Comparison of pain and postoperative stress in dogs undergoing natural orifice transluminal endoscopic surgery, laparoscopic, and open oophorectomy

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Background: Few studies are available to compare the potential benefits of natural orifice transluminal endoscopic surgery (NOTES) approaches to traditional surgery.

Objective: To compare complications, surgical stress, and postoperative pain.

Design: Prospective study in dogs.

Setting: Research laboratory.

Subjects: Thirty dogs.

Interventions: Oophorectomy procedures were performed via NOTES and laparoscopic and traditional open surgery.

Main Outcome Measurements: Operative time, pain scores, systemic stress parameters (cortisol, glucose), surgical stress markers (interleukin 6, C-reactive protein), 3-day observation.

Results: Median operative times were 76, 44, and 35 minutes for the NOTES, laparoscopic, and open procedures, respectively, with the NOTES procedure being significantly longer than the other 2 procedures. All ovaries were completely excised, and all the animals survived without complications. The NOTES animals had greater increases in serum cortisol concentrations at 2 hours but no statistically significant differences in glucose concentrations compared with the other groups. Serum interleukin 6 and C-reactive protein concentrations were significantly increased at specific times compared with baseline in the NOTES group, but not in the open or laparoscopic surgery groups. Based on the cumulative pain score and nociceptive thresholds, the animals in the NOTES group demonstrated less evidence of pain.

Limitations: Small sample size, limited follow-up.

Conclusions: Although the NOTES oophorectomy procedures took approximately twice as long and there may be more evidence of tissue damage as judged by increases in serum cortisol and interleukin 6 concentrations, the dogs in the NOTES group had lower pain scores, especially when compared with animals undergoing open surgery. (Gastrointest Endosc 2010;72:373-80.)

Abbreviations: CRP, C-reactive protein; IL-6, interleukin 6; NOTES, natural orifice transluminal endoscopic surgery.

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Laparoscopic approaches are clinically well accepted as being less painful and resulting in less stress than traditional open procedures. In natural orifice transluminal endoscopic surgery (NOTES),[1] a flexible endoscope is used to gain access to the abdominal cavity via the stomach, vagina, rectum, or bladder. Several researchers have undertaken comparative studies of NOTES procedures in swine, evaluating stress parameters and postoperative outcomes; however, none have thoroughly evaluated differences in postoperative pain.[2-6]

The dog was selected for this study because the peritoneal cavity's response to injury is very similar to that of a human,[7] the dog's stomach is anatomically similar to the human stomach, and there are validated models for the evaluation of postoperative pain[8] and studies demonstrating an ability to detect differences in pain with open and laparoscopic surgery.[9] Previously, NOTES techniques for performing bilateral oophorectomy were developed in dogs with 10 animals followed clinically and evaluated with postmortem examination after 10 to 14 days.[10] There is general societal and veterinary acceptance that neutering is in the best interest of the dog's health and increases the likelihood of adoption. To thoroughly assess the impact of minimally invasive surgical techniques such as NOTES on metabolic and stress responses as well as postoperative pain, we designed a clinical study comparing such factors in dogs undergoing laparoscopic, open, and NOTES oophorectomy. From an ethical view, we prefer this type of preclinical trial in which study endpoints do not require euthanasia.

Take-home Message

- Dogs undergoing oophorectomy with natural orifice transluminal endoscopic surgery had less pain postoperatively, but differences were not explained by decreased tissue inflammation. More research is needed to understand the relationship of postoperative pain and inflammation after surgery.

MATERIALS AND METHODS

Animal model

Thirty healthy female dogs, weighing 11.2 to 38.6 kg, were used for the study. The study was approved by the Purdue University Institutional Animal Care and Use Committee, and client consent was obtained. The NOTES procedures were performed in 10 research animals, and 20 dogs from a local animal shelter underwent either a laparoscopic or an open procedure.

