Post-operative outcomes of surgical and chemical castration with zinc gluconate in dogs presenting to veterinary field clinics

Brian A. DiGangi a,*, Jaime Grijalva b, Erika Pamela Puga Jaramillo c, Ivette Dueñas d, Christine Glenn e,f, María Emilia Calero Cruz f, Renán Patricio Mena Pérez c

a Department of Small Animal Clinical Sciences, University of Florida College of Veterinary Medicine, Gainesville, FL 32610, United States
b Department of Large Animal Clinical Sciences, University of Florida College of Veterinary Medicine, Gainesville, FL 32610, United States
c Universidad Central del Ecuador, Facultad de Medicina Veterinaria y Zootecnia, Ciudadela Universitaria Av. América, Quito, Ecuador
d Universidad San Francisco de Quito, Escuela de Medicina Veterinaria, Diego de Robles s/n y Pampite, Quito, Ecuador
e American Society of Veterinary Pathology, 1570 34th Avenue, Tampa, FL 33607, United States
f Centro de Gestión Zootecnaria, CIGEZOO URBANIMAL, Calle las Semillas, Quito, Ecuador

ARTICLE INFO

Article history:
Accepted 22 October 2017

Keywords:
Chemical
Non-surgical
Castration
Zinc gluconate
Field clinic

ABSTRACT

The objective of this study was to characterize post-operative outcomes of chemical castration as compared to surgical castration performed by existing municipal field clinics. Fifty-four healthy adult male dogs underwent chemical castration with zinc gluconate solution and 55 healthy adult male dogs underwent surgical castration in veterinary field clinics. Dogs in each group were evaluated for swelling, inflammation, and ulceration (chemical castration) or dehiscence (surgical castration) at Days 3, 7, and 14 following castration. More surgically castrated dogs required medical intervention than chemically castrated dogs (P = 0.0328); the number of dogs requiring surgical repair within each group did not differ (P = 0.3421). Seven chemically castrated dogs and 22 surgically castrated dogs experienced swelling, inflammation, and/or ulceration; all were managed medically. Two chemically castrated dogs experienced scrotal ulceration requiring surgical castration at Days 3 and 7. One surgically castrated dog experienced partial incisional dehiscence requiring surgical repair at Day 3. Our results suggest that chemical castration of dogs in field clinics is a feasible alternative to surgical castration, but proper follow-up care should be ensured for at least 7 days post-procedurally.

© 2017 Elsevier Ltd. All rights reserved.

Introduction

Non-surgical contraception for companion animals has been an area of active research for many years, however few products have successfully made it to market for regular use. An injectable sterilant for male dogs containing zinc gluconate neutralized by arginine was first approved by the FDA and introduced in the United States in 2003 (ACC&D, 2016). Shortly thereafter production and distribution was discontinued for business reasons unrelated to safety and efficacy. After release in select Central and South American countries from 2008 to 2010, the product was reintroduced in the United States by a new manufacturer. At this time, mandatory manufacturer-led pre-purchase training programs for veterinarians were instituted to ensure correct administration technique and minimize associated risks (Griffin, 2013). In 2016, the product was removed from the market citing poor sales, distribution difficulties, and poor acceptance in the veterinary community (Lau, 2016).

According to the product manufacturer, intra-testicular injection of zinc gluconate results in local necrosis of testicular tissue. Initial atrophy of the testicles, epididymides, and seminiferous tubules are followed by scar tissue formation and permanent fibrosis, preventing normal movement of sperm from the seminiferous tubules to the epididymis (Product insert. Zeuterin™, Ark Sciences, Inc. New York). Absorption and metabolism of the compound is complete within 72 h of injection (ACC&D, 2016). Although highly variable, testosterone production can be expected to decrease following treatment. In a dose determination study in Beagles ≥4 months of age, testosterone levels were 41–52% lower but remained in the same range as control dogs 2 years after treatment (NADA, 2003). A field study of free-roaming dogs ≥4 months of age found that testosterone levels were equivalent to surgically castrated dogs in 66% of cases 6 months after injection (Vanderstichel et al., 2015). Despite the continued presence of

https://doi.org/10.1016/j.tvjl.2017.10.016
1090-0233 © 2017 Elsevier Ltd. All rights reserved.
testosterone, dogs are rendered sterile 30 days after treatment with zinc gluconate, a similar time frame to that found with surgical castration (ACC&D, 2016).

