on L3 vertebra level, and for the last operated sheep (91370), the middle was positioned upper, on L1-L2 vertebrae level. For the control article, the middle of the paddle was positioned on L1-L2 vertebra level. Due to its conformation, the control article easily slipped on the right or left side of the spinal canal (Fig. 3), but one control article could be implanted on the center of the spinal cord (sheep 93144).

Clinical Observations

Globally all the clinical abnormalities observed throughout the study such as skin wounds or meteorism were not related to the experimental procedure and were commonly observed clinical signs in sheep. Moreover, as they were similarly observed in the test and control groups, they could not be related to the test article. Regarding im-

Table 3. Implanted control articles.

Control group	Animal number	Location of subcutaneous pocket	Final location of implant	Observations
	92095	On the left	On the left of the spinal cord (in the epidural space). Cranial extremity on L1 and caudal on L2.	Slight movement of the sheep back when sliding the article in the epidural space.
	01157	On the right	On the right of the spinal cord (in the epidural space). Cranial extremity on L1 and caudal on L2.	Nothing to report
	93144	On the left	In the middle of the spinal cord (in the epidural space). Cranial extremity on L1 and caudal on L2.	Nothing to report

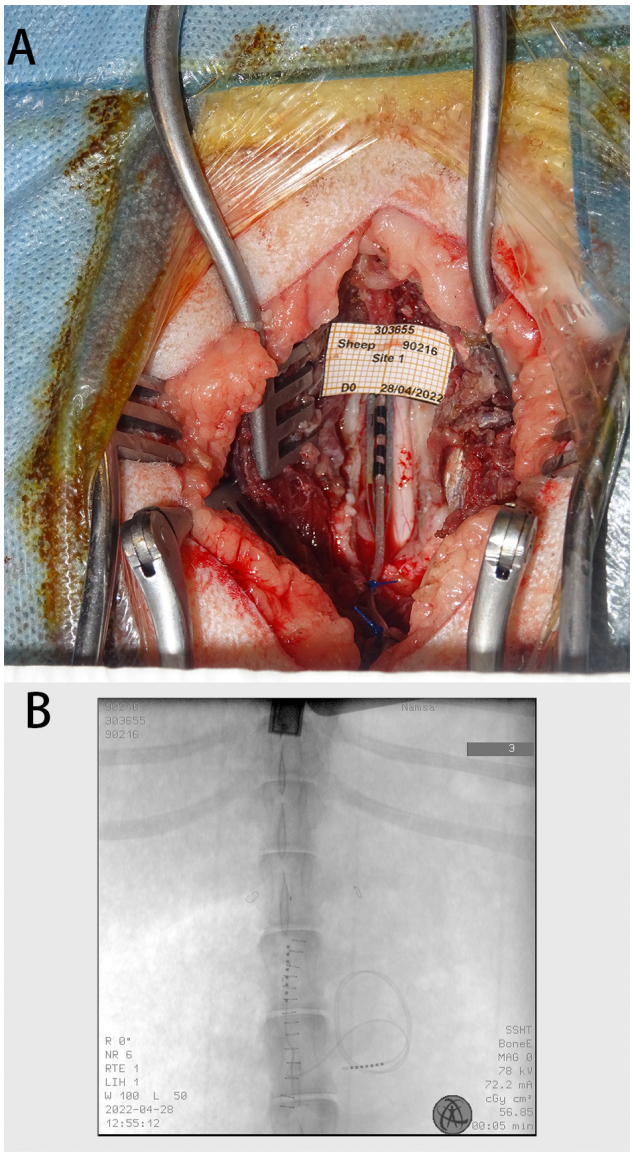

Fig. 2. Test article implantation. Test article placed on the *dura mater* (panel A) and fluoroscopic image at Day 0 (panel B) for sheep 90216.

