



Comparison of macroscopic resorption time for a self-locking device and suture material in ovarian pedicle ligation in dogs

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Abstract

A resorbable self-locking device (LigaTie) was developed to enable safe and easy surgical ligation of blood vessels. The aim of this study was to compare the long-term in vivo resorption of the device to a commercially available suture of equivalent material (Maxon) following ovarian pedicle ligation. After ovariohysterectomy follow-up ultrasound examinations were performed monthly on 21 dogs ligated with the device and 22 dogs ligated with the suture material until no hyperechoic remnants, acoustic shadowing or local tissue reactions were detected. In both groups, the ovarian pedicles gradually decreased in size. Ligation material was considered macroscopically resorbed when ultrasound showed no signs of the device or suture, ovarian pedicle or tissue reaction. Macroscopic resorption had occurred without signs of complications and was complete by four months for sutures and 5.5 months for the device. The results show that resorption time in vivo for the resorbable self-locking device is mildly longer than suture of the same material and that no complications of device resorption were detected, supporting that the resorbable self-locking device is safe for in vivo use.

Introduction

A resorbable self-locking device for surgical ligation that facilitates a safer and easier surgical procedure is being tested.¹⁻⁷ The material used in the device, a block copolymer of glycolic acid and trimethylene carbonate (TMC), is equivalent to the suture Maxon, a monofilament resorbable suture which was introduced in the mid-1980s.⁸ The degradation and resorption of the Maxon suture is well described⁹⁻¹⁵ and this resorbable suture is one of several alternatives for ligation of the canine ovarian pedicle.¹⁶

In a previous study, the device was tested for ligation of the ovarian pedicle in canine ovariohysterectomy, showing reduced duration of surgery and time needed for ligation of the ovarian pedicle compared with traditional suture ligation.¹ Furthermore, the ligation time was shorter compared with findings of a previous study of vessel sealing and suture ligation of the canine ovarian pedicle.¹⁷

The resorption of the device has been studied with ultrasound and histology following ligation of the spermatic cord in male dogs.² Additionally, the mechanical properties over time of the device in vitro are described.¹⁸ In the previous studies of the device it was manufactured using an in-house built injection moulding machine in a research and development laboratory. However, the device in the present study was serial produced and sterilised in an industrial setting and may have different mechanical and physical properties compared with the devices used in earlier studies. Its resorption profile may also differ from that of the previous study² due to differences in manufacturing and sterilisation processes between present and previous studies, all of which will affect the material at

Veterinary Record (2019)

doi: 10.1136/vr.104732

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Provenance and peer review Not commissioned; externally peer reviewed.

Received October 3, 2017

Revised October 19, 2018

Accepted February 7, 2019

a molecular level and the mechanical properties of the device.

The aim of this study was to follow the long-term resorption of the device used for ligation of the ovarian pedicles with diagnostic ultrasound and compare it with that of a commercially available suture made of the equivalent polymer material. The hypothesis was that the device and suture would degrade and resorb at similar rates and without signs of complications.

Methods

Animals

Forty-five female mixed-breed mongrel dogs were included in the study. The dogs were divided into two groups according to the method used for ligation of the ovarian pedicle: 24 dogs were included in the suture group where Maxon (size 0, 3.5 metric, monofilament polyglyconate synthetic absorbable suture, manufactured by Syneture, Norwalk, Connecticut, USA) was used for ligation and 24 dogs were included in the device group where a resorbable self-locking device (LigaTie, legal manufacturer Resorbable Devices, Uppsala, Sweden, www.LigaTie.com) was used.