Injection complications are relatively few, though can be severe in nature. After chemical castration with zinc gluconate, the most common local reaction reported by the product manufacturer was scrotal pain, associated with testicular swelling the first 2 days after injection, in 6.3% of dogs. The most common systemic reactions reported included neutropenia, vomiting and anorexia (Product insert. ZeuterinTM , Ark Sciences, Inc. New York). The most common local reaction reported by an independent retrospective study was necrotizing injection-site reactions requiring surgical correction (Levy et al., 2008). Such reactions are reportedly due to improper injection technique and/or self-trauma, although reactions are not always associated with the injection site, suggesting the influence of other factors (Forzán et al., 2014).

Based on the studies submitted for FDA approval, the commercial solution of zinc gluconate neutralized by arginine was only labeled for use in male dogs between 3 and 10 months of age with testicular widths 10–27 mm (Product insert. ZeuterinTM , Ark Sciences, Inc. New York). However, it has been successfully used in adult dogs and the product formulation has been licensed for use in any dog over 3 months of age in countries other than the United States (Esquivel LaCroix, 2006; Forzán et al., 2014). Its use may be desirable in cases where anesthetic risks are high, where inhalant anesthesia and surgical facilities are not available, where cultural or societal pressures value the presence of testicles in male dogs, or where the continued presence of testosterone without fertility is desired.

Veterinary field clinics are a widely used model for delivering veterinary care throughout the world, including elective sterilization. Operating in the model of Mobile Army Surgical Hospitals (MASH), such programs bring supplies and equipment to remote locations for the provision of veterinary care. The model carries the benefits of low start-up costs, quick start-up times, and the ability to work directly in areas of greatest need regardless of geographic, economic, or other limitations. Such clinics typically utilize a temporary and/or volunteer veterinary work force (Makolinski, 2013). Due to the nature of this work, follow-up care is often limited. Although standard veterinary care guidelines relevant to the operation of all types of spay-neuter clinics have been published (Griffin et al., 2016), full adherence remains a significant challenge for field clinics operating in remote locations with limited infrastructure and strict pharmaceutical regulations. For these reasons, chemical castration could be utilized to provide a safe and affordable means of controlling pet overpopulation in such operations. The objective of this study was to characterize post-operative outcomes of chemical castration as compared to surgical castration as performed by existing municipal field clinics.

Materials and methods

Study locations

Three University of Florida-Universidad Central del Ecuador cooperative veterinary clinics in the metropolitan area of Quito, Ecuador in June 2014 were selected as study sites for chemical castration. Five areas in the metropolitan area of Quito, Ecuador in October–November 2015 were selected as study sites for surgical castration. Clinic locations were each selected by URBANIMAL, a municipal organization charged with implementing animal welfare ordinances in Ecuador. Adherence to standard guidelines for spay-neuter clinic operation varied across each of the clinic sites for surgical castration; no attempts were made to alter existing clinic protocols.

Animals

Dogs presenting to the field clinics underwent physical examination by program veterinarians and veterinary students to determine overall fitness for each procedure. All healthy dogs presenting for castration were eligible for inclusion provided their testicular width was between 10–27 mm and there was no evidence of previous irritation or trauma of the scrotal tissue. Standardized medical health forms were completed with information on each dog including patient signalment and physical examination findings.

Chemical castration

To ensure patient comfort and consistent injection technique, all dogs were sedated with dexmedetomidine (10 mg/kg). IV. All procedures were conducted by veterinarians who had undergone manufacturer-provided training in proper product usage, including injection technique. Briefly, the injection site was gently cleaned with a dilute chlorhexidine solution (no hair clipping was performed) and calipers were used to determine testicular width. A commercially-available solution of zinc gluconate neutralized by arginine (ZeuterinTM , Ark Sciences, Inc. New York) was drawn into two new 1cc syringes at a dose according to the manufacturer’s recommendations based on testicular width. A new needle (28G-1/2” or 30G-3/4”) was placed on each syringe and the right testicle was gently grasped in order to insert the needle in a dorso-cranial to ventro-caudal direction just ventral to the head of the epididymis. The solution was injected slowly over 10–12 s and the needle withdrawn while the testicle was released. The procedure was repeated on the left side with the second needle and syringe. Each dog was marked as sterilized with a scoring tattoo consisting of two small parallel lines placed in the prescrotal region. The dogs were allowed to recover in a designated recovery area and atipamezole (5 mg/kg) was administered IM. Once recovered, all dogs were discharged with 3 doses of firocoxib (5 mg/kg PO once daily). No attempt was made to confine the dogs or prevent access to the injection site (i.e., through the use of an Elizabethan collar).