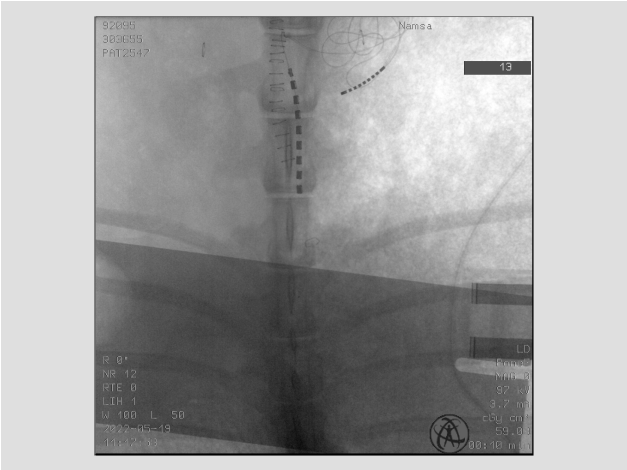

Fig. 3. Control article implantation. Fluoroscopic image at Day 0 for sheep 92095.

planted site observations, the sheep implanted with the control article showed more severe local reaction (swelling) during the post-operative follow-up, with no incidence on wound healing. Swelling lasted for an average of 6.3 days in the test group as compared to 11.3 days in the control group (Table 4). Nine of ten animals had experienced swelling for at least one day. Only one test animal (91370, operated last) did not show any sign of swelling. Scab formation occurred in two sheep of the control group on Day 14 and none of the sheep in the test group. Details related to observations of the surgical site by day/week can be found in **Supplementary Tables 2,3**. All but one surgical site were healed at 14 days post-surgery. The last site (control article group: sheep 93144) postoperative observations had to be prolonged for seven more days due to persistent swelling. Additional abnormalities observed include increased crust formation for two control animals (92095 and 93144) on Day 14, surgical wound dehiscence for one test animal (91309) at Day 2 that was resolved by Day 14 with no specific action taken, and surgical wound oozing for one control animal (93144) at Day 14.

Table 4. Wound Swelling Days.

Group	Animal number	Number of days with swelling	Mean (days)
Test	91351	11	6.3
	90216	5	
	91299	7	
	91181	9	
	91309	9	
	91107	3	
	91370	0	
Control	92095	11	11.3
	01157	9	
	93144	11	

Nevertheless, test animals lost weight during the first day's post-surgery, which was not observed in control animals. All test animals had a significant weight loss just after surgery (3 to 11% loss in the first six to eight days). Except for the one who lost 11% after surgery, they all regained their normal body weight by the end of the study (0 to 9% gain compared with their pre-operative body weight). The one who lost 11% of body weight in the first eight days post-surgery (91370) regained weight at Week 4 (+3% compared with her Day 8 weight) and Week 8 (+8% compared with her Day 8 weight), before losing again Week 12 (–4% compared with her Week 8 weight), reaching a 6 % global loss compared with her pre-surgical weight. This final loss is hard to explain, as it is not associated with any other abnormality (no sign of pain, lameness, or general condition abnormality). None of the three control animals did lose body weight after surgery. They all gained 9 to 13% between the day before surgery and the termination.

Regarding pain, no clear difference was observed in pain scores between the two groups. During the postoperative observation period, global pain score mean was between 0 and 1.7 for the control group and between 0.4 and 1.6 for the test group. It is to be noticed that in the control group, no pain sign was observed after Day 10 (global pain score mean of 0 from Day 11 to Day 14). That never occurred during the 14 post-operative days in the test group (global pain score mean of 0.4 on Day 14). The maximum global pain score occurred between Day 1 and Day 3 in the control group and between Day 3 and Day 7 in the test group, suggesting that pain peak occurred later and lasted longer in the test group, compared to the control group.

Finally, some sheep showed neurological disability post-surgery. The incidence of such abnormalities was higher in the test group than in the control group, but this difference was not significantly different and has to be mitigated based on the different number of animals in those two groups. Moreover, the neurological signs improvement appeared to be related to technical refinement of the surgical procedures, as first operated animals showed more neurological signs than the last operated ones (three of the four last operated animals happened to be in the control group, due to the study design, which is a bias to this analysis). Tremor was only observed between Day 1 and Day 7 for four test animals (90216, 91181, 91309 and 91107 for respectively 4, 1, 2 and 2 days) and two control animals (92095 and 93144 for one day). As this sign was not observed later during the post-operative follow-up and as it is known to be a sign of pain in sheep, veterinarians assume it is more related to pain than to a real neurological disability. One test animal (90216) presented convulsions on Day 3 and Day 4 during manipulations. Stress or pain may have been a favoring cause for this occurrence as it has never been observed again later until the study termination. One test animal (91351) showed an important neurological deficit during the whole duration of the study, leading to an anticipated termination for ethical reasons at Week 6. Another test animal (90216) showing a mild neurological deficit with an improvement at the end of the post-operative follow-up but still discreetly present until the study termination (Week 13). A third test animal (91299) showed no sign of neurological deficits until Week 10, but a slight deficit at Week 10 and Week 12. One control animal (92095) showed intermittent signs of neurological deficits until Week 6 but had a normal neurological exam after that and until the study termination. No dysphagia was observed in any sheep of either group.