The ovariectomies were performed by the same surgeon and followed standard procedures except that the device was used to ligate the ovarian pedicles in the device group. The surgical procedures and data of the animals were previously reported.¹ In the procedure, uterine horns and ovaries were localised manually and a hole was made in the broad ligament close to the ovary. The tissue of the ovarian pedicle was not clamped with forceps. The flexible band of the device was applied around the ovarian pedicle and introduced into the locking case, thus a loop was formed. The loop around the ovarian pedicle was tightened and the tissue and blood vessels within the loop were compressed, without prior crushing of tissue. A pair of forceps was placed in-between the device and the ovary, and the ovarian pedicle was transected between the forceps and the device. After haemostasis was verified, excess band was cut off at locking case, leaving 2–3 mm of the flexible band.¹

In the suture group, a pair of haemostatic forceps was used to clamp the ovarian pedicles and make a groove. The forceps were then repositioned distally, closer to the ovary and one ligature was placed in the compressed tissue. The ovarian pedicle was cut between the ligature and the forceps.

Surgery was done on the suture group first due to delayed delivery of devices. The initial order of registration and group assignment of the patients was adhered to.

The resorbable device

The implanted device (LigaTie, legal manufacturer Resorbable Devices, www.LigaTie.com) consisted of a flexible band, in part perforated, and a case

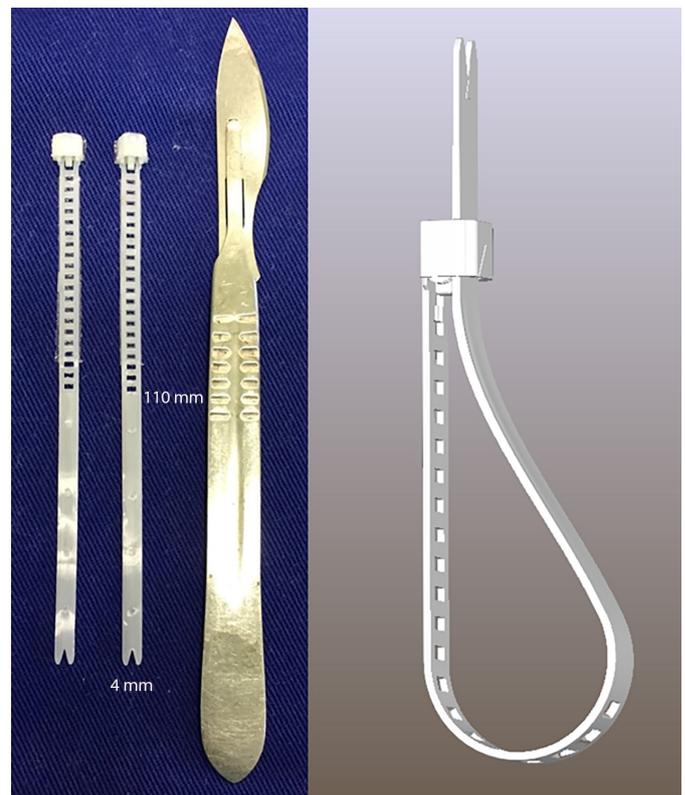


Figure 1 The resorbable device LigaTie, a self-locking loop designed for ligation purposes. Left: devices with scalpel. Right: flexible band introduced into the locking case.

with a locking mechanism where the band could be introduced, pulled through and a self-locking loop was formed (figure 1). Design features for tissue engaging properties, aimed to achieve a secured tissue grip, were added to the locking case to increase friction between the device and the tissue that was compressed inside the loop of the device. The measurements of the flexible band of the device were 0.65 mm x 4 mm and the measurements of the locking case were width 6 mm, height 4.7 mm and length 4.5 mm.

Glycolide and TMC were polymerised into a block copolymer. The resorbable polymer was injection moulded into LigaTie products. The produced devices were placed in Tyvek bags, two devices per bag. The Tyvek bags were sealed in a clean room, placed in aluminium foil pouches and allowed to dry under vacuum for at least seven days. Pouches were then sealed in a moisture-free environment. Devices were sterilised while inside the sealed aluminium foil pouches by using electron beam radiation at a dose of 25 kGy.

