Research Article

Title: Effects of epidural, spinal, and combined spinal-epidural anesthesia on cardiorespiratory variables and postoperative analgesia in dogs undergoing ovariohysterectomy

Authors: Maedeh Javaheri [a], Hadi Imani Rastabi [a*], Masoumeh Ezzati Givi [b], Bahman Mosallanejad [a]

[a] Department of Clinical Sciences, Faculty of Veterinary Medicine, Shahid Chamran University of Ahvaz, Ahvaz, Iran.
[b] Department of Basic Sciences, Faculty of Veterinary Medicine, Shahid Chamran University of Ahvaz, Ahvaz, Iran.

Corresponding author: Hadi Imani Rastabi
Postal address: Faculty of Veterinary Medicine, Shahid Chamran University of Ahvaz, Ahvaz, Iran
Email: h.imani@scu.ac.ir
ORCID ID: 0000-0002-1564-7240
Tel. number: +98 9133823324

Running (short) title: Combined spinal-epidural anesthesia in dogs

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Abstract

Epidural and spinal anesthesia are frequently used in small animals, although they may also cause undesirable side effects. A combined spinal-epidural approach might reduce individual drug doses and yield more favorable outcomes. This prospective, randomized, blinded study **c**ompared the cardiorespiratory effects and analgesic efficacy of epidural, spinal, and a combined spinal-epidural technique in dogs undergoing ovariohysterectomy. Nineteen healthy mongrel dogs were premedicated with acepromazine and morphine, induced (6 mg/kg) and maintained (0.4 mg/kg/min) with propofol. Dogs then received bupivacaine through epidural (1 mg/kg with a final volume of 0.35 mL/kg, n = 6), spinal (0.22 mg/kg with a final volume of 0.16 mL/kg, n = 7), or a combined epidural and spinal anesthesia (n = 6).

For the Combination, equal volumes and half the doses were used. Physiologic variables, recovery times, and pain scores were recorded at predetermined intervals. In all groups, heart rate increased during surgery, while mean arterial pressure decreased below baseline at several time points. Pain scores did not differ significantly among treatments, and all three techniques provided acceptable perioperative analgesia. Postoperatively, rescue fentanyl was administered to two dogs in the spinal group and two in the Combination group, with no significant difference among groups. Shorter times to head elevation and standing were observed in the Combination group compared with the epidural group. Overall, the combined spinal-epidural approach may provide comparable cardiorespiratory stability with effective analgesia and faster recovery, proposing it as a useful option for dogs undergoing ovariohysterectomy.

Keywords
Bupivacaine, Dog, Epidural anesthesia, Ovariohysterectomy, Spinal anesthesia

Abbreviations

Epidural anesthesia: EA

Spinal Anesthesia: SA

Heart rate: HR,

Respiratory rate: f_R

Rectal temperature: RT

Systolic arterial pressures: SAP

Diastolic arterial pressure: DAP

Mean arterial pressure: MAP

Visual Analogue Scale: VAS

University of Melbourne Pain Scale: UMPS

The short form of the Glasgow Composite Measure Pain Scale: CMPS-SF

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Introduction

Neuraxial anesthesia encompasses epidural and spinal anesthesia (EA and SA, respectively), which are administered to deliver highly effective localized anesthesia and analgesia in small animals [1]. EA and SA methods have been demonstrated to lower anesthetic requirements, eliminate muscle tone, and promote a quicker recovery from surgery [2]; they are also effective in managing pain in non-surgical cases [3].

Studies have shown that EA is effective in posterior half-body surgeries, whether used alone or with other drugs, in dogs [4-7]. However, incomplete and inefficient analgesia may result from the fat deposits within the epidural space [2]. Hypotension resulting from sympathetic block has also been reported as a potential complication following EA [8]. SA has demonstrated advantages over EA, including adequate analgesia resulting from the drug's direct action on the spinal cord and decreased systemic absorption of anesthetics [9-12]. Nevertheless, bradycardia and hypotension are potential complications of SA in dogs [10].

Combining EA and SA may offer complementary advantages over either technique alone. The direct delivery of anesthetic into the cerebrospinal fluid with SA can provide a rapid and reliable onset of neuraxial blockade, whereas epidural administration may supplement and prolong analgesia through a different site and pattern of drug distribution. Thus, combining the two techniques may allow an adequate anesthetic and analgesic effect to be achieved while reducing the dose required through each route, potentially limiting dose-related adverse effects such as excessive sympathetic blockade and associated cardiovascular changes. In human patients, the combined technique has been associated with a faster onset of anesthesia and immobilization, a longer duration of action, and improved block quality [13, 14]. A case report has also described its effectiveness in providing high-quality intra- and postoperative analgesia during pelvic canal surgery in a dog [9].

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Since, to the authors' knowledge, no prior research has investigated how combined EA and SA influence physiological parameters and pain during and after dog surgeries, this study aimed to compare these anesthetic techniques individually and together in dogs undergoing ovariohysterectomy under general intravenous anesthesia with propofol.

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Results

All the dogs tolerated anesthesia procedures well, and no complications were observed during the 2-week follow-up, according to the shelter owner. Comparison of the animals' weights, the amount of propofol used for induction, the volume of injected anesthetic drug, the duration of anesthesia, and the duration of surgery (Table 1) did not reveal significant differences between the three groups ($p > 0.05$).

Table 1. Mean ± standard deviation of some evaluated parameters in dogs receiving epidural (EA; n = 6), spinal (SA; n = 7), or spinal-epidural anesthesia (Combination; n = 6) with bupivacaine, under total intravenous anesthesia with propofol in ovariohysterectomy.

	EA	SA	Combination	p Value
Weight (kg)	21.9 ± 5.5	18.9 ± 3.3	23.3 ± 3.3	0.1781
Amount of propofol used for induction (mL)	12.7 ± 4.7	10.0 ± 3.9	14.0 ± 2.0	0.1652
The volume of injected anaesthetic drug (mL)	7.2 ± 1.9	2.9 ± 0.3	8.1 ± 1.1 (EA) 3.6 ± 0.5 (SA)	-
Duration of anaesthesia (minutes)	90.0 ± 10.0	81.7 ± 13.7	93.0 ± 26.8	0.6125
Duration of surgery (minutes)	41.7 ± 5.8	40.7 ± 7.9	41.7 ± 5.8	0.2508

Intraoperative evaluations

Table 2 displays changes in HR, blood pressure, f_R, RT, SpO2, and EtCO2 values during anesthesia. No significant differences were observed among the groups for these parameters during anesthesia ($p > 0.05$).