Surgical preparation

Preoperative evaluation included hematocrit, total protein, and blood glucose evaluations. Baseline physiologic parameters were determined just before surgery (t = 0). After a 24-hour fast, all animals were administered the same general anesthesia and were monitored and managed similarly. Perioperative antibiotics (cefazolin 22 mg/kg intravenously administered every 2 hours intraoperatively) were given, and aseptic procedures for clipping, preparing, and draping the abdomen were followed. Sterile instruments were used for all open and laparoscopic procedures. For the NOTES procedures, the endoscopes and other equipment underwent high-level disinfection and an overtube (U.S. Endoscopy, Mentor, Ohio) was used to reduce oral contamination.

NOTES procedure

A transgastric approach with percutaneous endoscopic gastrostomy technique was used to perform NOTES bilateral oophorectomy using techniques described previously.[10] To minimize issues with overinsufflation, a combination of air from the endoscope and CO_2 from an automatic insufflator set at 12 to 14 mm Hg through a percutaneous catheter was used to distend the abdominal cavity. A 3.0 × 4.5-cm hexagonal snare (AcuSnare; Cook Medical Inc, Bloomington, Ind) with monopolar electrosurgery was used to coagulate and cut the ovarian pedicle. Each ovary was then removed and examined to ensure complete removal. If the ovary was not present in the tissue removed, another excision was performed. After removal of both ovaries, the gastrotomy was closed with prototype T fasteners (developed by Cook Medical) and assessed visually from inside the stomach.

Laparoscopic procedure

Bilateral laparoscopic oophorectomy was performed through a 10-mm port placed at the umbilicus and a second 5-mm port placed on midline approximately 5 cm below the umbilicus. Insufflation with CO_2 was provided via an automatic insufflator with pressure set at 12 to 14 mm Hg. Each ovary was elevated with grasping forceps and suspended from the body wall by passing a percutaneous needle and suture or weighted hook (SPAY Hook; Karl Storz Veterinary Endoscopy, Goleta, Calif) through the body wall and through the tissue adjacent to the proper ovarian ligament. A 5-mm ultrasonic scalpel (Harmonic ACE; Ethicon Endosurgery, Cincinnati, Ohio) was used to coagulate and cut the suspensory ligament, ovarian pedicle, and fallopian tube. Each ovary was then removed from the umbilical port, and the port sites were closed with sutures in the body wall, subcutaneous tissue, and skin.

Open surgery

A standard 40- to 60-mm ventral midline incision was made from 3 cm caudal to the umbilicus toward the pubis with a no. 10 scalpel blade through the skin, subcutaneous tissue, and linea alba. A Snook ovariectomy hook (Miltex

Inc, York, Pa) and traction on the suspensory ligament were used to gain exposure to each ovary. A 3-forceps technique was used to ligate each ovarian pedicle with 2 ligatures. The pedicle was transected, the fallopian tube and proper ovarian ligament were ligated with suture, and the ovary was removed. The abdominal, subcutaneous, and skin layers were sutured routinely.

Monitoring and postoperative care

Baseline values for heart rate, respiratory rate, rectal temperature, blood pressure, and blood samples were obtained for analysis before surgery and postoperatively at 2, 4, 6, 12, 18, 24, 36, 48, and 72 hours after extubation. Serum samples were stored at 0°C and then assayed for cortisol and glucose at the end of the collection period by the University of Illinois College of Veterinary Medicine Clinical Pathology Laboratory. Serum from the 0-, 2-, 6-, 12-, 24-, 36-, and 72-hour samples were stored at −80°C and shipped to AniLytics, Inc (Gaithersburg, Md) for interleukin 6 (IL-6) (Quantikine canine IL-6 enzyme immunoassay kit reagents; R&D Systems, Inc, Minneapolis, Minn) and C-reactive protein (CRP) (enzyme-linked immunosorbent assay reagents; Life Diagnostics, Inc, West Chester, Pa) analysis. Each test was validated in the dog for research use only.

For postoperative analgesia, dogs were given 2 doses of hydromorphone 0.05 mg/kg intramuscularly, one at the end of the surgical procedure and another dose 6 hours later. Pain scores were determined and recorded by 1 of 2 observers preoperatively and at each time point as described previously.[8] The nociceptive threshold was determined in each dog immediately after blood sampling according to the techniques reported previously.[9,10] Dogs, which tolerated higher pressures in the cuff placed around the abdominal cavity, were interpreted as having less evidence of abdominal pain.