Ultrasonography

The dogs were placed in dorsal recumbency and the left and right caudal abdominal quadrants were scanned with a multifrequency of 3.0–7.0 MHz convex transducer (Medison SonoAce 8000 EX ultrasound, LTDA, São Paulo, Brazil) with frequencies set as high as possible in relation to the size of the dog and the distance to the area of interest. Acoustic gel was used and hair was clipped when necessary to improve the quality of

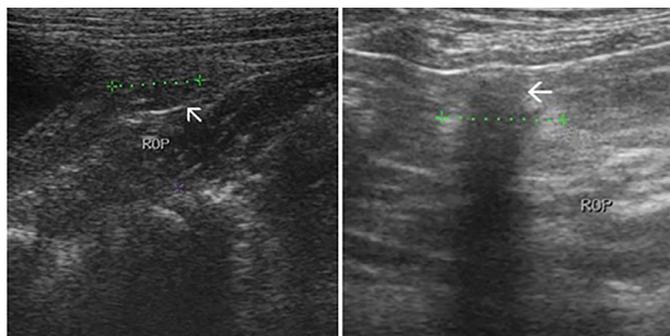


Figure 2 Ultrasound images of the right ovarian pedicles (ROP) ligated with Maxon suture (arrow) 28 days after surgery (left) and the LigaTie (arrow) device at 21 days after surgery (right). Parasagittal plane images, measurements made in cranial (left) to caudal (right) direction.

the acquired images. The dogs were not sedated during the examination. The location of the ligation area, that is, the ovarian pedicle (mesovarium), defined as tissues of the suspensory ligament with its vessels, the ovarian vessels and variable amounts of fat, was identified. The area was examined for remnants of suture or device represented by a hyperechoic structure with or without acoustic shadowing and changes suggestive of a local tissue reaction such as anechoic or echogenic fluid or surrounding hyperechoic tissues. The diameter of each ovarian pedicle (left ovarian pedicle (LOP) and right ovarian pedicle (ROP)) including the ligation and the tissue reaction was measured in a sagittal plane. The ultrasound examinations were performed by the same radiologist on a monthly basis until no hyperechoic remnants or acoustic shadowing or local tissue reactions were observed. The mean±sd number of days at each postoperative examination of each group is reported.

Several ultrasound images of the LOP and ROP were saved and for each ovarian pedicle the diameter measurement was done on the image considered to have the best quality and definition of the ovarian pedicle. Results were reported at group level as mean cm±sd of LOP and ROP for each group's ovarian pedicles at each follow-up.

Complete macroscopic resorption of the suture or device was considered to be the point where in ultrasound images there was subjectively no difference of acoustic impedance between the suture or device and surrounding soft tissues.^{2 19}

Statistics

Measured diameters at different time points were compared within and between groups. $P < 0.05$ was considered significant for the analysis. The data on remaining device size (ROP, LOP and the average of these) were analysed as repeated-measures data. A mixed model approach²⁰ as implemented in the Mixed procedure of the SAS²¹ system was used.^{20 22} The models included method, time and the interaction between these, as fixed factors. The relations between time points within dogs were modelled using an autoregressive covariance structure. Generally, this is

a two-way analysis of variance that takes account of the fact that several observations were made on the same dog. In this situation, there was a dependence between observations within dogs, which this model compensated for. Post hoc comparisons between groups and examinations were adjusted for multiplicity using Tukey's method.

The assumptions were checked using diagnostic plots. No apparent deviations from normality and homoscedasticity were detected.

Data on length of time until the device or suture had completely disappeared were analysed using survival analysis methods.²³ The Lifetest procedure of the SAS (2014) package was used to obtain non-parametric tests and estimates of the survival function.

Results

The mean (±sd) bodyweight and age of the dogs in the suture group was 13.1±6.6 kg and 3.1±1.9 years and in the device group was 10.7±5.6 kg and 4.1±2.2 years. There was no significant difference between the mean bodyweight or mean age of the suture and device group dogs.

