



Canine Research

Effect of levobupivacaine, administered intraperitoneally, on physiological variables and on intrasurgery and postsurgery pain in dogs undergoing ovariohysterectomy



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ABSTRACT

The aim of this study was to evaluate intraoperative and postoperative efficacy and cardiovascular effects of levobupivacaine compared with bupivacaine, administered intraperitoneally in dogs undergoing ovariohysterectomy surgery. Thirty female dogs were divided into three groups B, L, and E, each comprising ten subjects. All subjects received 5 mcg kg⁻¹ dexmedetomidine and 0.3 mg kg⁻¹ methadone intramuscularly, 4 mg kg⁻¹ propofol intravenously, and isoflurane after intubation. After laparotomy, 2.5 mg kg⁻¹ bupivacaine (B group), 2.5 mg kg⁻¹ levobupivacaine (L group), and 0.9% saline solution (E group) were sprayed on ovarian stalks and on the neck of the uterus. Heart rate, respiratory rate, hemoglobin saturation (SpO₂), noninvasive systolic blood pressure, carbon dioxide at the end of expiration (ETCO₂), and concentration of inspired isoflurane were recorded. Evaluation of intraoperative analgesia was performed with a cumulative pain scale, whereas evaluation of postoperative analgesia was performed using the University of Melbourne Pain Scale. Intraoperative analgesia was significantly different among the groups $P = 0.000$; L group scores were lower than groups B and E. Total pain score, during the 24 hours after extubation, was significantly different between the groups. In fact, in groups B and L, scores were statistically lower than group E. In our study, there were no differences in anesthetic power between the two local anesthetics. No patients manifested side effects. Intraperitoneal anesthesia, with levobupivacaine represents an effective and safe method to control intraoperative and postoperative pain in abdominal surgery.

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Introduction

In pets and humans, the use of local anesthetics is widespread: ropivacaine, mepivacaine, bupivacaine, and its racemic form, levobupivacaine, are new generation anesthetics used alone or in combination with anesthetic drugs, analgesics, and opioids as a supplement to general anesthesia. They are usually administered epidurally, intrarticularly, perineurally, or intraperitoneally to create a better multimodal intraoperative and postoperative analgesia (Agarwal et al., 2017; Bartel et al., 2016; Bidika et al., 2017;

Cerasoli et al., 2017; Gao et al., 2017; Hashimoto et al., 2010; Kalchofner Guerrero et al., 2016; Rausch-Derra et al., 2016; Shaikh et al., 2017; Wall et al., 2017).

Intraperitoneal anesthesia is an economic, effective, and safe method for controlling intraoperative and postoperative pain in abdominal surgery (Jairath et al., 2017).

Levobupivacaine, the left isomer of bupivacaine, is a long-acting local anesthetic that has shown lower toxicity on the central nervous system and cardiovascular system in cases of overdose or involuntary intravascular injections, although its anesthetic power is slightly lower than that of bupivacaine (Gürbüz et al., 2016; Wang et al., 2017). This local anesthetic is widely used in humans and dogs in epidural and locoregional anesthesia; however, in domestic animals, there are no bibliographic data on the use of levobupivacaine applied intraperitoneally (Das and Deshpande, 2017; Gvozdenović et al., 2015; Honca et al., 2014; Kalchofner et al., 2016;

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Rivard et al., 2015). The aim of this study is to evaluate intra-operative and postoperative efficacy and cardiovascular effects of levobupivacaine compared with bupivacaine, administered intraperitoneally in dogs undergoing ovariohysterectomy.

Methods

The study was approved by the University of Messina Review Board for Animal Care. Experiments were performed in accordance with Italian law (D.M. 116192), European law (O.J. of E.C. L 358/1 12/18/1986), and US laws (Animal Welfare Assurance No A5594-01, Department of Health and Human Services, USA). Moreover, informed consent was obtained from the owners of each dog.