Clinical evaluation

Water was offered when the animal was ambulatory, and moistened dog food was offered at 6 hours after surgery. The time of first defecation was recorded. After 3 days, the animal was returned to the care facility or animal shelter for subsequent adoption. Of the 30 animals enrolled in the study, 25 were ultimately adopted.

Statistical analysis

Data are presented as mean and standard deviation, and $P < .05$ was considered significant. Non-normally distributed variables were log-transformed (serum glucose, cortisol, CRP, and IL-6 concentrations) or ranked (pain score) before statistical analysis was performed. Repeated-measures analysis of variance (PROC MIXED, SAS 9.1; SAS Inc, Cary, NC) was performed to investigate the main effects of the surgical procedure (3 levels), time, and the interaction between surgical procedure and time. When indicated by a significant F test, Bonferroni-adjusted post-tests for each group were conducted to the baseline (time = 0) value or between surgical procedures at each time. Primary variables of interest were indices of systemic stress (serum cortisol concentration) and surgical stress (serum IL-6 and CRP concentrations), and postoperative nociceptive threshold. A power analysis was conducted using freeware (Win Episcope 2.0; Facultad de Veterinaria, Zaragoza, Spain) based on published or anticipated mean and standard deviation values and an effect size of 50% reduction in maximum serum cortisol, IL-6, and CRP concentrations and a 50% increase in maximum postoperative nociceptor threshold. The power analysis indicated that 7 to 10 dogs per group would provide adequate power ($\beta = .80$) for $\alpha = .05$. Spearman's correlation coefficient (r_s) was used to explore the relationship between serum IL-6 and cortisol concentrations.

RESULTS

Table 1 summarizes the comparative results of this study. Body weights were similar for dogs in all 3 groups (NOTES 21.7 ± 10.5 kg; laparoscopic 18.8 ± 4.4 kg; open 20.4 ± 3.8 kg). The NOTES procedures were performed first in 10 animals to expedite scheduling. The laparoscopic and open procedures were then performed in 20 animals in a randomized manner. The operating time for the NOTES procedure was significantly longer ($P < .001$) than the that of the other 2 procedures. All the procedures were completed successfully with complete removal of both ovaries, as confirmed by visual inspection by a veterinary pathologist (P.S.). There were no significant operative complications in any of the animals. There was no evidence of hemorrhage at any of the ovarian sites and no areas of iatrogenic trauma from introduction of surgical instruments. Four animals in the NOTES group required multiple attempts to remove the ovary and when this occurred, the operating time was longer by approximately 9 minutes per ovary. The NOTES animals also experienced short periods (ie, <1 minute) in which the intra-abdominal pressure exceeded the preset threshold because of excessive air insufflation. The zone of coagulation around the electrosurgical sites was 1 to 2 mm wider than that with the harmonic scalpel. There was no coagulation around the ligatures. All the animals recovered from surgery and sampling, and 72-hour follow-up was available for all but 1 animal in the NOTES group that was excluded from monitoring because of handling issues.

Physiologic parameters and clinical findings

All the monitoring was done by trained veterinary technicians. Physiologic parameters measured before surgery (baseline) and at the designated time points after surgery were all within normal limits, except for hypothermia (temperature <37.8°C) during postoperative recovery (Fig. 1). Other physiologic parameters remained in the expected range of normal values for

TABLE 1. Results of comparative study of NOTES, laparoscopic, and open oophorectomy in dogs