Surgical castration

Surgical castration was performed by veterinarians according to existing standard operating procedures of the municipal field clinics. In order to compare chemical castration to surgical castration as typically performed, no attempts were made to alter the existing anesthetic, surgical or analgesic protocols of the surgical clinics. All dogs were pre-medicated with a combination of tramadol (2 mg/kg), acepromazine (0.1 mg/kg) and atropine (0.025 mg/kg) given SC or IM; anesthesia was induced and maintained with a combination of ketamine (10 mg/kg), and diazepam (0.25 mg/kg) IV. After completion of the procedure, dogs were allowed to recover in a designated recovery area; no anesthetic reversal was administered. Each patient was treated with an injectable penicillin procaine, benzathine and dipyridostegymycin combination product (30,000 U/kg) as well as long-acting flunixin meglumine (1.5 mg/kg) SC. No attempt was made to confine the dogs or prevent access to the injection site (i.e., through the use of an Elizabethan collar).

Follow-up

Each dog was evaluated for degree of swelling and inflammation, and either ulceration (chemical castration) or dehiscence (surgical castration) on Days 3, 7, and 14 after the procedure. Swelling and inflammation were recorded as mild, moderate, or severe according to standardized definitions (see Appendix A: Supplementary material). Ulceration was recorded as present or absent; if present, the length of the ulcerated region was noted. Dehiscence was recorded as absent, partial, or complete. Follow-up evaluations of chemically castrated dogs were conducted by at least one of the authors (BD, JG, EP, CG); however, evaluation duties were overlapped on each individual’s first evaluation to ensure consistency of scoring. Follow-up evaluations of surgically castrated dogs were all conducted by one of the authors (EP). Patients found to have moderate or severe swelling or inflammation were treated according to standardized protocols which included the following measures: application of an Elizabethan collar, activity restriction, extended courses of firocoxib, injectable or oral antibiotics. Instances of ulceration or dehiscence were surgically corrected if indicated or non-responsive to medical management (see Appendix A: Supplementary material).

Statistical analysis

Descriptive statistics were calculated for each group. Chi square or Fisher’s exact tests, as appropriate, were performed to compare differences in treatment groups (Epi Info Version 7.2.1.0, Centers for Disease Control and Prevention). P < 0.05 was considered significant.

The study protocol was approved by the Institutional Animal Care and Use Committee at the University of Florida.

Results

A total of 109 dogs were enrolled in the study: 54 underwent chemical castration and 55 were surgically castrated. All dogs were between 4 months and 8 years of age and had a median body weight of 10 kg (range 3–37 kg). Testicular width was a median of
21 mm (range 0.7–29 mm right, 0.6–29 mm left). Six dogs that were chemically castrated were unavailable for follow-up and were excluded from further analyses. Among the remaining 48 chemically castrated dogs, 47 (97.9%) were available for follow-up evaluation on Days 3 and 14. Forty-four dogs (91.7%) were available for follow-up on Day 7. All surgically castrated dogs were available for follow-up on Days 3, 7, and 14.

Most chemically castrated dogs (n = 37, 77%) and all surgically castrated dogs exhibited some degree of post-operative swelling and inflammation throughout the study period. However, the majority of these complications were deemed mild and no specific treatment was prescribed by the attending veterinarian. [Table 1] Among dogs for whom post-operative complications were identified, more surgically castrated dogs required medical intervention than chemically castrated dogs (P = 0.0328). The number of dogs with complications requiring surgical intervention did not differ between those that were chemically or surgically castrated (P = 0.3421).

After chemical castration, 9 (18.8%) dogs had post-operative complications requiring further veterinary care. [Table 2] Seven (14.6%) dogs required medical management for mild to moderate post-operative swelling and/or inflammation; treatment was initiated on Day 3 (n = 1), Day 7 (n = 3), Day 14 (n = 1), and Day 27 (n = 2). The only complications identified for the two dogs treated on Day 27 were mild (1 dog) and moderate (1 dog) inflammation on Day 14. Two (4.2%) dogs required surgical management for scrotal ulceration after chemical castration. Both dogs that experienced scrotal ulceration were identified at Day 7, one of which required surgical castration and scrotal ablation on Day 7. The second dog was initially managed medically, but required surgical castration and scrotal ablation on Day 19.

After surgical castration, 23 (41.8%) dogs had post-operative complications that required further veterinary care. [Table 2] Twenty-two (40%) dogs required medical management for mild to moderate post-operative swelling and/or inflammation; treatment was initiated on Day 3 (n = 15), Day 7 (n = 5), and Day 14 (n = 2). One (1.8%) dog required surgical management for an incisional dehiscence after surgical castration; dehiscence was identified and repaired on Day 3.

