In ferrets with hyperadrenocorticism, does use of deslorelin acetate implants compared to adrenalectomy result in a superior prognosis?

A Knowledge Summary by

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KNOWLEDGE SUMMARY

PICO question

In ferrets with hyperadrenocorticism, does use of deslorelin acetate implants compared to adrenalectomy result in a superior prognosis?

Clinical bottom line

Category of research question

Treatment

The number and type of study designs reviewed

One study was reviewed, a retrospective cohort study that directly compared the outcomes of these treatments

Strength of evidence

Weak

Outcomes reported

The study found that in ferrets with hyperadrenocorticism, use of deslorelin acetate implants resulted in a longer average time to recurrence of clinical signs and a lower mortality rate than adrenalectomy. However, the strength of evidence for this study is weak and it has several design limitations

Conclusion

In view of the evidence, both deslorelin acetate implants and adrenalectomy are valid treatments for a ferret with hyperadrenocorticism, but it cannot be concluded based on the current literature that deslorelin acetate implants result in a superior prognosis

How to apply this evidence in practice

The application of evidence into practice should take into account multiple factors, not limited to: individual clinical expertise, patient's circumstances and owners' values, country, location or clinic where you work, the individual case in front of you, the availability of therapies and resources.

Knowledge Summaries are a resource to help reinforce or inform decision making. They do not override the responsibility or judgement of the practitioner to do what is best for the animal in their care.

Clinical Scenario

A client presents their female spayed ferret as she has become symmetrically alopecic, has vulvar swelling and is showing sexual behaviour. You recognise this presentation as hyperadrenocorticism (HAC), also known as ferret adrenocortical disease (ACD). The clinical disease seen in ferrets is not the same as Cushing's disease in dogs, when cortisol levels are elevated due to a pituitary tumor. Neoplasms of the adrenal cortex have the potential to overproduce steroids (glucocorticoids, mineralcorticoids, androgens) of the adrenal glands, leading to the syndrome of HAC. In ferrets, adrenal cortex neoplasms usually overproduce one or more of the sex hormones oestradiol, androstenedione, or 17α-hydroxyprogesterone and in contrast to Cushing's disease,

the contralateral adrenal gland usually does not atrophy (Chen, 2010). Following diagnosis based on these clinical signs and further testing, you consider your treatment options.

Whilst adrenalectomy has been a mainstay treatment for HAC, you are aware of its limitations. Research into the use of deslorelin acetate implants, a synthetic analogue of gonadorelin and sold under the brand name Suprelorin®, has led this medical therapy to become more popular in non-surgical candidates. You want to know whether there is evidence that treating this ferret with a deslorelin acetate implant compared to adrenalectomy surgery will result in a superior prognosis.

The evidence

The literature search yielded one relevant paper (Lennox & Wagner, 2012) that found that treatment with deslorelin acetate implants resulted in a longer average time to recurrence of clinical signs and a lower mortality rate than adrenalectomy. However, this study has limitations; it is a retrospective study so has weak evidentiary value and as a cohort study there is likely to be confounding factors. Furthermore, the small sample size affects reliability of results and because no statistical analysis was carried out, the results cannot be assumed to be clinically significant. Therefore, the strength of evidence for this PICO is very low and therefore further studies are required before any recommendations can be made.

Summary of the evidence

Lennox & Wagner (2012)	
Population:	• Ferrets exhibiting overt clinical signs consistent with adrenocortical disease (ACD) that either received adrenalectomy surgery or subcutaneous 4.7 mg deslorelin acetate implants alone. • Adrenalectomy surgery was defined as complete removal of the left gland alone and/or subtotal removal of the right gland. • Ferrets were not included if they received surgery and medical therapy simultaneously, or if they were euthanised soon after surgery for problems not related to ACD or ACD surgery.
Sample size:	89 ferrets
Intervention details:	Medical records were analysed for: • time of recurrence to clinical signs, • response to therapy, • mortality rate. For time of recurrence to symptoms: 1. Received surgical therapy (n = 28) 2. Received 4.7 mg deslorelin acetate implant (n = 35) This smaller surgical group included ferrets for which follow-up to evaluate time to return to disease was possible. For response to treatment: 1. Received surgical therapy (n = 51) 2. Received 4.7 mg deslorelin acetate implant (n = 35) For mortality rate: 1. Received surgical therapy (n = 54) 2. Received 4.7 mg deslorelin acetate implant (n = 35)
Study design:	Retrospective, observational cohort study