	NOTES (n = 9 or 10)	Laparoscopic (n = 10)	Open (n = 10)
Body weight (kg)	21.7 ± 10.5	18.8 ± 4.4	20.4 ± 3.8
Operative results			
Insufflation gas	Air and CO_2	CO_2	None
Ligation means	Monopolar electrosurgery	Harmonic scalpel	Suture ligature
Median operating time (min)	76* (range 41-136)	44 (range 35 -65)	35 (range 25-65)
Intraoperative complications	Wider zone of coagulation; multiple attempts to remove ovaries in 4 animals	None	None
Physiologic parameters			
Rectal temperature (Fig. 1)	Hypothermia after surgery; WNL†	Hypothermia after surgery; WNL†	Hypothermia after surgery; WNL‡
Heart rate	WNL	WNL	WNL
Respiratory rate	WNL	WNL	WNL
Blood pressure	WNL	WNL	WNL
Time to first defecation (h)	9† (range 3-12)	18† (range 3-72)	42‡ (range 1-72)
Metabolic response			
Cortisol (Fig. 2)	Increased from baseline at 2 h†	Increased from baseline at 2 h‡	Increased from baseline at 2 h†
Glucose (Fig. 3)	Increased from baseline at many time points	Increased from baseline at many time points	Increased from baseline at many time points
Surgical stress markers			
IL-6 (Fig. 4)	Increased at 2, 6, 12 hours compared with baseline†	Not significantly increased over baseline	Not significantly increased over baseline
C-reactive protein (Fig. 5)	Lower at baseline than the other groups, increased after surgery	Not significantly increased over baseline	Not significantly increased over baseline
Pain evaluation			
Cumulative pain score (Fig. 6)	0.0-1.8	0.9-2.9	1.3-2.9
Nociceptive threshold (Fig. 7)	Decreased from baseline after surgery; tolerated significantly higher pressures at 18 h	Decreased from baseline after surgery	Significantly lower from baseline at all times after surgery

WNL, within normal limits.
*the operating time for the NOTES procedure was significantly longer ($P < .001$) than that of the other 2 procedures.
†,‡significant differences shown by different character designation across rows.

dogs, with no differences between groups (data not shown). All the animals ate 6 to 12 hours after surgery and began to be interested in their environment at 12 hours after surgery. The time to first defecation was shorter ($P = .005$) for the NOTES group than for the open group and tended to be shorter ($P = .063$) for the NOTES group than the laparoscopic group. All of the dogs were considered to have returned to their normal activity levels by 36 hours, and there were no wound complications evident by the end of the study.

Systemic stress parameters

The animals undergoing NOTES procedures had greater elevations in serum cortisol at the 2-, 4-, and 36-hour periods than those undergoing a laparoscopic procedure (Fig. 2). When all data were considered,

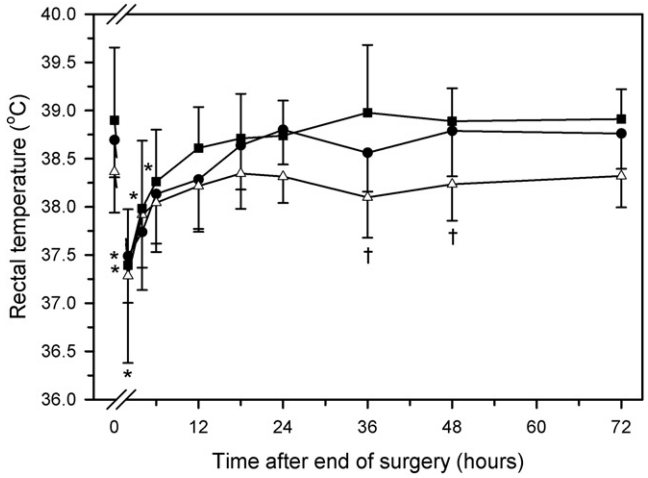

Figure 1. Rectal temperature in dogs undergoing bilateral oophorectomy with NOTES, laparoscopic, and open surgical approaches (10 dogs per group). Data are mean ± standard deviation. NOTES procedure (**open triangles)**, laparoscopic surgery (**solid circles**), and open laparotomy (**solid squares**). *Significantly different from time = 0 value within a group. †NOTES procedure significantly different from open procedure at the same time point. At 36 and 48 hours after surgery, the dogs undergoing NOTES procedures had significantly lower body temperatures than the dogs undergoing an open procedure.