Thirty dogs were registered at the veterinary teaching hospital of the Veterinary Science Department, University of Messina, in the morning on the day of ovariohysterectomy and examined the following: mucous membrane color, heart rate, respiratory rate, systolic blood pressure, rectal temperature, and complete blood count. The patients were chosen for their docile temperament and for absence of pain signs on abdominal palpation. They were divided into three groups of ten subjects: the treatment to be administered to each group—B, L, or E—was decided by a lottery.

All the subjects were premedicated with 5 mcg kg⁻¹ dexmedetomidine (Dexdomitor 0.5%; Pfizer, Italy) and 0.3 mg kg⁻¹ methadone (Eptadone 1%; Molteni, Italy) intramuscularly.

After sedation, a venous catheter was inserted in the cephalic vein and lactated Ringer's solution was administered (10 mL kg⁻¹ hr⁻¹). Anesthesia was induced with propofol 4 mg kg⁻¹ (Proposure 1% Merial Italia), and maintained with isoflurane in oxygen (Isoflò Esteve Spagna) after endotracheal intubation. After laparotomy, 2.5 mg kg⁻¹ of bupivacaine (Bupivacaina 0.25% Angelini Italia) in B group, 2.5 mg kg⁻¹ of levobupivacaine (Chirocaina 0.5% Abbott Italia) in L group, and 0.9% saline solution (10 mL) in E group were

sprayed on ovarian pedicles, on the neck of the uterus, and in the rest of the peritoneum. Five minutes after the administration of local anesthetic or saline solution, the surgeon removed the ovaries and the uterus, and after closure of the laparotomy incision and suture of the skin, isoflurane was stopped.

Heart rate (HR), respiratory rate (RR), and noninvasive systolic blood pressure (SAP) were recorded with the animal awake (baseline values), and after premedication, intubation—skin incision, traction of the ovarian pedicles, ligation of the cervix, and suture of the skin. After intubation, hemoglobin saturation (SpO₂), carbon dioxide at the end of expiration (ETCO₂), and concentration of inspired isoflurane (CI) were also recorded at the same time points.

Evaluation of intraoperative analgesia was performed with a cumulative pain scale by giving a score based on percentage variations of HR, RR, and SAP, compared with the values recorded after skin incision, according to the following scheme:

- 0 ≤ 0%
- 1 ≥ 0% but ≤ 10%
- 2 ≥ 10% but ≤ 20%
- 3 ≥ 20% but ≤ 30%
- 4 ≥ 30%

The sum of the scores gave us the total score. We have established that if total score was ≥ 10, a bolus of 2 mcg kg⁻¹ of fentanyl (Fentadon 50 mcg ml⁻¹ Dechra) was given as rescue analgesia. The choice of this cut off point was based on the evaluation that if a subject shows an increase between 20% and 30% or greater of the three parameters (HR, RR, SAP) at the same time, it was indicative of severe pain.

Evaluation of postoperative analgesia was performed using the University of Melbourne Pain Scale (Hellebrekers, 2000, pp 59–64). This pain scale rating included six categories defined by physiological data (heart rate, respiratory rate, rectal temperature), response to palpation, activity, mental state, posture and

Table 1

Physiological parameters and concentration of inspired isoflurane after administration of 5 mcg kg⁻¹ dexmedetomidine, 0.3 mg kg⁻¹ eptadone IM, and 4 mg kg⁻¹ propofol (groups B, E, L)