Outcome studied:	1. Time of recurrence to symptoms. 2. Mortality rate. 3. 3. Number of animals with no response to treatment.
Main findings: (relevant to PICO question):	1. Time to recurrence of symptoms in the small surgery group had a mean of 13.6 months and range of 0–38 months, whilst the medical group had a mean of 16.5 months and range of 3–30 months. 2. Mortality rate in the large surgery group was 5.6% (3/54), with patients dying within 24 hours of the procedure, whilst it was 0% (0/35) in the medical group. 3. 5.9% (3/51) animals in the small surgery group showed no response to therapy, while all ferrets in the medical group responded – though the response in one of these ferrets lasted only 3 months.
Limitations:	• Retrospective study with no randomisation, so other factors such as severity of disease at presentation could be confounding. • Possible bias due to lack of blinding. • Small sample size which affects reliability of results. • The records examined were from only two veterinary facilities so may be poorly representative of the wider population. • Confounding between clinician and treatment measure as data is from two veterinary facilities. • No statistical analysis so cannot guarantee clinical significance. • Do not report standard deviation so difficult to assess how heterogenous the time taken until recurrence of clinical symptoms was for the majority of patients, with the measure reported potentially distorted by the presence of one or more outliers. Also, there was no reporting on the distribution of responses or whether the distribution justified reporting the mean time taken (a median, first and third quartile may have been more appropriate). • Different group sizes were used to assess each outcome so this can cause a skewed view of the results. • 'Surgical therapy' included complete removal of left gland alone and/or subtotal removal of right gland, so these variations in surgical methods may be confounding. • 'Time to recurrence of clinical signs' is a subjective variable, so there may be observer bias. • No indication of a standardised protocol to assess clinical signs, if this was done by the owner this may not be reliable. • Follow-up methods were not described and losses to follow-up can bias the results if there was an absence of data. • Necropsies were unavailable for the ferrets that died, so it cannot be confirmed that the mortality was a direct result of surgery. • Mistakes in the summary of data table which affect both apprehension of the findings and confidence in the quality of the research.

Appraisal, application and reflection

One paper (Lennox & Wagner, 2012) was found to directly address the topic of this Knowledge Summary, and this was a retrospective cohort study. Whilst there are multiple papers about the prognosis of either surgery (Swiderski et al., 2008; and Weiss et al., 1999) or deslorelin acetate implants (Wagner et al., 2005; and Wagner et al., 2009) for treatment of ferret HAC, the study by Lennox & Wagner (2012) was the only paper yielded from the literature search to compare the outcomes of both and was therefore the only study deemed to have evidence worthy of inclusion.

Medical treatment for ferret HAC is aimed at controlling clinical signs through hormone manipulation and is typically used for non-surgical candidates or for treating recurrence of clinical signs after an adrenalectomy (Chen, 2010). The benefits include a non-invasive approach and few side effects, however, medical therapies have not shown to directly affect the adrenal tumour itself and autonomous production of steroids by the adrenal gland may occur over time, resulting in a loss of efficacy of the implant and recurrence of clinical signs (Shoemaker & van Zeeland, 2021). In comparison, the limitations of adrenalectomy are the challenging surgical technique and risk of complications, such as deterioration or death of compromised patients, and recurrence (Shoemaker, 2017).

Lennox & Wagner (2012) reviewed the medical records of two groups of ferrets exhibiting overt clinical signs consistent with HAC, that either received an adrenalectomy or subcutaneous 4.7 mg deslorelin acetate implants alone, to identify if there was a difference in clinical outcomes. However, authors failed to carry out statistical analysis of their results and so the clinical significance of their findings is questionable.