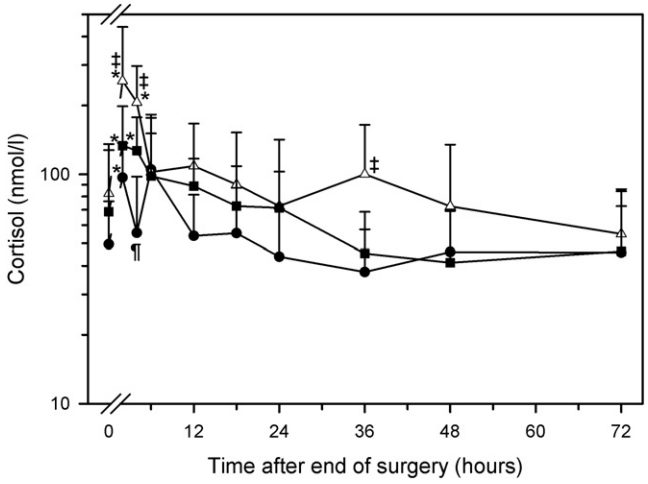

Figure 2. Serum cortisol concentrations in dogs undergoing bilateral oophorectomy with NOTES, laparoscopic, and open surgical approaches (10 dogs per group). Data are mean ± standard deviation. NOTES procedure (**open triangles**)**,** laparoscopic surgery (**solid circles**), and open laparotomy (**solid squares**). *Significantly different from time = 0 value within a group. ‡NOTES procedure significantly different from open procedure at the same time point. ‡NOTES procedure significantly different from laparoscopy procedure at the same time point.

there was a weak but significant correlation between serum IL-6 and cortisol concentrations ($r_s = +0.24$, $P = .0006$). Although serum glucose concentrations were significantly increased at many time points after surgery, there were no statistically significant differences between groups (Fig. 3).

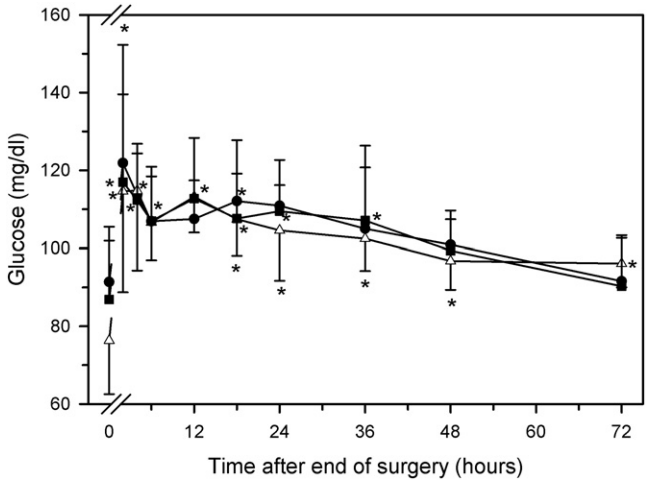

Figure 3. Serum glucose concentration in dogs undergoing bilateral oophorectomy with NOTES, laparoscopic, and open surgical approaches (10 dogs per group). Data are mean ± standard deviation. NOTES procedure (**open triangles**), laparoscopic surgery (**solid circles**), and open laparotomy (**solid squares**). *Significantly different from time = 0 value within a group.

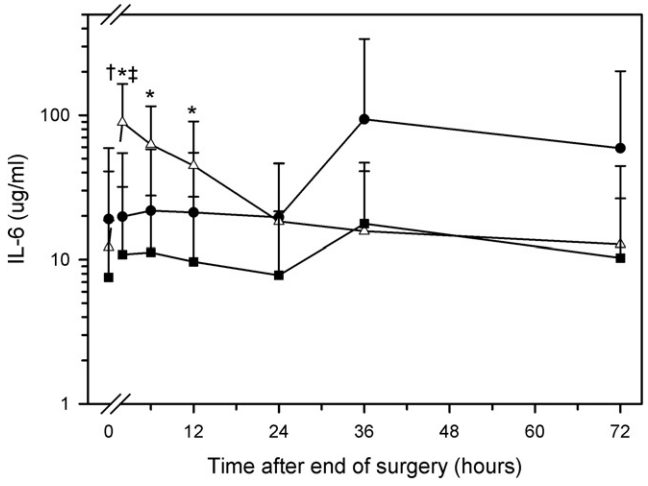

Figure 4. Serum IL-6 concentrations (logarithmic scale) in dogs undergoing bilateral oophorectomy with NOTES, laparoscopic, and open surgical approaches (10 dogs per group). Data are mean ± standard deviation. NOTES procedure (**open triangles**)**,** laparoscopic surgery (**solid circles**), and open laparotomy (**solid squares**). *Significantly different from time = 0 value within a group. †NOTES procedure significantly different from open procedure at the same time point. ‡NOTES procedure significantly different from laparoscopy procedure at the same time point.