Measured data	Group	B	SD	Time I	IS	TP	LC	SS	P =
Mean ± SD	B	150 ± 37	99 ± 20 ^a	75 ± 8 ^a	81 ± 4 ^a	72 ± 3 ^{a,b}	66 ± 10 ^{a,b}	95 ± 23 ^a	0.000
	E	138 ± 34	89 ± 14 ^a	78 ± 10 ^a	78 ± 4 ^a	94 ± 5 ^{a,b}	95 ± 4 ^{a,b}	83 ± 7 ^a	0.000
HR beats/min	L	149 ± 33	100 ± 18 ^a	76 ± 4 ^a	85 ± 4 ^a	85 ± 3 ^a	85 ± 1 ^a	100 ± 14 ^a	0.000
RR breaths/min	B	43 ± 4	20 ± 1 ^a	11 ± 1 ^a	10 ± 1 ^a	11 ± 3 ^a	12 ± 2 ^{a,b}	10 ± 1 ^a	0.000
	E	45 ± 3	23 ± 2 ^a	9 ± 1 ^a	11 ± 1 ^a	36 ± 4 ^{a,b}	40 ± 5 ^{a,b}	11 ± 2 ^a	0.000
	L	44 ± 5	22 ± 2 ^a	10 ± 1 ^a	12 ± 1 ^a	11 ± 2 ^{a,b}	10 ± 1 ^{a,b}	12 ± 2 ^a	0.000
NIBP mm Hg	B	143 ± 9	142 ± 38	156 ± 34	130 ± 26	152 ± 25 ^b	159 ± 34 ^b	128 ± 22	0.001
	E	147 ± 13	164 ± 20	158 ± 33	130 ± 53	165 ± 32 ^b	170 ± 29 ^b	130 ± 24	0.000
SAP	L	145 ± 10	149 ± 34	163 ± 27	137 ± 23	152 ± 20 ^b	157 ± 33 ^b	129 ± 24	0.000
ETCO ₂ %	B			36 ± 4	34 ± 3	36 ± 2 ^b	36 ± 4 ^b	34 ± 2	0.018
	E			34 ± 2	36 ± 2	48 ± 5 ^{a,b}	40 ± 3 ^{a,b}	42 ± 3 ^a	0.000
	L			35 ± 3	32 ± 3 ^a	34 ± 2 ^{a,b}	35 ± 3 ^b	36 ± 2	0.000
CI%	B			3 ± 0	2.3 ± 1 ^a	1.5 ± 0.1 ^{a,b}	1.5 ± 0.2 ^{a,b}	2 ± 0.2 ^a	0.000
	E			3 ± 0	2.2 ± 0.5 ^a	2.8 ± 1	3 ± 0.1	2 ± 0.1 ^a	0.000
	L			3 ± 0	2.3 ± 0.2 ^a	1.6 ± 0.2 ^{a,b}	1.5 ± 0.1 ^{a,b}	2 ± 0.2 ^a	0.000
SpO ₂ %	B			100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0	0.000
	E			98 ± 2	98 ± 1	99 ± 1 ^a	99 ± 1 ^a	98 ± 2	0.000
	L			99 ± 1	98 ± 2 ^a	98 ± 2 ^a	97 ± 1	100 ± 0 ^a	0.000
TC ^c	B	39 ± 0	39 ± 0	39 ± 0	38 ± 0.5 ^a	38 ± 0.2 ^a	38 ± 0.1 ^a	38 ± 0	0.000
	E	39 ± 0	39 ± 0	39 ± 0	38 ± 0.3 ^a	38 ± 0.3 ^a	38 ± 0.3 ^a	38 ± 0.2 ^a	0.000
	L	39 ± 0	39 ± 0	39 ± 0	38 ± 0.5 ^a	38 ± 0.3 ^a	38 ± 0.2 ^a	38 ± 0.2 ^a	0.000

B, baseline; CI, concentration of inspired isoflurane; ETCO₂, carbon dioxide at the end of expiration; HR, heart rate; I, intubation; IS, incision skin; LC, ligation of the cervix; RR, respiratory rate; SpO₂, hemoglobin saturation; SAP, noninvasive systolic blood pressure; SD, administration of injectable anesthetics (dexmedetomidine eptadone); TP, traction of the ovarian pedicles; SS, suture of the skin.

Group B: 2.5 mg kg⁻¹ bupivacaine, group L: 2.5 mg kg⁻¹ levobupivacaine, group E: 10 mL 0.9% physiological solution, intraperitoneally administered.

^a Significant difference compared with the baseline.

^b Difference in each group during TP and LC compared with IC; P value changes with time in each group, changes between groups.

Table 2
Total score after intraperitoneal administration

Time	Score median and range	Groups	TP	LC	P =
		B	1 (0–4) ^b	2 (0–3) ^{a,b}	0.000
		E	3 (1–4) ^{b,c}	4 (1–4) ^{b,c}	0.000
		L	0 (0–2) ^c	0 (0–2) ^{a,c}	0.000
					0.000

LC, ligation of the cervix; TP, traction of the ovarian pedicles.

