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Original Article

Oral Administration of Ginger Rhizome Powder and Postoperative Inflammation Indices in Ovariohysterectomized Dogs

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ABSTRACT

With regard to the importance of prescribing medicinal plants in the traditional veterinary medicine and the anti-inflammatory role of ginger, the current study was conducted to evaluate the effects of the oral administration of the ginger rhizome powder following ovariohysterectomy in puppies. Ten healthy young female puppies were randomly assigned to two equal groups, including a control and an experimental group. Two hours before surgical neutering by ovariohysterectomy, a Zintoma Capsule (*Zingiber officinale*) was administered orally in the experimental group and continued daily for 10 days after surgery. Several inflammatory markers were measured to evaluate the postsurgical status of the animals in the different times. Although there was no difference in the albumin and glucose level between the experimental and control groups at the different times, a statistically significant reduction in the inflammatory markers C-reactive protein (CRP), fibrinogen, tumor necrosis factor α (TNF-α), and interleukin 6 (IL-6) was observed in the experimental group compared to the control group. These preliminary findings suggest the usefulness of ginger rhizome powder, a traditional herbal dietary supplement, in the reduction of postoperative inflammatory reactions in dogs undergoing ovariohysterectomy.

Introduction

Ginger rhizome (*Zingiber officinale Roscoe*) is a member of the Zingiberaceae family of plants and is used in various parts of the world as a well-liked spice as well as medicinal herb since ancient times because of its very favorable content of antioxidants and anti-inflammatory properties.[1,2] Ginger rhizome is increasingly used for nutritional and therapeutic purposes in fresh, dried, aqueous and ethanolic extracts and ginger oil.[3] A variety of therapeutic effects, including analgesic and anti-inflammatory activities, have been attributed to gingerol, which is the major constituent of ginger.[4-6] Ueda *et al*. reported that repeated oral administration of squeezed ginger extract in mice gradually induced ginger anti-inflammatory effect.[7] In a human study, it was found that two months of oral administration of ginger (*Zingiber officinale*) could decrease serum levels of tumor necrosis factor α (TNF-α) and high-sensitivity C-reactive protein (CRP).

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So, it was concluded that ginger can control low-grade inflammation as a common feature in patients with type 2 diabetes.[8] In addition, the oral use of ginger with its analgesic effects on human musculoskeletal injuries has been reported. Ginger powder has demonstrated curing properties in patients with musculoskeletal disorders through impeding the cyclooxygenase and lipoxygenase pathway in synovial fluid.[9] The efficacy of ginger extract in patients with osteoarthritis has demonstrated its pain reducing impact without any side effects.[10,11] Van Breemen *et al*. reported the mechanism of the anti-inflammatory effect of ginger constituents. They found that 10-gingerol, 8-shogaol, and 10-shogaol strongly inhibited cyclooxygenase 2 (COX-2) and thereby significantly reduced inflammation.[6] Although ginger exhibits its anti-inflammatory effect by blocking COX-2 enzymes, Grzanna has reported blocking the activities of both COX-1 and COX-2.[12] Moreover, it is also showed that ginger could suppress leukotriene biosynthesis by inhibiting 5-lipoxygenase.[6] It is reported that gingerols, as a major biologically effective ingredient of ginger, have several pharmacological and physiological effects, including analgesic, anti-inflammatory, cardiotonic, antipyretic, and inhibition of prostaglandin and leukotriene biosynthesis.[4,5] The inhibition of COX-1 activity by ginger was also demonstrated by Nurtjahja-Tjendraputra and coworkers. Their study revealed that 8-paradol of ginger was a potent COX-1 inhibitor.[13] In fact, gingerol has been shown to reduce inflammation by suppressing reactive oxygen-species (ROS) activated nuclear factor kappa B (NF-κB)/COX-2 pathway.[14]