Within-group assessment indicated that HR in all three groups at each assessed time point during anesthesia was significantly higher than baseline ($p \leq 0.0039$, $p \leq 0.0017$, $p \leq 0.0007$, respectively, for the EA, SA, and Combination treatments). SAP in the EA treatment was significantly lower than baseline at T0, T1, and T2 ($p \leq 0.0025$). Additionally, within the SA group, SAP at T0, T1, T2, and T4 ($p \leq 0.0010$) were significantly lower than the baseline. SAP in the Combination group was significantly lower than baseline at T0, T1, and T2 ($p \leq 0.0358$). DAP levels in the EA and SA groups were significantly lower than the baseline at multiple time points: T0, T1, T2, and T4 ($p \leq 0.0447$ and $p \leq 0.0023$, respectively). DAP levels were significantly lower in the Combination group at T0, T1, and T2 ($p \leq 0.0003$). MAP values in the EA and SA groups were significantly lower than the baseline at T0, T1, T2, and T4 ($p \leq 0.0002$). Regarding the Combination group, the measured MAP values at T0, T1, and T2 ($p \leq 0.0059$) were significantly lower than the baseline. Two dogs in EA developed transient hypotension (MAP below 60 mmHg), managed by increasing the crystalloid rate; no vasopressors were required. No hypotension was observed in SA or Combined groups.

f_R values in both EA and Combination treatments were lower than the baseline ($p = 0.0490$ and $p = 0.0007$, respectively) at all measured points during anesthesia. Concerning the RT in the EA, SA, and the Combination treatments, the measured values were significantly lower than the baseline at T1, T2, T3, and T4 time points ($p \leq 0.0159$). No other significant difference was observed in the intra-treatment assessment concerning the studied parameters during anesthesia ($p > 0.05$).

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Table 2. Mean ± standard deviation of changes in heart rate (HR), blood pressure (SAP, DAP, MAP), respiratory rate (f_R), rectal temperature (RT), oxygen saturation (SpO_2), and end-tidal carbon dioxide ($EtCO_2$) during before anesthesia (base), at five minutes before the beginning of surgery (T0), skin incision (T1), incision and opening of the abdominal muscles (T2), ligation of the uterine structures (T3), and skin suturing (T4)) in dogs receiving epidural (EA; n = 6), spinal (SA; n = 7), or spinal-epidural anesthesia (Combination; n = 6) with bupivacaine, under total intravenous anesthesia with propofol in ovariohysterectomy.

	Group	Base	T0	T1	T2	T3	T4
HR (beats minute^{-1})	EA	70 ± 13	111 ± 17†	112 ± 16†	117 ± 18†	125 ± 23†	132 ± 29†
	SA	86 ± 6	117 ± 6†	113 ± 12†	114 ± 17†	119 ± 24†	131 ± 13†
	Combination	74 ± 11	107 ± 13†	111 ± 16†	110 ± 18†	109 ± 21†	104 ± 18†
SAP (mmHg)	EA	109 ± 19	80 ± 11†	78 ± 13†	85 ± 17†	115 ± 21	99 ± 13
	SA	136 ± 8	90 ± 9†	93 ± 6†	92 ± 8†	136 ± 27	107 ± 6†
	Combination	133 ± 29	96 ± 23†	91 ± 22†	95 ± 25†	128 ± 32	128 ± 33
DAP (mmHg)	EA	70 ± 8	42 ± 3†	43 ± 13†	48 ± 14†	62 ± 13	56 ± 11†
	SA	85 ± 13	46 ± 3†	47 ± 8†	50 ± 7†	82 ± 17	63 ± 5†
	Combination	84 ± 18	47 ± 9†	50 ± 7†	54 ± 9†	71 ± 17	75 ± 17
MAP (mmHg)	EA	97 ± 11	57 ± 7†	57 ± 12†	67 ± 15†	90 ± 15	71 ± 9†
	SA	109 ± 11	63 ± 5†	64 ± 8†	63 ± 5†	99 ± 18	81 ± 6†
	Combination	107 ± 24	75 ± 16†	70 ± 6†	69 ± 9†	86 ± 18	87 ± 16
f_R (breaths minute^{-1})	EA	17 ± 2	9 ± 5†	13 ± 6†	12 ± 7†	11 ± 6†	11 ± 2†
	SA	15 ± 3	11 ± 5	12 ± 4	14 ± 5	16 ± 7	13 ± 5
	Combination	16 ± 4	9 ± 3†	8 ± 3†	10 ± 4†	8 ± 3†	7 ± 3†
RT (˚C)	EA	38.1 ± 0.4	37.6 ± 0.5†	37.6 ± 0.5†	37.5 ±0.6†	37.2 ± 0.6†	37.1 ±0.7†
	SA	38.8 ± 0.3	37.3 ± 0.5†	37.5 ± 0.2†	37.4 ± 0.1†	37.3 ± 0.2†	37.1 ± 0.5†
	Combination	38.7 ± 0.2	37.8 ± 0.4†	37.7 ± 0.4†	37.7 ± 0.4†	37.5 ± 0.4†	37.2 ± 0.4†
SpO_2 (%)	EA	-	97 ± 1	90 ± 3	95 ± 2	90 ± 3	93 ± 3
	SA	-	96 ± 3	97 ± 2	97 ± 2	94 ± 2	93 ± 5
	Combination	-	95 ± 3	93 ± 7	94 ± 3	95 ± 3	95 ± 4

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	EA	-	50 ± 1	51 ± 5	52 ± 5	52 ± 5	55 ± 9
$EtCO_2$ (mmHg)	SA	-	50 ± 3	50 ± 6	52 ± 2	51 ± 2	50 ± 7
	Combination	-	52 ± 5	47 ± 4	50 ± 4	47 ± 6	55 ± 2

†Significant difference compared to baseline ($p < 0.05$).

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Postoperative evaluations

1- Physiologic variables

Changes relating to physiologic variables in the postoperative period across all treatments are shown in Figure 1.