Firstly, the study by Lennox & Wagner (2012) found that post-treatment, the medical group had superior outcomes, including numerically a longer time to recurrence of clinical signs than the surgical group (16.5 months vs 13.6 months). This is similar to a study in which 30 ferrets with HAC were given 4.7 mg deslorelin acetate implants and the average time to return of clinical signs was reported as 17.6 months (Wagner et al., 2009). Interestingly, the time to relapse was quite variable, both in this study (8–30 months) and in the reviewed study (3–30 months), therefore inter-species variation in clinical response should be acknowledged for this treatment. Nevertheless, in the paper by Lennox & Wagner (2012), the authors acknowledged that 'time to return to clinical signs' may not correlate with progression of disease, so this outcome may not be a true assessment of prognosis. As follow-up methods were not described, the results may be unreliable especially if the assessment of clinical signs was carried out by the owner. Furthermore, loss to follow-up can bias the data and as this is a subjective variable there may be observer bias.

Lennox & Wagner (2012) found that the medical group also had a lower mortality rate (5.6% vs 0%) which could imply better patient safety. Nevertheless, a two-tailed Fisher's exact test indicates a non-significant difference (P = 0.276) between mortality in the surgical group, with a prevalence of 5.6% (3/54), compared to the medical group, with a prevalence of 0% (0/35). In addition, as cause of death in the surgical group was not confirmed by necropsy, direct causation cannot be proved. Comparatively, a retrospective study by Swiderski et al. (2008) looked at long-term outcomes of surgical intervention in 130 ferrets and found a 98% 1 year survival and 70% 5 year survival, which indicates that surgical treatment has a good prognosis. However, 14.3% ferrets that underwent bilateral adrenalectomy developed signs of hypoadrenocorticism (Swiderski et al., 2008), a negative outcome that is not reported with deslorelin acetate implants as they do not affect the adrenal tumour itself (Morrisey, 2013).

Finally, in the paper by Lennox & Wagner (2012) it is difficult to interpret 'no response to treatment' as there were mistakes in the data and a lack of clarity in reporting the findings. For example, the main text leads the reader to think that the sample size for this outcome was 28 rather than 51. This study stated that all ferrets in the medical group responded, a superior outcome to surgery, however a two-tailed Fisher's exact test shows this outcome was not significant (P = 0.267) between the surgical group (3/51) and the medical group (0/35). On the other hand, there are rare reports in the literature of non-response to hormonal therapy. For example, a case study by Brezina et al. (2019) reported that a ferret showed no improvement after 4 months following 9.4 mg deslorelin acetate implantation. As a result, adrenalectomy was performed resulting in complete

resolution of clinical signs, which demonstrates that this therapeutic option may be preferable in some cases. In fact, in the article by Lennox & Wagner (2012) they state that since preparing the paper, both authors identified at least one patient that did not respond to the deslorelin acetate implant. Nevertheless, there are currently no studies reporting on prospectively identifying which ferrets will not respond to implants.

Interestingly, the author found a study that reviewed deslorelin acetate implants by Wagner et al. (2005), where the duration of clinical effects in ferrets with HAC that had previously undergone adrenalectomy was almost 4 months longer than that of ferrets with no previous surgery. The difference in time to clinical relapse between adrenalectomised and non-adrenalectomised ferrets was significant ($P<0.05$) and so this study suggests the need for further research into the benefits of combining these therapies.

In conclusion, whilst the pilot study by Lennox & Wagner (2012) proposes that deslorelin acetate implants have good safety, efficacy and some advantages over adrenalectomy, there is currently insufficient evidence to prove that this medical treatment leads to a superior prognosis than adrenalectomy in ferrets with HAC. Undoubtedly, further experimental studies, ideally randomised control trials, which directly compare these options would be necessary before conclusions can be made.