**Discussion**

In the field clinics described in the current study, dogs undergoing chemical castration with zinc gluconate neutralized by arginine were less likely to require follow-up medical treatment when post-operative complications arose than those undergoing surgical castration. When more severe post-operative complications occurred (i.e., those requiring surgical intervention), they did so up to 7 days post-procedurally.

The FDA approval clinical trial for the product used in this report described an ulceration rate of 0.4% with only 1 of 270 dogs requiring surgical intervention (NADA, 2003). Such complications were identified on Days 3, 7 and 17 post-injection and product training materials state that erythema will usually begin 1–2 days post-injection developing into ulceration 2–3 days post-injection (Ark Sciences, 2014). These findings are inconsistent with those reported by the current and previous field studies (Levy et al., 2008; Forzán et al., 2014).

Approximately 2% of surgically castrated dogs experienced wound dehiscence. A previous retrospective medical record review of a similar population reported surgical dehiscence in 3.4% of surgically castrated dogs (Levy et al., 2008). In that report, for dogs undergoing chemical castration, 3.9% of necrotizing injection site reactions required surgical management; these reactions were identified 4–6 days after injection. Another report found necrosuppurative and ulcerative dermatitis in 5.5% of dogs 7–8 days after chemical castration with a zinc gluconate solution (Forzán et al., 2014). We found similar proportions of complications (4.2%), however, ulceration did not occur until Day 7 after injection. In one case, the dog exhibited moderate swelling and inflammation on Day 3, while in the other there was no evidence of any post-operative complications on Day 3. In each of these reports, the same manufacturer-recommended administration technique

**Table 1**

<table>
<thead>
<tr>
<th>Treatment required</th>
<th>Chemical castration no. (%)</th>
<th>Surgical castration no. (%)</th>
<th>Odds ratio</th>
<th>Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>28 (75.7)</td>
<td>32 (58.2)</td>
<td>2.2</td>
<td>0.89–5.63</td>
<td>0.0840</td>
</tr>
<tr>
<td>Medical</td>
<td>7 (18.9)</td>
<td>22 (40)</td>
<td>0.35</td>
<td>0.13–0.94</td>
<td>0.0328</td>
</tr>
<tr>
<td>Surgical</td>
<td>2 (5.4)</td>
<td>1 (1.8)</td>
<td>U/D</td>
<td>0.15–185.35</td>
<td>0.5624</td>
</tr>
</tbody>
</table>

S = swelling; I = inflammation; U/D = ulceration/dehiscence; CC = chemical castration; SX = surgical castration; 0 = none; 1 = mild; 2 = moderate; 3 = severe; NA = not available for follow-up.

* Surgical treatment.
described herein was utilized. Because observations on each dog were not recorded daily, it is possible that ulcerations in both dogs may have begun as early as Day 4. However, since procedural days were staggered, study personnel were in each community on a daily basis to monitor other dogs and likely would have been alerted to serious complications noted by caregivers.

The low frequency of complications requiring further treatment that we observed suggests chemical castration might have improved long-term outcomes when compared to surgical castration as conducted in the municipal clinics described. By the nature of such clinics, where follow-up care is necessarily limited, the method of sterilization with the lowest possible complication rate is desired. The authors are unaware of other reports that have prospectively evaluated post-operative outcomes in a field clinic setting, however, the frequency of complications following surgical castration requiring further treatment (41.6%) is subjectively high. Post-operative complication rates for elective sterilization in standard veterinary surgical facilities have ranged from 2.5 to 8.5% (Vasseur et al., 1988; Burrow et al., 2005). The range of aseptic practices in the clinics where surgical procedures were conducted in this report varied widely and did not adhere to standard guidelines (Griffin et al., 2016). Although by nature field clinics face significant challenges, adherence to such guidelines is possible and likely would have decreased the rate of surgical complications in the study population. However, in order to effectively evaluate the feasibility of the chemical castration protocol in the field clinic setting, it was important to compare the complication rate to that of surgical procedures as they were being conducted at that time. This information warrants review of existing municipal clinic practices including aseptic technique; preparation of the patient, surgeon, and surgical instruments; and tissue handling and surgical technique. The risk-benefit ratio of conducting such procedures in light of their implications for both community and individual animal welfare should be evaluated.