HR measurements in the Combination group were significantly lower at 15 and 30 minutes after surgery than the EA and SA treatments ($p = 0.0007$ and $p = 0.0108$ at the 15-minute time point, and $p = 0.0032$ and $p = 0.0017$ at the 30-minute time point, respectively). Moreover, HR values in the Combination treatment were significantly lower than in the EA group at 45 and 60 minutes after the end of ovariohysterectomy ($p = 0.0004$ and $p = 0.0017$, respectively). Intra-treatment evaluation revealed that the post-operation HR measurements were significantly higher than baseline values at various time points: in the EA group, at 15, 30, 45, 60 ($p \leq 0.0001$), and 75 minutes ($p = 0.0074$), in the SA treatment, at 15 and 30 minutes ($p \leq 0.0001$), and 45 minutes ($p = 0.0029$), and in the Combination treatment at 15 minutes after the end of surgery ($p = 0.0251$).

The SAP level was significantly lower in the SA group compared to the Combination group at the 15-minute time point ($p = 0.0251$). Furthermore, the measured SAP values at 60, 90, 150, and 180 minutes ($p \leq 0.0360$) after ovariohysterectomy were lower in the EA group compared to the Combination treatment. DAP levels in the EA group at 15, 30, 60, 75, 90, 120, 150, and 180 minutes ($p \leq 0.0418$) postoperatively were lower than in the Combination group. At 15 minutes post-operation, the DAP value in the Combination group was significantly higher

than in the SA group ($p < 0.0001$). The MAP values in the EA group were significantly higher than the Combination group at time points of 60, 75, 90, 120, and 180 minutes ($p \leq 0.0422$) after the surgery. Among the studied treatments, the SAP levels were significantly higher than the baseline at 300 minutes post-surgery in the EA group ($p = 0.0268$), at 240 minutes in the SA group ($p = 0.0052$), and at 120, 150, 240, and 270 minutes ($p \leq 0.0352$) in the Combination group. The MAP showed significant differences in the SA treatment at 15 minutes ($p = 0.0333$), and in the Combination treatment at 60, 90, 150, and 180 minutes ($p \leq 0.0393$). The MAP values were significantly higher compared to the baseline in the Combination group at 60, 75, 120, and 180 minutes ($p \leq 0.0498$).

Statistical analysis did not reveal any significant change in the f_R values both between and within the studied groups ($p > 0.05$). No significant differences in RT values were observed between the studied groups ($p > 0.05$). RT levels at time points 45 to 150 minutes in the EA group ($p \leq 0.0439$), 15 to 240 minutes in the SA treatment ($p \leq 0.0420$), and 15 to 120 minutes after surgery in the Combination group ($p \leq 0.0002$) were significantly lower than baseline.

2- Recovery times

The comparison of recovery times- including the reversal of the swallowing reflex, head elevation, sternal recumbency, and ability to stand- shown in Table 3, revealed no significant difference at the time of the swallowing reflex returning and when sitting on the sternum ($p > 0.05$). However, the times for head elevation and the ability to stand in the Combination group were significantly shorter than in the EA group ($p = 0.0335$ and $p = 0.0468$, respectively).

3- Pain assessments

The values associated with the pain scores are displayed in Figure 2.

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Comparison of the given VAS pain scores among the studied groups showed that, compared to the Combination group, the values were higher in the SA treatment 6 hours after the operation ($p = 0.0039$). Furthermore, it was observed that the VAS pain scores were significantly higher compared to baseline measurements in the EA and the Combination treatments at 3, 4, 5, and 6 hours ($p \leq 0.0313$) after surgery. In the SA treatment, the VAS pain scores were significantly higher than the baseline at 1, 2, 3, 4, 5, and 6 hours ($p \leq 0.0313$) post-operation. Comparison of the UMPS and CMPS-SF scores between groups showed no significant difference ($p > 0.05$). In the EA group, UMPS and CMPS-SF scores were significantly higher at 3, 4, 5, and 6 hours after surgery than baseline measurements ($p \leq 0.0313$). Regarding the SA treatment, scores were significantly higher than baseline values at 2, 3, 4, 5, and 6 hours ($p \leq 0.0313$) after surgery. UMPS and CMPS-SF scores were significantly higher than baseline levels at 4, 5, and 6 hours following ovariohysterectomy in the Combination group ($p \leq 0.0313$).

Two dogs in the SA treatment and one dog in the Combination treatment received fentanyl during surgery. Additionally, two dogs in the SA group (on two occasions) and two dogs in the Combination group received fentanyl as a rescue analgesic after surgery (one of them twice and the other once). There were no significant differences with regard to rescue analgesia administration among groups ($p > 0.05$). Electrocardiogram evaluation did not reveal any considerable arrhythmias among the studied groups.

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Discussion

Neuraxial anesthesia techniques are frequently utilized in conjunction with general anesthesia during small animal surgical procedures to decrease the dose of general anesthetics and mitigate their adverse effects. Furthermore, the addition of local anesthesia offers effective pain relief during and following surgery [2, 3]. Nevertheless, neuraxial techniques may be

associated with specific side effects [2, 8, 10], which have been addressed through the implementation of a combined approach. The integration of SA and EA reduces the doses of both methods and has yielded satisfactory results in human patients [13, 14, 22] and in a single canine case [9]. Based on the authors' knowledge, this study is the first to experimentally assess the physiological and analgesic effects of combined spinal-epidural anesthesia in dogs undergoing ovariohysterectomy under total intravenous anesthesia with propofol. In this study, spinal anesthesia was performed first to establish the spinal component of the neuraxial block through direct intrathecal administration, which is characterized by a rapid onset of action. Epidural anesthesia was subsequently administered as the complementary component, with the aim of supplementing and prolonging the neuraxial analgesic effect. This sequence was therefore selected to obtain the rapid onset associated with spinal anesthesia followed by the potentially longer-lasting contribution of epidural administration.