A search on the Internet can sometimes reveal published non-academic information showing the use of ginger in the canine field. It should be noted that most of these prescriptions have a local and traditional basis. Surgical interventions can threaten the patient's health due to uncontrollable or extensive tissue damage. Complications of elective surgeries such as open ovariohysterectomy (OHE) in dogs and cats are not uncommon. These include bleeding, surgical inflammation, and infection.[15,16] Therefore, using an appropriate surgical approach and sometimes prescribing medications and anti-inflammatory agents can provide a normal and controlled postsurgical inflammatory response for small animals undergoing surgical neutering. As a result, wound healing and recovery of surgical injuries are provided optimally with minimal complications.

Among the relevant considerations for achieving good postoperative status is the study of effective medicinal plants after surgery. With regard to the anti-inflammatory role of ginger, the current study was conducted to evaluate the effects of the oral administration of ginger rhizome powder following OHE in puppies. Finally, the effectiveness of this treatment is studied by measuring several inflammatory markers. The hypothesis of the present study is that the administration of this herbal medicine can provide better postoperative status in animals undergoing neutering surgery.

Materials and Methods

The study procedure was approved by the Research Council of the Department of Veterinary Clinical Sciences (1396-12-15).

Animals

Ten healthy female puppies aged 2-3 months and weighing 5 ± 1.12 kg that were admitted for elective open OHE at the Surgery Section of Veterinary Medicine Hospital, Shahrekord University, Iran, were in the current study. These mixed breed puppies were vaccinated and treated for heartworm and visceral parasite infections. The puppies were found to be healthy based on the medical background and physical examination, and hematobiochemical profile. The dogs were randomly assigned to the experimental (n = 5) or the control (n = 5) groups.

Surgery Preparation and Procedure

One day prior to surgery, a 20-gauge heparinized intravenous (IV) catheter was placed aseptically into a cephalic vein to facilitate collection of blood and to reduce stress associated with obtaining the blood samples on the day of surgery.

Two hours before induction of anesthesia, 250 mg ginger rhizome powder (Zintoma Capsule 250 mg; Goldaru Co. Iran) was administrated orally using a pill popper in the experimental group. The company states each ginger capsule contains 250 mg of 100% pure ginger root powder with active ingredients including alkaloids (gentialutine, gentianine), glycosides (anaroswerin, amaropanin), and volatile oils (bisabolene, zingiberene, gingerols, and zingiberole).

Hair was clipped over the ventral abdominal area and skin was aseptically made ready before induction of anesthesia. The surgery was planned so that all animals underwent surgery at the same time interval (11-12 am). All the puppies were premedicated with a combination of morphine (0.4 mg/kg, IV; Temad Co.

Iran) and midazolam (0.2 mg/kg, IV; Caspian Tamin Co. Iran). Additionally, meloxicam (0.2 mg/kg; Razak Co. Iran) was injected subcutaneously. Anesthesia was induced by means of administration of ketamine (6 mg/kg, IV; Rotexmedica Germany) and diazepam (0.3 mg/kg, IV; Caspian Tamin Co. Iran), and, after tracheal intubation, anesthesia was continued with isoflurane (Terrel Isoflurane, USA) in oxygen and air. Warm lactated Ringer's fluid (10 mL/kg/h) was administrated IV until the animal was extubated. Prophylactic antibiotics were not administered.

Neutering of all animals was performed by one surgeon with a constant assistant. Standardized surgical conventions were considered for all procedures. After surgical incision and access to the ovaries and uterine horns according to the standard approach,[17] the ovarian vessels (artery and vein) were double ligated (Size 2-0 polyglactin 910) cranial to the ovarian bursa and the mesovarium was incised with scissors. Subsequently, the round ligaments were separated with scissors; finally, the uterine body and uterine vessels were double ligated with size 2-0 polyglactin 910 suture material cranial to the cervix. A small clamp was applied cranial to the ligature site, and the uterine body was cut sharply between the suture site and the preplaced clamp. After removal of the uterus, the uterine pedicle was replaced in their normal anatomic location. After inspection of all the ligated vessels and confirmation of the absence of bleeding, the abdominal cavity was closed routinely.[17,18] The oral administration of 250 mg ginger rhizome powder at mealtime was continued daily for 10 days in the experimental group.