2.5 mg kg⁻¹ of bupivacaine group B; group L 2.5 mg kg⁻¹ of levobupivacaine; 10 mL of physiological solution 9% group E.

Evaluation of intraoperative analgesia was performed with a cumulative pain scale by giving a score based on percentage variations of HR, RR, and SAP, compared with the values recorded after skin incision, according to the following scheme.

0 ≤ 0%; 1 ≥ 0% but ≤ 10%; 2 ≥ 10% but ≤ 20%; 3 ≥ 20% but ≤ 30%; 4 ≥ 30%.

^a Significant difference between groups B and L.

^b Significant difference between groups B and E.

^c Significant difference between groups L and E, p difference between groups.

vocalization of the subject. Each of these categories contained descriptions of the various behaviors, to which numerical values were assigned. The observer, unaware of the treatment received by each patient, assigned scores for each category based on the dog's behavior. The sum of the scores of the individual categories determined the total score ranging from 0 up to a maximum of 27 points, corresponding to severe pain (Hellebrekers, 2000). Postoperative analgesia evaluation was performed immediately after extubation (time 0) and after I, II, III, IV, V, VI, XII, and XXIV hours. If the score exceeded 10 points additional analgesia was administered (methadone 0.2 mg kg⁻¹ IM).

Statistical analysis of data was performed using SPSS 15.0 (IBM Company, Italy): physiological data, expressed with mean ± standard deviation, were compared with two-way ANOVA for repeated measures, followed by Bonferroni test; scores, expressed with median and range, were compared with Friedman test ($P < 0.05$).

Results

Heart rate decreased after premedication in all groups, while during pedicle traction and cervix ligation, compared to values at the skin incision, it decreased in B group, remained constant in L group and increased in E group.

Respiratory rate significantly decreased in all groups along the time line compared to baseline. However, throughout the surgical procedure, in B and L groups RR recorded values were not significantly different compared to values at skin incision, while in E group there was a significant increase.

Systolic pressure did not show significant differences compared to baseline values at any time during monitoring, in all groups. However, there was an increase in systolic pressure during traction of the pedicle and cervix ligation compared to the data recorded at the time of skin incision in all groups, more significant in E group

compared to the other two groups. (Group B: $P = 0.000$ – $P = 0.001$; Group E: $P = 0.000$ – $P = 0.000$; Group L: $P = 0.060$ – $P = 0.030$).

Carbon dioxide at the end of expiration (ETCO₂) rested in physiological ranges between 32% and 48% in all groups, with values in the E group higher than those in groups B and L during surgery.

Isoflurane requirements (CI%) were statistically lower in groups B and L during traction of the peduncle and cervix ligation compared to the isoflurane requirements at the time of skin incision ($P = 0.000$), while in group E isoflurane requirements were not statistically significant during traction of the peduncle and cervix ligation, compared with the isoflurane requirements at the time of skin incision ($P = 1.000$).

Hemoglobin saturation (SpO₂) was between 97%–100% in all groups.

Body temperature remained within a range of 38 to 39°C in all groups (Table 1).

Intraoperative analgesia was significantly different among the groups ($P = 0.000$), with L group scores lower than groups B and E (Table 2).

The total pain score, during the 24 hours after extubation was significantly different among groups. In fact, in B and L groups scores were statistically lower than in E group ($P = 0.000$) (Table 3).

Discussion

The analgesia scores recorded in our study for group E show that anesthesia performed with dexmedetomidine, methadone, propofol and isoflurane provided intraoperative and postoperative analgesia. No patient received additional analgesic drugs. However, in the groups treated with bupivacaine and levobupivacaine, in addition to the basic protocol (B and L groups), HR, RR, and SAP were statistically lower than in the control group (E group) during

Table 3
University of Melbourne Pain Scale (0–27 points).