Although blood pressure reduction in the Combination and SA groups did not exceed the thresholds for hypotension (MAP below 60 and SAP below 80), two cases of hypotension were observed in the EA treatment, which were managed by increasing the Ringer's solution infusion rate. It has been stated that a reduction in blood pressure is a common finding after EA and SA administration, which is caused by local anesthetic drugs [10, 11, 16, 17]. Nevertheless, some studies have not observed hypotension following the administration of EA [23]. The cause of hypotension after EA is the blockade of ganglionic sympathetic afferent fibers, which leads to decreased vascular contractility in the area. The severity of hypotension depends on the balance between sympathetic and parasympathetic systems, the extent of sympathetic blockade, the systemic effects of the local anesthetic, and the level of cardiac filling and efficiency [24]. Regarding the results from the present study, despite the observation of blood pressure decrease after the administration of anesthetics, it seems that

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EA, SA, and combined methods did not cause severe hypotension, and there was no difference among the studied groups in this regard. Furthermore, the increase in HR values after administering anesthetics can be attributed to the reflex tachycardia following a decrease in blood pressure.

f_R decreased in both the EA and Combination groups during surgery, but remained largely unchanged in the SA group. All groups showed EtCO2 levels above the normal 35-45 mmHg range. Reduced f_R combined with elevated EtCO2 signals respiratory depression across the EA and Combination groups. For the SA group, tidal volume was not monitored in the present study; therefore, the mechanism underlying this finding cannot be determined directly. One possible explanation is a reduction in VT and consequently in alveolar ventilation, which could increase $EtCO_2$ despite a stable respiratory frequency. Almeida et al. [4] observed a decline in f_R after EA with bupivacaine in dogs under total intravenous anesthesia with propofol. They attributed this decrease to propofol, noting that normal breathing resumed once anesthesia stopped. Similarly, in this study, reductions in f_R and increases in EtCO2 are likely due to propofol effects, since respiration rates returned to baseline after the cessation of anesthesia.

During postoperative evaluation, overall, HR increased in all groups after surgery, but the earliest return to baseline was observed in the Combination group, followed by the SA group, and then the EA group. Also, SAP and MAP levels were lower in the EA treatment than in the Combination treatment from 60 to 180 minutes after surgery. Therefore, until about three hours post-surgery, blood pressure in the EA group was lower than in the Combination group. Furthermore, blood pressure values in the SA group were between those of the other two groups. Almeida et al. [4] reported that HR values in dogs anesthetized with propofol and receiving EA with bupivacaine had a declining trend up to 90 minutes after ovariohysterectomy, which is contrary to the results of the present study; the researchers also

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reported that blood pressure values were below the baseline measurements from 30 minutes to 90 minutes post-operation in dogs. The cause of low blood pressure in dogs after surgery appears to be similar to that during surgery: the sympathetic block. However, based on the results of the current study, it seems that sympathetic block in the Combination group resulted in a smaller decline in blood pressure compared to the SA and EA groups. It appears that, similar to the previously mentioned issue regarding the increase in HR during anesthesia, HR values rose in all groups after surgery as a reflex response to the drop in blood pressure. Pain is another possible reason for increased HR and blood pressure, particularly in the Combination group. However, this cannot be confirmed because, at the time points when both HR and blood pressure values increased simultaneously, there was no significant difference among the studied groups in terms of pain scores.

Recovery times were shorter in the SA group than in the EA group, although the difference was not statistically significant. Almeida et al. [4] reported a return to movement time in dogs receiving EA bupivacaine of 229 ± 75 minutes. In the present study, the recovery of motor block was not assessed, but the standing time in the EA treatment was 150 ± 22.8 minutes. Sarotti et al. [16] demonstrated that more dogs receiving SA, compared to those receiving EA, could stand 3 and 4 hours post-surgery. Additionally, Sarotti et al. [11] found that 90% of dogs receiving SA could stand for 5 hours after injection, which is probably 0.5% faster than with EA using bupivacaine [8, 25]. In this study, although the recovery times in the SA treatment appeared faster, the difference was not statistically significant. The head elevation and standing times in the Combination treatment were significantly shorter than in the EA treatment. Human research indicates that patients receiving both EA and SA recover movement faster than those receiving only SA [13, 22]. However, a meta-analysis of human studies found no significant difference between the two methods regarding the return of motion [26].

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In this experiment, two dogs in the SA group and one dog in the Combination group received fentanyl during surgery. Therefore, it appears that the analgesia provided by the local anesthetic injection was not sufficient in the aforementioned dogs to manage pain during the operation. The success rates of the three methods used to induce analgesia during surgery were 100% for EA, 71.5% for SA, and 83% for the Combination group. Adami et al. [27] reported that the success rate of the SA following injection of ropivacaine was 100%. In another study, 29% of dogs that received SA required fentanyl injections during surgery [17]. In another experiment by Sarotti et al. [10], SA could not prevent cardiovascular changes caused by pain during surgery in dogs. Regarding EA, after administration of EA, three of the eleven dogs received fentanyl for pain during surgery in a study by Caniglia et al. [28]. A clinical report in a dog evaluated analgesia during surgery after using a combined EA and SA as effective [9]. Concerning the matters as mentioned earlier, it appears that although there is a chance of failure in all three methods, each has the necessary effectiveness to provide adequate analgesia during surgery.

Comparison of the measured VAS pain scores among the studied groups showed they were higher at 6 hours after surgery in the SA group compared to the EA; however, evaluated pain scores in both the UMPS and CMPS-SF methods did not show a significant difference between the studied groups. Overall, the intra-treatment comparison revealed that pain began to reappear sooner in the SA treatment, with the EA and Combination treatments showing later return, respectively. It should be noted that two dogs in the SA group and two dogs in the Combination group exhibited pain symptoms during the assessment and were given fentanyl as rescue analgesia. Almeida et al. [4] assessed EA blockade with bupivacaine in dogs and reported that none of the animals needed rescue analgesia until 6 hours post-surgery. In another study, dogs that received a combination of lidocaine and bupivacaine for EA did not require analgesic injections until 6 hours after surgery [28]. Following EA in dogs that

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underwent tibial plateau levelling osteotomy, McCally et al. [29] reported that two of fourteen dogs required rescue analgesia after the operation. In another study conducted by Odette and Smith [30], one of twenty dogs required an analgesic injection after surgery following the EA injection with bupivacaine. The CMPS pain score was below six after SA for at least 5 hours post-surgery in dogs, and no analgesics were needed [16]. In a clinical report, Novello and Corletto [9] stated that the combination of EA and SA can offer effective postoperative pain relief in a dog. Regarding the abovementioned matter, it appears that the rate of complete analgesia with EA is high, whereas with SA, the requirement for analgesics in the postoperative period is greater, and these findings are in accordance with the results of the present study.