Methodology Section

Search Strategy	
Databases searched and dates covered:	CAB Abstracts on OVID Platform [1985–2021] PubMed via the NCBI Interface [1938–2021] Web of Science All Databases [1998–2021]
Search terms:	(ferret* OR mustel*) AND (adrenal* OR adreno* OR hyperadren* OR cushing*) AND ("Deslorelin acetate" OR Deslorelin OR Ovuplant OR SucroMate OR Suprelorin OR "GnRH analogue" OR "GnRH agonist") AND (surger* OR adrenalectom*)
Dates searches performed:	22 May 2021

Exclusion / Inclusion Criteria	
Exclusion:	Not relevant to PICO. No direct comparison. No English publication available.
Inclusion:	Studies in English that are relevant to the PICO and compare outcomes of surgery versus deslorelin acetate implants.

Search Outcome					
Database	**Number of results**	**Excluded – Not relevant to PICO**	**Excluded – Non-comparative**	**Excluded – Non-English publication**	**Total relevant papers**
CAB Abstracts	16	8	6	1	1
PubMed	2	0	2	0	0
Web of Science	12	6	5	0	1
Total relevant papers when duplicates removed					**1**

CONFLICT OF INTEREST

The authors declare no conflicts of interest.
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REFERENCES

1. Brezina, T., Thöle, M., Klotz, D., Herder, V. & Fehr, M. (2019). Surgical therapy of a non-deselin-responsive adrenal gland adenocarcinoma in a four-year-old ferret (Mustela putorius furo). *Kleintierpraxis.* 64(5), 280–290. DOI: https://doi.org/10.2377/0023-2076-64-280
2. Chen, S. (2010). Advanced Diagnostic Approaches and Current Medical Management of Insulinomas and Adrenocortical Disease in Ferrets (*Mustela putorius furo*). *Veterinary Clinics of North America: Exotic Animal Practice*. 13(3), pp.439–452. DOI: https://doi.org/10.1016/j.cvex.2010.05.002
3. Lennox, A. & Wagner, R. (2012). Comparison of 4.7-mg Deslorelin Implants and Surgery for the Treatment of Adrenocortical Disease in Ferrets. *Journal of Exotic Pet Medicine*. 21(4), pp.332–335. DOI: https://doi.org/10.1053/j.jepm.2012.09.001
4. Schoemaker, N. (2017). Ferret Oncology: Diseases, Diagnostics, and Therapeutics. *Veterinary Clinics of North America: Exotic Animal Practice*. 20(1), 183–208. DOI: https://doi.org/10.1016/j.cvex.2016.07.004
5. Shoemaker, N. & van Zeeland, Y. R. A. (2021). *Endocrine Disorders Of Ferrets*. [online] MSD Veterinary Manual. Available at: https://www.msdvetmanual.com/exotic-and-laboratory-animals/ferrets/endocrine-disorders-of-ferrets [Accessed 19 October 2021].
6. Swiderski, J., Seim III, H., MacPhail, C., Campbell, T., Johnston, M. & Monnet, E. (2008). Long-term outcome of domestic ferrets treated surgically for hyperadrenocorticism: 130 cases (1995–2004). *Journal of the American Veterinary Medical Association*. 232(9), 1338–1343. DOI: http://dx.doi.org/10.2460/javma.232.9.1338
7. Wagner, R., Finkler, M., Fecteau, K. & Trigg, T. (2009). The Treatment of Adrenal Cortical Disease in Ferrets with 4.7-mg Deslorelin Acetate Implants. *Journal of Exotic Pet Medicine*. 18(2), 146–152. DOI: https://doi.org/10.1053/j.jepm.2008.11.003

8. Wagner, R., Piche, C., Jochle, W. & Oliver, J. (2005). Clinical and endocrine responses to treatment with deslorelin acetate implants in ferrets with adrenocortical disease. *American Journal of Veterinary Research*. 66(5), 910–914. DOI: https://doi.org/10.2460/ajvr.2005.66.910
9. Weiss, C. A., Williams, B. H., Scott, J. B. & Scott, M. V. (1999). Surgical treatment and long-term outcome of ferrets with bilateral adrenal tumors or adrenal hyperplasia: 56 cases (1994–1997). *Journal of the American Veterinary Medical Association*. 215(6), 820–823.