Two dogs from the device group did not return for evaluation and another one was attacked by another dog and died, leaving 21 animals in the device group. Two dogs from the suture group did not return for evaluation leaving 22 dogs in the suture group.

Suture group

The dogs in the suture group were examined on average 3.8 times after surgery. Eighteen dogs were examined four times, four dogs had three follow-up examinations.

The mean number of days between the surgical procedure and the first examination was 34 (±8.4). In the first examination of the ovarian pedicles, it was possible to see a hyperechoic area that was compatible with local tissue reaction. Additionally, faint hyperechoic structures that caused faint acoustic shadows were noted and interpreted as the ligatures (figure 2). In the second examination, performed at a mean of 63 (±9.1) days after surgery, it was still possible to see hyperechoic areas suggestive of local tissue reactions, but no hyperechoic structures or acoustic shadows could be detected. The third examination done at mean of 87 (±6.0) days after surgery still showed a local tissue reaction. In the fourth examination, 122 (±6.4) days after surgery, no local tissue reaction could be seen. The pattern of findings was the same for all dogs. Anechoic or echogenic fluid in or around the ligation area was not seen in any of the dogs.

The results of the measurements are reported in table 1. The measurement of the third and fourth examinations of the suture group differed significantly when compared with the first examination and with their previous examinations. In the device group, results of the third, fourth and fifth examinations differed from

Table 1 The size of the ovarian pedicle at postoperative follow-up examinations of the suture (22 dogs) and device (21 dogs). Time of examination reported as mean (\pm sd). Measurement data reported as LSM (\pm SEM)

Diameter of ovarian pedicles, mean of left and right LSM (\pm SEM)	Postoperative time of examination Mean (\pm sd)
Suture group	
1.25 \pm 0.06 cm	First examination: 34 (\pm 8.4) days
1.13 \pm 0.06 cm	Second examination: 63 (\pm 9.1) days
0.79 \pm 0.06 cm*†	Third examination: 87 (\pm 6.0) days
Not seen*†‡	Fourth examination: 122 (\pm 6.4) days
Device group	
1.35 \pm 0.06 cm	First examination: 27 (\pm 7.6) days
1.19 \pm 0.06 cm	Second examination: 55 (\pm 8.3) days
0.95 \pm 0.06 cm*	Third examination: 80 (\pm 7.7) days
0.81 \pm 0.06 cm*	Fourth examination: 102 (\pm 4.9) days
Not seen*†	Fifth examination: 166 (\pm 5.6) days

*Differs significantly from first examination.
†Differs significantly from previous examination.
‡Differs significantly between methods.
LSM, least squares mean.

the first examination, and the fifth examination of the device group differed significantly from the previous examination. In the comparison between ligation methods, the estimated size of the ovarian pedicles differed at the fourth examination.

Device group

Dogs in the device group were examined on average 4.3 times after surgery. Nine dogs had five examinations, 10 had four examinations, one had three examinations and one had two follow-up examinations.

The first examination of the dogs in the device group was performed at a mean (\pm sd) of 27 (\pm 7.6) days after the surgical procedure. The mean days after surgery until the second, third, fourth and fifth examinations were 55 (\pm 8.3), 80 (\pm 7.7), 102 (\pm 4.9) and 166 (\pm 5.6), respectively. In the first examination of the ovarian pedicles, it was possible to see a hyperechoic area that was compatible with local tissue reaction. Additionally, a hyperechoic structure along with a well-defined acoustic shadow was noted and interpreted as the device (figure 2). In the second examination, the hyperechoic area compatible with tissue reaction in the region of the ovarian pedicles could still be seen. Despite the marked presence of an acoustic shadow, the hyperechoic structure became less evident when compared with the first evaluation. In the third examination, the previous hyperechoic local tissue reaction was heterogeneous, and it was not possible to see any hyperechoic structure or acoustic shadowing. In the fourth examination, the local tissue reaction was less evident and poorly defined. In the fifth and last examination, no local tissue reaction could be seen. The pattern of findings was the same for all dogs. Anechoic or echogenic fluid in or around the ligation area was not seen in any of the dogs.