This study has several limitations. Foremost, no prior sample size calculation was performed, and a relatively small sample size was used, which may limit the generalizability of the findings; a larger cohort could reveal significant differences among treatment groups in both physiological variables and the administration of rescue analgesia. Budget and resource limitations, including restricted facility access, reduced our ability to enroll more dogs and broaden the scope of the investigation. Second, motor block was not evaluated because animals tolerated general anesthesia and in the time of motor recurrence might not have been enough alertness to show motor activity changes. Because the primary objective of this study was to compare analgesic efficacy rather than motor-sparing effects, motor assessment was omitted to avoid misinterpretation. Third, the 6-hour postoperative evaluation provides only a short-term perspective and does not capture longer-term analgesic outcomes. Although this duration supports initial conclusions, a longer follow-up would yield a more comprehensive understanding of sustained pain control and recovery. Despite these limitations, the study provides valuable foundational data on the comparative effects of epidural, spinal, and

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combined spinal-epidural analgesia in dogs and offers a framework for future, more expansive work that can inform clinical decision-making and translational applications.

Conclusions

All three methods employed in the current study effectively provided analgesia for dog surgery. Moreover, the combined anesthesia showed comparable cardiorespiratory stability with effective analgesia; a faster head elevation and standing time were observed for combined anesthesia vs. epidural only, requiring confirmation in further studies.

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Materials and Methods

Study design

A prospective, randomized, and experimental study was designed. All experimental procedures were approved by the Faculty of Veterinary Medicine ethics committee at the Shahid Chamran University of Ahvaz (EE/1400.24.3.88369/SCU.ac.ir). All animal experiments were performed in accordance with relevant national and international guidelines.

A total of 19 healthy mongrel female dogs, ages ranging from 1.5 to 2.5 years, with an average weight of 21.2 ± 4.4 kg, and American Society of Anesthesiologists (ASA) I-II were used. The studied dogs were randomly (https://randomizer.org/) divided into three groups: EA (n = 6), SA (n = 7), and combined EA and SA (Combination; n = 6). All dogs, belonging to a private shelter aimed to preserve mongrel dogs and controlling their population, were brought to the faculty's surgery lab and kept in individual cages for two weeks before the experiment. All animals underwent a thorough examination, including a complete physical examination, a complete blood count (CBC), and a total protein (TP) test. Dogs were excluded from the study if any signs of anatomic abnormalities, skin infection at the injection sites, or pregnancy

were diagnosed. Before the procedures began, food was withheld for 12 hours; however, animals had free access to water for up to two hours prior to surgery.

Procedures

The dogs were weighed on the day of examination. Next, they were taken to the surgery room and given 30 minutes to acclimatize to the environment. Then, their heart rate (HR), respiratory rate (f_R), and rectal temperature (RT) were recorded before premedication. Non-invasive arterial blood pressure (systolic [SAP], diastolic [DAP], and mean [MAP] arterial pressures) was also measured using a multiparametric monitoring device (Burtons Veterinary patient monitor PM-9000-2, UK) with an appropriately sized cuff placed over the dogs' metatarsal region.

Anesthetic protocol

All animals were premedicated with intramuscular acepromazine (0.05 mg/kg; Sedam, Pasteur-Filiala Filipeşti S.R.L., Romania) and morphine (0.5 mg/kg; Morphin Sulphate 10 mg/mL, Darou Pakhsh Pharmaceutical MFG Co, Iran). Then, the dogs were placed on a table, an intravenous catheter was inserted into their cephalic veins, and their skin hair over the third lumbar to the first sacral vertebrae area, along with the ventral abdominal area from the xiphoid to the pubis, was clipped. The dogs received 100% oxygen through the flow-by method for five minutes. Forty minutes after the premedication, anesthesia was induced using intravenous propofol (6 mg/kg, Propofol 1%, Fresenius Kabi Ltd, UK) administration through the pre-placed catheter. The injection was titrated until endotracheal intubation was possible. Following endotracheal intubation, the dogs were connected to an anesthetic machine and received 100% oxygen (100 mL/kg/min). Using a syringe pump, Anesthesia was maintained with a continuous infusion rate (CRI) of propofol (0.4 mg/kg/min). During anesthesia, all dogs received Ringer's solution (5 mL/kg/h, Ringer, Shahid Ghazi Pharmaceutical Co, Iran)

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intravenously. Ventrodorsal and lateral radiographs were then taken from the dogs to confirm the absence of pregnancy and detect any spinal abnormalities.

Local anesthetic injections

About 5 minutes after the initiation of anesthesia, the animals were positioned in sternal recumbency, with each dog's hindlimbs flexed symmetrically into a frog-legged position and carefully adjusted until there was no tension felt in the hindlimb muscles and joints [15]. The area over the animal's lumbar to sacral region was then prepared aseptically using 70% alcohol and 7.5% scrub solutions. Subsequently, 1 ml of lidocaine (Lidocaine 2%, Pasteur Institute, Iran) was injected into the subcutaneous tissues at the designated injection sites. Afterwards, the dogs were randomly assigned to three groups: SA (n = 7), EA (n = 6), and Combination (n = 6).

Concerning the EA group, the mixture comprised bupivacaine (Bupivacaine, 5 mg/mL, Mylan, France) administered at a dose of 1 mg/kg [16]. The final volume was 0.35 mL/kg; therefore, Normal saline solution (Sodium chloride 0.9%, SAMEN Pharmaceutical Co., Iran) was employed to achieve the targeted volume in this group [4]. The injection was performed using a Tuohy needle (Disposable epidural needle, 20G, Zhejiang Runqiang Medical Instruments Co., China), which was inserted perpendicularly into the epidural space through a median approach between the L7 and S1 vertebrae. The entry into the epidural space was confirmed by a sudden loss of resistance, the absence of blood or cerebrospinal fluid (CSF) in the needle hub, and the use of the hanging drop method.

Regarding the SA group, the mixture contained bupivacaine (0.22 mg/kg); its final volume was 0.16 mL/kg [17]. Similar to the EA group, Normal saline solution was used to reach the aforementioned volume. The mixture was injected using a spinal needle (Disposable spinal needle 20G & 22G × 90mm, Dr. Japan Co, Japan) via a median or paramedian approach at the intervertebral space between L6 and L7. The needle was inserted at an angle of 30 to 45

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degrees. The landmarks for entering the subarachnoid space included observing CSF in the needle hub or noting tail or hindlimb muscles twitching [18].