Necropsy Observations

In the test sheep 91181 prematurely terminated at Week 4, a thick fibrous tissue was observed at the laminectomy site and the article was surrounded by a fibrous capsule. The paddle was in contact with the *dura mater*, except on its caudal part (curved by the cable). No macroscopic finding was observed on the *dura mater* and on the surface of the spinal cord. In the test sheep 91351 prematurely euthanized at Week 6 due to persistent paresis, a layer of hard fibrous tissue was observed at the location of the laminectomy. The article was partially encapsulated. Upon post-fixation macroscopic examination, the spinal cord presented on caudal position from the paddle location a few randomly distributed white areas in the funiculi (Fig. 4). This type of observation suggests a chronic lesion, with replacement of the axons by astrogliosis as a repair process. This chronic lesion can be due to the incidental contact between the surgical instrument and the spinal cord, leading macroscopically to a modification of the white matter. These white areas are not directly linked to the touch of the burrs but suggest a chronic lesion due to repair processes.

In the five other test sheep implanted for 13 weeks (90216, 91299, 91309, 91107, 91370), hard mesenchymal tissue (fibrous/cartilaginous/osseous tissue) was always observed at the location of the laminectomy (Fig. 5). The article was mostly surrounded by a capsule causing adhesions between the *dura mater* and the paddle. Among the five test sheep, two presented white areas in the spinal cord

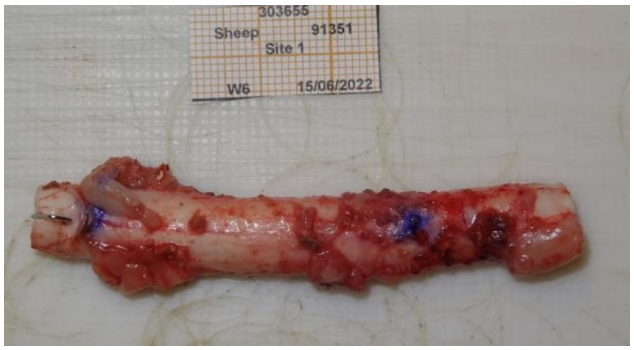

Fig. 4. Macroscopic observation of the spinal cord under the paddle location. *Dura mater* was removed, blue spots correspond to the paddle extremity location.

white matter, over the whole length where the paddle was implanted. Sheep 90216 presented white areas of 0.5 mm in diameter, randomly distributed but mostly in dorsal funiculus. This animal did show neurological signs (mild then discreet) throughout the study. Sheep 91370 presented a white focal area of 1 mm in diameter in the right dorsolateral funiculus, where the paddle was in contact with the *dura mater*. In caudal position of the paddle, the cut surface of the spinal cord was discolored, and the distinction between grey and white matter was difficult to make. This animal presented neurological signs during the first 14 days post-surgery, then had a normal neurological exam. The white focal area on the spinal cord can be due to the incidental contact between the surgical instrument and the spinal cord or to a potential pressure of the paddle or inflamed tissues around it on the spinal cord, leading macroscopically to a modification of the white matter (very small white (1 mm) areas observed on the section of spinal cord).

In the three-control sheep (92095, 93144, 01157), the fibrous/cartilaginous/osseous repair tissue was similarly observed for the test group at the location of the laminectomy. The control paddle was always encapsulated in a thin translucent fibrous tissue, which was adherent to the *dura mater*. The paddle was removed after cutting the capsule and was always macroscopically intact. One out of three control sheep (sheep 92095) presented a white focal area of 1 mm in diameter in the left dorsolateral funiculus, where the paddle was located, and the white and grey matter of the spinal cord were hardly distinguishable. The paddle of this animal was found completely on the left side of the spinal cord at termination. At implantation, this animal moved when the spinal cord was touched by the paddle, during the placement of the paddle in the epidural space. This animal showed intermittent neurological signs until Week 6, then had a normal neurological exam after and until termination.