An additional factor that might have contributed to the high surgical complication rate in surgically castrated dogs was the analgesic protocol employed. Although tramadol has been demonstrated to be an effective analgesic for elective sterilization (Kongara et al., 2013; Morgaz et al., 2013), recent reports have called its efficacy, variability, and duration of action in dogs into question (Davila et al., 2013; Delgado et al., 2014; Benitez et al., 2015a and b). These factors could have contributed to increased post-operative discomfort and increased self-trauma requiring treatment in the surgically castrated patients. Unfortunately, the use of pure opioids in veterinary patients is prohibited in Ecuador. Both chemically and surgically castrated dogs were treated with similar duration courses of post-operative NSAIDs. Although use of the cyclo-oxygenase-2 selective firocoxib in the chemically castrated patients is likely to have fewer adverse effects than the non-selective flunixin meglumine used in the surgically castrated patients, this selectivity alone should not impact analgesic efficacy (KuKanich et al., 2012).

Aside from the absolute number of complications requiring further intervention, which was lower in the chemically castrated dogs evaluated, some consideration should be given to complication severity. Although some pain and discomfort was presumed to be associated with complications found in each group and treatment was provided, no attempt was made to directly quantify the welfare implications of these complications. The study design presumed that all medical complications and all surgical complications were of equal weight across treatment groups, however, it is plausible that one technique might have had greater or lesser impact on the individual subject experience. In other words, the seven dogs that had medical complications resulting from chemical castration could have experienced a greater or lesser degree of pain or discomfort than the 22 dogs that had medical complications resulting from surgical castration — either individually or collectively as a group. Similarly, the two dogs that experienced surgical complications resulting from chemical castration experienced scrotal ulceration then underwent medical management followed by a second veterinary procedure (i.e., surgical castration with scrotal ablation) which could have resulted in an overall greater degree of pain or discomfort than the one dog whose surgical incision partially dehisced and was quickly identified and repaired. Clinicians evaluating the use of chemical and surgical castration in the field should consider the impact of each treatment modality in light of the risks and benefits for the individual patients as well as those of other animals in the population. A variety of tactics can be employed to weigh the consequences of such clinical decision-making including quantification of welfare of treated and untreated animals, prioritization of certain outcomes over others, or some combination thereof (Yeates, 2013).

Our study has several limitations. Instances of swelling and inflammation were recorded subjectively by 3 different observers. Although standardized definitions for complication severity were described, some individual variation is likely to occur, and the clinical response protocol allowed for clinician discretion in the administration of treatment for dogs having a “moderate” score for swelling and inflammation. Despite these factors, review of individual patient records suggests that they are not likely to have resulted in a clinically significant difference in any patient. While observers at times worked alone, each observer accompanied another observer on their initial day of observation to minimize variation in scoring. Secondly, injections of zinc gluconate solution were administered by three different individuals. Although each was trained in proper injection technique and no clinical distinction in technique was evident, experience with intratesticular injection varied. In the two cases of scrotal ulceration, the zinc-gluconate was administered by different individuals. Finally, it was not possible to blind observers to the procedure type given the presence or absence of testicles or surgical incision.

Surgical sterilization is safe, effective, and its effects on both individual animal and population health and welfare are well established. While the cost, equipment, and expertise required limit its utility in many parts of the world, the indications for elective sterilization of companion animals in those regions still remain. Non-surgical methods of sterilization could provide a practical means of overcoming some of these barriers and expand options for controlling fertility in companion animals (Griffin, 2013; ACC&D, 2014).

Conclusions

Although the product evaluated in this report is no longer being manufactured, similar products are currently in active use and these results have important implications for the future use of chemical sterilants and practitioners working in field clinics around the world. The length of follow-up care required to address the medical and surgical needs of field clinic patients was longer than anticipated and likely longer than most field clinics are equipped to provide. Given the variation in aseptic practices encountered in field clinics and the fact that access to veterinary care is typically limited in the locations where field clinics are in operation, provisions for proper follow-up care should be ensured for at least 7 days post-procedurally.

Conflict of interest statement

None of the authors of this paper have a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.


Acknowledgements

The authors would like to thank Drs. Patricia Dingman, N. Luzuriaga, and Sandy MacArthur for their support and technical assistance. Portions of these results were presented in a graduate thesis at Universidad Central del Ecuador, Facultad de Medicina Veterinaria, “Determinación y comparación evolutiva de los efectos adversos de castración quirúrgica con relación a castración química (gluconato de zinc), por vía intraepididimal como método opcional de esterilización en caninos (machos) para la aplicación en el control de fauna urbana en el Distrito Metropolitano de Quito,” April 2016. Preliminary results were presented as an Abstract at the 21st Annual ABVP Symposium, San Antonio, October 2016. The chemical sterilant used in this study was donated by Ark Sciences, Inc., New York.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tvjl.2017.10.016.

References


Burrow, R., Batchelor, D., Cripps, P., 2005. Complications observed during and after ovariomyectomy of 142 bitches at a veterinary teaching hospital. The Veterinary Record 157, 829–833.