All animals were hospitalized in solitary confinement during the study at the animal husbandry center of the faculty of veterinary medicine and daily monitoring of their surgical wounds, feeding and cleaning of their beds were done carefully after surgery. Additionally, postoperative pain management included oral administration of carprofen (2 mg/kg) every 12 hours for 2 days after surgery.

Evaluation of Inflammatory Markers

At time 0 (the day of surgery but before any intervention as base data), day 1, 3, 7, and 14 after surgery when the animals were hospitalized, whole blood samples (5 ml) were collected from a cephalic vein to measure various parameters related to inflammation. The collected blood samples placed in the tubes containing EDTA (2 ml), 3.2% sodium citrate (1 ml), and in a plain tube (2 ml). Plain tubes were centrifuged (750 g for 5 min) to obtain serum. Blood works were performed within 1 hour from blood collection. Serum concentrations of glucose, CRP, and albumin were measured using an automated biochemistry analyzer (BT1500, Biotecnica, Italy) by means of standard methods and commercial reagents (Dialab, Austria). Fibrinogen concentration was measured by Clauss' coagulometric method using citrated blood samples. In addition, plasma TNF-α concentration was measured by ELISA using a monoclonal human anti-TNFa-antibody, 61E71, and a polyclonal rabbit anti-hTNF-α. ELISA tests utilizing this human antibody experimentally in canine plasma have shown a detection limit of 15 pg/mL, which is 1/60 of the levels achieved after sub-lethal doses of endotoxin.[19] The activity of interleukin 6 (IL-6) in plasma samples was determined by a method introduced by Fransson *et al.*, which is based on the assay of IL-6 using IL-6-dependent hybridoma B-9.[19]

Statistical Analysis

Measured data were analyzed using a statistical software program (SPSS for Windows, version 20, USA). The means and standard error for each variable were evaluated. According to the number of animals in the evaluated groups, the differences between the means of both groups were compared using non-parametric statistical test Mann-Whitney. Furthermore, data for these parameters were analyzed over time using the Kruskal-Wallis test. A p value of < 0.05 was considered statistically significant.

Results

The effect of oral administration of ginger rhizome powder on the mean (± SE) measured parameters are shown in Table 1. The analyzed results indicated that there were no statistically significant differences in the albumin and glucose level between the experimental and control groups at the different times. However, it was observed that on day 7 of the study in both groups there was a significant increase in mean glucose compared to time 0 ($p < 0.05$). The results showed that on days 1, 7 and 14 of the study, the mean (± SE) of CRP decreased significantly in the experimental group compared to the control group ($p < 0.05$). The first day after surgery in both control and experimental groups showed a significant increase in this parameter compared to time 0, which was a significant increase in its mean until the end of the study. Mean (± SE)

Table 1. Effect of *Zingiber officinale* on the inflammatory markers in the experimental and control groups of dogs (mean ± SE)