In the Combination treatment, the bupivacaine doses used for the EA and SA injections were half (0.5 mg/kg and 0.11 mg/kg, respectively), yet the volumes remained unchanged (adjusted to 0.35 mL/kg and 0.16 mL/kg, respectively, using Normal saline solution). In this group, the SA injection was administered before the EA injection, with a 5-minute interval between procedures.

The injection rate was maintained at 1 mL over 40 seconds across all groups. Furthermore, dogs were excluded from the study following three consecutive unsuccessful attempts if the aforementioned criteria remained unmet.

Performing surgery and monitoring

About 15 minutes after the injections were administered, the animals were placed in dorsal recumbency, their ventral abdominal areas prepared aseptically, and they underwent ovariohysterectomy surgery following the standard method [19].

HR, indirect blood pressure (SAP, DAP, MAP), f_R, RT, peripheral capillary oxygen saturation (SpO2), and end-tidal carbon dioxide (EtCO2) were continuously monitored during anesthesia and surgery. All patients breathed spontaneously unless EtCO2 exceeded 45 mmHg, at which point manual intermittent positive pressure ventilation was used to restore and maintain normocapnia. During surgery, efforts were made to maintain the animals' body temperature between 37-38 °C using blankets and warm water bags. During operation, an increase of at least two parameters—HR, MAP, or f_R—by 20% or more above the baseline (pre-incisional values) was considered a sign of pain (Sarotti et al. 2011), and fentanyl at a dose of 3 μg/kg was administered intravenously to induce analgesia (Adami et al. 2016). Additionally, if the MAP fell below 60 mmHg for 5 minutes or any MAP dropped below 55 mmHg, the rate of Ringer's solution injection would be increased until the MAP rose above

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60 mmHg (Sarotti et al. 2011). Electrocardiograms (Lead II) were recorded from the animals during anesthesia and surgery.

At the end of the surgical procedure, propofol and Ringer's solution were discontinued; however, the animals continued to receive oxygen via the tracheal tube until the swallowing reflex reappearance. Then, the tracheal tube was withdrawn, and all subjects were administered intramuscular cefazolin (20 mg/kg, Cefazolin 1g, Dana Pharmaceutical Co., Iran) every 12 hours for three days.

All anesthesia procedures, including anesthesia induction, maintenance, and local anesthesia administration, were done by HIR. All data were measured and recorded by MJ. MJ, anesthetists, surgeons, and the statistician were unaware of the treatments.

Assessments

Anesthesia, surgical procedure, and recovery durations were documented, including the return of the swallowing reflex, head elevation, lying on the sternum, and standing. The anesthesia duration is defined from the initiation of tracheal intubation to the removal of the tracheal tube. Additionally, the surgical time was calculated from the commencement of skin incision to the final skin suture. HR, indirect blood pressure, f_R, and RT values were recorded as baseline (before anesthesia) and five minutes prior to the beginning of surgery (T0). Subsequently, during the surgery, alongside the parameters mentioned above, SpO2 and EtCO2 levels were recorded at the following intervals: skin incision (T1), incision and opening of the abdominal muscles (T2), ligation of the uterine structures (T3), and skin suturing (T4). After the surgical procedure, HR, blood pressure, f_R, and RT were recorded at 5, 15, 30, 45, 60, 75, and 90 minutes, followed by measurements every 30 minutes up to 6 hours post-operation. These measurements were obtained using a monitoring device, an appropriately-sized cuff, a stethoscope, and a digital thermometer.

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During the postoperative period, animals' pain levels were monitored and scored using the Visual Analogue Scale (VAS), University of Melbourne Pain Scale (UMPS), and the short form of the Glasgow Composite Measure Pain Scale (CMPS-SF) at 30 minutes, 1 hour, and then hourly up to 6 hours after ovariohysterectomy. When evaluating the animals' pain, if the VAS score was three or higher, or the UMPS score was above 8, or the Glasgow system score surpassed 5 out of 20 or 6 out of 24, fentanyl (1 µg/kg) was administered intravenously as a rescue analgesic [20, 21].

After the 6 h assessment, all dogs received flunixin meglumine (Flunixin Meglumine 50 mg/mL, Razak, Iran) 0.1 mg/kg SC once daily for 3 days. Dogs were monitored twice daily by the veterinarian for appetite, wound, pain, and adverse events for 2 weeks. No additional rescue or wound complications were observed.

Statistical analysis

Data were analyzed using GraphPad Prism Version 9.0 (GraphPad Software Inc., CA, USA). The Shapiro-Wilk test was used to evaluate the normal distribution of the data. To compare dogs' weights, the amount of propofol used for induction, the amount of bupivacaine used, anesthesia and surgery durations, recovery time, and alterations in HR, blood pressures, f_R, RT, SpO2, and EtCO2, one-way ANOVA was employed, and subsequently, the Bonferroni test was utilized if needed. HR, blood pressures, f_R, RT, SpO2, and EtCO2 were tested for normality by the Shapiro-Wilk test and analysed by two-way repeated-measures ANOVA with group as the between-subject factor and time as the within-subject factor, including group × time interaction. Sphericity was assessed by Mauchly's test, with Greenhouse-Geisser correction when violated. When the omnibus F was significant ($P<0.05$), Bonferroni-adjusted pairwise between-group comparisons were performed at each time-point. To compare pain scores among and within treatments, Kruskal-Wallis and Dunn's multiple comparison tests and the Friedman test were employed, respectively. A Fisher-Freeman-Halton exact test was

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used to compare the number of rescue analgesia administrations among groups. Post-rescue observations after the time of rescue were censored from subsequent time-points; pre-rescue data were retained. Normal values were reported as mean ± standard deviation (SD), while non-parametric values were presented as a median (minimum-maximum). A significance level was considered at $p < 0.05$.

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Figure legends

Figure 1- Mean ± standard deviation of heart rate (HR), systolic, diastolic and mean arterial blood pressure (SAP, DAP, and MAP, respectively, respiratory rate (f_R), and rectal temperature (RT) in the postoperative period in dogs receiving epidural (EA; n = 6), spinal (SA; n = 7), or spinal-epidural combination (Combination; n = 6) with bupivacaine, under total intravenous anesthesia with propofol in ovariohysterectomy.
* Significant difference from the EA and SA groups, ** Significant difference between the EA and Combination groups, *** Significant difference between the SA and Combination groups, τ Significant difference compared to timepoint in the EA group, θ Significant difference compared to baseline in the SA group, δ Significant difference compared to baseline in the Combination group ($p < 0.05$).