Group	Extubation	Hour							
		I	II	III	IV	V	VI	XII	XXIV
Group E	2 (1–3) ^b	3 (3–3) ^{a,b}	3 (3–6) ^{a,b}	3 (3–6) ^{a,b}	5 (4–6) ^{a,b}	5 (4–6) ^{a,b}	5 (4–6) ^{a,b}	7 (6–8) ^{a,b}	7 (6–8) ^{a,b}
Group B	0 (0–0)	1 (0–3) ^a	1 (1–4) ^a	1 (1–4) ^a	2 (1–3) ^a	3 (1–3) ^a	3 (1–4) ^a	3 (1–4) ^a	3 (1–4) ^a
Group L	0 (0–0)	1 (0–3) ^a	1 (1–3) ^a	1 (1–3) ^a	2 (1–3) ^a	2 (1–3) ^a	3 (1–4) ^a	3 (1–4) ^a	3 (1–4) ^a

University of Melbourne Pain Scale (0–27 points): from 0 to 4 total score, pain is considered minimal; from 4 to mean 8 total score, pain is considered moderate. We considered a total point score ≥ 10 appropriate to use as cutoff, exceeded which rescue analgesia was administered.

^a Statistically significant difference from time 0.

^b Statistically significant difference between the three groups University of Melbourne Pain Scale scores, expressed in median and range, obtained after ovarian hysterectomy, with intraperitoneally administration of saline 10 mL (group E), bupivacaine 2.5 mg kg⁻¹ (group B), and levobupivacaine 2.5 mg kg⁻¹ (group L). ($P < 0.05$) Hour after extubation.

pedicle traction and cervix ligation. Cumulative intraoperative pain scores and isoflurane concentration used were lower in the two groups receiving local anesthetic. We have decided to administer rescue analgesia when cutoff point of ≥ 10 , corresponding to an increase of HR, RR, and SAP between 20% and 30% or more, is occurred. In our knowledge, for the intraoperative pain evaluation, there does not exist a scientific accordance that established a cutoff point, exceeding which rescue analgesia is administered. In two recent studies, cutoff point was subjectively established. Caniglia et al. 2012 have used a cut-off point $> 10\%$, whereas for Portela et al. 2013, the cutoff point was $> 25\%$.

Postoperative analgesia scores were higher in E group compared with B and L groups; in these latter two groups, the scores were superimposable. The dosage of bupivacaine used in our study was lower than dosages intraperitoneally used by other authors in dogs (Kalchofner Guerrero et al., 2016), but the pain scores recorded in our study were low. No patients manifested side effects with the combination of the drugs used (intraperitoneal levobupivacaine or bupivacaine and methadone).

A limitation of our study is the subjective evaluation of intraoperative and postoperative analgesia that was performed with point scales. Evaluation of postoperative analgesia was performed using the University of Melbourne Pain Scale (0–27 points): from 0 to 4 total score, pain is considered minimal; from 4 to mean 8 total score, pain is considered moderate (Firth 1999). We considered a total point score ≥ 10 appropriate to use as cutoff, exceeding which rescue analgesia was administered.

A possible method for measuring analgesia in an objective way is electroencephalographic entropy determination, but we do not have the equipment (Mahidol et al., 2015).

Conclusions

Levobupivacaine, a long-acting local anesthetic, was developed as an alternative to bupivacaine, which can lead to severe toxic phenomena. It is the pure left isomer of bupivacaine and, thanks to its three-dimensional structure, it appears to have a low toxic potential on the central nervous system and cardiovascular system (Gürbüz et al., 2016; Wang et al., 2017).

Despite the slight difference in anesthetic strength (bupivacaine racemic $>$ levobupivacaine), our study did not show any difference in anesthetic power between the two drugs; consequently the use of levobupivacaine may be preferable in those cases where there is a risk of systemic toxicity overdose or accidental intravascular injection (Gürbüz et al., 2016; Wang et al., 2017).

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Ethical Considerations

The study was approved by the University of Messina Review Board for Animals Care. Experiments were performed following Italian law (D.M. 116192), Europe law (O.J. of E.C. L 358/1 12/18/1986), and USA laws (Animal Welfare Assurance No A5594-01, Department of Health and Human Services, USA). Moreover, the owners of each dog were informed about the study and signed a consent.

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