Surgical stress markers

IL-6 was increased more in the NOTES group than the other 2 groups at 2 hours (Fig. 4). For unknown reasons, the serum CRP concentrations were lower in the NOTES group at baseline than the other 2 groups and increased after surgery in the NOTES group (Fig. 5).

Pain evaluation

Table 2 lists the median and range of pain scores for each group of animals postoperatively. None of the ani-

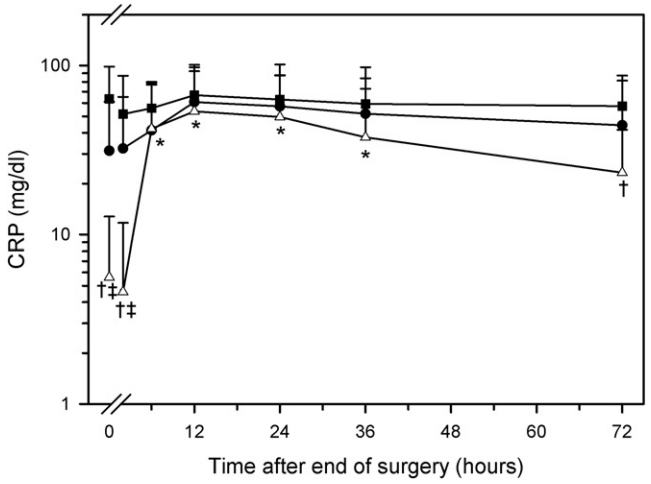

Figure 5. Serum CRP concentrations in dogs undergoing bilateral oophorectomy with NOTES, laparoscopic, and open surgical approaches (10 dogs per group). Data are mean ± standard deviation. NOTES procedure (**open triangles**), laparoscopic surgery (**solid circles**), and open laparotomy (**solid squares**). *Significantly different from time = 0 value within a group. †NOTES procedure significantly different from open procedure at the same time point. ‡NOTES procedure significantly different from laparoscopy procedure at the same time point.

mals had a pain score requiring additional postoperative analgesia (ie, >10 of a possible 27) at any time after surgery (Fig. 6). When the pain scores were examined for the relative contributions of posture, vocalization, mental status, and palpation, it seemed that the palpation score was the most sensitive measure of pain in these animals (data not shown). The NOTES group had the lowest pain scores at all postoperative intervals. The animals undergoing open surgery had significantly lower nociceptive thresholds at all times after surgery. The animals in the NOTES group tolerated significantly higher pressures at 18 hours than the open group (Fig. 7).

DISCUSSION

NOTES oophorectomy requires skill in performing flexible endoscopy and using endoscopic instruments through dual working channels. By using the same surgical team and a standardized approach to the NOTES procedure, we determined that when we used existing equipment, the estimated asymptotic operating time had been reached before beginning this study.[11] One limitation of this study was that different techniques were used for ovarian pedicle ligation and for insufflation of the abdominal cavity. A wider zone of coagulation injury was seen with the NOTES technique and could have influenced the results of this study.[12,13]

More rapid return of GI motility was seen postoperatively in the NOTES group compared with the open group. Other studies also demonstrate earlier recovery of bowel motility with laparoscopic compared with open procedures.[14-19] Time to first defecation and mouth to anus transit times have been previously shown to be shorter in dogs undergoing laparoscopic surgery compared with open partial pancreatectomy.[20]