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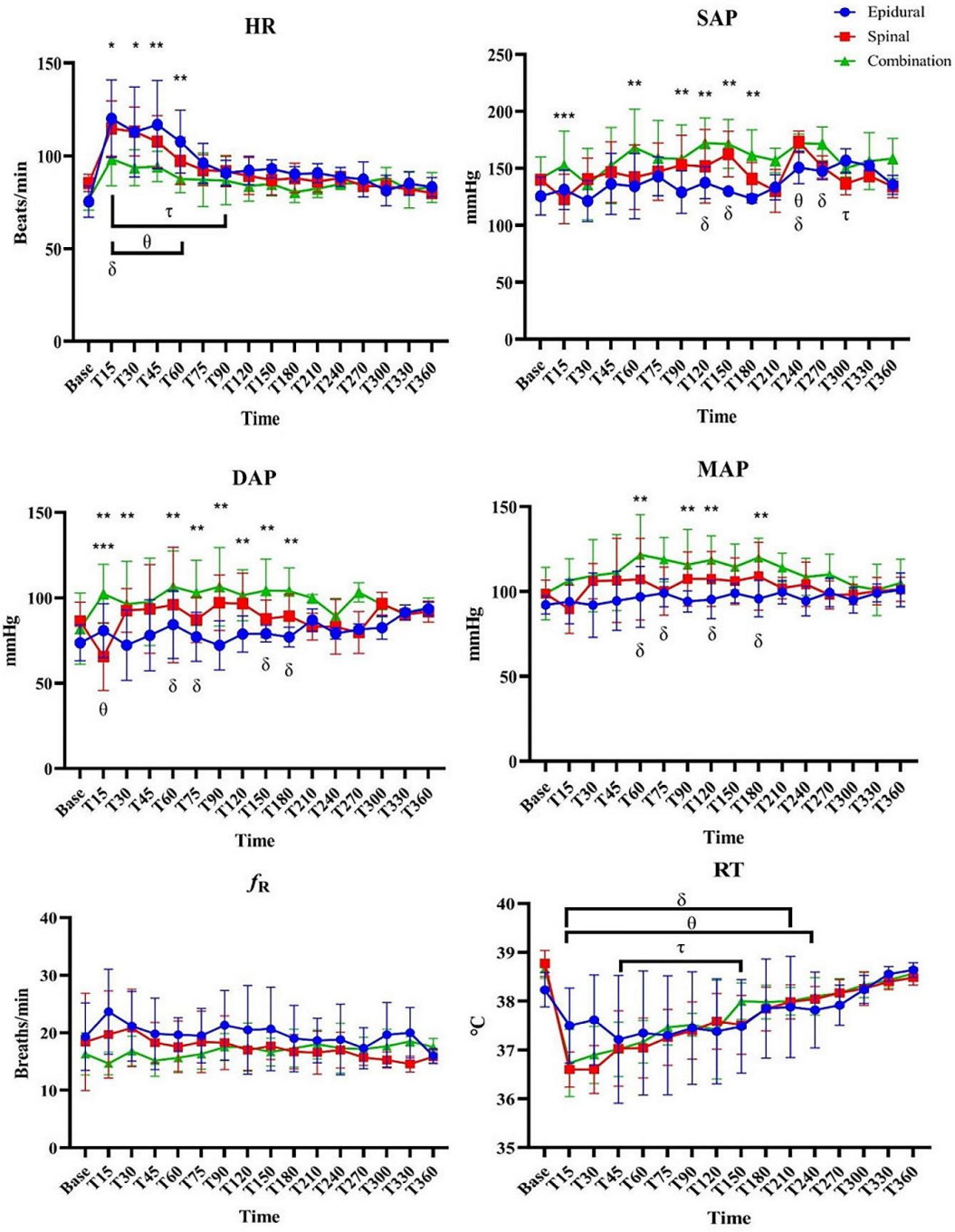
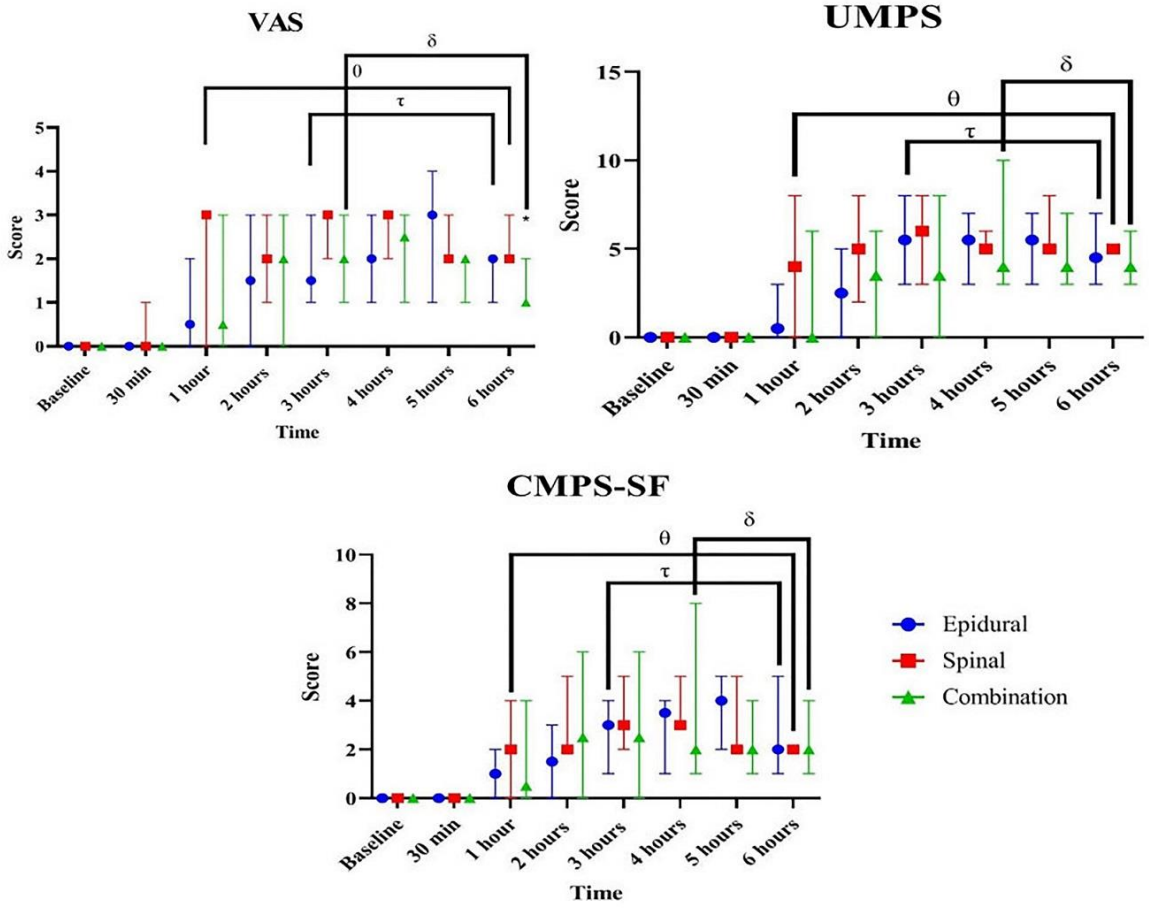