Parameter	Group	Time (day after surgery)				
		0	1	3	7	14
Glu (mg/dl)	Control	113.00 ± 12.72	111.50 ± 14.84	111.50 ± 10.25	135.33 ± 21.01	110.60 ± 13.12
	Experimental	111.50 ± 14.84	99.50 ± 17.23	106.50 ± 18.16	162.33 ± 13.31	105.25 ± 34.26
	p value	0.83	0.70	0.68	0.53	0.72
Alb (mg/dl)	Control	2.45 ± 0.21	2.70 ± 0.34	2.77 ± 0.50	2.97 ± 0.31	2.95 ± 0.45
	Experimental	2.55 ± 0.07	2.72 ± 0.26	2.28 ± 0.67	3.16 ± 0.21	2.54 ± 0.43
	p value	0.66	0.86	0.50	0.47	0.28
CRP (µg/dl)	Control	7.50 ± 0.71	14.20 ± 1.92	17.66 ± 2.51	15.66 ± 2.88	18.25 ± 1.89
	Experimental	7.00 ± 1.41	10.66 ± 0.57	14.75 ± 3.59	10.00 ± 1.73	13.00 ± 1.00
	p value	0.72	0.04	0.29	0.04	0.02
Fibrinogen (mg/dl)	Control	225 ± 65.6	246.1 ± 47.5	348 ± 123.44	554 ± 183.8	408.4 ± 34.88
	Experimental	232.24 ± 25.11	231 ± 75.22	337.33 ± 69.57	426.6 ± 34.7	371 ± 58.4
	p value	0.33	0.53	0.27	0.03	0.10
TNF-α (pg/mL)	Control	0.11 ± 0.01	5.05 ± 0.08	4.08 ± 0.18	0.15 ± 0.05	0.18 ± 0.01
	Experimental	0.13 ± 0.05	3.11 ± 0.01	2.11 ± 0.63	0.16 ± 0.04	0.14 ± 0.02
	p value	0.17	0.03	0.04	0.44	0.16
IL-6 (pg/mL)	Control	35.3 ± 9.1	47.17 ± 10.35	154.44 ± 8.41	166 ± 10.3	57.35 ± 15.45
	Experimental	38.22 ± 11.2	51.24 ± 6. 6	102.58 ± 13.07	93.36 ± 6.08	45.34 ± 10.62
	p value	0.18	0.42	0.03	0.02	0.09

Glu: glucose; Alb: albumin; CRP: C-reactive protein; TNF-α: tumor necrosis factor alpha; IL-6: interleukin 6.

comparison of fibrinogen, TNF-α and IL-6 at a few days later after surgery showed a significant decrease in the mean of these parameters in the experimental group compared to the control group ($p < 0.05$). However, in both control and experimental groups, over time, fibrinogen from day 7 of the study and TNF-α and IL-6 from day 1 and 3 had a significant increase compared to baseline data (day 0), respectively.

Discussion

The current experiment was conducted to evaluate whether the postoperative inflammation indices of puppies undergoing OHE were influenced by oral administration of ginger rhizome powder as a natural anti-inflammatory treatment. In fact, this study was planned based on the anti-inflammatory potential of ginger and the importance and attractiveness of prescribing medicinal plants in the field of small animals. Therefore, it was decided to perform this study at the same time as surgery (OHE) and during the period when the surgical wound is healing, oral administration of ginger should be done daily and during this period, the inflammatory condition of animals undergoing OHE should be evaluated. The point to be noted is the small number of animals studied. Since no scientific and academic paper was found in the oral administration of ginger after OHE, the minimum number of animals were considered in the study in order to respect animal rights. Obviously, this study could provide the basis for future evaluations of oral ginger administration after surgery in dogs.

Post-operative incisional swelling/inflammation, pain and redness, and also seroma formation through the ventral midline are delineated OHE complications.[16] The pain and inflammation associated with the open procedure are ascribed to the manipulation and desiccation of exposed viscera and disturbance of the peritoneal surface.[20] Furthermore, digital detachment of the suspensory ligament damages the peritoneal space and can potentially cause peritoneal and general inflammation.[21] Obviously, extensive or uncontrolled inflammation can delay or disrupt the patient's recovery.[22] Although NSAIDs are commonly used to control postoperative pain, it sometimes appears that these drugs impair healing by over-inhibiting inflammation because inflammation is an important part of the healing process.[23] Although this is controversial, the question is, can the administration of carprofen as a NSAIDs not affect the purpose of the study, which is to evaluate the effect of oral ginger? First, all animals in both groups received this drug for a limited time (for two days) after OHE. Another point is that there is still no accurate and documented information about the analgesic effect of ginger after surgery in dogs. However, in situations such as short-term administration of NSAIDs, as well as the patient's health and the absence of diseases such as diabetes and chronic wounds, the postsurgical healing is not affected by NSAIDs.[23,24] However, it should be noted that the main purpose of the study was not to evaluate the effect of ginger analgesic after OHE in dogs. Therefore, paying attention to medicinal plants for acceptable control of inflammation after surgery can be a new approach of managing postoperative inflammatory status of the patient.