Comparison between suture and device group

Due to the design of the LigaTie device with straight borders and a larger size, a more distinct hyperechoic structure and clear acoustic shadowing was observed at the ligation site compared with the suture group.

At fourth examination of the suture group, no tissue reaction was seen whereas it was still evident in the device group.

In the Lifetest procedure of the survival function, ovarian pedicles ligated with the device could be seen for a longer time compared with ovarian pedicles ligated with suture, that is, four examinations versus three examinations differed significantly (log-rank and Wilcoxon, $P < 0.001$).

Discussion

This follow-up study of the resorbable self-locking ligation device^{1 2} demonstrated that the resorption of the device was similar to traditional suture material. The ovarian pedicles gradually decreased in size over time and no long-term complications related to the device or the suture in the suture group were observed. At the end of follow-up, structures representing the ovarian pedicles could not be seen on ultrasound examinations, which suggested resorption of the devices and suture material.

Self-locking loops in the form of traditional nylon cable ties have been used in veterinary surgery in the past.^{24 25} However, long-term complications such as chronic granulomas and fistulas were reported, and their use as permanent implants in surgery cannot be recommended.^{26–30} The present study, the first follow-up study of the device manufactured in an industrial setting, demonstrated the resorption time of the device. The results were in agreement with a previous study where the device was manufactured in a research laboratory setting and used for ligation of the canine spermatic cord.² The previous study included follow-up with ultrasound and histopathology. The results were also in agreement with initial studies of development of prototype devices where polydioxanone was used.^{19 31 32}

An exact comparison of time needed for complete resorption of the device versus suture was not possible to perform due to the time difference of fourth examination, 102 versus 122 days. However, our interpretation of the data was that the time needed for complete resorption of the device was approximately one month longer compared with that of the suture material. This could partly depend on the size of the device and of the manufacturing processes, injection moulding versus fibre spinning. Sutures have a highly oriented crystalline structure which would increase the resorption time. On the other hand, the implanted device has a higher mass compared with the suture. At the fifth examination of the device group at a mean of 166 days after surgery, the ovarian pedicles and remains of devices could not be seen which suggested loss of geometrical structure

and what may be referred to as macroscopic resorption. From an ultrasound perspective, as the material degraded and was resorbed, at end stage there was no difference in acoustic impedance between introduced material and normal body tissues. We conclude that macroscopic resorption of suture material had occurred at four months, whereas for the ligation device it had occurred at 5.5 months. The total volume and mass of the implanted material was considerably larger for the LigaTie device compared with the reference suture, which may explain our results, interpreted as a slightly longer resorption time for the device compared with the suture material. This difference does not appear to have clinical relevance.

It is recommended to apply a double ligation to the ovarian pedicle.^{33 34} In this study, a single ligation was used. The results regarding resorption time for double suture ligation may be different from the present study's single ligation.

The resorption of the Maxon suture has been studied previously. One study reported a full resorption of 8-0 polyglyconate suture material in 24 weeks (168 days) after arterial anastomosis in a rat and rabbit model evaluated by light microscopy.¹⁵ In another study, the resorption of suture sizes 2-0 and 4-0 was assessed histologically after subcutaneous implantation in rabbits. The resorption time was six to seven months (180–210 days). Size of suture and therefore amount of suture material affected resorption time. At six months, around 83 per cent of size 2-0 suture material and 93 per cent of size 4-0 suture material were absorbed, respectively.⁸ In the present study, size 0 Maxon was used in all dogs, which was considered large for the small-sized patients. Similarly, one size of device was used for all dogs. As expected, the implanted material was resorbed.