HR
Beats/min
Time
SAP
mmHg
Time
Epidural
Spinal
Combination
DAP
mmHg
Time
MAP
mmHg
Time
f_R
Breaths/min
Time
RT
°C
Time
Base
T15
T30
T45
T60
T75
T90
T120
T150
T180
T210
T240
T270
T300
T330
T360

Figure 2- Median and range (minimum-maximum) of pain scores (Visual Analogue Scale (VAS), University of Melbourne Pain Scale (UMPS), and the short form of the Glasgow Composite Measure Pain Scale (CMPS-SF)) in the postoperative period in dogs receiving epidural (EA; n = 6), spinal (SA; n = 7), or spinal-epidural combination (Combination; n = 6) with bupivacaine, under total intravenous anesthesia with propofol in ovariohysterectomy. * Significant difference between the SA and Combination groups, τ Significant difference compared to baseline in the EA group, θ Significant difference compared to baseline in the SA group, δ Significant difference compared to baseline in the Combination group ($p < 0.05$).



عنوان مقاله: اثرات بی‌حسی اپیدورال، اسپاینال و ترکیبی اسپاینال–اپیدورال بر متغیرهای قلبی–تنفسی و بی‌دردی پس از عمل در سگ‌های تحت عمل جراحی برداشت رحم و تخمدان

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نویسندگان:

مائده جواهری[۱]، هادی ایمانی راستابی [۱]، معصومه عزتی گیوی[۲]، بهمن مصلی‌نژاد[۱]

[۱] گروه علوم درمانگاهی، دانشکده دامپزشکی، دانشگاه شهید چمران اهواز، اهواز، ایران

[۲] گروه علوم پایه، دانشکده دامپزشکی، دانشگاه شهید چمران اهواز، اهواز، ایران

نویسنده مسئول: دکتر هادی ایمانی راستابی

آدرس پستی: گروه علوم درمانگاهی، دانشکده دامپزشکی، دانشگاه شهید چمران اهواز، اهواز، ایران

ایمیل سازمانی: h.imani@scu.ac.ir

شماره تلفن: ۰۹۱۳۳۸۲۳۳۲۴

خلاصه فارسی: بی‌حسی اپیدورال و اسپاینال به‌طور مکرر در حیوانات کوچک استفاده می‌شوند، هرچند ممکن است عوارض جانبی نامطلوبی نیز ایجاد کنند. استفاده ترکیبی از بی‌حسی اپیدورال-اسپاینال ممکن است دوز داروهای مجزا را کاهش داده و نتایج مطلوب‌تری به همراه داشته باشد. این مطالعه آینده‌نگر، تصادفی و کور اثرات قلبی-تنفسی و کارایی ضددردی بی‌حسی اپیدورال، اسپاینال و ترکیب اسپاینال-اپیدورال را در سگ‌های تحت عمل جراحی برداشت رحم و تخمدان مقایسه کرد. نوزده قلاده سگ نژاد مخلوط سالم با آسپرومازین و مورفین دریافت کردند و با پروپوفول القا (۶ میلی‌گرم بر کیلوگرم) و نگهداری (۰/۴ میلی‌گرم بر کیلوگرم در دقیقه) شدند. سپس سگ‌ها بوپیواکائین را از طریق اپیدورال (۱ میلی‌گرم بر کیلوگرم با حجم نهایی ۰/۳۵ میلی‌لیتر بر کیلوگرم، تعداد =۶)، اسپاینال (۰/۲۲ میلی‌گرم بر کیلوگرم با حجم نهایی ۰/۱۶ میلی‌لیتر بر کیلوگرم، تعداد =۷)، یا ترکیبی از بی‌حسی اپیدورال و اسپاینال (تعداد =۶) دریافت کردند. در گروه ترکیبی، حجم‌ها برابر و دوزها نصف شد. متغیرهای فیزیولوژیک، زمان‌های بهبودی و نمرات درد در بازه‌های زمانی از پیش تعیین‌شده ثبت شدند. در همه گروه‌ها، ضربان قلب در حین جراحی افزایش یافت، در حالی که فشار متوسط شریانی در چند نقطه زمانی از سطح پایه کاهش نشان داد. نمرات درد تفاوت معنی‌داری بین گروه‌های درمانی نداشت و هر سه روش بی‌دردی قابل قبولی در دوره حین و پس از عمل فراهم کردند. فنتانیل رهایی‌بخش به دو سگ در گروه اسپاینال و دو سگ در گروه ترکیبی تجویز شد و تفاوت معنی‌داری بین گروه‌ها مشاهده نشد. زمان کوتاه‌تری برای بلند کردن سر و ایستادن در گروه ترکیبی نسبت به گروه اپیدورال مشاهده شد. در مجموع، روش ترکیبی اسپاینال-اپیدورال ممکن است تغییرات قلبی-تنفسی قابل مقایسه و بی‌دردی مؤثر همراه با ریکاوری سریع‌تری ایجاد نماید.

واژگان کلیدی: بوپیواکائین، سگ، بی‌حسی اپیدورال، جراحی برداشت رحم و تخمدان، بی‌حسی اسپاینال