The present study is the first to investigate the postoperative inflammation indices of dogs after OHE. The therapeutic properties of ginger are attributed to several of its active compounds. The important constituents in ginger are the powerful vanilloids, gingerol, shogaols, paradol, and zingerone.[4,6] It is known that blood glucose as well as serum cortisol concentrations are helpful indicators of surgical stress.[21] For example, it was found that in open OHE surgery of adult dogs, postoperative glucose levels were higher for a longer period of time than laparoscopic OHE.[21] The results of our study on glucose concentration indicated that there was no significant difference between the two control and experimental groups at different times. Other studies have shown that the effect of ginger on serum glucose should be found in long-term administration of ginger.[25,26] Similarly, significant differences in serum glucose concentrations were observed in the present study. Albumin is commonly used as a non-invasive, useful, and available indicator for the diagnosis of some inflammatory diseases in dogs.[27] In addition, albumin is a nonspecific, slow-reaction negative acute-phase protein and its plasma concentration decreases with increasing severity of inflammation.[27] Any damaging process, such as surgery, infection, or burns, can disrupt protein metabolism, including albumin production.[28,29] However, in our study it was found that oral administration of ginger did not cause a significant change in plasma albumin levels compared to the control group. The reason should be considered that albumin is an early biomarker that changes immediately after surgical stress and can be observed in the early hours after surgery,[30] while the measurement of this marker in our study was not immediately after surgery.

CRP is an inflammatory marker in that its levels increase after surgery intervention and also in response to trauma and other inflammatory conditions.[31] It can be used to quantify the inflammatory response in various surgeries in dogs.[32] It has previously been shown that OHE causes a mild increase in CRP in dogs.[33,34] However, invasive interventions such as orthopedic surgery have been shown to further increase this inflammatory marker due to more damage.[33] In both groups, the amount of CRP showed a significant increase after surgery, but interestingly, the results of the present study showed an obvious decrease in the CRP levels in the experimental group (compared to the control group at similar times) and confirmed the anti-inflammatory activity of ginger supplementation. One could question why the administration of carprofen as an NSAID did not change the level of postoperative CRP compared to day 0. On the one hand, it has been suggested that NSAIDs do not directly inhibit the production of IL-6 (the main inducer of CRP).[33,35] On the other hand, it has been stated that CRP is not affected in humans after NSAID administration. It is similarly stated in the veterinary field that the administration of meloxicam or carprofen after OHE surgery in dogs did not cause a significant reduction in CRP.[36] Similarly, due to the change in the level of postoperative CRP in both groups of our study, it is concluded that the postsurgical carprofen administration could not prevent the CRP rising after OHE.

Fibrinogen has been introduced in many species as an acute phase protein. Fibrinogen testing is common in the diagnosis of hemostatic disorders in small animals and is less commonly used as a biomarker in inflammation.[37] Because it has little specificity and responds slowly and during inflammation increases moderately in both our studied groups, a significant increase in fibrinogen was observed compared to baseline data (day 0) on day 7 of the study, which was delayed compared to CRP change.