Synthetic sutures at dimensions 2-0 and 4-0 (USP) have approximately 0.3 and 0.15 mm thickness, respectively. The flexible band of the device, 0.65 x 4 mm, and its locking case represented proportionately more materials compared with the suture. An estimation of the volume of the implanted material, represented by the locking case and 2 cm of the flexible band, was approximately 117 mm³. The used suture material for a single ligation of the ovarian pedicle was approximated to 5 cm, representing a volume of 51 mm³. This difference made it easier to see the device on ultrasound. At a mean time of 80 days, the acoustic shadowing of the device was not seen. Previous studies^{8 15} suggested a slightly longer resorption time with greater dimension sutures which was in agreement with our results that indicated a somewhat longer resorption time for the device compared with the suture. We concluded our results were in agreement with the previous studies of resorption of the Maxon suture.^{8 15}

A secondary result was the description of the resorption of the remaining ovarian pedicles

after ovariectomy at repeated ultrasound examinations. In both groups, the statistical analysis showed a reduction in ovarian pedicle sizes over time. In the device group, at the fourth examination at 102 days the ovarian pedicle could be seen, whereas the ovarian pedicle could not be seen in the suture group in the corresponding fourth examination at 122 days. Our assumption was that if the ovarian pedicle could be seen on ultrasound, ligation material still remained. However, if a suture ligation material with a shorter resorption time would result in a shortened duration for reorganisation and resorption of the ovarian pedicles remains to be investigated.

A study limitation was the absence of histopathological evaluation and limited number of dogs. In previously performed studies,^{2 19} both histopathology and ultrasound examinations were used, but our knowledge of the exact correlation between results of histopathology and ultrasound examinations is incomplete. In agreement with the 3R (Replacement, Reduction and Refinement)³⁵ no animals were euthanased or had repeat surgery in the study and thus tissue for histopathology could not be obtained. Instead, the follow-up was restricted to ultrasound examinations which showed that suture and device structures gradually disappeared which was interpreted as macroscopic degradation and resorption. However, as described previously, the suture and device material has been in clinical use for decades. There are resorbable devices available on the market that by volume represent a greater amount of resorbable polymer material, that is, surgical meshes.³⁶ The natural expected response after implantation of a resorbable polymer material, a foreign body reaction, is transient. The tissue reaction and resorption of those materials are well described, and after complete resorption of the material, only connective tissue will remain.^{36 37} Potential individual differences could have been minimised if suture and device were both used in the same dog on separate sides. Re-examination of groups did not occur at identical time intervals and due to logistical issues the time between the last two exams was longer than the other time periods, which were other study limitations.

In conclusion, the macroscopic resorption of suture material and the LigaTie ligation device, and any signs of resorption complications, were assessed by repeated ultrasound examinations. Ultrasound images showed that the ligated ovarian pedicle tissue progressively decreased in size, that the ligation material became undetectable in the ultrasound image, which was considered to be the point of macroscopic resorption, and that no signs of complications of resorption were detected. The equivalent suture materials Maxon and LigaTie were considered to be macroscopically resorbed by four months and 5.5 months, respectively. The results show that the *in vivo* macroscopic resorption

time for the LigaTie resorbable self-locking device is only mildly longer than suture of the same material, and that no complications of device resorption were detected, supporting that the resorbable self-locking device^{38–40} is safe for in vivo use.

Correction notice This article has been updated since it was published Online First. The license is now CC-BY-NC.

Acknowledgements We thank Carla Feitosa for the organisation, support and care with the patients of the study, and Dr Michelle Lopes Avante for providing second opinion on the ultrasound images. We also express our sincere gratitude to VINNOVA (Sweden's innovation agency) which supported cost of manufacturing of the used LigaTie devices through a grant to Resorbable Devices, Sweden.

Funding Grant to Resorbable Devices AB, Sweden, from VINNOVA (Sweden's innovation agency).

Competing interests OVH is the inventor of the LigaTie device. Resorbable Devices, Sweden controls the patents describing the self-locking device and trademark LigaTie. Both OVH and NOB are part-owners of Resorbable Devices.

Ethics approval Approval to perform the study was obtained from the local ethical committee, reference UENF-CEUA 435813.

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