Lead Migration Observations

The lead migration was evaluated by comparing the positioning of each article at the surgery (Day 0), four weeks after the surgery (Week 4) and at the explantation day through fluoroscope images (Week 13, or Week 4 and 6 in sheep 91181 and 91351 respectively). No lead migration event was reported for the test articles. 1 lead migration event was reported in sheep 92095 with control article. The lead was found completely on the left side of the spinal cord.

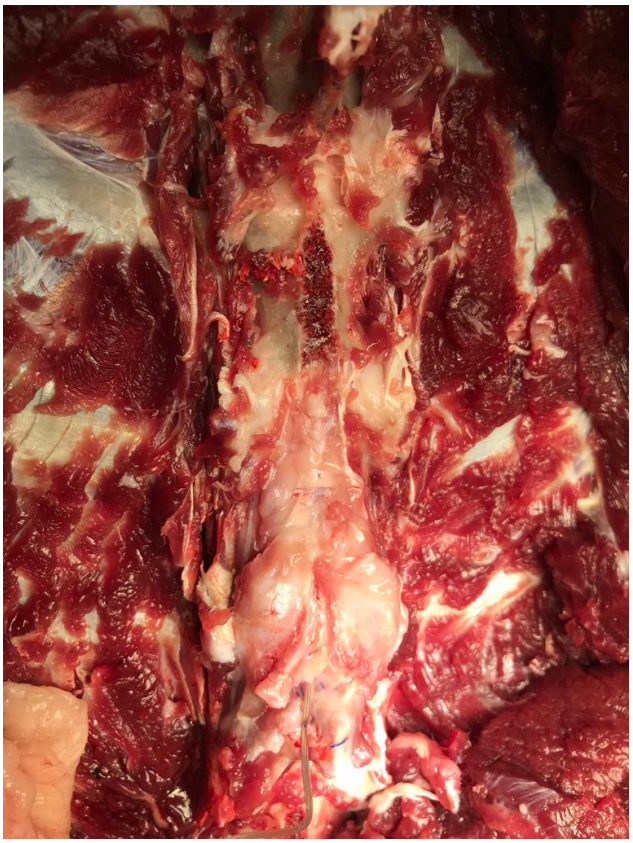

Fig. 5. Hard mesenchymal tissue at site of laminectomy. Fibrotic, cartilaginous, and osseous tissue over the lead of sheep 91107.

Protocol Deviations

Sheep 91351, 90216, 91299 and 91181 were operated on the same day (i.e., Apr-28th). Since a few days after surgery, it seemed that fentanyl patches did not provide a better pain management than the analgesic treatment (i.e., buprenorphine injections), the veterinarians decided to modify the analgesic treatment for the following sheep (i.e., buprenorphine injections). Moreover, the renewal of the patches on awakened sheep was not easy in sheep 91351, 90216, 91299 and 91181 and could generate stress to the animals, in comparison to an injection of buprenorphine. The veterinarians suggested that pain signs collected in the first operated sheep following the surgery could be due to the fact that the fentanyl patches did not stay in place correctly on the first day and were re-applied at the end of the surgery. Therefore, for following operated sheep, the veterinarians administered IV injection of diazepam and

methadone, continuous IV injection of propofol, and isoflurane inhalant anesthetic on the day of the surgery. Postoperatively, buprenorphine was administered twice after the end of the surgery and three times a day for 3 days, then two times a day for 2 days.

Taking into account the considerations listed above, material and methods were adapted and slightly modified in comparison with the protocol, when necessary, to improve the surgical procedure, or to adapt to technical difficulties. The modifications were minor and did not negatively impact the study outcome, as they were implemented to optimize the study design of this study.

Discussion

In accordance with the aim of the study, the local tissue effects of the test article after its implantation in the epidural space of the sheep were evaluated through macroscopic observations during article explantation. In all sheep in which the test article (91351, 90216, 91299, 91181, 91107, 91309, 91370) and the control article (93144, 01157, 92095) were implanted, fibrosis developed around the article, as described in the clinical scientific literature (at 13 Weeks, but also at Week 6 and Week 4, as reported in sheep 91351 and sheep 91181, respectively) [14]. There was no significant difference between the two groups in term of fibrosis reaction around the leads. It can be suggested that using a real percutaneous implantation, without exposure of the *dura mater* through a laminectomy (as performed in humans), the process of reactive fibrosis around the test article could be less important.