Metabolic response

The metabolic response to surgery has been studied by measuring serum glucose and cortisol concentrations. The magnitude of the metabolic response is thought to be attributed to the perception of pain because of the magnitude of surgical trauma, with cortisol concentrations increasing after the start of surgery and increasing to a maximum at 4 to 6 hours.[21-23] In this study, all groups had increased glucose concentrations from their respective baseline after surgery, lasting for at least 36 hours, but there were no significant differences in mean serum glucose concentrations in any of the groups. These observations are consistent with our feasibility study and observations by others.[9-10,23] In this study, cortisol concentrations were significantly more increased in the animals undergoing NOTES procedures at the 2-, 4-, and 36-hour time periods than those undergoing open and laparoscopic procedures. The higher cortisol concentrations in the NOTES animals can potentially be explained by pneumoperitoneum with higher intra-abdominal pressures,[23] longer operating times,[24] or differences in thermal injury.[12,13,25]

Systemic stress response

IL-6 is a cytokine and CRP is an acute-phase protein initiated by surgical trauma, and plasma concentrations may be an effective measure of the extent of trauma.[26,27] IL-6 stimulates acute-phase protein production by the liver and has been shown to increase shortly after major abdominal surgery and peaking in 24 hours.[22,27,28] Therefore, CRP is affected by IL-6. In this study, compared with baseline, IL-6 was increased at 2, 6, and 12 hours in the NOTES group, but not in the open and laparoscopic groups, with IL-6 being higher in the NOTES group than the other 2 groups at the 2-hour time point. Increases in IL-6 have been demonstrated in experimental models with exposure of the peritoneum to atmospheric air, with increased surgical time and with incisions made in the peritoneum.[27,28] Previous studies comparing IL-6 concentrations and other mediators of inflammation after open and laparoscopic surgery have yielded conflicting results, with some showing less increase in IL-6 after laparoscopic surgery and others showing no differences.[29-31] Previous studies comparing NOTES with laparoscopic and open surgery in swine did not evaluate IL-6 at the early time points, and no differences were detected.[2,4] Our findings that IL-6 was significantly increased from baseline at 2, 6, and 12 hours in the NOTES group only are consistent with IL-6 being an early indicator of inflammation and tissue injury.[28-30] Previously, others demonstrated a positive correlation between IL-6 concentration and cortisol in postsurgical patients,[32] and this finding was seen in our study also.

TABLE 2. Cumulative pain score in dogs undergoing bilateral oophorectomy with NOTES, laparoscopic, and open surgical approaches (10 dogs per group)

	2 h	4 h	6 h	12 h	18 h	24 h	36 h	48 h	72 h
NOTES	0 (0-3)*	2 (0-4)	1 (0-6)*	0(0-2)*	0 (0-2)*	0 (0-2)*	0 (0-2)*	0 (0-2)*	0*
Lap	2 (0-4)†	2.5 (0-5)	2.5 (0-4)†	2.5 (1-6)†	1.5 (0-4)*	1 (0-3)†	1 (0-3)*	1 (0-3)†	1 (0-2)*
Open	2 (0-5)†	3 (0-4)	3 (2-4)†	3 (1-5)†	2 (1-4)†	1 (0-5)†	1.5 (0-3)†	1 (0-3)†	1.5 (0-3)†

Lap, Laparoscopy; *NOTES*, natural orifice transluminal endoscopic surgery.
Observations were made at 2, 4, 6, 12, 18, 24, 35, 48, and 72 hours after surgery. Data are median (range) of scores. Baseline pain score for all 3 groups was 0.
Values within a column with the same character designation (*,†) are not significantly different at a 0.05 significance level.