In addition, on days 7 and 14 of the study, the mean fibrinogen in the ginger receiving group was significantly lower than the control group, which may be due to ginger's anti-inflammatory activity. However, it has been reported that 3-month oral administration of ginger (4 g/day) in patients with coronary artery disease does not alter fibrinogen levels in these patients.[38] Of note is the induction of fibrinogen synthesis from primary hepatocytes by IL-6.[39] IL-6 as a pro-inflammatory cytokine activates acute-phase protein production (such as CRP, serum amyloid A), lymphocytes, and increases antibody production.[40] IL-6 can forecast an inflammatory process before circulating CRP increases and clinical signs appear.[41,42] In veterinary medicine, studies have been performed on the prognostic role of IL-6 concentrations in inflammatory diseases, sepsis, and inflammatory systemic response syndrome.[43-45] Measuring IL-6 concentrations has been suggested as a suitable indicator for determining the health of dogs after OHE.[46] Therefore, the measurement of IL-6 in our experiment, before surgery (time 0), confirmed the health of the puppies and showed that they did not have inflammatory condition before OHE. The results of our study showed that 3 days after OHE IL-6 concentrations in both groups increased significantly. So, this incremental change can be considered a sign of surgical stress. In addition, it was found that following oral administration of ginger on days 3, 7 and 14, IL-6 concentrations were lower than the control group (no oral intake of ginger). Therefore, it can be concluded that the anti-inflammatory effect of ginger is (at least partially) IL-6 mediated. Ginger appears to induce its anti-inflammatory effect by selectively inhibiting the production of pro-inflammatory cytokines, including IL-6, from macrophages.[47]

Another pro-inflammatory cytokine used to assess inflammation includes TNF-α. Plasma TNF-α has been shown to be elevated in people as well as dogs with systemic inflammation syndrome.[48,49] For example, it has been shown that 3-month daily consumption of ginger powder in people with knee osteoarthritis reduce inflammation and disease and measuring TNF-α concentrations used as the indicator for the therapeutic effectiveness of ginger.[50] The results of some studies show that ginger intake can lead to a decrease of TNF-α levels.[51-53] on days 1 and 3 of our study, plasma TNF-α was significantly lower in the ginger receiving group (experiment) than in the control group. However, over time, in both groups on days 1 and 3, TNF-α levels increased significantly compared to time 0, after which they decreased. It should be noted that TNF-α has a short half-life[54] and tends to precede the acute-phase response reflected by increased CRP and decreased albumin.[55] In addition, it is stated that IL-6 also has anti-inflammatory effects and can inhibit the production of TNF-α.[56] The results of our study are in accordance to these previous findings and describe TNF-α changes. In our study, it was found that the decrease in TNF-α levels in the experimental group compared to the control group that did not receive ginger was only until the third day of the study. After this time, a significant difference between the two groups can be seen in the level of IL-6. It appears that this effect may be due to the inhibitory effect of IL-6 on TNF-α. Similarly, oral administration of ginger has been shown to have a therapeutic effect in people with active rheumatoid arthritis, leading to a reduction in some pro-inflammatory cytokines, including TNF-α.[57] But the mechanism of TNF-α reduction after ginger administration is attributed to the compounds of this plant. It is stated that ginger ingredients also reduce TNF-α by impacting up-stream gene expression in its pathway.[53] For example it has been reported that 6-Shogaol (an important ingredient of ginger) acts as a proliferator-activated receptor-gamma (PPAR-γ) agonist, reducing inflammation and TNF-α levels by activating PPAR-γ.[58] Of course, 6-shogaol also has an anti-inflammatory effect by suppressing the production of PGE2 and pro-inflammatory cytokines. This is due to down regulating COX-2, p38 mitogen-activated protein kinase (MAPK), and NF-kB gene expression.[59]

In conclusion, oral administration of dried ginger significantly reduced inflammatory markers including CRP, fibrinogen, TNF, and IL-6 in dogs undergoing OHE. So, based on these findings, the traditional herbal dietary supplement ginger rhizome powder is a useful supplement in dogs undergoing elective neutering.

Conflict of Interest

The authors have declared that no competing interests exist.

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