Despite a careful surgical technique, as epidural space is more or less virtual in sheep, neurological signs were observed in several animals in relation to spinal cord contusion during the surgical approach. The incidence was higher in the test group (3 out of 6; Sheep No. 91351, 90216 and 91299) than in the control group (1 out of 3; Sheep No. 92095), but this difference is not significantly relevant and has to be mitigated in light of the different numbers of animals in those two groups. Moreover, the neurological signs improvement appeared to be related to technical refinement of the surgical procedure, as first operated animals showed more neurological signs than the last operated ones (three of the four last operated animals happened to be in the control group, due to the study design, which is a bias to this analysis).

Macroscopic examination at termination showed that two test sheep and one control sheep presented macroscopic modification of the white matter, suggestive of a chronic lesion. For one out of 2 test sheep and for the control sheep, this observation was in line with the long-lasting neurological signs observed, while the other test sheep did not present persistent neurological signs. Repair tissue composed of fibrous-cartilaginous-osseous tissue was similarly observed in both groups, at the location of the laminectomy. Therefore, it is possible to conclude that when the test article is implanted with the same procedure as the control article, the safety profile is identical for both the test and the control article.

A further goal of the study is the evaluation of the likelihood of migration by comparing the positioning of the article at the time of surgery (Day 0), one month after surgery (Week 4) and at the day of article explantation through fluoroscopic imaging (Week 13, or Week 4 and 6 in sheep 91181 and 91351 respectively). Results demonstrate that the test article is correctly fixed and does not move when implanted for the entire duration of the study even in the absence of anchors. This result also confirms that the test article has a great ability to adhere to the *dura mater* and suggests that the lead migration events can be reduced as compared to the current clinical practice.

Although test and control articles were implanted surgically through a laminectomy, both articles are compatible with a mini-invasive percutaneous procedure. For years there has been a debate about using paddle leads versus percutaneously placed leads for spinal cord stimulation. Paddle lead has the advantages of much less migration and less energy consumption but it requires a laminectomy for placement which can also complicate the explanation of the lead if needed after years of implantation. The presented Heron lead prototype brings this discussion out of interest. A percutaneous procedure is at reach of the majority of pain specialists, eliminates complications consequent to laminectomy and is much quicker. The proposed device allows the placement of a multicolumn, directional lead conforming to the *dura mater* with the same procedure currently used for cylindrical leads. This enables to increase the precision and the efficiency of the stimulation without having to pay a tribute to the complexity and the risks of the implantation procedure.

Conclusions

The goals of this work were first to observe the scar reaction around the Heron lead prototype at the location of the laminectomy that was similar to that created with a control article. Secondarily, there was no migration event of the test article in this animal model.

Therefore, it is possible to conclude that the Heron lead is as safe as currently available paddle leads, and that lead migration can be reduced.

Availability of Data and Materials

All data sources are available, but due to ongoing development work, the datasets generated and/or analyzed in this study are not yet publicly available and can be obtained from the corresponding author upon reasonable request.

Author Contributions

According to ICMJE guidelines, all authors contributed to the conception and design of the study. PM performed the surgeries. PM, MCC, AA, SF, VF, AAE interpreted and analysed data. All authors prepared the manuscript. All authors assisted with reviewing the manuscript and reviewed study results. Final approval was given by all authors. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by NAMSA Ethical Committee. The project authorization number associated with this study for NAMSA is APAFIS#22914-2019091916114859 v10 (100%). The study was conducted in the NAMSA facility in Chasse-sur-Rhône, France.

Acknowledgment

Not applicable.

Funding

This work was funded by: European Commission – European Innovation Council and SMEs Executive Agency. PercPad - GA No. 959546. MiMit - Agreements for Innovation. SCS Expert - B29J23000210005.

Conflict of Interest

Dr. Alaa Abd-Elsayed is serving as one of the Editorial Board members of this journal. We declare that Dr. Alaa Abd-Elsayed had no involvement in the peer review of this article and has no access to information regarding its peer review. Heron® lead comes from WISE S.r.l.. The authors declare no conflict of interest. Dr. Patrick Mertens reports consultant fees from WISE S.r.l. during the conduct of the study. Dr. Alaa Abd-Elsayed reports consultant fees from WISE S.r.l.. The other authors are employees of WISE S.r.l..

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202335177.62.

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