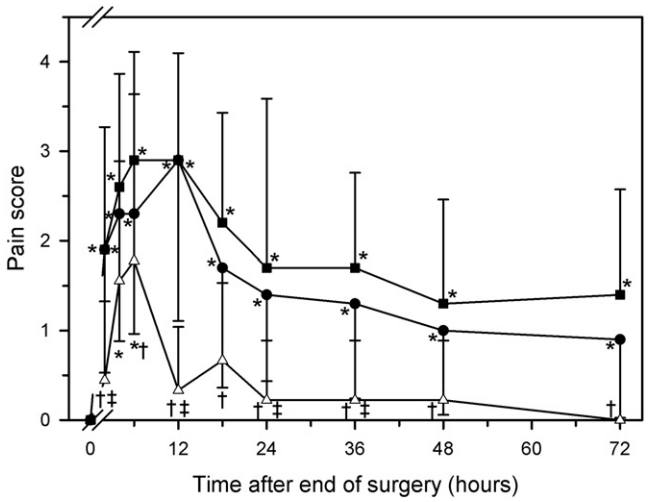

Figure 6. Pain scores in dogs undergoing bilateral oophorectomy with NOTES, laparoscopic, and open surgical approaches (10 dogs per group). Data are mean ± standard deviation. NOTES procedure (**open triangles**), laparoscopic surgery (**solid circles**), and open laparotomy (**solid squares**).*Significantly different from time = 0 value within a group. †NOTES procedure significantly different from open procedure at the same time point. ‡NOTES procedure significantly different from laparoscopy procedure at the same time point.

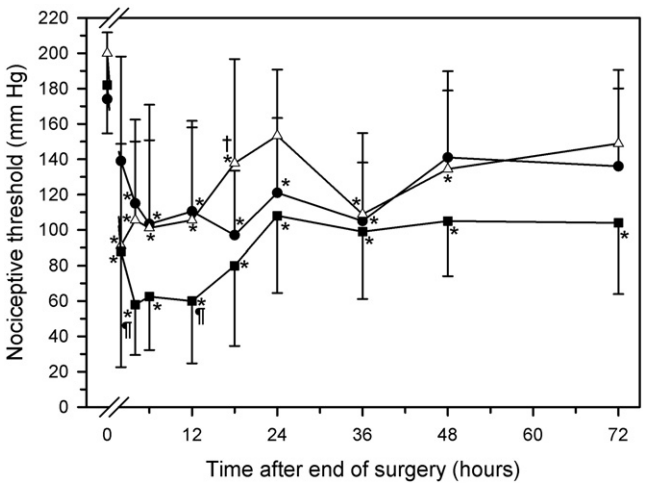

Figure 7. Mean nociceptive threshold values in dogs undergoing bilateral oophorectomy with NOTES, laparoscopic and open surgical approaches (10 dogs per group). Data are mean ± standard deviation. NOTES procedure (**open triangles**), laparoscopic surgery (**solid circles**), and open laparotomy (**solid squares**). *Significantly different from time = 0 value within a group. †NOTES procedure significantly different from open procedure at the same time point. ¶Open procedure significantly different from laparoscopy procedure at the same time point.

Serum CRP concentration in all animals and groups followed a trend of increasing after surgery to a peak at 12 hours and then decreasing. Cruickshank et al[33] reported on trends in IL-6 and CRP production after surgery in humans and showed that CRP increased 8 to 12 hours after the incision and peaked at 24 to 48 hours. Concentrations were weakly correlated with the duration of surgery. Compared with baseline, serum CRP was significantly increased in the NOTES group from 6 to 72 hours and in the laparoscopic group at 12 hours. These values followed the trend seen in our previous study[10] and in other studies involving ovariohysterectomy procedures in dogs.[34]

Pain evaluation

Physiologic parameters, the pain score, and nociceptive threshold were used to evaluate postoperative pain. Although the pain scores were lower than previously reported in other studies, they follow the trend seen in minimally invasive procedures being associated with less pain.[9,35] With the palpation score accounting for the largest difference among the groups, there was close agreement with the use of the nociceptive threshold to evaluate and measure pain. The NOTES animals had a significantly higher nociceptive threshold at 18 hours than the open group, indicating that these animals experienced less postoperative pain than the animals undergoing open surgery, consistent with the findings of other studies.[9,10]

CONCLUSION

NOTES oophorectomy in dogs results in minimal pain and postoperative stress, as evident by clinical and physiologic monitoring, including markers of surgical and systemic stress. Although operating times are longer, the

results of the study reported here suggest that NOTES procedures may be less painful and thereby enable a faster recovery time. Additional studies in a larger number of cases seem indicated.

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